**Appendix D: Characteristics of Included Studies [ordered by study ID]**

**Amr 2010**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 3 arms, placebo-controlled trial for 6 months | |
| **Participants** | 150 patients scheduled for either partial or radical mastectomy with axillary dissection | |
| **Interventions** | In the (Group 1) venlafaxine group, patients received 37.5 mg of venlafaxine extended release along with another capsule (identical in appearance to the gabapentin capsules) once daily at bed time. Patients in the (Group 2) gabapentin group received 300 mg of gabapentin and another capsule (identical in appearance to the venlafaxine extended release capsules) once daily at bed time. Patients in the (Group 3) placebo group received 2 capsules that were filled with thin sugar (1 identical in appearance to the gabapentin capsules and the other identical to venlafaxine extended release capsules) once daily at bed time. Administration of the drugs started the evening before surgery and continued for the first 10 postoperative days, including the day of the surgery. | |
| **Outcomes** | Pain scores at rest and movement-induced, morphine consumption, and side effects profile | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Anesthesia was induced with thiopental and fentanyl. Intubation of the trachea was facilitated with rocuronium, anesthesia was maintained with isoflurane, 70% nitrous oxide in  oxygen, and incremental rocuronium doses were repeated  to maintain neuromuscular block.  Post-op: morphine the first 24 hours; acetaminophen + codeine during the rest of the follow-up (POD 2-10) | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | Shuffling envelopes: "A prospective, randomized (sealed envelopes indicate the group of assignment) ... |
| Allocation concealment (selection bias) | Low risk | "An independent anesthesiologist, who did not participate in the study or data collection, read the number contained in the envelope and made group assignments". |
| Blinding of participants and personnel (performance bias) | Low risk | "Control (sugar filled) and/or treatment capsules for each group were packaged in group-specific bottles and coded as Bottle 1, Bottle 2, and Bottle 3 for Groups 1, 2, and 3, respectively. Yellow hard gelatin capsules (identical in appearance to the gabapentin capsules) and gray/peach capsules (identical in appearance to the venlafaxine extended release capsules) were filled with thin sugar. Envelopes, bottles with capsules, and coding were prepared by the pharmacy of the hospital. |
| Blinding of outcome assessment (detection bias) | Low risk | "double-blind design was used, with both patients and postoperative assessors blinded to management protocol" |
| Incomplete outcome data (attrition bias) | Low risk | The authors reported no missing outcome data |
| Selective reporting (reporting bias) | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | Low risk | No other potential sources of bias were detected |

**Anwar 2019**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicentre (2 centres), randomized, double-blind, 3 arm, placebo controlled trial, follow-up for 6 months. | |
| **Participants** | 150 patients scheduled for cardiac surgery via sternotomy | |
| **Interventions** | Pregabalin: 1 preoperative day and 14 postoperative days of 150-mg pregabalin capsules, alongside 48 postoperative hours of placebo (normal saline) infusion.  Pregabalin + Ketamine: 1 preoperative day and 14 postoperative days of 150-mg pregabalin capsules, alongside 48 postoperative hours of ketamine infusion at 0.1 mg · kg−1 · h−1.  Placebo: Placebo capsules and IV normal saline | |
| **Outcomes** | Primary outcome: The proportion of patients with clinically meaningful pain at 3 and 6 months after cardiac surgery.  Secondary outcomes: Clinically meaningful acute pain scores at the sternotomy and saphenectomy sites, total morphine consumption. Recovery from surgery, time to extubation, times to readiness for discharge from intensive care and hospital, and safety measures of respiratory rate and arterial carbon dioxide partial pressure at 24 h after surgery and any episode of inpatient diplopia, a common transient side effect of pregabalin use in naïve patients. Changes in sensory testing after surgery were also recorded as secondary outcomes, as well as potential biomarkers of drug efficacy. | |
| **Notes** | Co-analgesia:  Pre-op: None reported  Intra-op: Anesthesia was induced with propofol and fentanyl (restricted to a total intraoperative dose of 7.5-20 μg/kg) and maintained with isoflurane, before cardiopulmonary bypass, before converting to intravenous infusion of propofol for the remainder of the perioperative period. Remifentanil was prohibited in this study.  Post-op: All patients received the usual care of patient-controlled analgesia (morphine at 1 mg/ml per bolus with a  lockout period of 5 min) and regular paracetamol at 1 g  every 6 h for the duration of the hospital stay. Supplementary regular oral codeine was provided after drain removal, and in addition, oral tramadol was available on demand for breakthrough pain. | |
| **Source(s) of funding** | Supported by the European Association of Cardiothoracic Anaesthesiologists (Rome, Italy). | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "patients were recruited and block-randomized 1:1:1 (in groups of 30) to one of the following three treatment groups, using a computer-generated randomization sequence, created and managed in a blinded manner by the Barts Trials Pharmacy" |
| Allocation concealment (selection bias) | Low risk | "Allocation concealment was achieved by the use of study capsules and intravenous infusions with identical appearance for active and placebo drugs. Pregabalin study capsules were supplied by Pfizer (Surrey, UK) with no other contribution to the design, conduct, analysis, or publication of this trial. Sealed 50-ml syringes containing clear ketamine or placebo (0.9% saline) solution were prepared in a blinded manner by the clinical trials unit at St. Bartholomew’s Hospital, with no other involvement in patient care. Per-patient release of drug to the research assistants (after evaluation of eligibility, informed consent, and enrolment of participants) ensured that blindness was maintained throughout until all follow- up assessments were completed, and the data sets were locked and submitted to the trials pharmacy for release of the randomization code." |
| Blinding of participants and personnel (performance bias) | Low risk | "Allocation concealment was achieved by the use of study capsules and intravenous infusions with identical appearance for active and placebo drugs... Per-patient release of drug to the research assistants (after evaluation of eligibility, informed consent, and enrolment of participants) ensured that blindness was maintained throughout until all follow- up assessments were completed, and the data sets were locked and submitted to the trials pharmacy for release of the randomization code." |
| Blinding of outcome assessment (detection bias) | Low risk | "Per-patient release of drug to the research assistants (after evaluation of eligibility, informed consent, and enrolment of participants) ensured that blindness was maintained throughout until all follow- up assessments were completed, and the data sets were locked and submitted to the trials pharmacy for release of the randomization code." |
| Incomplete outcome data (attrition bias) | Low risk | Missing data <20%. Lost to follow-up of 2 patients at 3 and 6 months unlikely related to study drugs (1 death 7 days post-surgery and 1 emigration) |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | Low risk | Unable to find additional potential bias. 50 participants per study arm and persistent pain was the primary outcome. |

**Aveline 2014**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 3 arms, placebo-controlled trial, follow-up for 12 months. | |
| **Participants** | 75 patients scheduled for elective unilateral total knee arthroplasty performed with a midline skin incision and parapatellar approach | |
| **Interventions** | In the (Group 1) ketamine patients received: 0.2mL/kg  bolus over 20 minutes started before surgical incision, followed  by a continuous infusion of 120 mg/kg/h until the end  of surgery, and then 60 mg/kg/h until the second postoperative  day. In the (Group 2) nefopam patients received: 0.2mL/kg  bolus over 20 minutes started before surgical incision, followed  by a continuous infusion of 120 mg/kg/h until the end  of surgery, and then 60 mg/kg/h until the second postoperative  day. Patients in the (Group 3) placebo group received an equal volume of saline considered as placebo. | |
| **Outcomes** | The incidence of CP, 1 year after surgery, unrelated to surgical complication, and defined by VAS-M score ≥ 40 mm during stair-climbing with walking up and down 10 stairs of 15 cm height. | |
| **Notes** | Co-analgesia:  Pre-op: Alprazolam one hour before surgery.  Intra-op: General anaesthesia was induced with propofol, remifentanil, and a single bolus of cisatracurium for tracheal intubation. Anaesthesia was maintained with sevoflurane with 50% nitrogen in oxygen. Twenty minutes before skin closure, all patients received an IV bolus of morphine and droperidol.  Post-op: first 48 hours, PCA morphine hydrochloride, 400mg paracetamol and 30mg dextropropoxyfen every 6 hours, 150mg ketoprofen twice daily, and immediate release morphine sulfate up to 4 tablets a day. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "They were allocated randomly to one of the three groups, according to a computer-generated list of random numbers." (see primary article Aveline 2009) |
| Allocation concealment (selection bias) | Unclear risk | "An opaque and sealed envelope was prepared for each patient." The use of assignment envelopes is described but it remains unclear whether envelopes were sequentially numbered. |
| Blinding of participants and personnel (performance bias) | Low risk | "Double-Blinding was ensured by using blinded syringes prepared by a nurse not involved in any part of the study who opened the envelope on the morning of surgery."… "Patients, surgeons and health care providers involved in patient care, data collection, and postoperative follow-up, were unaware of the group allocation." |
| Blinding of outcome assessment (detection bias) | Low risk | "The current study is a 6-month (M6) and 12-month (M12) follow-up of the patients included in the first study. These patients received a phone call by an observer blinded to their allocation in the 3 groups of the first study and to the results of this study, and were invited to participate in an outcome study at M6 and 1 year after surgery. All patients provided a written informed consent to participate. All measurements were taken by the same physiotherapist not involved in the original study." |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was below 20%. Lost to follow-up: 1/25 Ketamine group, 3/25 Nefopam group, 2/25 Placebo group |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. |

**Beaussier 2018**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicentre, randomized, double-blind, 3 arms, placebo controlled trial, follow-up for 6 months. | |
| **Participants** | 95 patients scheduled for laparoscopic left colectomy | |
| **Interventions** | Lidocaine: a continuous infusion of intravenous lidocaine 1.5% (Autofuseur elastomeric pump) was set at 4 ml/h for 48 h, after an initial starting bolus of 6 ml lidocaine 1%. An infusion of saline was concomitantly delivered through the wound catheter for 48 h.  CWI group: wound catheter with a solution of 0.2% ropivacaine 10 ml/h for 48 h immediately after an initial starting bolus of 10 ml. An infusion of saline solution was concomitantly delivered through the intravenous peripheral analgesic line for 48 h.  Saline: both the analgesic intravenous line and the multi-hole wound catheter were perfused with a saline solution for 48 h. | |
| **Outcomes** | Primary outcome: the ratio between the area of hyperalgesia around the abdominal wound incision and the incision size at postoperative hour 72  Secondary outcomes: Postoperative pain intensity was evaluated at rest and during movement (peak-flow manoeuvre) ... every day until the patient’s discharge from hospital. Residual postoperative pain at 3 and 6 months was evaluated with a telephone call. Patients were asked about pain or discomfort located around the abdominal incision. If a sensation of pain persisted, the DN4 questionnaire was used to verify its neuropathic origin | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Anaesthetic induction used propofol, sufentanil and atracurium. Endotracheal intubation was performed and minute ventilation was adjusted to keep PCO2 between 35 and 40 mmHg during the procedure. Anaesthetic maintenance was provided by desflurane in a mixture of 50/50% O2/N2O and continuous infusion of sufentanil and atracurium according to neuromuscular monitoring. Additionally, all patients received repeated intravenous administration of acetaminophen (Perfalgan 1 g) every 6 h for 48 h.  Post-op: Once in the recovery room, according to pain intensity, intravenous morphine titration was started using repeated boluses of 2 mg every 5 min until VAS ≤ 30 mm. Thereafter, the PCA device was connected and set to deliver boluses of 1 mg morphine with a free interval of 5 min. | |
| **Source(s) of funding** | The sponsor was Assistance Publique – Hôpitaux de Paris  (Departement de la Recherche Clinique et du Developpement). The study was funded by a grant from Assistance Publique – Hôpitaux de Paris (PHRC no. 08028). | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Patients were randomized in a 1:1 ratio. Centralized block balance randomization was prepared by URC-Est." |
| Allocation concealment (selection bias) | Low risk | "Centralized block balance randomization was prepared by URC-Est." |
| Blinding of participants and personnel (performance bias) | Low risk | "The area of hyperalgesia was determined by punctuate mechanical stimulation using calibrated von Frey hairs... by investigators blinded to the administered treatment. Statistical analyses were performed blind to treatment allocations." "double-blind controlled study" |
| Blinding of outcome assessment (detection bias) | Unclear risk | "Residual postoperative pain at 3 and 6 months was evaluated with a telephone call. Patients were asked about pain or discomfort located around the abdominal incision." There is no mention that investigators conducting the telephone call were blinded. |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20% |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Bergeron 2009**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double blind, placebo-controlled trial with long-term follow-up for 6 weeks and one year | | |
| **Participants** | 18 years or older patients undergoing elective primary total hip arthroplasty using spinal anesthesia to receive either dexamethasone (40 mg intravenous, n = 25) or saline placebo (n = 25) | | |
| **Interventions** | A research collaborator, who did not participate in data collection, prepared an IV infusion bag containing 40 mg of dexamethasone or an equal volume of saline diluted into 40 mL of normal saline according to group allocation. Dexamethasone is colorless and causes no pain when given intravenously. | | |
| **Outcomes** | Pain Scores, Harris Hip Score | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Standard lumbar spinal anesthesia using bupivacaine.  Post-op: Morphine PCA, acetaminophen and Ibuprofen | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Not reported |
| Allocation concealment (selection bias) | | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | | Low risk | "A research collaborator, who did not participate in data collection, prepared an IV infusion bag containing 40 mg of dexamethasone or an equal volume of saline diluted into 40 mL of normal saline according to group allocation. Dexamethasone is colorless and causes no pain when given intravenously". |
| Blinding of outcome assessment (detection bias) | | Low risk | "The patients, anesthesiologists, nurses, and research coordinators gathering the data were blinded to the study arms". |
| Incomplete outcome data (attrition bias) | | Low risk | "We lost 10 patients to follow-up for nonmedical reasons due to a large referral network outside our province where patients are routinely followed radiographically and by phone interview". |
| Selective reporting (reporting bias) | | Unclear risk | Insufficient information to permit judgment |
| Other bias | | Unclear risk | Fewer than 50 patients per arm |

**Bilgen 2012**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double blind, four arm, placebo-controlled trial, follow-up for 12 months. | | |
| **Participants** | 140 ASA I-II term pregnant, nulliparous women in whom Cesarean delivery was indicated, using Pfannenstiel incision. | | |
| **Interventions** | Group 1: ketamine 0.25 mg kg-1; group 2: ketamine 0.5  mg kg-1; group 3: ketamine 1 mg kg-1; group 4: placebo (0.9% normal saline). After preoxygenation, the study drug or placebo was given to patients. | | |
| **Outcomes** | Patients were evaluated for persistent postoperative pain at 2 weeks, 1 and 6 months, and 1 year. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Anaesthesia was induced with propofol. Muscle relaxation was provided by rocuronium. Anesthesia was maintained with 50% oxygen in N2O and sevoflurane.  Post-op: PCA morphine chloride for 48h, rescue analgesia with intramuscular diclofenac sodium. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Enrolled participants were randomized to one of four groups (N.=35 each) using a computer-generated random number table" |
| Allocation concealment (selection bias) | | Unclear risk | "Randomization and allocation of the enrolled participants into intervention groups according to the computerized numbers was performed by an anaesthesiologist who did not participate in the conduct of the trial. Study drugs were prepared by an anesthesiologist independent of the study. " The method of concealment is not described. |
| Blinding of participants and personnel (performance bias) | | Low risk | "The participants, care givers, and those assessing the outcomes were blinded to group assignment." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Low risk | "...those assessing the outcomes were blinded to group assignment." |
| Incomplete outcome data (attrition bias) | | Low risk | No missing data or participants lost to follow-up reported. All 140 participants appear to be included in the analysis at 6 months and 1 year. |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. |

**Bouzia 2017**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, 3 arms, placebo-controlled trial, follow-up for 3 months. | |
| **Participants** | 101 patients scheduled for elective primary cardiac surgery with median sternotomy and extracorporeal circulation | |
| **Interventions** | Arm 1: Pregabalin 75mg single dose  Arm 2: Pregabalin:150mg single dose  Placebo: Placebo capsule (formulation not specified) | |
| **Outcomes** | Primary outcome is morphine consumption at 24 hours  3 months after surgery, inquired about the impact of the operation on their lives, and asked specific questions about the presence and severity of pain after surgery | |
| **Notes** | Co-analgesia:  Pre-op: None reported  Intra-op: General anesthesia was induced using etomidate and fentanyl, and intubation was facilitated with vecuronium. Anesthesia was initially maintained using sevoflurane until insertion of a cordis in the right internal jugular vein and placement of a continuous cardiac output/mixed venous oximetry pulmonary artery catheter. Anesthesia was maintained using propofol and remifentanil infusion and sevoflurane was discontinued.  Post-op: Patients received a single 5mg dose of intravenous morphine and patient control analgesia (PCA). Analgesia was supplemented with IV paracetamol 1 gm every 8 hours for the first 24 hours after surgery. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Based on a computer custom number generator, patients were randomly assigned to one of three groups" |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | Unclear risk | "The study drug (pregabalin or placebo) was given to patients by a research coordinator and was documented in the medical record as “study drug.” All anesthesia personnel taking care of patients in the operating room were blinded to group assignment." Identical matching of placebo capsules is not explicitly described |
| Blinding of outcome assessment (detection bias) | Low risk | "An anesthesiologist blinded to group assignment visited the patients in 8 hours and 24 hours after extubation, recorded VRS after a deep breath, documented the presence and severity of nausea and vomiting, and collected data on PCA use and morphine consumption from the Gemstar pump. In addition, a blinded searcher interviewed all patients by telephone 3 months after surgery, inquired about the impact of the operation on their lives, and asked specific questions about the presence and severity of pain after surgery." |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20% |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Brogly 2008**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 6 months | | |
| **Participants** | 50 patients aged 18-75 yr., ASA I-III, undergoing scheduled total or partial thyroidectomy without lymph node dissection | | |
| **Interventions** | Gabapentin 1200 mg PO 2 hours before surgery or matching placebos (placebos are not described) | | |
| **Outcomes** | Primary outcome: analgesic drug consumption was assessed during the procedure and postoperatively in the post anesthesia care unit and after discharge to the ward. Over the first 24 h, pain levels at rest and during swallowing were measured. The day before operation and 6 months after patients were asked to answer a neuropathic pain diagnostic questionnaire (DN2). | | |
| **Notes** | Co-analgesia:  Pre-op: Premedication with oral hydroxyzin 2h preoperatively.  Intra-op: General anesthesia was induced with propofol, sufentanil. Atracurium was injected IV to facilitate orotracheal intubation. A bilateral superficial cervical plexus block (SCPB) was performed. Anesthesia was maintained with propofol and sufentanil.  Post-op: analgesic rescue: paracetamol + tramadol 50 mg | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Randomization was performed by subgroups of 10 patients with a randomization table". |
| Allocation concealment (selection bias) | | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | | Unclear risk | Not reported |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data (3/50) was minimum |
| Selective reporting (reporting bias) | | Unclear risk | Insufficient information to permit judgment |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Brulotte 2015**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arms, placebo controlled trial, follow-up for 3 months | | |
| **Participants** | 114 patients scheduled for elective thoracotomy for various surgeries | | |
| **Interventions** | Pregabalin: 150 mg orally twice daily started 1 hour before the induction of general anesthesia and continued until 4 days after the surgery (total of 10 doses) or matching placebos (placebos are not described) | | |
| **Outcomes** | Primary outcome: The proportion of patients with PTPS 3 months after surgery.  Secondary outcomes PTPS intensity, analgesic requirement to treat PTPS, and the impact of pain on daily activities, all measured with the BPI questionnaire. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: General anesthesia.  Post-op: Thoracic epidural anesthesia bupivacaine + fentanyl, acetaminophen, shoulder pain (VNS, ≥4) was treated with subcutaneous hydromorphone. Pain control after discharge from the hospital consisted of oral hydromorphone, as needed, and acetaminophen for 2 weeks. | | |
| **Source(s) of funding** | This work was supported by a grant from the Department of Anesthesiology, University of Montreal. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were block-randomized (blocks of 4) to 1 of 2 groups based on a computer-generated randomization list prepared by the pharmacy." |
| Allocation concealment (selection bias) | | Low risk | "Placebo and pregabalin capsules were purchased from Galenova/Gentès et Bolduc Pharmacy, Montreal, Quebec, Canada, and were indistinguishable from one another. The capsules were kept at the research pharmacy and distributed to a blinded member of the research team, according to the randomization list. This research team member administered the study drug to the patient, who was also blinded to group allocation." |
| Blinding of participants and personnel (performance bias) | | Low risk | "The capsules were kept at the research pharmacy and distributed to a blinded member of the research team, according to the randomization list. This research team member administered the study drug to the patient, who was also blinded to group allocation." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was below 20%. Lost to follow-up: 6/56 Pregabalin and 7/58 Placebo |
| Selective reporting (reporting bias) | | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Buchheit 2019**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicentre (3 centres), randomized, double-blind, 2 arms, placebo controlled trial, follow-up for 3 months. If a patient was not available at three months, the study outcome was determined at the six-month research visit. | |
| **Participants** | 128 patients presenting for amputation, stump revision, or surgery for a mangled limb | |
| **Interventions** | Valproic acid: oral solution 250 mg 3x per day (750 mg/d)  The initial dose was given by the perioperative anesthesia team. Subsequent doses were stored on the hospital ward or in the intensive care unit (depending on patient disposition) with the patient’s other medications and administered by the nurse every eight hours, up to seven days or until the time of patient discharge from the hospital, whichever came first...the average number of study drug days was 3.7 days  Placebo: similar tasting flavored syrup: | |
| **Outcomes** | Primary outcome: Incidence of chronic pain (defined as pain >=3/10 on the numeric rating scale over the previous week) ...  Secondary outcomes: change in BPI (Pain and Interference scores), DVPRS (Pain and Supplemental scores), opioid use, and neuropathic pain subtypes | |
| **Notes** | Co-analgesia:  Patients in both the placebo and intervention study arms received regional anesthesia (either peripheral nerve or epidural), with multimodal perioperative management according to the standard of care at each of the three institutions. Common non-opioid multimodal analgesics utilized at the study sites included preoperative acetaminophen, nonsteroidal anti-inflammatory drugs (unless contraindicated), gabapentin, and intraoperative ketamine. If patients were already taking gabapentin or pregabalin as part of their outpatient pain control regimen for medical disease, the medications were continued through the perioperative period. | |
| **Source(s) of funding** | This work was supported by the Department of Defense, Congressionally Directed Medical Research Program (CDMRP, PT110575), and CDMRP W81XWH-15–2-0046. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | "randomization was performed within the respective investigational drug pharmacy according to the schedule provided by our statistician. Randomization was stratified by site and surgical intervention with mixed block size, i.e., amputation, amputation revision, or surgery for mangled limb with equal probability of assignment to the valproic acid group or the controlled placebo group" The method for sequence generation is not stated. |
| Allocation concealment (selection bias) | Low risk | "randomization was performed within the respective investigational drug pharmacy according to the schedule provided by our statistician." |
| Blinding of participants and personnel (performance bias) | Low risk | "Patients, investigators, treating medical/surgical team, and study personnel were blinded to the assignment. At each of the study sites, following randomization, an order was then placed to the Investigational Drug Service (IDS). The IDS pharmacist assigned treatment class according to the randomization schedule. The Investigational Drug Pharmacist was the only person aware of treatment allocation until the close and unblinding of the study data for analysis. "The study medication (valproic acid oral solution or placebo [similar tasting flavored syrup]) was then transported to the patient in the preoperative area." |
| Blinding of outcome assessment (detection bias) | Low risk | "The Investigational Drug Pharmacist was the only person aware of treatment allocation until the close and unblinding of the study data for analysis." "Blinding was kept intact throughout the study for all patients." |
| Incomplete outcome data (attrition bias) | High Risk | Missing data >20% in the placebo arm (14/66) vs. treatment arm (7/62) |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | Unclear risk | "use of comprehensive perioperative care and regional anesthetic techniques may have biased the results toward the null" "Selection bias is also a potential criticism given the high screen-to-enrollment ratio. There were several factors that led to a high screen-to-enrollment ratio." 11 patients assessed at 6-months due to missing the 3-month exam were included with those analyzed at 3 months. |

**Burke 2010**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 3 months | | |
| **Participants** | 40 ASA physical status I and II patients, aged 18 - 60, with chronic lumbar sacral radiculopathy undergoing elective lumbar discectomy | | |
| **Interventions** | Pregabalin 300 mg 2h preoperatively + 150 mg POP at 12 h + 150 mg at 24h | | |
| **Outcomes** | Primary outcome was the change in the present pain intensity (PPI) (visual analog scale [VAS], 0–100 mm [PPI-VAS, McGill Pain Questionnaire]) from preoperatively to 3 months postoperatively | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: General anesthesia was induced with fentanyl and propofol followed by vecuronium to facilitate tracheal intubation  and ventilation. Anesthesia was maintained using sevoflurane and intermittent vecuronium as clinically indicated. Paracetamol, morphine, NSAID and SC infiltration of bupivacaine.  Post-op: codeine, acetaminophen and diclofenac. | | |
| **Source(s) of funding** | Supported in part by the Pfizer Pain Research Fellowship Programme | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | "In this double-blind study, patients received pregabalin or placebo (sucrose) according to random allocation" |
| Allocation concealment (selection bias) | | Low risk | "The medication was prescribed according to instructions in a sealed, opaque envelope by an anesthesiologist with no further involvement in the study". |
| Blinding of participants and personnel (performance bias) | | Unclear risk | Not reported |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "At 3 months postoperatively, patients once again completed the same 6 questionnaires in the presence of the same investigator". |
| Incomplete outcome data (attrition bias) | | Low risk | 2 patients dropped out from the study, only |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Buvanendran 2010**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 6 months | | |
| **Participants** | 228 patients scheduled to undergo a primary total knee arthroplasty using an abbreviated medial parapatellar approach, with a diagnosis of osteoarthritis of the operative knee. | | |
| **Interventions** | Patients randomized to the experimental arm of the study received pregabalin 300 mg orally (per os [PO]), 1–2 h before surgery, 150 mg twice daily for the first 10 postoperative days, 75 mg twice daily on Days 11 and 12, and 50 mg twice daily on Days 13 and 14 | | |
| **Outcomes** | Adverse events related with the medication, Leeds Assessment of Neuropathic Symptoms and Signs pain scale, knee injury and Osteoarthritis Outcome Score–Physical function Short-form, Range of motion, epidural drug use and postoperative pain assessment | | |
| **Notes** | Co-analgesia:  Pre-op: All patients received preoperative celecoxib.  Intra-op: Epidural Infusion of bupivacaine and fentanyl (PCEA). Patients were sedated with IV propofol for the duration of the surgery.  Post-op: Epidural infusion of fentanyl and bupivacaine for 32-42h. Patients were then transitioned to oral opioid medications as  needed for adequate pain control. All patients  received celecoxib 200 mg PO twice daily for 3 days while in the hospital, to conform to the multimodal  analgesia protocol used at our facility. | | |
| **Source(s) of funding** | Supported by a Medical School Grant from Pfizer, Inc. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomized to a treatment group using a computer-generated randomization sequence". |
| Allocation concealment (selection bias) | | Low risk | "During the study, only the dispensing pharmacist had knowledge of the study codes". |
| Blinding of participants and personnel (performance bias) | | Low risk | "Control patients received PO-matched placebo tablets, at identical time points, with both pregabalin and placebo capsules provided by Pfizer" |
| Blinding of outcome assessment (detection bias) | | Low risk | "The personnel involved with postoperative pain assessments and management of the epidural infusion, physical therapists, and the study patients were blinded to group assignment". |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups |
| Selective reporting (reporting bias) | | High risk | Outcomes reported are clinically meaningful and validated. However, we detected some discrepancies in the definition of primary and secondary outcome between the published protocol (NCT00558753) and the publication. |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Chan 2011**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Multicenter, randomized, double-blind, controlled trial with long-term follow-up for at least three months | | |
| **Participants** | 640 patients that were 18 yr. or older scheduled, under general anesthesia, for surgery that included a skin incision and that was anticipated to exceed 2 hours, and were expected to be in the hospital for at least 3 days after surgery | | |
| **Interventions** | Intraoperative 70% nitrous oxide | | |
| **Outcomes** | The primary outcome of this follow-up study was chronic postsurgical pain according to the definition by the International Association for the Study of Pain. Secondary outcomes were the impact of chronic postsurgical pain on daily living. | | |
| **Notes** | This study had a very high mortality rate at follow-up (34%)  Co-analgesia: In patients receiving nitrous oxide-free anesthesia, the attending anesthesiologist was allowed to use a range of inspired oxygen concentration (25%–100%), if there was a strong personal preference or if clinically indicated. All other aspects of perioperative care, including postoperative analgesia, were left to the discretion of the attending anesthesiologists and surgeons. | | |
| **Source(s) of funding** | supported by General Research Fund (461409), Research Grants Council of Hong Kong and the National Health and Medical Research Council, Australia (236956). The follow-up study was supported by a Project Grant (07/010) from the Australian and New Zealand College of Anaesthetists and a Direct Grant for Research, The Chinese University of Hong Kong (2041315). | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "…. using a computer-generated code, accessed via an automated telephone voice recognition service". |
| Allocation concealment (selection bias) | | Low risk | "…. automated telephone voice recognition service. Treatment assignment was stratified by site and elective/emergency status of the surgery, using permuted blocks". |
| Blinding of participants and personnel (performance bias) | | Low risk | "Attending anesthesiologists were required to have knowledge of group identity for the safe administration of anesthesia, but group identity was concealed from the surgeon using drapes or cardboard to screen the anesthesia machine". |
| Blinding of outcome assessment (detection bias) | | Low risk | "At the end of the procedure, the intraoperative case report form and documentation of group identity were faxed to the data management center and then placed in an opaque envelope by the anesthesiologist. The envelope was then sealed to ensure blinding of research staff conducting the postoperative follow-ups". |
| Incomplete outcome data (attrition bias) | | Unclear risk | This secondary analysis included the Hong Kong population only |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported for this secondary analysis are clinically meaningful and validated |
| Other bias | | High risk | "Pain intensity was not described as an outcome in the original 2007 report". |

**Chan 2016**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicentre (19 centres in 5 countries), randomized, double-blind, 2 arm, follow-up 12 months | |
| **Participants** | 3325 patients aged 45 or older undergoing non-cardiac surgery at risk of a perioperative major cardiac event | |
| **Interventions** | Nitrous Oxide: 70% nitrous oxide in 30% oxygen or no nitrous Oxide (70% nitrogen in 30% oxygen). | |
| **Outcomes** | The primary outcome was the presence of chronic postsurgical pain. The secondary outcome was severe pain defined as average pain throughout the previous 24 h rated by the patient at equal or greater than 50 of 100 points. | |
| **Notes** | Co-analgesia: All other perioperative clinical care was according to standard practice at each site, as this is an effectiveness trial designed to represent “real-world” practice. This includes choice of anesthetic drugs, analgesic regimens and/or regional analgesia techniques, antiemetics, and initiation or continuation of perioperative cardiac medications including anticoagulant and antiplatelet therapy. | |
| **Source(s) of funding** | This study was supported by a project grant (11121051) from Health and Medical Research Fund, Hong Kong Special Administrative Region, China and project grants (10/014 and 12/008) from the Anaesthesia and Pain Medicine Foundation, Australian and New Zealand College of Anaesthetists. The ENIGMA-II Trial was supported by a project grant (435015) from the Australian Government National Health and Medical Research Council and a project grant from General Research Fund (461409), Research Grants Council, Hong Kong Special Administrative Region, China. P.S.M. is supported by the National Health and Medical Research Council, Practitioner Fellowship scheme. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "After the patient's consent has been obtained, center personnel will telephone a central 24-hour interactive voice recognition system that prompts the researcher or study coordinator to identify their study site, and randomly allocates patients to a treatment group (1:1) from a computer-generated list. Randomization is stratified by site." (See primary article by Myles 2009) |
| Allocation concealment (selection bias) | Low risk | "Anesthesiologists will have knowledge of group after randomization (for safe use of nitrous oxide), but administration and group identity will be concealed from the surgeon. Anesthesiologists participating in the conduct of the study will receive education explaining the importance of, reasoning for, and methods to ensure blinding from surgeons and others. The anesthetic machine flow meters will be concealed from the surgical staff, using drapes or cardboard screen. To ensure blinding of all the other staff, the anesthesiologist will place the original anesthesia record after surgery in a sealed opaque envelope; the envelope is to be stored in the patient's hospital record and should not be opened until after the 30- day follow-up unless there is a clinical imperative." (Myles 2009) |
| Blinding of participants and personnel (performance bias) | Low risk | "Patients, surgeons, and research staff collecting data and interviewing patients postoperatively will be blind to treatment allocation." (Myles 2009) "Patients, surgeons, and the assessors for all outcome measures were blinded to treatment allocation." (Chan 2016) |
| Blinding of outcome assessment (detection bias) | Low risk | "the assessors for all outcome measures were blinded to treatment allocation." (Chan 2016) |
| Incomplete outcome data (attrition bias) | Unclear risk | Figure 1 portrays approximately 5% have been lost-to follow up, however the actual proportions lost to follow-up are 208/1654 (12.6%) in the Nitrous Oxide group and 193/1671 (11.5%) in the Placebo group. According to the manuscript "Adjustment for missing data did not substantially alter the risks for chronic postsurgical pain". |
| Selective reporting (reporting bias) | High risk | One or more reported outcomes were not pre-specified. According to ClinicalTrials.gov there is no mention of any outcomes of interest beyond the 30-day time-point. "Before the start of the trial, the steering committee planned a 12-month follow-up study to evaluate the long-term effect of nitrous oxide on disability, stroke, myocardial infarction, and death. A protocol amendment was submitted in February 2010" This information was not amended on ClinicalTrials.gov and was subsequently approved by the ethics committees of all participating centres to undergo additional evaluation of chronic postsurgical pain. |
| Other bias | Low risk | No other potential sources of bias were detected |

**Chaparro 2010**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with long-term follow-up for one year | | |
| **Participants** | 106 patients scheduled to Esthetic Augmentation Mammoplasty were followed one year after the surgery | | |
| **Interventions** | Ketamine 25 IV before the beginning of the surgery plus additional 50 mg mixed with the IV anesthetic (2 mg of remifentanil) | | |
| **Outcomes** | Pain Scores, opioid consumption and adverse effects profile | | |
| **Notes** | Co-analgesia: Dipyrone and meperidine. Acetaminophen+Codeine and NSAIDs after discharge. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | Throwing coin |
| Allocation concealment (selection bias) | | High risk | Randomization and allocation in groups of 4 patients. Two patients in a row receiving one treatment will predict the treatment for the next 2 |
| Blinding of participants and personnel (performance bias) | | Low risk | A registered nurse prepared the bags of saline and ketamine. She did not participated of the outcomes assessment |
| Blinding of outcome assessment (detection bias) | | Low risk | Outcomes assessors were not aware of the treatment that the patients received |
| Incomplete outcome data (attrition bias) | | High risk | Significant missing outcome data: 53% |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Choi 2013**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 3 arms, placebo controlled trial, follow-up 6 months | | |
| **Participants** | 120 patients aged 20-70 scheduled to undergo elective lumbar laminectomy with or without fusion. | | |
| **Interventions** | Pregabalin: 150mg orally every 12 hours starting 1 hour before anesthetic induction and until the third postoperative day for a total of 8 doses.  Pregabalin + Dexamethasone: Pregabalin 150mg orally every 12 hours starting 1 hour before anesthetic induction and until the third postoperative day for a total of 8 doses. Dexamethasone 16mg was injected before the induction of anesthesia.  Placebo: Placebo capsules and IV normal saline | | |
| **Outcomes** | Primary outcomes: postoperative pain intensity during rest and movement and the frequency of rescue analgesic administered during the first 72 hours after surgery.  Secondary outcomes were to compare back and leg pain relief and functional outcome in terms of daily activity performance over a 6-month period after surgery. | | |
| **Notes** | Co-analgesia:  Pre-op: Anesthesia was induced with propofol and remifentanil,  and orotracheal intubation was facilitated with rocuronium. Anesthesia was maintained by a continuous infusion of remifentanil, rocuronium, and sevoflurane.  Intra-op: Neuromuscular blockade with glycopyrrolate and pyridostigmine.  Post-op: Ondansetron and fentanyl. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomly allocated to 1 of 3 groups using a computerized randomization table 1 day before surgery" |
| Allocation concealment (selection bias) | | Low risk | "Medications were prepared in capsules of identical color and appearance by a staff nurse who was not involved in the study. Furthermore, identical syringes containing the same volume of liquid were prepared by the staff nurse." |
| Blinding of participants and personnel (performance bias) | | Low risk | "the surgeon who was blinded to the group allocation." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Low risk | "An independent investigator blinded to the group allocation assessed these variables." "After discharge from the hospital, VAS pain scores at rest and during daily activity performance were assessed at 1, 3, and 6 months after surgery at the outpatient clinic by the surgeon who was blinded to the group allocation." |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was below 20%. Lost to follow-up: 4/40 Pregabalin and 4/40 Placebo |
| Selective reporting (reporting bias) | | High risk | The study protocol is available, however only the Primary Outcome is described a priori. The study title eludes to Chronic Pain as an outcome, but there is no mention on ClinicalTrials.gov of how they intended to measure this. |
| Other bias | | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. Patients’ characteristics and pre-operative data were similar among the groups, with the exception of baseline back pain intensity, which was significantly higher in group PD than group P (P=0.005). |

**Choi 2017**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arms, placebo controlled trial, follow-up 3 months | | |
| **Participants** | 90 patients aged 20-65 scheduled to undergo elective robot-assisted thyroidectomy via transaxillary single-incision approach | | |
| **Interventions** | Intravenous Lidocaine: 0.1 ml/kg of 2% lidocaine (2 mg/kg) was infused intravenously for 10 min immediately after anesthesia induction, and then, it was continuously infused at a rate of 0.15 ml/kg/h of 2% lidocaine (3 mg/kg/h) until the patients were extubated  Placebo: Saline 0.9% | | |
| **Outcomes** | Postoperative quality of recovery, acute postsurgical pain, Chronic postsurgical pain (CPSP) was evaluated 3 months after surgery. Sensory disturbances in the anterior chest were assessed at 24 h and 3 months after surgery. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Anesthesia was induced with propofol and remifentanil and maintained with sevoflurane and remifentanil. Before the end of the operation, patients received propacetamol.  Post-op: Oral ibuprofen until discharge. | | |
| **Source(s) of funding** | This research was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) that was funded by the Ministry of Science, ICT and  Future Planning (NRF-2014R1A1A1002001). | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "On the day before surgery, the principal investigator randomly allocated the patients to either the control or the lidocaine group, using a randomization sequence generated by the web site www.randomizer.org/form.htm." |
| Allocation concealment (selection bias) | | Unclear risk | "An anesthetic nurse, who did not participate in the study, prepared the 2% lidocaine or the 0.9% normal saline in 50-ml syringes in accordance with the principal investigator’s instructions. These injections were administered to the patients by the attending anesthesiologists who did not know the patients’ group allocations." |
| Blinding of participants and personnel (performance bias) | | Low risk | "The other investigators, including the anesthesiologists responsible for the patients’ intraoperative care, the surgeons, and the nursing staffs, and the patients were blinded with regard to the groups to which the patients were assigned during the entire study period." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Low risk | "All of the preoperative and postoperative data for this study were obtained by one investigator who was unaware of the groups to which the patients had been allocated." |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was below 20%. Lost to follow-up: 4/41 in the Lidocaine Group and 2/44 in the placebo group |
| Selective reporting (reporting bias) | | High risk | One or more reported outcomes were not pre-specified. There is no mention of a 3-month follow-up on ClinicalTrials.gov. According to ClinicalTrials.gov the Current Secondary outcome measure is "Assessing the presence of chronic postsurgical pain(CPSP) [ Time Frame: 24hours after operation day]" |
| Other bias | | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. |

**Chumbley 2019**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 12 months | |
| **Participants** | 77 patients scheduled for either thoracotomy or video assisted thoracic surgery | |
| **Interventions** | Patients received a bolus of 0.1 mg/kg of ketamine/placebo prior to starting the infusion. Study infusions were due to continue for 96 hr. | |
| **Outcomes** | Primary outcome measures: incidence of pain (0-10) at 6 weeks after surgery, brief Pain Inventory, and Leeds Assessment of Neuropathic Symptoms and Signs.  Secondary long-term outcome measures: analgesic consumption at 3, 6 and 12 months. Sensory testing at 6 months & 12 months. Incidence of pain (0-10) at 3, 6 and 12 months, Brief Pain Inventory, and Leeds Assessment of Neuropathic Symptoms and Signs | |
| **Notes** | Co-analgesia:  This was a pragmatic study in a busy London teaching hospital, and therefore, it was not possible to standardize anaesthetic techniques or perioperative pain management. Patients either received a thoracic epidural infusion post‐operatively or patient‐controlled analgesia (PCA) +/− a paravertebral local anaesthetic infusion depending on the choice of the anaesthetist and patient. | |
| **Source(s) of funding** | This research study was funded by a personal clinical lectureship, awarded to Dr GM Chumbley, by the National Institute of Health Research (NIHR). | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "A simple random allocation sequence generated by computer was used to randomize patients to receive either a ketamine infusion or saline placebo, and this was kept concealed by the pharmacists in the clinical trials pharmacy." |
| Allocation concealment (selection bias) | Low risk | "A simple random allocation sequence generated by computer was used to randomize patients to receive either a ketamine infusion or saline placebo, and this was kept concealed by the pharmacists in the clinical trials pharmacy." "The infusions were made and labelled in the clinical trials pharmacy." (central allocation) |
| Blinding of participants and personnel (performance bias) | Low risk | ... this was kept concealed by the pharmacists in the clinical trials pharmacy. Patients, staff and researchers were blinded as to which infusion patients received. Patients were recruited and followed up by the researchers (GC, LT, JS) and assigned the next study number in the order they were recruited." "The infusions were made and labelled in the clinical trials pharmacy." |
| Blinding of outcome assessment (detection bias) | Low risk | "Patients, staff and researchers were blinded as to which infusion patients received." "The study was not unblinded until the last patient had completed the 12‐month follow‐up." |
| Incomplete outcome data (attrition bias) | Unclear risk | Missing data > 20% after 6 Month Time-point At 3 months 10/77 (13%): 6 lost to follow-up Ketamine arm 4 lost to follow-up Placebo arm At 6 months 14/77 (18%): 8 lost to follow-up Ketamine arm 6 lost to follow-up Placebo arm At 12 months 21/77 (27%): 11 lost to follow-up Ketamine arm 10 lost to follow-up Placebo arm |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Clarke 2009**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 6 months | | |
| **Participants** | 126 patients, ASA I-III undergoing total hip arthroplasty | | |
| **Interventions** | Patients were randomly assigned to one of 3 treatment groups (G1: Placebo/Placebo; G2: GBP/Placebo; and G3: Placebo/ GBP). Group 2 received gabapentin 600mg p.o. 2 h before surgery; the other groups received an identical-looking placebo capsule. Upon arrival to the recovery room, group 3 received gabapentin 600mg p.o.; the other groups received an identical-looking placebo capsule. | | |
| **Outcomes** | Pain scores at rest and movement-evoked; patients were also assessed for the incidence and severity of sedation, nausea, vomiting and pruritus. Patients were administered 3 questionnaires: a follow-up Hip Arthroplasty Pain questionnaire, The Neuropathic Pain Scale and The Hospital Anxiety and Depression Scale. Pain intensity was measured using a 0-10 numeric rating scale (NRS). | | |
| **Notes** | Co-analgesia:  Pre-op: Acetaminophen, celecoxib and dexamethasone  Intra-op: Midazolam. Spinal anesthesia with bupivacaine and fentanyl. Sedation was administered by an IV propofol infusion.  Post-op: PCA morphine | | |
| **Source(s) of funding** | This study was made possible through a grant by the Physicians’ Services Incorporated. Joel Katz is supported by a Canada Research Chair in Health Psychology at York University. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "A computer-generated randomization schedule was used to assign patients at random in blocks of 6 to one of the 3 treatment groups". |
| Allocation concealment (selection bias) | | Low risk | "The schedule was created by the hospital investigational pharmacy, which was otherwise not involved in the clinical care of the patients or in the conduct of the trial. The randomization schedule was kept in the pharmacy and none of the investigators had access to it". |
| Blinding of participants and personnel (performance bias) | | Low risk | "Gabapentin and placebo medications were encapsulated in identically colored gelatin capsules and packaged in identical individual blister packs by the Sunnybrook Health Sciences Centre Investigational Pharmacy in order to maintain double-blind conditions". |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Incomplete information |
| Incomplete outcome data (attrition bias) | | High risk | Missing outcome data balanced across groups, but > 20% |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Clarke 2014**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled, follow-up 3 months. | |
| **Participants** | 179 patients scheduled for total knee arthroplasty. | |
| **Interventions** | Gabapentin: 600 mg 2 hours before operation followed by 4 days of gabapentin 200 mg TID  Placebo: Placebo capsules (cellulose and lactose monohydrate) | |
| **Outcomes** | WOMAC, Anxiety & Depression, and Functional Outcomes (Knee range of motion, timed get up and go, stair test, walk test) | |
| **Notes** | Co-analgesia:  Pre-op: Celecoxib 2h before operation  Intra-op: Midazolam. Femoral and sciatic nerve blocks. Spinal anesthesia was performed with bupivacaine and fentanyl. Sedation was provided with IV propofol.  Post-op: PCA morphine for 24h. Upon discharge from PACU celecoxib plus PCA morphine for 24h. Oxycontin. | |
| **Source(s) of funding** | This study was made possible through grants by the Canadian Anesthesiology Society, the Sunnybrook Health Sciences Centre Practice Based Research Fund, and a grant from the Orthopedic Foundation of Canada. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "A computer- generated randomization schedule was used to assign patients at random, in blocks of six, to one of the two treatment groups. The schedule was created by the hospital investigational pharmacy using randomization.com (http://www.jerrydallal.com/ random/randomize.htm)." |
| Allocation concealment (selection bias) | Low risk | "Gabapentin and placebo medications were encapsulated in identically coloured gelatin capsules and packaged in identical individual blister packs by the Sunnybrook Health Sciences Centre Investigational Pharmacy in order to maintain double-blinded conditions." "The investigational pharmacy was otherwise not involved in the clinical care of the patients or in the conduct of the trial. The randomization schedule was kept in the pharmacy and none of the investigators had access to it. The pharmacy dispensed the capsules according to the randomization schedule when the investigators informed them that a patient had been recruited into the trial." |
| Blinding of participants and personnel (performance bias) | Low risk | "Researchers were also blind to drug assignment during data analysis." "The attending anaesthesiologist was not involved in the patients’ evaluation after operation." Double-blind study design |
| Blinding of outcome assessment (detection bias) | Low risk | "Blinding was maintained throughout the study until the code was broken upon the completion of our statistical analysis." |
| Incomplete outcome data (attrition bias) | Unclear risk | Higher proportion of lost to follow-up in the treatment group 16/95 (17%) vs. 8/84 (9.5%) in the control group. The dropout rate was below 20%. |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | Low risk | No other potential sources of bias were detected |

**Clarke 2015**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 3 months. | | |
| **Participants** | 184 patients scheduled for primary total hip arthroplasty | | |
| **Interventions** | Pregabalin: 150mg two hours before surgery and 75mg BID starting 8 hours after surgery until 7 days after discharge  Placebo: placebo capsules contained a mixture of 50% cellulose and 50% lactose monohydrate | | |
| **Outcomes** | Pain, Anxiety/Depression, and Functional Outcomes (e.g. stair test, walk test). [Clinical Trials.gov: Physical function 6 weeks and 3-months post-total hip arthroplasty. Time Frame: Up to 3 months. Secondary outcomes not described.] | | |
| **Notes** | Co-analgesia:  Pre-op: All patients received celecoxib 400 mg 2h before surgery  Intra-op: Spinal anaesthesia with hypobaric bupivacaine with fentanyl, sedation was provided with propofol infusion.  Post-op: PCA morphine and celecoxib for 24h, oxycontin. | | |
| **Source(s) of funding** | Department of Anaesthesia at the University of Toronto (Merit Awards to H.C. and C.M.); Canadian Institute of Health Research Fellowship (to H.C.); Canada Research Chair in Health Psychology at York University (to J. Katz); Pfizer Canada (physician-initiated peer-reviewed Neuropathic Pain Competition). | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "A computer-generated randomization schedule was used to assign patients at random, in blocks of six, to one of the two treatment groups." |
| Allocation concealment (selection bias) | | Low risk | "The schedule was created by the hospital investigational pharmacy, which was otherwise not involved in the clinical care of the patients or in the conduct of the trial. The randomization schedule was kept in the pharmacy, and none of the investigators had access to it. " |
| Blinding of participants and personnel (performance bias) | | Low risk | "Pregabalin capsules were provided by Pfizer Canada Inc., and placebo medications were encapsulated in identically coloured gelatin capsules and packaged in identical individual blister packs by the Sunnybrook Health Sciences Centre Investigational Pharmacy in order to maintain double-blind conditions." "The pharmacy dispensed the capsules according to the randomization schedule when the investigators informed them that a patient had been recruited into the trial. Researchers were also blind to drug assignment during data analysis." "The attending anaesthetist was not involved in the patients’ postoperative evaluation." |
| Blinding of outcome assessment (detection bias) | | Low risk | "Blinding was maintained throughout the study until the code was broken upon the completion of our statistical analysis." |
| Incomplete outcome data (attrition bias) | | Unclear risk | "The major limitation to the present study is the dropout rate at the 3-month time point. We examined baseline differences between patients who did vs did not complete the 3-month follow-up." Outcome data missing for 32/92 in Placebo group and 22/92 in Pregabalin group. The dropout rate was >20%. |
| Selective reporting (reporting bias) | | High risk | The study protocol is available, however only the Primary Outcome is described a priori. The paper reports secondary outcomes are opioid consumption, pain in hospital, adverse effects, NRS scores 1 week post discharge, and anxiety/depression scores. |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Cohen 2013**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Multicentre, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for twelve months. | | |
| **Participants** | 77 patients scheduled for open, unilateral inguinal hernia repair with mesh. | | |
| **Interventions** | Subcutaneous etanercept 50 mg administered 90 minutes before surgery vs. saline | | |
| **Outcomes** | The primary outcome measure was a 24-hour numerical rating scale pain score. Secondary outcome measures were post anesthesia care unit pain scores, 24-hour opioid requirements, time to first analgesic, and pain scores recorded at 1 month, 3 months, 6 months, and 12 months. | | |
| **Notes** | Co-analgesia:  Pre-op: IV midazolam.  Intra-op: Either general anesthesia or monitored anesthetic  care, depending on clinical circumstances and the preference  of the surgeon and anesthesiologist. Aside from the use of IV fentanyl and surgical local anesthesia with bupivacaine or a 50:50 mixture of lidocaine and bupivacaine for intraoperative analgesia, the anesthetic plan was catered to the individual patient and could include propofol or a volatile anesthetic. Ketamine, regional anesthetic techniques, local anesthetic infusions, and nonsteroidal anti-inflammatory drugs were not permitted intraoperatively.  Post-op: Systemic opioids PRN, Before PACU discharge, patients were given prescriptions for oxycodone/acetaminophen PRN. | | |
| **Source(s) of funding** | Supported in part by a Congressional Grant from the Defense and Veterans Center for Integrative Pain Management, Rockville, MD. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "subjects were randomized 1 to 2 weeks before surgery in a 1:1 ratio in blocks of 8 at each institution via a computer-generated randomization table. " |
| Allocation concealment (selection bias) | | Low risk | "A research pharmacist prepared the clear injectate solution for each subject in an unlabeled syringe, which was picked up the day of surgery. The appearance of the syringe was identical for the treatment and control groups" |
| Blinding of participants and personnel (performance bias) | | Low risk | "The patient, surgeon, anesthesiologist, injecting physician, nursing staff, and evaluators were all unaware of treatment allocation until after the 3-month follow-up" |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "The patient, surgeon, anesthesiologist, injecting physician, nursing staff, and evaluators were all unaware of treatment allocation until after the 3-month follow-up" Methods describe they were unaware of treatment allocation for the first 3 months, however pain scores were recorded up to 1 year. |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was below 20%. Lost to follow-up: 1/34 in the Etanercept Group and 2/43 in the placebo group. |
| Selective reporting (reporting bias) | | Unclear risk | The study protocol is available however there were amendments made to the pre-specified outcomes of interest. Original primary outcome submitted in 2009 was "Numerical Rating Pain Score [ Time Frame: First 24 hours, then 1,3,6 and 12 months postoperatively]" and the amended primary outcome submitted after the article was published was "Numerical Rating Scale Pain Score [ Time Frame: 24 hours]" |
| Other bias | | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. |

**Comez 2015**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 3 arm, follow-up for 6 months | | |
| **Participants** | 60 patients scheduled for elective major thoracotomy operations. | | |
| **Interventions** | Dexketoprofen + Epidural Group (Group PED): 50 mg dexketoprofen trometamol was given within 100 ml 0.9% NaCl with i.v. infusion in 15 minutes, and it was finished 15 minutes before the surgical incision. Levobupivacaine was given to cases in 5 ml with intervals of 5 minutes pre-emptively through an epidural catheter before the anaesthesia induction to provide the analgesia at two dermatome levels below and above the surgical incision dermatome (T4-T10). Intraoperative analgesia was provided with 10 ml 0, 125% Levobupivacaine injection, which was repeated every 60 minutes through epidural catheter. A postoperative 50 mg dexketoprofen trometamol was given to Group PED with i.v. infusion in 15 minutes within 100ml 0.9% NaCl, 12 hours after the first dexketoprofen dose.  The Pre-emptive Epidural Group (Group PE): Levobupivacaine was given to cases in 5 ml with intervals of 5 minutes pre-emptively through epidural catheter before the anaesthesia induction to provide the analgesia at two dermatome levels below and above the surgical incision dermatome (T4-T10). Sufficiency of the analgesia was determined by performing hot-cold test and the anaesthesia induction was then started. Intraoperative analgesia was provided with 10 ml 0.125% Levobupivacaine injection, which was repeated every 60 minutes through epidural catheter.  Group C (Control arm): Fentanyl citrate and O2/N2O 40-60%. | | |
| **Outcomes** | The existence of chronic post-thoracotomy pain was accepted in cases with a VAS score of ≥3 during the 1st, 3rd, and 6th postoperative months. Patient satisfaction was also questioned and recorded following the discharge of the cases and during postoperative month 6. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: For all cases, propofol induction, muscle relaxation provided with rocuronium bromide. Maintenance of anaesthesia was provided with Desflurane. Morphine + fentanyl through epidural catheter while stitching the skin sutures.  Post-op: Epidural analgesia for 48h. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "The cases were divided into 3 groups involving 20 individuals with the random envelope method." |
| Allocation concealment (selection bias) | | Unclear risk | Not reported. |
| Blinding of participants and personnel (performance bias) | | Unclear risk | "The cases, who were not informed about which study group they were included in…" "the VAS score was questioned and recorded by making face-to-face interviews with the cases who could come for the examination, and calling those who could not, during the 1st, 3rd, and 6th postoperative months, without knowing the groups of the cases." Double-blind study design. Unclear, only patients and the outcome assessor was blinded. |
| Blinding of outcome assessment (detection bias) | | Low risk | "the VAS score was questioned and recorded by making face-to-face interviews with the cases who could come for the examination, and calling those who could not, during the 1st, 3rd, and 6th postoperative months, without knowing the groups of the cases." |
| Incomplete outcome data (attrition bias) | | Low risk | No missing data or participants lost to follow-up reported. |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Fewer than 50 participants per arm. There is no study protocol to verify if chronic pain as the primary outcome was pre-specified. The numbers screened to obtain 20 participants in each study arm is not described. Description of blinding is unclear. |

**Crousier 2008**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with long-term follow-up for 3 months | | |
| **Participants** | 36 patients, no limit of age, requiring radical mastectomy with axillary lymph node dissection | | |
| **Interventions** | Ketamine 0.5 mg/kg previous to surgical incision + infusion during surgery at 0.25/mg/kg/h versus saline bolus + infusion | | |
| **Outcomes** | Pain scores, side effects profile | | |
| **Notes** | Co-analgesia: Morphine, acetaminophen/codeine | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | The method of the sequence generation is not reported |
| Allocation concealment (selection bias) | | Unclear risk | Method for allocation concealment is not stated |
| Blinding of participants and personnel (performance bias) | | Unclear risk | The method to keep blinded the intervention is not stated |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Blinding of the outcomes assessors at 3 months follow-up is unclear |
| Incomplete outcome data (attrition bias) | | High risk | The proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate |
| Selective reporting (reporting bias) | | Low risk | The trial was registered and non-significant differences with the protocol were noticed |
| Other bias | | High risk | 25% (n:3/12) in the ketamine group versus 50% (9/18) in the placebo group, reported presurgical neuropathic pain |

**Curtin 2017**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 1 year. | |
| **Participants** | 131 patients with carpal tunnel syndrome or trigger finger and undergoing release surgery | |
| **Interventions** | Minocycline: 200 mg 2 hours prior to procedure, and then minocycline, 100 mg 2 times a day for 5 days given at the same intervals  Placebo: Placebo (lactose) | |
| **Outcomes** | Primary outcome: reducing time to pain resolution (TPR) to a clinically meaningful extent. A failure to find evidence of futility would then be taken as reason to plan a larger multisite randomized controlled trial of perioperative minocycline.  Secondary outcome: change in hand function. | |
| **Notes** | Co-analgesia:  Patients underwent open CTR or open TFR using local-only anesthesia (50/50 mixture of bupivicaine and lidocaine). | |
| **Source(s) of funding** | C.M.C. received support through an RR&D pilot grant RX000487 from the U.S. Department of Veterans Affairs Rehabilitation and Research and Development Service. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Patients were randomly assigned to receive either minocycline or placebo using a computer-generated randomization table using a biased coin approach." |
| Allocation concealment (selection bias) | Low risk | "The randomization table was prepared by a third party not otherwise involved in collecting study data, dispensing medication, or enrolling patients. The randomization table was provided directly to the Veterans Administration research pharmacist. Based on this table, the research pharmacist allocated patients according to the randomization list, while concealing randomization assignment from the study team enrolling patients." |
| Blinding of participants and personnel (performance bias) | Low risk | "Participants and all study team members—health care providers, data collectors, data analysts, except for the research pharmacist—were blinded to randomized treatment group." "Minocycline was prepared by overencapsulating a 100-mg minocycline capsule. The placebo was identical in appearance and consisted of the same large capsule filled with lactose and then overencapsulated." |
| Blinding of outcome assessment (detection bias) | Low risk | "Participants and all study team members—health care providers, data collectors, data analysts, except for the research pharmacist—were blinded to randomized treatment group." |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20% |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | Low risk | Unable to find additional potential bias. >50 participants per study arm. |

**Czarnetzki 2019**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 1 year. | |
| **Participants** | Adults, ASA I-III, undergoing back surgery (laminectomy, lumbar arthrodesis (Posterior Lumbar Interbody Fusion - PLIF, Transforaminal Lumbar Interboby Fusion - TLIF, Postero-lateral Fusion, semi-rigid fixation | |
| **Interventions** | 50 ml syringes containing 1% ketamine or 0.9% NaCl. After induction and before start of surgery, patients received an intravenous bolus of 0.025 ml/kg of the study solution (corresponding to 0.25 mg/kg ketamine). Maintenance with a syringe driver at a rate of 0.025 ml/kg/h (corresponding to 0.25 mg/kg/h ketamine) until one hour before the end of surgery, and then be decreased to a rate of 0.01 ml/kg/h (corresponding to 0.1 mg/kg/h ketamine) throughout the stay in the recovery room (usually 2 to 3 hours). The infusion stopped when the patient left the recovery room. | |
| **Outcomes** | Primary outcome measures: 6 and 12 months effect of perioperative intravenous low-dose ketamine on chronic neuropathic pain in patients undergoing major back surgery.  Secondary long-term outcome measures: short-term (during hospitalisation) effect of perioperative intravenous low-dose ketamine in patients undergoing major back surgery: tolerability and safety, opioid-sparing effect, pain intensity, morphine-related adverse effects. To study psychosocial factors that may be involved in the perception of acute and chronic postoperative pain in patients with or without chronic back pain undergoing back surgery | |
| **Notes** | Co-analgesia:  Pre-op: Midazolam 7.5 mg 1 hr prior to induction of anaesthesia  Intra-op: Anaesthesia was induced with propofol and sufentanil. Rocuronium was used to facilitate tracheal intubation. Anaesthesia was maintained with isoflurane or sevoflurane and a standardized regimen of sufentanil intravenously. No nitrous oxide was used in any patient.  Post-op: IV Morphine until pain ≤4 on a 0 to 10 then PCA Morphine. Ketorolac as rescue analgesia or ibuprofen. After 48h oral morphine, ibuprofen and acetaminophen. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "The pharmacy of Geneva University Hospitals performed randomization in a 1:1 ratio according to a computer-generated randomization list" |
| Allocation concealment (selection bias) | Low risk | "The pharmacy of Geneva University Hospitals performed randomization in a 1:1 ratio according to a computer-generated randomization list and prepared study medications in numbered and indistinguishable 50 ml syringes of ketamine (1%) and placebo (physiological saline)." COMMENT: Central allocation |
| Blinding of participants and personnel (performance bias) | Low risk | "The pharmacy... prepared study medications in numbered and indistinguishable 50 ml syringes of ketamine (1%) and placebo (physiological saline)."  "Patients, caregivers and observers were blinded to study drug assignment. The allocation sequence  was concealed until the final 12-month follow-up (study end)."  "Study nurses blinded to study treatments performed all postoperative evaluations." |
| Blinding of outcome assessment (detection bias) | Low risk | "Patients, caregivers and observers were blinded to study drug assignment. The allocation sequence  was concealed until the final 12-month follow-up (study end)."  "Study nurses blinded to study treatments performed all postoperative evaluations." |
| Incomplete outcome data (attrition bias) | Low risk | Missing data < 20%  At 6 months 7/80 Ketamine and 12/80 placebo  At 12 months 8/80 Ketamine and 13/80 placebo |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | Unclear risk | Reasons for lost to follow-up not reported. |

**De Kock 2001**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, 5 arms, placebo-controlled trial with long-term follow-up for 3 months | | |
| **Participants** | 100 Patients aged 55-75 undergoing curative surgical resection of rectal carcinoma via xypho-pubic incision | | |
| **Interventions** | Control: saline infusion, Low IV dose: i.v. ketamine at the bolus dose of 0.25 mg/kg followed by an infusion of 0.125 mg/kg per h, High IV dose: 0.5 mg/kg and 0.25 mg/kg per h; Low epi dose: epidural ketamine 0.25 mg/kg and 0.125 mg/kg per h; high Epi dose: 0.5 mg/kg and 0.25 mg/kg per h. | | |
| **Outcomes** | Cumulative morphine request up to 48 h after surgery; pain scores at rest and movement-evoked; area of hyperalgesia; global quality of analgesia management; Long term: any pain in the scar area and any unpleasant experience since the operation | | |
| **Notes** | Co-analgesia:  Pre-op: Lormetazepam sublingual 12h and 1h before.  Intra-op: Epidural bupivacaine, sufentanil, clonidine. General intravenous anesthesia with propofol and an oxygen/air mixture.  Post-op: PCA morphine. | | |
| **Source(s) of funding** | The cost of this work was exclusively borne by the Department of Anesthesiology of the University of Louvain, St. Luc Hospital. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "According to a computer-generated table of random number assignments"... |
| Allocation concealment (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | | Low risk | "All studied solutions were prepared by an anesthesiologist who was not involved in the patient's care. The patient and the anesthesiologist who delivered anesthesia and evaluated analgesia also were blinded to the study solutions". |
| Blinding of outcome assessment (detection bias) | | Unclear risk | The incidence and importance of postoperative residual pain was evaluated at 2 weeks, 1 month, 6 months and 1 year after surgery. Patients were asked to answer the following questions…. This inquiry was performed by phone and confirmed by mail. |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups and < 20% |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Duale 2009**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with long-term follow-up for 6 weeks and 4 months | | |
| **Participants** | 86 patients between 20 and 75 years of age scheduled for elective partial pneumonectomy under thoracotomy | | |
| **Interventions** | Racemic ketamine was diluted to 500 mg in 500 mL of isotonic saline.1 mL per kg of the solution was given 5 min before surgical incision, and 1 mL per kg/h until skin closure. For the postoperative period, 1 mg per kg of ketamine was diluted in isotonic saline in a 48 mL-syringe, then infused at the rate of 2 mL per h (i.e. 1 mg per kg for 24 h), then discontinued. In the placebo group, isotonic saline was given alone following the same protocol. | | |
| **Outcomes** | The primary endpoint was to assess whether ketamine was able to reduce the pain score at the 6th week after surgery, compared to placebo. The secondary endpoints were to compare the early postoperative pain parameters, the rate of side effects, the late parameters of pain and the quality of life between the 2 groups. Morphine consumption (in mg), pain at rest (VAS from 0 to 10), sedation (scale from 0 to 3), nausea, vomiting, dizziness, pruritus, sensation of dry mouth, and current vital parameters. Area of sensory abnormalities (hypoesthesia, allodynia, hyperalgesia. The neuropathic pain symptom inventory and the SF-36 were also filled out. | | |
| **Notes** | Co-analgesia:  Pre-op: Lorazepam on the night preceding and 1 h before.  Intra-op: Anaesthesia involved intravenous midazolam, propofol or etomidate, sufentanil, cistracurium. The patient was maintained with desflurane, sufentanil, cistracurium. Before skin closure, the edges of the thoracotomy as well as the chest drainage orifices were infiltrated with 0.1% ropivacaine.  Post-op: Interpleural 0.2% ropivacaine, intravenous paracetamol  (1 g every 6 h), nefopam (80 mg per 24 h) and morphine. Morphine bolus on patient demand and then via PCA. | | |
| **Source(s) of funding** | Acknowledgments of financial and material support: Programme Hospitalier de Recherche Clinique – Appel d’Offres Régional 2003. CHU Clermont-Ferrand, France. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Sequence generation is not stated |
| Allocation concealment (selection bias) | | Low risk | "Randomisation was undertaken by a research assistant who was not involved in the observations. An inclusion number was allocated randomly and kept in a sealed envelope". |
| Blinding of participants and personnel (performance bias) | | Low risk | "When the patient arrived at the operating theatre, the anaesthetist checked the randomisation, which was kept secret to the patient throughout the study". |
| Blinding of outcome assessment (detection bias) | | Low risk | "All the observers of the study (i.e. nurses in recovery room and surgical ward, investigators and research assistants) were unaware of the treatment given, throughout the study". |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups |
| Selective reporting (reporting bias) | | Low risk | Protocol was registered and no differences were noticed compared with publication |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Dullenkopf 2009**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, 3 arms, placebo-controlled trial with long-term follow-up for 3 months | | |
| **Participants** | 120 adult patients undergoing general or orthopedic operations anticipated to last 30 to 120 minutes | | |
| **Interventions** | The study medication for all 3 groups was prepared and blinded by the hospital pharmacist. A syringe containing 12 ml was provided for every patient. One ml of the study solution contained 1.5 mg, 5 mg or 0 mg of ketamine in groups Kl, Km and P, respectively. In all patients, 1 ml of the study solution was administered for every 10 kg of body weight, resulting in 0.15 mg/kg ketamine IV, 0.5 mg/kg ketamine IV or normal saline in groups Kl, Km and P, respectively. | | |
| **Outcomes** | Anesthetic consumption, time from skin closure to emergency, sedation score, ketamine side effects profile, pain management categorical score. At 3 months: pain scores at rest and movement evoked, pain management score from excellent to poor | | |
| **Notes** | Co-analgesia:  Pre-op: Midazolam 45 minutes before.  Intra-op: General anesthesia was induced with propofol and fentanyl IV. Anesthesia was maintained with propofol and nitrous oxide in oxygen supplemented with fentanyl if required and remifentanil. Fifteen minutes before the end of surgery patients given novaminsulfone 1 gram  Post-op: IV morphine and paracetamol | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "On the basis of a computer-generated block randomisation" |
| Allocation concealment (selection bias) | | Low risk | "The study medication for all 3 groups was prepared and blinded by the hospital pharmacist". |
| Blinding of participants and personnel (performance bias) | | Low risk | Solutions were prepared in a blinded fashion by the pharmacist |
| Blinding of outcome assessment (detection bias) | | Low risk | Patients replied by mail 3 months later. Unclear if they were still blinded |
| Incomplete outcome data (attrition bias) | | High risk | The proportion of missing outcomes (27.3%) compared with observed event risk enough to induce clinically relevant bias |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Eisenberg 2007**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with long-term follow-up for 1 and 6 months | | |
| **Participants** | 22 Patients aged 18 to 75 years with breast cancer requiring mastectomy and axillary lymph node dissection. Subjects with any kind of chronic pain were excluded | | |
| **Interventions** | Treatment was initiated on the day before surgery and continued daily for 14 consecutive days. The dosing schedule was 100 mg of amantadine sulfate tablets twice daily. Patients in the placebo group received equal numbers of identical-looking placebo tablets according to the same schedule. | | |
| **Outcomes** | 0-10 pain scores, rescue medications, multidimensional pain evaluation. 3 months evaluation: 0-10 pain intensity across 5 different anatomical areas, coanalgesia and non pharma treatments, chemotherapy, hormone or Rxtherapy, Short Form-McGill Pain Questionnaire, sensory examination at medical visit (1 month and 6 months) | | |
| **Notes** | Co-analgesia:  Pre-op: Not reported.  Intra-op: Not reported.  Post-op: Patients were allowed to use rescue medications, including opioids, simple analgesics (paracetamol or dipyrone), and non-steroidal anti-inflammatory drugs (NSAIDs) | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | "Randomization was done in blocks of 4 according to a pre-prepared random code"...unclear how the sequence generation was created. |
| Allocation concealment (selection bias) | | Unclear risk | Not stated in the publication |
| Blinding of participants and personnel (performance bias) | | Unclear risk | "Both the amantadine and the placebo tablets were supplied by Merz  Co, Frankfurt, Germany"…unclear if the placebos matched the active drug. |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Unclear if outcomes assessors were blinded |
| Incomplete outcome data (attrition bias) | | High risk | Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups. However the proportion of missing data was > 20% |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | Unclear risk | Fewer than 50 patients per arm |

**Fassoulaki 2001**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled, 4 arms trial for 3 months | | |
| **Participants** | 100 adult female patients, ASA I or II, scheduled for modified  radical mastectomy or lumpectomy plus axillary node dissection | | |
| **Interventions** | 4 arms combining ropivacaine (brachial plexus + Intercostal infiltration); mexiletine 200 mg BID for 6 days starting the night before surgery, and placebos | | |
| **Outcomes** | Pain scores at rest and movement-evoked in the acute setting; Three months after surgery, all patients responded to a structured phone interview to determine if they had: radiotherapy and/or chemotherapy; pain in the chest, axilla, arm of the operated side; reduced or absent sensation in the same areas; the average pain score (from 0 to 10) during the 3 months, if present; and the need for analgesics since they were discharged from the hospital. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported  Intra-op: All patients received IV metoclopramide 10 mg and droperidol before induction of anesthesia. Anesthesia induced with thiopental, propofol, and rocuronium. Anesthesia was maintained with sevoflurane and nitrous oxide 70% in oxygen.  Post-op: IM Propoxyphene and paracetamol PRN for 24h. 24 hours after surgery: codeine + paracetamol PRN. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Allocation concealment (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | | Unclear risk | Insufficient information to permit judgement |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Three months after surgery, all patients responded to a structured phone interview to determine if they had…unclear if the interviewer was blinded |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups and < 20% |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Fassoulaki 2002**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 3 months | | |
| **Participants** | 75 ASA I or II female patients scheduled for modified radical mastectomy or lumpectomy with axillary lymph node dissection | | |
| **Interventions** | Patients were blindly randomized to one of 3 groups. In the mexiletine group, patients received 200 mg of mexiletine along with placebo capsules (identical in appearance to the gabapentin capsules) 3 times per day. Patients in the gabapentin group received 400 mg of gabapentin and placebo capsules (identical in appearance to the mexiletine capsules) 3 times per day. Patients in the placebo group received both placebo capsules 3 times per day. Administration of the active and/or placebo drugs started the evening before surgery and continued 3 times a day for the first 10 postoperative days, including the day of surgery. | | |
| **Outcomes** | The visual analog scale score assessed pain at rest and after movement. 3 months later, all patients were interviewed to identify intensity of chronic pain and analgesic requirements | | |
| **Notes** | Co-analgesia:  Pre-op: Premedication was omitted.  Intra-op: Anesthesia was induced with thiopental and propofol. Intubation was facilitated with rocuronium, and anesthesia maintained with 2% sevoflurane and 70% nitrous oxide in oxygen.  Post-op: Propoxyphene and paracetamol given intramuscularly (IM) on demand. Paracetamol and codeine (POD 2-10) | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Each patient was randomly assigned to a treatment group, and the first dose was given the evening before surgery" |
| Allocation concealment (selection bias) | | Low risk | "Seventy-five envelopes were prepared, coded as Group 1, Group 2, and Group 3, sealed, and opened for each patient to indicate the group of assignment". |
| Blinding of participants and personnel (performance bias) | | Low risk | "Envelopes, bottles with capsules, and coding were prepared by an anesthesiologist in cooperation with the hospital’s pharmacy. This anesthesiologist did not participate in the study, evaluation of the patients or data, or in report of the findings." |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "Three months after surgery, patients were interviewed by phone to identify whether they received postoperative chemotherapy, radiotherapy, or both and if they experienced pain or abnormal sensations in the chest, axilla, or the arm of the operated side" |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups and < 20% |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Fassoulaki 2012**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double-blind, 2 arm, placebo-controlled trial, follow-up for 3 months. | | |
| **Participants** | 80 patients scheduled for total abdominal hysterectomy or myomectomy | | |
| **Interventions** | Pregabalin: 150mg 8-hourly starting on the day before surgery at 14:00 hours and continuing for the first five postoperative days.  Placebo: Placebo caps (thin sugar) | | |
| **Outcomes** | Postoperative intravenous morphine and Lonalgal (30 mg codeine with 500 mg paracetamol) tablet consumption, visual analogue pain scores at rest and on coughing, sedation, anxiety, dizziness, ataxia, blurred vision and diplopia were recorded. One and 3 months postoperatively patients were interviewed for the presence of pain and analgesic needs due to surgery. | | |
| **Notes** | Co-analgesia:  Pre-op: Premedication was omitted.  Intra-op: Ranitidine, droperidol and metoclopramide were administered intravenously. Anaesthesia was induced with fentanyl, thiopental, cis-atracurium to facilitate intubation of the trachea, and maintained with sevoflurane in a 50% nitrous oxide/oxygen mixture.  Post-op: PCA morphine for 48h, intravenous ranitidine and  metoclopramide, codeine with paracetamol PRN | | |
| **Source(s) of funding** | Financial support and sponsorship: this work was supported by Departmental funds (Aretaieio Hospital, University of Athens, Athens, Greece). | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomised to the control or treatment group using sealed envelopes, containing odd and even numbers obtained from a computer-generated table; for odd numbers, patients were allocated to the control (code A) group and for even numbers to the pregabalin (code B) group." |
| Allocation concealment (selection bias) | | Low risk | "The active and placebo capsules were coded accordingly and kept in two different containers. Placebo capsules were prepared by emptying the pregabalin capsules and filling them with thin sugar. Capsule preparation and allocation into the containers (containers coded as A for the placebo and as B for the pregabalin capsules) were undertaken by an anaesthesiologist who did not participate in the study data collection or analysis. Anaesthesiologists, surgeons and patients were not aware of the contents of capsules." |
| Blinding of participants and personnel (performance bias) | | Low risk | "Anaesthesiologists, surgeons and patients were not aware of the contents of capsules." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | No reported. |
| Incomplete outcome data (attrition bias) | | High risk | Lost to follow-up: 12/39 (31%) vs. 6/41 (15%) were lost to follow-up in the treatment and control groups, respectively. The dropout rate was >20% |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. |

**Fransen 2006**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Multicenter, randomized, double-blind, placebo-controlled trial for a variable follow up time (6-14 months) | | |
| **Participants** | 902 Patients identified within 24 hours of completed THR (primary or revision), irrespective of age, reason for surgery, or procedure performed | | |
| **Interventions** | Ibuprofen 1200 mg Daily (TID) for 14 days | | |
| **Outcomes** | Primary outcomes: changes from baseline to follow-up in WOMAC. We standardised scores to a range of 0-10, with 0 indicating no hip pain or no difficulty with daily activities and 10 indicating severe hip pain or severe difficulty with daily activities. Secondary outcomes: Short form 36, compared with before surgery; hip status today with 5 response levels; frequency of use of analgesia for hip pain during the past week; ability to get “about the house” and ability to get “out of the house” with 5 response levels ranging from “not at all” to “no difficulty”; time spent participating in physical activity during the past week; objective measures of physical performance (hip flexion, time to walk 50 feet (about 15 metres), and timed “up and go”; radiographic evidence of ectopic bone formation according to the Brooker classification and major bleeding complications during hospital admission. | | |
| **Notes** | Co-analgesia was up to treatment group. No changes in the NSAIDs were allowed. Patients could not take other NSAIDs (with the exception of low dose aspirin) during the study period. The protocol required no other changes to usual preoperative or postoperative care. | | |
| **Source(s) of funding** | Funding: National Health and Medical Research Council of Australia and the Medical Benefits Fund of Australia provided funding through competitive peer reviewed processes | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Randomisation was performed centrally by using a computer based system" |
| Allocation concealment (selection bias) | | Low risk | "We used a minimisation program to stratify treatment by study centre and type of surgery performed (primary or revision). Treatment allocation was blinded and concealed from patients and study staff until the database was locked". |
| Blinding of participants and personnel (performance bias) | | Low risk | "All study tablets were packaged in identical blister packs". |
| Blinding of outcome assessment (detection bias) | | Low risk | "All assessments were standardised and performed blind to randomised treatment allocation". |
| Incomplete outcome data (attrition bias) | | Low risk | No statistical significant difference in the rate of dropouts. (P=0.06). The proportion of missing outcome data < 20% |
| Selective reporting (reporting bias) | | Low risk | Protocol was registered and no differences were noticed compared with the publication |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Gianesello 2012**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up for 2 days, 3 months and 1 year after surgery | | |
| **Participants** | 60 adult patients of either sex, having American Society of Anesthesiologists physical status I-II, scheduled for elective decompressive lumbar laminectomy with spinal fusion for degenerative spinal stenosis. | | |
| **Interventions** | Patients were randomly assigned to 2 equal groups of 30 each using a computer-generated table of random numbers to receive either a matching PL or PG 300 mg (Lyrica; Pfizer) and PL or PG 150 mg, twice a day for 48 hours postoperatively. | | |
| **Outcomes** | Pain scores at rest and movement-evoked, Ramsay sedation scale, incidence of respiratory depression, hypotension and other side effects. Patients were called at 3 months to evaluate EuroQoL and perceived general health status. | | |
| **Notes** | Co-analgesia:  Pre-op: Midazolam  Intra-op: General anesthesia with propofol and fentanyl, and orotracheal intubation was facilitated by cisatracurium. Anesthesia was maintained with sevoflurane and air in oxygen. Intraoperative analgesia was provided by remifentanil. Ondansetron and dexamethasone for prophylaxis of  nausea and vomiting. IV morphine. At the end of surgery, neuromuscular block with neostigmine and atropine.  Post-op: Morphine and ketorolac tromethamine infusion for 48h. | | |
| **Source(s) of funding** | No funding. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomly assigned to 2 equal groups of 30 each using a computer-generated table of random numbers". |
| Allocation concealment (selection bias) | | Low risk | "All of the medications were identical, were provided by the hospital pharmacy". |
| Blinding of participants and personnel (performance bias) | | Low risk | "All of the medications were identical" |
| Blinding of outcome assessment (detection bias) | | Low risk | "Patients were questioned during the first 1 hour in the postanesthesia care unit and were later evaluated in the ward at 4, 8, 12, 24, and 48 hours by an independent observer blinded to group allocation". |
| Incomplete outcome data (attrition bias) | | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Grigoras 2012**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with a daily follow-up for 7 days, and sensory examination 3 months after surgery | | |
| **Participants** | 36 American Society of Anesthesiology physical status I or II patients undergoing breast surgery (mastectomy or wide local excision+axillary node dissection, including sentinel node mapping or clearance) were undertaken | | |
| **Interventions** | Immediately after orotracheal intubation, patients of the lidocaine group (L) received an IV bolus of lidocaine (1.5 mg/kg in 10 min) followed by a continuous IV infusion at 1.5 mg/kgh. The infusion was stopped 60 minutes after skin closure. Patients in the control group (C) received an equivalent saline regimen. | | |
| **Outcomes** | Visual analog scale (VAS) pain scores at rest and on arm movement was recorded at 2, 4, 24, 48, and 72 hours postoperatively, or at these time points until discharge from hospital; analgesic use was recorded for each group; A questionnaire was also used to assess the presence or absence of persistent pain, the time of onset, location and character of the pain, medications used for pain relief and impact on the patients’ daily life, a history of chemotherapy or radiotherapy, and further surgery. PPSP was considered to be present if the answer to “Have you had pain in the last week which you attribute to your breast surgery?” was “Yes.”; Three months postoperatively, patients had the area of peri-incisional hyperalgesia measured by the same blinded investigator and completed the short-form McGill Pain Questionnaire, the Pain Catastrophizing Scale, and the Hospital Anxiety and Depression Scale. | | |
| **Notes** | Co-analgesia:  Pre-op: Patients received no preanaesthetic medication.  Intra-op: Anesthesia was induced with propofol and fentanyl and maintained with sevoflurane and 70% nitrous oxide in oxygen. Muscle relaxation was achieved with vecuronium. Intraoperative analgesia in both groups consisted of paracetamol IV 1 g, diclofenac IV 75 mg, and morphine sulphate PRN IV. Morphine was administered after induction of general anesthesia and titrated according to patient response to surgical stimuli.  Post-op: Patients in both groups received a standard analgesic regimen (morphine sulphate PCA, diclofenac sodium, paracetamol). Tramadol IM/PO PRN as rescue medication). | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomly allocated to 1 of 2 groups based on computer generated codes that were maintained in sequentially numbered opaque envelopes". |
| Allocation concealment (selection bias) | | Low risk | "None of the investigators involved in patient management or data collection were aware of the group assignment". |
| Blinding of participants and personnel (performance bias) | | Low risk | "On the morning of surgery an anesthetist who was not involved in the patient’s evaluation opened the envelope and prepared either 1% lidocaine or normal saline in coded 50mL syringes". |
| Blinding of outcome assessment (detection bias) | | Low risk | "Three months postoperatively, patients had the area of peri-incisional hyperalgesia measured by the same blinded investigator".... |
| Incomplete outcome data (attrition bias) | | Low risk | The study reported no missing outcome data at 3 months |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per group |

**Grosen 2014**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow up for 6 months. | | |
| **Participants** | 104 patients with pulmonary malignancies scheduled for anterior thoracotomy. | | |
| **Interventions** | Gabapentin: an initial single oral dose of 1200 mg gabapentin 2 h before scheduled surgery followed by an increasing oral dose of gabapentin over 5 consecutive days in a step-up multi-dose manner: postoperative day 1: 300 mg twice a day; postoperative day 2: 300 mg three times a day; and postoperative days 3–5: 300 mg four times a day, equivalent to a total dose of 6300 mg.  Placebo: Placebo pill (formulation not specified) | | |
| **Outcomes** | Primary outcome: the effect of gabapentin on the incidence of persistent post-thoracotomy pain, and the potentially protective role of gabapentin… measures of pain intensity, interference with function and mood.  Secondary outcomes: acute postoperative pain intensity, post-op recovery, analgesia related adverse effects. Persistent post-thoracotomy pain was assessed according to responses to the short forms of the Brief Pain Inventory (BPI) and the McGill Pain Questionnaire (MPQ) at 3 and 6 months postoperatively. Clinically relevant persistent post-thoracotomy pain was defined as BPI average pain during the past week equal to or higher than 4/10 on the NRS. | | |
| **Notes** | Co-analgesia:  Pre-op: Oral diazepam and acetaminophen 2h before surgery.  Intra-op: Epidural blockade with bupivacaine plus IV hydroxyethyl starch. General anesthesia was initiated with fentanyl, propofol, and cisatracurium. Epidural analgesia was provided with continuous infusion of bupivacaine + morphine.  Post-op: Standardized multimodal analgesia. Non-opioid analgesic treatments with acetaminophen and ibuprofen and constipation prophylaxis were initiated from the day of surgery in all patients. Pain relief was tailored with epidural analgesia and/or systemic opioids PRN. Controlled-release morphine. Bolus IV morphine as rescue analgesia. | | |
| **Source(s) of funding** | This work was supported by the M.L. Jørgensen and Gunnar Hansen’s Foundation, Copenhagen, Denmark (grant no. 2956 to Kasper Grosen), the Danish Council for Strategic Research and the  Danish Agency for Science, Technology and Innovation, Copenhagen, Denmark (grant no. 10-092786 to Asbjørn Mohr Drewes). | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "An external trial pharmacist from the Hospital Pharmacy at Aarhus University Hospital, Denmark, prepared a computer-generated concealed treatment allocation schedule randomizing the two treatments in blocks of eight at a 1:1 ratio to a consecutive series of patient numbers (001–104)." |
| Allocation concealment (selection bias) | | Low risk | "The Hospital Pharmacy kept the allocation sequence concealed during the entire study period. Each participant’s allocation was concealed in sequentially numbered, opaque and sealed envelopes and kept in the medical records." |
| Blinding of participants and personnel (performance bias) | | Low risk | "The identical gabapentin or placebo capsules were then pre- packed in numbered containers according to the randomization schedule to obtain double blinding. As patients entered the trial, they were assigned in turn to the next consecutive number and subsequently received the capsules in the corresponding pre- packed container." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Low risk | "The Hospital Pharmacy kept the allocation sequence concealed during the entire study period." |
| Incomplete outcome data (attrition bias) | | Unclear risk | Numbers analyzed for primary outcome: 30/52 (Gabapentin) and 37/52 (Placebo). The dropout rate was >20%. "...potential source of bias in this trial was the overall amount of missing questionnaire forms during followup, with more patients leaving the gabapentin group. The attrition rate was high for obvious reasons; however, the reason why forms were missing was unknown in ~15% of patients. These missing cases could, if they were different from those providing data, have biased the estimate of the rate of persistent post-thoracotomy pain. We performed a sensitivity analysis based on best case/worst case scenarios (i.e. absence/presence of persistent pain in nonrespondents) to assess the effects of potential bias. In the worst case, if all of the non-respondents who did not provide data on the primary outcome had persistent post-thoracotomy pain, the incidence would have been 57% in the placebo group versus 58% in the gabapentin group. If, on the other hand, none of these patients had persistent post-thoracotomy pain, the incidence would have been 41% for placebo-treated patients compared with 37% for gabapentin-treated patients. Therefore, even if the worst possible bias had been present, inability to get the data would not have considerably changed any of the effect measures." |
| Selective reporting (reporting bias) | | High risk | The study report fails to include results for a key outcome that would be expected to have been reported for such a study. According to ClinicalTrials.gov, the following was a pre-specified primary outcome: "Persistent post surgical pain [Time Frame: 12 months following surgery] Pain is assessed by means of the Brief Pain Inventory (BPI-SF) and The McGill Pain Questionnaire (SF-MPQ). Persistent postoperative pain is measured both on a 11-point numeric pain rating scale and on a 10 cm visual analog scale (VAS). A score >=3 is considered as moderate pain." There is no mention of a 12-month follow up in the paper. |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Hah 2018**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 2 arm, placebo controlled trial, follow-up for up to 2 years. | |
| **Participants** | 422 patients scheduled for an eligible surgery (thoracotomy, video-assisted thoracoscopic surgery, primary or revision total hip replacement, primary or revision total knee replacement, unilateral or bilateral mastectomy, and breast lumpectomy with or without sentinel node biopsy or axillary node dissection) | |
| **Interventions** | Gabapentin: The treatment group received 4 capsules of gabapentin, 300mg (1200mg total), preoperatively and 2 capsules of gabapentin, 300mg, 3 times a day (600mg 3 times a day) postoperatively (10 total doses).  Placebo: Active placebo (lorazepam, 0.5mg) preoperatively followed by inactive placebo postoperatively for 72 hours | |
| **Outcomes** | Primary outcome: time to pain resolution (5 consecutive reports of 0 of 10 levels of average pain at the surgical site on the numeric rating scale of pain).  Secondary outcomes: time to opioid cessation (5 consecutive reports of no opioid use) and the proportion of participants with continued pain or opioid use at 6 months and 1 year. | |
| **Notes** | Co-analgesia:  Various: Intravenous Ketamine, Spinal analgesia, Epidural analgesia, Regional anesthetic technique (see Table 2) | |
| **Source(s) of funding** | Funding/Support: Drs Hah (grant K23DA035302), Carroll (grant K23DA025152), and Mackey (grant K24DA029262) received funding from the National Institute on Drug Abuse, National Institutes of Health for this project. This project was also funded by the Stanford Department of Anesthesiology, Perioperative, and Pain Medicine. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "The randomization list was computer-generated with corresponding randomization log sheets provided to the operating room pharmacy. One log sheet was generated per combination of surgeon/surgery." |
| Allocation concealment (selection bias) | Low risk | "The randomization list was… provided to the operating room pharmacy." "The pharmacist documented the patient’s information on a randomization card that was placed in a sealed envelope indicating which medication was prescribed." "Participants, clinicians, and researchers were blinded to allocation until completion of statistical analyses." |
| Blinding of participants and personnel (performance bias) | Low risk | "Participants, clinicians, and researchers were blinded to allocation until completion of statistical analyses." "All analyses were completed before the data were unblinded." "Patients were not able to correctly guess randomization status (χ2 P = .30) suggesting that blinding was successful." |
| Blinding of outcome assessment (detection bias) | Low risk | "Participants, clinicians, and researchers were blinded to allocation until completion of statistical analyses." "All analyses were completed before the data were unblinded." |
| Incomplete outcome data (attrition bias) | High Risk | Missing data >20%. Actual lost to follow-up 59 placebo, 54 gabapentin (see Figure). 410 included in intent-to-treat analysis. |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | Low risk | Unable to find additional potential bias. >50 participants per study arm. |

**Han 2019**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 12 months | |
| **Participants** | 80 patients scheduled for elective abdominal hysterectomy. | |
| **Interventions** | Dexmedetomidine: 0.5 μg/kg/hour of dexmedetomidine was infused by a microinjection pump from 15 minutes prior to the initiation of anesthesia until peritoneum closure  Placebo: Saline 0.9% | |
| **Outcomes** | The goal of this study was to determine the effect of pre-emptive dexmedetomidine (Dex) on the incidence of CPHP | |
| **Notes** | Co-analgesia:  Pre-op: Patients were not given any premedication.  Intra-op: General intravenous anesthesia was induced with midazolam, etomidate, fentanyl and vecuronium. All patients were intubated and mechanically ventilated with 100% oxygen during surgery procedure. Propofol and remifentanil were used to maintain anesthesia. Intermittent administration of vecuronium was used to keep muscle relaxation as required.  Post-op: Rescue analgesia was provided with tramadol 50 mg intravenous if the patient’s NRS pain score was > 3. Before discharge to ward, all patients were received patient-controlled intravenous analgesia (PCIA) using an analgesia pump filled with sufentanil, tropisetron with normal saline. | |
| **Source(s) of funding** | This work was supported by Fund of Six Best Talent of Jiangsu, 2016 (WSW-113) and Jiangsu Young Medical Talents (grant no. QN-RC2016209). | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "The patients were randomly assigned into two groups each of 40 using a computer-generated randomization scheme" |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | Low risk | "double-blind" "NRS, sufentanil dose by PCIA and adverse reactions were recorded at 2, 6, 12, 24 and 48 hours after the surgery by a specified anesthesiologist blinded to group allocation." |
| Blinding of outcome assessment (detection bias) | Unclear risk | Blinding only described for early outcomes: "NRS, sufentanil dose by PCIA and adverse reactions were recorded at 2, 6, 12, 24 and 48 hours after the surgery by a specified anesthesiologist blinded to group allocation." |
| Incomplete outcome data (attrition bias) | High Risk | Missing data >20%. 4/40 lost to follow-up in the Dex group and 7/40 lost to follow-up in the placebo group. |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | High Risk | Fewer than 50 participants per study arm. No study protocol, so no way to verify if chronic pain was a pre-specified primary outcome. |

**Hayes 2004**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 3, 6 + 6 months after surgery | | |
| **Participants** | 45 Patients presenting for above- or below-knee amputation because of peripheral vascular disease, cancer or chronic infection | | |
| **Interventions** | The Ketamine patients received a pre-induction intravenous (IV) bolus of ketamine 0.5 mg.kg–1, + IV infusion at 0.15 mg.kg/h. Control patients received a pre-induction IV bolus of normal saline, followed by IV infusion. Trial solutions were continued for 3 days postoperatively. If side-effects considered attributable to ketamine occurred (vivid dreams, hallucinations or confusion), the infusion rate was halved. If side-effects then continued or were severe, the infusion was ceased. | | |
| **Outcomes** | Opioid consumption at 24 and 72 hours, complications, patient satisfaction, phantom or stump pain incidence. 0-10 Pain scores (highest, lowest, usual and current level). Sensory examination with von Frey filaments including measurement of the area of sensitization. | | |
| **Notes** | Co-analgesia: morphine PCA. Amitriptyline and sodium valproate were used to treat phantom limb pain. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomized (via a random number generator) to receive"... |
| Allocation concealment (selection bias) | | Unclear risk | Not stated |
| Blinding of participants and personnel (performance bias) | | Low risk | "The patient, anaesthetist, Acute Pain Service (APS) personnel, ward staff and investigators were blinded to the contents of the trial solution". |
| Blinding of outcome assessment (detection bias) | | Low risk | "The patient, anaesthetist, Acute Pain Service (APS) personnel, ward staff and investigators were blinded to the contents of the trial solution". |
| Incomplete outcome data (attrition bias) | | High risk | Significant proportion of missing outcome data (>20%) |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per group |

**Hu 2014**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up 6 months. | | |
| **Participants** | 81 lung tumor patients scheduled for thoracotomy for lung tumor using muscle sparing axillary thoracotomy (no sternotomy) | | |
| **Interventions** | Ketamine: intravenous ketamine 1 mg/kg before incision, followed by 2 μg/kg/min infusion for 72 hours.  Placebo: Normal saline | | |
| **Outcomes** | This study aimed to investigate whether continuous intravenous ketamine during the first 72 hours after thoracotomy could reduce the incidence and intensity of CPTP and to define the incidence and risk factors of CPTP. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: General anesthesia was induced with propofol, midazolam, and sufentanil. Intubation of the trachea was facilitated with rocuronium. Anesthesia was maintained with sevoflurane and propofol. Incremental intraoperative rocuronium and sufentanil doses were repeated if necessary.  Post-op: PCIA sufentanil and azasetron during the first 72 hours after surgery. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Not reported |
| Allocation concealment (selection bias) | | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | | Unclear risk | Not reported Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | | Unclear risk | The number lost to follow-up by group is not reported. Only the total lost to follow-up for the whole sample. 78/81 patients were analyzed in this study |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Fewer than 50 participants per arm. There is no study protocol so no way to verify if chronic pain as the primary outcome was pre-specified. |

**Hyer 2015**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 3 months. | | |
| **Participants** | 101 patients scheduled for elective spine neurosurgery (lumbar micro discectomy, anterior cervical discectomy & fusion, and lumbar decompression and fusion). | | |
| **Interventions** | Duloxetine: One 30mg capsule per day for 5 days, one 60mg capsule per day for 30 days, and one 60mg capsule per day for 60 days  Placebo: Placebo capsule (inert pill) | | |
| **Outcomes** | Pain (Brief Pain Inventory), Opioid utilization, SF-36 Pain Sub-scale, SCL-90-R somatization subscale, function, depression, anxiety | | |
| **Notes** | Co-analgesia:  Pre-op: Not reported.  Intra-op: Not reported.  Post-op: Not reported. | | |
| **Source(s) of funding** | This study was supported by a research grant through Eli Lilly and Company. The current study was investigator initiated and had no obligation to Eli Lilly and Company. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | "Randomization (a coin flip for every two people and accounting for surgery type) was applied at presurgery. We identified the type of spine surgery at entry and would make adjustments over time for randomization but none were needed." |
| Allocation concealment (selection bias) | | High risk | "We identified the type of spine surgery at entry and would make adjustments over time for randomization but none were needed." |
| Blinding of participants and personnel (performance bias) | | Unclear risk | Not reported. "Placebo and active drug bottles were differentiated by patient number" |
| Blinding of outcome assessment (detection bias) | | Low risk | This is not reported in the methods however, in the results section it states: "Recall that the CIBIC is assessed by a blind interviewer" |
| Incomplete outcome data (attrition bias) | | Unclear risk | Over 30% were lost to follow-up 15/51 in the Duloxetine group and 16/50 in the placebo group. There is no mention in the discussion regarding the large proportion lost to follow-up nor whether any sensitivity analyses were conducted for non-completers. |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Methodology and reporting of the results are poorly communicated. There are no details regarding the concomitant analgesic procedure, surgical procedure, and details about medication administration is vague. |

**Ibrahim 2018**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 3 months | |
| **Participants** | 44 patients undergoing spinal fusion surgery | |
| **Interventions** | Lidocaine: loading dose of IV lidocaine 2mg/kg slowly just before induction of anesthesia, then the lidocaine infusion started at a rate of 3mg/kg/h  Placebo: Sodium chloride infusion 0.9% | |
| **Outcomes** | Postoperative pain evaluation during rest was assessed by VAS (0=no pain, 10=most severe pain). The score was recorded at the following times: immediately at 1hour; 6hours; 12hours; 24 hours; at discharge time; 1 month; 2 months, and 3 months postoperation. Time to the first request for analgesia, and the total dose of rescue analgesia (morphine) in the first 24 hours after surgery was recorded. The long-term follow-up of postoperative back pain for 3 months was conducted through the outpatient orthopaedic clinic, or by telephone. | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: General anesthesia was induced by propofol, and cisatracurium to facilitate orotracheal intubation. In both the groups, anesthesia was maintained with isoflurane in oxygen/air mixture at sufficient concentration to maintain systolic blood pressure within the limit of 20% baseline value. All patients received 60 mg ketorolac IV infusion after induction of anesthesia, and fentanyl 1.5mg/kg IV before skin incision. Acetaminophen (paracetamol) 1gm was given by IV infusion to all patients before extubation.  Post-op: In the first 24hours postoperative; patients were given IV Ketorolac and paracetamol for 8hours. Morphine IV was given as rescue analgesia when VAS was ≥4, or if patient requested. After 24 hours post-operation; paracetamol and ketorolac were given orally for 2 weeks. | |
| **Source(s) of funding** | The authors received no financial support for the research, authorship, and/or publication of this article | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | "Randomization was performed using lidocaine group, and control group registers, which were placed in sealed envelopes…" There is insufficient information about how the randomization sequence was generated. |
| Allocation concealment (selection bias) | Unclear risk | "Randomization was performed using lidocaine group, and control group registers, which were placed in sealed envelopes prior to study initiation, and opened prior to anesthesia by a physician who prepared the IV solution, and identified it with the patient number, according to the envelope drawn. The solution was handed to another physician, blind to the prepared solutions’ content, who was responsible for the anesthesia. The solution volume was equal. The responsible investigator remained blind to the chosen group until the end of the study." The use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed. |
| Blinding of participants and personnel (performance bias) | Unclear risk | "a physician who prepared the IV solution, and identified it with the patient number, according to the envelope drawn. The solution was handed to another physician, blind to the prepared solutions’ content, who was responsible for the anesthesia. The solution volume was equal. The responsible investigator remained blind to the chosen group until the end of the study." Randomization and blinding methods are not clearly described |
| Blinding of outcome assessment (detection bias) | Unclear risk | "The responsible investigator remained blind to the chosen group until the end of the study." Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20% |
| Selective reporting (reporting bias) | High Risk | One or more reported primary outcomes were not pre-specified. The study was conducted from 2015-2016 but the trial was not registered until 2017. The original outcome when first submitted January 2017 was Postoperative opioid consumption. [ Time Frame: Postoperative 24 h] and this was changed to numerical rating scale (NRS), pain score. [Time Frame: Postoperative 3 months] in November 2017 |
| Other bias | High Risk | Fewer than 50 participants per study arm. The study protocol was submitted after the study was completed, so no way to verify if chronic pain was a pre-specified primary outcome. |

**Ilkjaer 2000**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 3 months after surgery | | |
| **Participants** | 50 patients scheduled for non-malignant elective abdominal hysterectomy with a supravaginal, horizontal approach | | |
| **Interventions** | One hour before surgery, patients received dextromethorphan 150 mg or placebo (5 tablets) orally as premedication | | |
| **Outcomes** | Pressure pain detection threshold, von Frey pain detection threshold and hyperalgesia to von Frey hair stimulation proximal to the surgical wound, were assessed 3 months after the operation, during a control visit at the hospital. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported other than the study drug/placebo.  Intra-op: General anesthesia was induced with fentanyl and thiopental. Vencuronium to facilitate intubation. General anesthesia was maintained with isoflurane, nitrous oxide in oxygen. Additional fentanyl every half hour. No other analgesics were administered during the operation.  Post-op: PCA morphine as the only analgesic. | | |
| **Source(s) of funding** | This study was supported by Danish Medical Research Council (Reg. no. 28809) and Novo Nordisk Foundation. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Allocation concealment (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | | Low risk | "The study drugs (identical tablets of dextromethorphan 30 mg, or vehicle without dextromethorphan)". |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias) | | Low risk | Excluded patients were replaced until 50 data sets were available for analysis |
| Selective reporting (reporting bias) | | High risk | the authors reported sensory examination, however, it would be more clinical meaningful the report of pain scores or at least the rate of residual pain |
| Other bias | | High risk | Fewer than 50 patients per group |

**Jendoubi 2017**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double-blind, 3 arm, placebo-controlled trial, follow-up for 3 months | | |
| **Participants** | 63 patients scheduled for elective open nephrectomy | | |
| **Interventions** | Lidocaine: IV lidocaine bolus of 1.5 mg/kg (0.075 ml/kg of lidocaine 2%) at the induction of anesthesia, followed by a continuous infusion of 1 mg/kg/h intraoperatively and for 24 h postoperatively.  Ketamine: IV ketamine bolus of 0.15 mg/kg (0.075 ml/kg of solution of ketamine diluted to a concentration of 2 mg/ml in normal saline) at the induction of anesthesia, followed by infusion of 0.1 mg/kg/h intraoperatively and for 24 h postoperatively.  Placebo: Saline 0.9% | | |
| **Outcomes** | Primary outcome was cumulative morphine consumption. Secondary outcome was incidence of Neuropathic Pain at 3 months, defined as >=4 on the DN4 | | |
| **Notes** | Co-analgesia:  Pre-op: hydroxyzine.  Intra-op: General anesthesia was induced with propofol, fentanyl, cisatracurium and maintained by boluses of fentanyl and inhaled sevoflurane 1 minimum alveolar concentration in 50% oxygen/air.  Paracetamol and nefopam 30 min before the end of the surgical procedure.  Post-op: titration of IV morphine (2 mg boluses every 5 min), then PCA morphine for 24h. Additional analgesia was provided with combination of the paracetamol and nefopam IV. | | |
| **Source(s) of funding** | No funding | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Not reported |
| Allocation concealment (selection bias) | | Unclear risk | "The patients were randomly assigned to one of the three treatment groups using the sealed envelope method. A “blinded” nurse prepared the study solutions." Methods of concealment are not described in sufficient detail. The use of assignment envelopes are described but it remains unclear whether envelopes were sequentially numbered and opaque. |
| Blinding of participants and personnel (performance bias) | | Low risk | A “blinded” nurse prepared the study solutions." "None of the other investigators involved in patient management or data collection were aware of the group assignment." Double-blind study design. |
| Blinding of outcome assessment (detection bias) | | Low risk | "None of the other investigators involved in patient management or data collection were aware of the group assignment." |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was below 20%. Lost to follow-up: 1/21 in each of the 3 study arms |
| Selective reporting (reporting bias) | | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. |

**Jeyamohan 2015**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 24 months. | |
| **Participants** | 112 patients scheduled for multilevel (≥ 2 motion segments) anterior cervical spine surgery | |
| **Interventions** | Dexamethasone: dexamethasone (Decadron; 0.2 mg/kg) followed by 4 postoperative doses of 0.06 mg/kg of steroid or placebo, respectively, administered every 6 hours for the first 24 hours.  Placebo: Saline. | |
| **Outcomes** | Fusion status, incidence of dysphagia and airway compromise  Other outcomes: At the 3-, 6-, 12-, and 24-month follow-up time points, the patients were assessed by using the FOSS and pain and functional scales | |
| **Notes** | Co-analgesia:  Pre-op: Not reported.  Intra-op: Not reported.  Post-op: Not reported. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | Not reported |
| Allocation concealment (selection bias) | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | Low risk | "double-blinded" "intravenous dexamethasone or an equivalent volume infusion of saline" "The patients and the investigators were blinded to the treatment for the duration of the study." |
| Blinding of outcome assessment (detection bias) | Low risk | "The patients and the investigators were blinded to the treatment for the duration of the study." |
| Incomplete outcome data (attrition bias) | High Risk | Missing data > 20% |
| Selective reporting (reporting bias) | High Risk | One or more reported primary outcomes were not pre-specified. According to Clinicaltrials.gov, the only outcome specified was "subjects will demonstrate good bony fusion [Time Frame: one year]". In the summary it states "The investigators hypothesize that the use of steroids intraoperatively provides a significant benefit to the patient, in terms of reduced incidence of dysphagia and airway compromise." There is no mention of collecting pain outcome data at 3, 6, 12, and 24 months. |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Joseph 2012**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 3 months. | | |
| **Participants** | 60 patients scheduled for elective thoracotomy for partial pneumonectomy by posterolateral or lateral thoracotomy | | |
| **Interventions** | Ketamine: Continuous i.v. infusion of ketamine for 48 h and patient-controlled thoracic epidural analgesia (PCEA) with ropivacaine 1.5 mg/ml during the thoracotomy postoperative period. An i.v. ketamine infusion was standardized as follows: 0.5 mg/kg of ketamine during anaesthesia induction and an intraoperative continuous i.v. infusion of ketamine 3 μg kg−1 min−1 following by a postoperative infusion of ketamine 1.5 μg kg−1 min−1 during the postoperative 48 h, starting at the end of the surgery.  Placebo: The standard/placebo group was given a combination of continuous i.v. infusion of saline solution and PCEA with ropivacaine 1.5 mg/ml during the thoracotomy postoperative period. The saline solution was administered using the same protocol and the same duration. | | |
| **Outcomes** | Early postoperative analgesia (ropivacaine consumption, post-op pain intensity, supplemental analgesic requirement), Pulmonary Function, Residual Pain at 1 and 3 months after surgery, Side Effects of treatments | | |
| **Notes** | Co-analgesia:  Pre-op: prescribed oral alprazolam.  Intra-op: PCEA device containing ropivacaine and sufentanil was started. General anaesthesia performed, using target-controlled infusion of propofol and remifentanil. IV paracetamol 1 g every 6 h with the first dose starting 1h before extubation.  Post-op: PCEA ropivacaine 1.5 mg/ml and sufentanil 0.4 μg/ml). | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomized to one of the two groups using a computer-generated randomization schedule." |
| Allocation concealment (selection bias) | | Unclear risk | "The syringes had a similar appearance allowing the double-blind schedule. The pharmacist did not take part in the patient management." Allocation concealment is not described, only blinding with similar looking syringes. |
| Blinding of participants and personnel (performance bias) | | Low risk | "The syringes had a similar appearance allowing the double- blind schedule. The pharmacist did not take part in the patient management.". Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "The patient’s subjective postoperative pain intensity was evaluated by a blinded observer". Blinding is described for the early postoperative assessment only. It is not clear whether assessors at 3 months were blinded. |
| Incomplete outcome data (attrition bias) | | High risk | Almost 40% lost to follow-up prior to the 3-month endpoint. Outcome data available for only 18/30 in Ketamine and 19/30 in the placebo groups. |
| Selective reporting (reporting bias) | | High risk | The study report fails to include results for a key outcome that would be expected to have been reported for such a study. According to ClinicalTrials.gov, the following was a pre-specified secondary outcome "pain postponed in 1, 3 and 6 months [Time Frame: 24 months]", however there is no mention of the 6 month outcome in either the methods or results. |
| Other bias | | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. The authors completed the CONSORT checklist, however there are gaps in the reporting as they pertain to allocation concealment and blinding. |

**Joshi 2013**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 3 months. | | |
| **Participants** | 40 patients scheduled for primary off-pump coronary artery bypass surgery (OPCAB) | | |
| **Interventions** | Pregabalin: 150 mg capsules 2 h before induction of anesthesia. Pregabalin capsules (75 mg) were given every 12 h for 2 post-operative days  Placebo: Placebo pill (sucrose) | | |
| **Outcomes** | Patients were interrogated for pain by VAS scoring system at rest and during deep breathing at 0 h (at extubation), thereafter at 4, 6, 12, 24,36, and 48 h from extubation. Chronic pain was assessed at 1 month and 3 months after discharge. | | |
| **Notes** | Co-analgesia:  Pre-op: Patients were pre-medicated with tab diazepam the night before and on the morning of surgery.  Intra-op: Anesthesia was induced with fentanyl, midazolam and propofol, endotracheal intubation was facilitated with vecuronium. Anesthesia was maintained with isoflurane, fentanyl infusion and intermittent doses of vecuronium as clinically indicated.  Post-op: Propofol infusion for 2h, intravenous paracetamol, oral paracetamol, rescue analgesics tramadol or intravenous diclofenac. | | |
| **Source(s) of funding** | No funding. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | "Randomization was conducted using the closed-envelope-method." |
| Allocation concealment (selection bias) | | Unclear risk | "Randomization was conducted using the closed-envelope-method." "In this double-blind, randomized, placebo-control design, patients in the pregabalin group received 150 mg pregabalin capsules (LYRICA®, Pfizer Inc., Germany.), and the control group received placebo (similar looking sucrose containing capsules prepared by the hospital pharmacy) 2 h before induction of anesthesia. |
| Blinding of participants and personnel (performance bias) | | Unclear risk | "The study drug or placebo was administered by an anesthesiologist who was not involved in the study." |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "Patients were interrogated for pain by VAS scoring system at rest and during deep breathing by an intensivist blinded to the study groups at 0 h (at extubation), thereafter at 4, 6, 12, 24, 36, and 48 h from extubation. Chronic pain was assessed at 1 month and 3 months after discharge by telephonic interview by an anesthesiologist who was not a part of the perioperative management of the enrolled patients." |
| Incomplete outcome data (attrition bias) | | Low risk | There does not appear to be any missing outcome data: "All the forty patients completed the study protocol". |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Fewer than 50 participants per arm. There is no study protocol so no way to verify if chronic pain as the primary outcome was pre-specified. There is no reporting on number screened, ineligible, etc. Very vague reporting for the 3 month outcome data. Only that pain scores and incidence of chronic pain was "comparable among groups". |

**Karanikolas 2011**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up for 6 months after surgery | | |
| **Participants** | 65 patients > 18 yr. with severe pain (VAS > 60 /100) one week before scheduled for above- or below-knee lower-limb amputation | | |
| **Interventions** | The study had five groups that received intravenous PCA Fentanil or Epidural fentanyl, which was started 2 days before surgery until the second postoperative day. One of the groups represented the "conventional analgesia" that included IM Meperidine and codeine/acetaminophen. | | |
| **Outcomes** | The results of the visual analog scale and the McGill Pain Questionnaire were recorded perioperatively and at 1 and 6 months | | |
| **Notes** | Co-analgesia: Patients received IV intraoperative remifentanil, too | | |
| **Source(s) of funding** | Support was provided solely from institutional and/or departmental sources. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Randomization was performed using computer-generated blocks". |
| Allocation concealment (selection bias) | | Low risk | "Each patient assigned to participate in the study had a sequentially numbered sealed envelope containing a randomization code. The envelopes were concealed until after consent was obtained". |
| Blinding of participants and personnel (performance bias) | | Low risk | "…. control group patients had an epidural catheter placed subcutaneously at the L4 interspace in the lumbar area and received N/S at 2 ml/h. In addition, they had a second infusion pump that administered patient-controlled intravenous N/S". |
| Blinding of outcome assessment (detection bias) | | Low risk | "...A second blinded investigator (G.M.) interviewed all patients before the beginning and after the end of the analgesic protocol (at 4- and 10-day and at 1- and 6-month follow-up), whereas a third blinded investigator (M.K.) conducted all interviews during the analgesic protocol (at least at 8-h intervals)". |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data were minimum and balanced across groups |
| Selective reporting (reporting bias) | | Low risk | Protocol was registered and no significant differences were noticed compared with publication…except for the pain intensity inclusion criteria (> 70/100 in the protocol) |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Katz 2004a**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 3, 14 and 6 months after surgery | | |
| **Participants** | 141 patients scheduled for radical prostatectomy for prostate cancer. Inclusion criteria were ASA I-II, age between 19 and 75 years | | |
| **Interventions** | Two 60 ml coded syringes were used labelled as pre-incision and post-incision. Every syringe had ketamine (1mg/ml) or saline. Group 1: PRE Ketamine POST: Saline; Group 2: PRE Saline POST Ketamine; Group 3: Both had saline. 10 minutes before incision. All patients received i.v. fentanyl (1 mcg/kg) every 80 min starting approximately 5 min before induction of general anesthesia. Approximately 10 min before skin incision, and after induction of general anesthesia, all patients received a bolus dose of i.v. fentanyl (0.5 mcg/kg). This was followed immediately by an i.v. bolus dose (0.2 ml/kg) and an i.v. infusion (0.0025 ml/kg/min) from the first syringe labelled ‘pre-incision’. Seventy minutes after incision, the first infusion was stopped and all patients received a bolus dose of i.v. fentanyl (0.5 mcg/kg). This was followed immediately by an i.v. bolus dose (0.2 ml/kg) and an i.v. infusion (0.0025 ml/kg//min) from the second syringe labelled ‘post-incision’. The second infusion was stopped after 80 min, approximately 150 min after incision. | | |
| **Outcomes** | Visual analogue pain scores at rest and movement (first 3 days); pain rating index, and present pain intensity. Touch and Pain Threshold using the von Frey filament (at 2 weeks follow up), Mental Health Inventory, Spielberg state-Trait Anxiety Inventory, at 6 months, patients were followed with the Follow-Up Questionnaire (FUPQ). | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: IV fentanyl and general anesthesia.  Post-op: PCA morphine. | | |
| **Source(s) of funding** | The study was supported by Grants MT-12052 and MOP-37845 from the Canadian Institutes of Health Research (CIHR), Ontario, Canada, and a CIHR Investigator Award to JK. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "A randomization schedule was computer-generated"… |
| Allocation concealment (selection bias) | | Low risk | "An opaque envelope containing the patient number and group assignment was prepared, sealed and numbered for each patient by the hospital pharmacist". |
| Blinding of participants and personnel (performance bias) | | Low risk | "All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated. The anesthesiologist in charge of the case was also unaware of group allocation". |
| Blinding of outcome assessment (detection bias) | | Low risk | "All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated. The anesthesiologist in charge of the case was also unaware of group allocation". |
| Incomplete outcome data (attrition bias) | | Low risk | A proper method for incomplete outcome data was performed for analysis |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Kendall 2018**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 6 months | | |
| **Participants** | 150 patients scheduled for unilateral or bilateral  mastectomy with or without lymph node involvement | | |
| **Interventions** | Lidocaine: 1.5 mg/kg bolus of IV lidocaine followed by a 2 mg/kg/hour infusion. The maximum allotted dose of lidocaine administered during the surgical procedure was 1,200 mg.  Placebo: Saline. | | |
| **Outcomes** | The primary outcome of this investigation was the frequency of chronic postsurgical pain as assessed using validated pain instruments in accordance with the IMMPACT recommendations | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: All patients received an anesthetic regimen consisting  of propofol, remifentanil, succinylcholine, and sevoflurane. All patients received ondansetron and dexamethasone for nausea and vomiting prophylaxis. At the end of surgery, all subjects received hydromorphone as part of the pain management protocol.  Post-op: IV hydromorphone, PCA IV hydromorphone. Oral hydrocodone/acetaminophen. No nonsteroidal anti-inflammatory medications or IV acetaminophen were administered during the first 24 hours postoperatively. | | |
| **Source(s) of funding** | This work was supported by the Northwestern Memorial Foundation-Evergreen Invitational Women’s Health Grants to G.S.D. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "subjects were randomized into 2 groups using random block sizes of 2, 4, and 6 and using an R script" |
| Allocation concealment (selection bias) | | Unclear risk | "Group allocation of random assignments was performed by a single investigator (R.J.M.) not involved in patient recruitment or assessment. Group assignments were placed in a sealed opaque envelope that was opened by a single investigator (G.S.D.) after obtaining written informed consent." "Sealed opaque envelopes were opened preoperatively, and the study medication was prepared by research personnel not involved in clinical care or the evaluation of outcomes." The use of opaque assignment envelopes are described but it remains unclear whether envelopes were sequentially numbered. |
| Blinding of participants and personnel (performance bias) | | Low risk | "The anesthesia team and study personnel involved in postoperative assessment were blinded to the study arm." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Low risk | "The anesthesia team and study personnel involved in postoperative assessment were blinded to the study arm." |
| Incomplete outcome data (attrition bias) | | Unclear risk | There is a large number of missing outcome data at 3 months for both groups (43% no contact/response) 31/75 and 34/75 were lost to follow-up at 3 months for the Lidocaine and placebo groups, respectively. Methods were changed for the 6 month follow-up to improve on data collection (19% no contact/response) |
| Selective reporting (reporting bias) | | High risk | One or more reported primary outcomes were not pre-specified. There is no mention of a 3-month follow-up on ClinicalTrials.gov. According to ClinicalTrials.gov the Current Primary outcome measure is "The development of chronic pain after surgery [Time Frame: 6 months]" |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Khan 2019**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicentre (2 centres), randomized, double-blind, 4 arm, placebo controlled trial, follow-up for 3 months. | |
| **Participants** | 100 female patients scheduled for unilateral or bilateral mastectomy or lumpectomy for prophylaxis | |
| **Interventions** | Lidocaine + Pregabalin: Lidocaine was administered with anesthetic induction using a 1.5-mg/kg bolus followed by a 2.0-mg/kg/h infusion until the start of surgical closure.  Pregabalin was administered 300 mg within 30−120 minutes before surgery and then received pregabalin 75 mg twice a day for 9 days after surgery.  Lidocaine: Lidocaine was administered with anesthetic induction using a 1.5-mg/kg bolus followed by a 2.0-mg/kg/h infusion until the start of surgical closure.  Pregabalin: 300 mg within 30−120 minutes before surgery and then received pregabalin 75 mg twice a day for 9 days after surgery.  Placebo: Lidocaine placebo (formulation not specified); Pregabalin placebo (formulation not specified) | |
| **Outcomes** | Primary outcome: Feasibility of conducting a larger adequately powered randomized trial  Secondary outcomes: Post-mastectomy pain syndrome at 6 months; Length of hospital stay; Quality of Life at 3 months; Somatic Pre-occupation and Coping Scale at 3 months; Acute postoperative pain. | |
| **Notes** | Co-analgesia:  Pre-op: The use of any oral pre-emptive or preoperative analgesics (e.g., such as preoperative acetaminophen, nonsteroidal anti-inflammatories) besides study medications were restricted.  Intra-op: Restricted any additional intravenous lidocaine as well as any neuraxial or regional anesthetic techniques, except local wound infiltration by the surgeon, which was restricted to 50 mg of bupivacaine. Other analgesics such as steroids, ketamine, and opioids were left to the discretion of the attending anesthesiologist.  Post-op: There were no restrictions on postoperative pain management. | |
| **Source(s) of funding** | Supported by the Physicians Services Incorporated [grant number R14-30] and an Innovation grant received from McMaster University, Hamilton, Ontario, the Alternate Funding Plan body for McMaster University and affiliated Hamilton Hospitals. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "We randomized patients the day before surgery using a centralized system using a computer-generated randomization scheme in a 1:1:1:1 allocation." |
| Allocation concealment (selection bias) | Low risk | "We randomized patients the day before surgery using a centralized system…" (central allocation) |
| Blinding of participants and personnel (performance bias) | Low risk | "Pregabalin and pregabalin placebo medications were compounded into identical blinded gelatin capsules. Lidocaine and lidocaine placebo were dispensed in identical blinded 60- mL syringes. All drugs were prepared and dispensed by the central pharmacy at each clinical site." "Our computerized randomization system alerted the central pharmacy on the next enrolled patient according to a unique ID. The pharmacy prepared the appropriate drug or placebo medications in their blinded capsules and syringes and provided them to the research assistant on the day of surgery." |
| Blinding of outcome assessment (detection bias) | Low risk | "The pharmacy prepared the appropriate drug or placebo medications in their blinded capsules and syringes and provided them to the research assistant on the day of surgery. Research assistants provided the blinded preoperative pregabalin medication to the patient and the blinded lidocaine syringe to the attending anesthesiologist. As such, all patients, clinicians, data collectors, outcome assessors, and analysts were all blinded to group assignments." |
| Incomplete outcome data (attrition bias) | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Khurana 2014**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 3 arm, placebo controlled trial, follow-up for 3 months. | |
| **Participants** | 90 patients scheduled for lumbar discectomy | |
| **Interventions** | Gabapentin: 300mg 60 minutes preoperatively and 8 hourly for 7 days postoperatively  Pregabalin: 75mg 60 minutes preoperatively and 8 hourly for 7 days postoperatively  Placebo: Placebo pill (formulation not specified) | |
| **Outcomes** | Postoperatively pain score, hemodynamics, oxygen saturation respiratory rate, sedation and side effects. 3 questionnaires were filled at 7 days, 21 days, and 3 months (VAS pain at rest and on movement, Oswestry Disability Index (ODI), Modified Prolo economic and functional score) | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Anesthesia was induced with fentanyl and propofol, followed by vecuronium, to facilitate tracheal intubation and ventilation. Anesthesia was maintained using isoflurane and vecuronium and fentanyl as clinically indicated. At the time of skin closure IV diclofenac sodium.  Post-op: IV tramadol | |
| **Source(s) of funding** | No funding. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "According to computer-generated random allocation" |
| Allocation concealment (selection bias) | Low risk | "The medication was prescribed according to instructions in a sealed, opaque envelope by an anesthesiologist with no further involvement in the study." |
| Blinding of participants and personnel (performance bias) | Low risk | "The medication was prescribed according to instructions in a sealed, opaque envelope by an anesthesiologist with no further involvement in the study." Double-blind study design |
| Blinding of outcome assessment (detection bias) | Low risk | "Then, the 3 questionnaires were filled at 7 days, 21 days, and 3 months by the same recorder who was not involved further in the study." "collection of the questionnaire was by a single blinded investigator" |
| Incomplete outcome data (attrition bias) | Unclear risk | There does not appear to be any missing outcome data. Numbers analyzed at 3 months not reported. Results state: "No patient was withdrawn from the study because of severe pain requiring additional analgesic beyond the recommended protocol." |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | High risk | Fewer than 50 participants per arm. Chronic pain is not specified as the primary outcome, nor is there any study protocol to verify this. There is no reporting on number screened, ineligible, dropouts, lost to follow-up, etc. |

**Kim 2010**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 3 months | | |
| **Participants** | 99 ASA class I–II patients, aged 20–65 years, with thyroid cancer were scheduled for elective robot-assisted endoscopic thyroidectomies using axillary approach | | |
| **Interventions** | According to their assigned study group, patients received pregabalin 150 mg or placebo twice—1 h before surgery and 12 h after the initial dose. All pills were administered by a nurse who was not involved in the study. | | |
| **Outcomes** | Pain scores, side effects profile, and incidence of anterior chest hypoesthesia | | |
| **Notes** | Co-analgesia:  Pre-op: Midazolam 30 min before surgery.  Intra-op: General anesthesia was induced with remifentanil and propofol and maintained with remifentanil and sevoflurane. At the time of skin suturing, ketorolac and ondansetron were administered.  Post-op: All patients received ibuprofen twice per day on the day after their operation. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | "Patients were randomly assigned to one of 2 groups to receive…. |
| Allocation concealment (selection bias) | | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | | Low risk | "The drugs were provided by the hospital pharmacy as identical capsules to ensure blinding." |
| Blinding of outcome assessment (detection bias) | | Low risk | "Patients, the surgeon, and the anesthesiologist responsible for follow-up during the postoperative period were blinded to group allocation." |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups and < 20% |
| Selective reporting (reporting bias) | | Low risk | Protocol was registered and no significant differences were noticed compared with publication |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Kim 2017**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double-blind, 3 arm, placebo controlled trial, follow-up for 3 months. | |
| **Participants** | 126 patients scheduled to undergo partial or total mastectomy with lymph node dissection - sentinel, axillary, or both | |
| **Interventions** | Lidocaine hydrochloride: Administered at 2 mg/kg for 15 minutes immediately after induction, followed by infusion at 2 mg/kg/h. Saline added to achieve total volume of 50ml.  Magnesium sulfate: Administered at 20 mg/kg for 15 minutes immediately after induction, followed by infusion at 20 mg/kg/ h infusion. Saline added to achieve total volume of 50ml.  Placebo: Saline | |
| **Outcomes** | Quality of recovery, acute pain and chronic pain measured with the Korean version of the McGill Pain Questionnaire (KSF-MPQ) | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Patients were administered glycopyrrolate intravenously, and anesthesia was induced with propofol and remifentanil; anesthesia was maintained using desflurane with an adjuvant infusion of remifentanil. Rocuronium bromide to facilitate tracheal intubation in all patients. 30 min before completion of the operation, propacetamol and nefopam. Palonosetron 15 min before end of surgery.  Post-op: opioids (not specified). | |
| **Source(s) of funding** | No funding. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "using a random number sequence created by an internet website (http://www.random.org), the patients were randomly allocated to one of three groups in a 1:1:1 ratio" "randomization was not blocked or stratified" |
| Allocation concealment (selection bias) | Unclear risk | "The assignments were concealed in a sealed envelope" There is no mention of proper safeguards such as the envelopes being opaque or sequentially numbered. |
| Blinding of participants and personnel (performance bias) | Low risk | "The surgeons, patients, and those assessing outcomes were blinded to the group assignment." "The study drugs were prepared by a researcher who was not otherwise involved in the study. Saline was added to the calculated drug doses to achieve a total volume of 50 ml, and the treatments were labeled as “study drug” to ensure double-blinded administration. " Double-blind study design |
| Blinding of outcome assessment (detection bias) | Low risk | "...those assessing outcomes were blinded to the group assignment." |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was below 20%. Lost to follow-up: 3/42 Lidocaine group, 4/42 Magnesium group, 3/42 Placebo group |
| Selective reporting (reporting bias) | High risk | The study protocol is available, however only the Primary Outcome is described a priori. According to Clinical Trials.gov, the Primary outcome was "The difference of QoR-40 global scores [ Time Frame: 24 hours after mastectomy]" There is no mention of a planned follow-up at 1 month and 3 months after surgery. |
| Other bias | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. |

**Kim 2018**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 3 months | |
| **Participants** | 58 patients scheduled for elective BABA robotic or endoscopic thyroidectomy | |
| **Interventions** | Nefopam: after the induction of anesthesia, the nefopam group received 0.2 mg/kg of nefopam intravenously, and then 120 ug/kg/h continuous infusion until the end of the operation (skin closure)  Placebo: saline. | |
| **Outcomes** | Primary outcome was acute postoperative pain scores.  Secondary outcomes were as follows: The need for postoperative rescue analgesics, recovery profiles, postoperative adverse events, and chronic pain and discomfort at 3 months after the operation. | |
| **Notes** | Co-analgesia:  Pre-op: Patients received IV midazolam for premedication.  Intra-op: Total intravenous anesthesia with propofol and remifentanil was used with target controlled infusion  Post-op: IV fentanyl was used as first-line rescue analgesics, and ketorolac tromethamine was used as second-line if NRS >30. In the ward, patients received IV ketorolac tromethamine if NRS was more than 30 or if patients wanted analgesic drugs. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "According to a computer-generated random number table (Random Allocation Software Version 1.0) with a block size of 4, patients were assigned to either the control group (n = 29) or the nefopam group (n = 29)." |
| Allocation concealment (selection bias) | Low risk | "Study solutions (normal saline or nefopam) were prepared by an anesthetic nurse and delivered to the operating room in identical 50-ml syringes to ensure blinding." |
| Blinding of participants and personnel (performance bias) | Low risk | "Patients, anesthesiologists responsible for the patients, and outcome assessors were blinded to the group assignment." |
| Blinding of outcome assessment (detection bias) | Low risk | "Patients, anesthesiologists responsible for the patients, and outcome assessors were blinded to the group assignment." |
| Incomplete outcome data (attrition bias) | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Kinney 2011**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 3 months | | |
| **Participants** | 120 patients aged 45 - 75 years undergoing elective thoracotomy | | |
| **Interventions** | Patients were allocated to receive either 600 mg of gabapentin or active placebo (diphenhydramine 12.5 mg) orally within 2 hours preoperatively | | |
| **Outcomes** | Pain scores in the acute setting + side effects of the medications. Telephone call: surgical site pain | | |
| **Notes** | Co-analgesia: thoracic epidural analgesia, POP fentanyl, ketorolac and acetaminophen | | |
| **Source(s) of funding** | Supported by the Mayo Foundation for Education and Research (ClinicalTrials.gov number NCT00588159). The project described was also supported by Grant Number 1 UL1 RR024150 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | "Using a block randomization schedule stratified by surgeon… |
| Allocation concealment (selection bias) | | Low risk | "All members of the surgical, nursing, and acute pain service teams were blinded to group assignment". |
| Blinding of participants and personnel (performance bias) | | Low risk | "Placebo capsules of identical shape and size to commercially available gabapentin were manufactured by the hospital pharmacy" |
| Blinding of outcome assessment (detection bias) | | Low risk | "All outcome assessors were blinded to group allocation". |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups and < 20% |
| Selective reporting (reporting bias) | | Low risk | Protocol was registered and no significant differences were noticed compared with publication |
| Other bias | | Low risk | No other potential sources of bias were detected |

**KjaerPetersen 2018**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicenter (3 centres), randomized, double-blind, 3 arm, placebo controlled trial, follow-up for 3-4 years | |
| **Participants** | 300 patients scheduled to undergo elective unilateral primary total knee arthroplasty | |
| **Interventions** | Gabapentin: High dose group: 1,300 mg/day: 900 mg preoperatively and 400 mg at 10:00 PM on the day of surgery, thereafter 400 mg at 8:00 AM and 900 mg at 10:00 PM. The capsules were administered twice a day for 7 days, starting 2 h preoperatively, again at 10 PM on the day of surgery, and thereafter at 8 AM and 10 PM on postoperative days 1–6  Gabapentin: Low dose group: 900 mg/day: 600 mg preoperatively and 300 mg at 10:00 PM, thereafter 300 mg at 8:00 AM and 600 mg at 10:00 PM. The capsules were administered twice a day for 7 days, starting 2 h preoperatively, again at 10 PM on the day of surgery, and thereafter at 8 AM and 10 PM on postoperative days 1–6  Placebo: Placebo (formulation not specified) | |
| **Outcomes** | Primary outcome: pain upon ambulation (walking 5 m with a walking aid) 24 hours after surgery. Other pain outcomes… days 2 to 6 after surgery. Follow-up study (3-4 years post-surgery): The pain intensity scores during walking, at rest (supine), upon 45 ° hip flexion with straight leg, and upon passive 60 ° knee flexion were collected. A 100-mm verbal numeric analog scale (NRS) was used (0 = no pain and 100 = worst pain imaginable). | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Surgery was performed under lumbar spinal anesthesia with bupivacaine and optional supplemental propofol.  Post-op: A basic analgesic regime was used consisting of oral slow release acetaminophen and celecoxib. Rescue analgesics consisted of IV sufentanil and subsequently of oral morphine at the ward and after discharge. In very few cases, other opioids (ketobemidone, oxycodone, and intravenous morphine) were used for resistant pain. | |
| **Source(s) of funding** | The study was supported with a research grant from The Lundbeck Foundation, Hellerup, Denmark, which is independent of the pharmaceutical company, Lundbeck Pharma, Denmark. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "A computer produced 1:1:1 random allocation sequence (A, B and C) was generated in blocks of 12 (25 blocks) without the use of stratification variables, using the free internet service “www. Randomization.com”." |
| Allocation concealment (selection bias) | Low risk | "...randomization and blinding procedures together with the study drug preparations were handled by a state-registered and certificated pharmacy, The Capital Regional Pharmacy, not otherwise involved in the trial." "The study drugs, oral gabapentin 300 mg and 400 mg, and placebo, were prepared by the pharmacy as small capsules, identical in appearance." |
| Blinding of participants and personnel (performance bias) | Low risk | "All trial participants, care providers, investigators, and outcome assessors (data collectors) were blinded to allocation. After termination of the study, the typing of data was performed by 2 independent and blinded individuals (double data entry). Subsequently, the blinded randomization list (allocation to group A vs B vs C) was dispatched by The Capital Regional Pharmacy to the principal investigator enabling blinded “group A vs B vs C” analyses. This list was unblinded with respect to intervention type and released by The Capital Regional Pharmacy only after all statistical analyses had been performed. Thus, all analyses were performed blinded." (Lunn 2015 Primary article) |
| Blinding of outcome assessment (detection bias) | High risk | "The primary study with data on pre- and six first postoperative days has previously been published [33]. The current secondary, exploratory work focuses on follow-up 3–4 years after TKA surgery." This is an exploratory study conducted 3-4 years later. The randomization codes would have been already broken to conduct the primary analysis. There is no mention of whether outcomes assessors conducting the follow-up assessment or patient were still blinded to allocation. |
| Incomplete outcome data (attrition bias) | High Risk | Missing data >20%. Group A 32/100, Group B 23/100, Group C 30/100 lost to follow-up for the 3-4 year follow-up |
| Selective reporting (reporting bias) | High Risk | One or more reported primary outcomes were not pre-specified. The current study is a secondary follow-up of a previously published primary RCT investigating the effect of gabapentin on acute postoperative pain after TKA |
| Other bias | Low risk | Unable to find additional potential bias. >50 participants per study arm. |

**Konstantatos 2016**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Multicenter (3 centres), randomized, double-blind, 2 arm, placebo-controlled trial, follow-up for 9 months. | | |
| **Participants** | 100 patients scheduled for video-assisted thoracoscopic surgery | | |
| **Interventions** | Pregabalin: Two tablets of pregabalin 150mg, 30 min before surgery and one tablet of pregabalin 150mg twice-daily for five postoperative days  Placebo: Placebo pill (formulation not specified) | | |
| **Outcomes** | Primary outcome was the average pain score over the incision site during deep breathing from the time of surgery up to nine postoperative months after surgery | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Anaesthesia was induced and maintained with propofol or volatile agents. During surgery, IV morphine and the thoracoscopic port sites were infiltrated with ropivacaine.  Post-op: PCA morphine, oral paracetamol, oxycodone. Additional analgesics were given as recommended by the independent pain physician. The type and dose of analgesics were recorded. | | |
| **Source(s) of funding** | This study was supported, in part, by an investigator-initiated research grant provided by Pfizer pharmaceuticals. Pfizer pharmaceuticals (New York, NY, USA) donated the pregabalin and placebo study drug, but they had no role in the design, conduct and analysis of the trial. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "The Pharmacy Department, independent of the investigators, generated a computer sequence with equal numbers allocated to placebo or pregabalin, stratified by hospital site, in blocks of four participants. " |
| Allocation concealment (selection bias) | | Low risk | "Assignment codes were concealed in opaque envelopes." "Participants were sequentially assigned…" |
| Blinding of participants and personnel (performance bias) | | Low risk | "The Pharmacy distributed envelopes and coded tablets to pharmacists at each of the three study sites. Placebo and pregabalin tablets were indistinguishable. " |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "Participants were reviewed by independent pain physicians while in hospital." |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was <20%. At 3 months 0 participants lost to follow-up. At 9 months 3/52 in the treatment group and 2/36 in the placebo group analyzed. |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | Unclear risk | >50 participants in treatment arm, but <50 in placebo arm and chronic pain was not the primary outcome. Unable to find additional potential bias. |

**Koyuncu 2018**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 3 months | |
| **Participants** | 140 patients scheduled for hysterectomy under general anesthesia | |
| **Interventions** | Acetaminophen: 1g acetaminophen in 100ml in 15 minutes, given every 6 hours starting with skin closure for a total of 72 hours. Women assigned to acetaminophen thus received 12g over the three-day study period, an amount generally regarded as safe.  Placebo: Saline | |
| **Outcomes** | Primary outcome: incisional VAS pain score at three months after surgery  Secondary outcomes: short term measurements within the initial 24 hours arrival to PACU | |
| **Notes** | Co-analgesia:  Pre-op: IV midazolam  Intra-op: Anesthesia was induced with propofol; intubation was facilitated by rocuronium; and anesthesia was maintained by sevoflurane in combination with nitrous oxide 50% in oxygen. Fentanyl was given 3-5 min before the surgical incision. All patients received tramadol intravenously at the time of skin closure.  Post-op: In the PACU patients were connected to patient-controlled analgesia (tramadol)... diclofenac was given as rescue analgesic. | |
| **Source(s) of funding** | The study was supported by a grant for life expenses from TUBITAK: Technology and Innovation Support Programs, Directorate of the Scientific and Research Council of Turkey | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Randomization was web-based and out of the control of any investigator." |
| Allocation concealment (selection bias) | Low risk | "The web system was accessed by an independent investigator who prepared the assigned drug which was covered with opaque plastic to keep the surgical team and anesthesiologists blinded to treatment." "The bags were labeled as "Study Drug" to maintain blinding." |
| Blinding of participants and personnel (performance bias) | Low risk | "double-blind study" "The web system was accessed by an independent investigator who prepared the assigned drug which was covered with opaque plastic to keep the surgical team and anesthesiologists blinded to treatment." "The bags were labeled as "Study Drug" to maintain blinding." |
| Blinding of outcome assessment (detection bias) | Low risk | "All postoperative measurements were conducted by a research assistant who was blinded to group allocation." |
| Incomplete outcome data (attrition bias) | Unclear risk | There were actually 144 randomized with 2 drop-outs in each group after surgery. The text and Figure 1 relay different results about numbers randomized and lost to follow-up. |
| Selective reporting (reporting bias) | High Risk | The study started in April 2012 but was not registered until March 2014, therefore unable to verify whether the primary outcome of chronic pain at 3 months was pre-specified. |
| Other bias | Low risk | Unable to find additional potential bias. >50 participants per study arm. |

**Lakdja 1997**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 6 months | | |
| **Participants** | 30 patients with adenocarcinoma requiring total or partial mastectomy with axillary dissection | | |
| **Interventions** | Ibuprofen: 400 mg 90 minutes before surgery, 2 h after and then q8h up to 32 hours after surgery | | |
| **Outcomes** | Pain Scores: VAS in the first 42 hours after surgery. At 6 months, consultation. They evaluated the need of adjuvant radiotherapy, the presence of dysesthesia, allodynia, paresthesia or hyperesthesia that lasted more than 3 months and was present during the exam: SDPM: postmastectomy pain syndrome. | | |
| **Notes** | Co-analgesia: 300 mcg of intraoperative fentanyl, POP analgesia: PCA morphine | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Allocation concealment (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | | Unclear risk | Insufficient information to permit judgement |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups and < 20% |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per group |

**Lee 2017**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 1 year | |
| **Participants** | 123 patients scheduled for Posterior Lumbar Interbody Fusion (PLIF) surgery | |
| **Interventions** | Vitamin C: vitamin C treatment was initiated on the first postoperative day and administered each following morning for 45 days. Dosage not specified.  Placebo: Placebo pill (formulation not specified) | |
| **Outcomes** | Primary outcome measure: pain intensity in the lower back around the surgical site. Pain intensity at the lower back was recorded using a visual analogue scale (VAS), whose scores were obtained before surgery and then again at 1, 3, 6 months, and 1 year post surgery.  Secondary outcome measures included: (1) clinical outcome; (2) fusion rate; and (3) complications. | |
| **Notes** | Co-analgesia: Analgesic approach not specified. All patients were managed with the same postoperative medications and rehabilitation program protocols. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Randomization was conducted by a computer-generated allocation program (nQuery Advisor PPS 6.01; Statistical Solutions Ltd., Saugus, MA, USA), which assigns numbers in strict chronological sequences and enters regular sequences for each study group. Randomization was stratified via 3 variables: (1) age (40s vs. 50s); (2) smoking status (smoker vs. nonsmoker); and (3) surgical level (L4–5 vs. L5–S1). Each study participant was allocated a unique randomization number upon completion of the screening process." |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | Unclear risk | "The treatment allocation was blinded to both the surgeon and the patient; thus, this was a double-blinded study." Identical matching of placebo capsules is not explicitly described |
| Blinding of outcome assessment (detection bias) | Unclear risk | "Questionnaires, chart data, and clinical records were analyzed by 1 surgeon who was not otherwise involved in this study." According to the clinicaltrials.gov record the study was Quadruple Blind (Participant, Care Provider, Investigator, Outcomes Assessor) Blinding for outcome assessment not explicitly stated in the manuscript. |
| Incomplete outcome data (attrition bias) | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | High Risk | One or more reported primary outcomes were not pre-specified. According to ClinicalTrials.gov the primary outcome was Pain scores on the VAS [Time Frame: Postoperative 1 month]. In the manuscript it states the primary outcome was pain on the VAS at 1,3, 6, and 12 month time-points. |
| Other bias | High risk | The dose of the intervention pill is not specified. The duration of administration of the study drug according to ClinicalTrials.gov was 1 month post surgery, yet the methods indicate it was administered for 45 days The trial was completed in May 2014 but only registered with ClinicalTrials.gov one month earlier in April 2014 |

**Lee 2018**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 3 months. | |
| **Participants** | 64 patients scheduled for robot-assisted thyroidectomy. | |
| **Interventions** | Ketamine: Patients in the ketamine group received a bolus dose of 0.15 mg/kg of racemic ketamine after anaesthetic induction. Racemic ketamine was also infused continuously until the end of the surgery at a rate of 2 mg/kg/min.  Placebo: Saline | |
| **Outcomes** | Primary outcome: Pain at 24 hour postoperatively  Secondary outcomes: Pain at 3, 6, 12, 48 and 72 hour postoperatively; Time to the first analgesics postoperatively; Analgesic requirements for 24 hours after surgery; Chronic pain at 3 month after surgery | |
| **Notes** | Co-analgesia:  Pre-op: No premedication.  Intra-op: General anaesthesia was induced using a target controlled continuous infusion of propofol and remifentanil. Rocuronium was administered for tracheal intubation.  Post-op: IV pethidine. Fentanyl in the post-anaesthesia care unit and ketorolac or pethidine on the ward were administered on request. | |
| **Source(s) of funding** | This research was supported by a Keimyung University Research Grant (No. 20170231). | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "The patients were randomly allocated into the control and ketamine groups using Random Allocation Software, version 1.0.0 (Isfahan University of Medical Sciences, Isfahan, Iran). The randomisation was generated using random blocks of four and six and performed by an investigator who was blind to the study protocol." |
| Allocation concealment (selection bias) | Unclear risk | "The assignments were placed in opaque envelopes and managed by anaesthetists who did not participate in either the patient care or the investigation." "The group assignment was revealed to the investigator on the morning of the surgery." The use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, and sealed. |
| Blinding of participants and personnel (performance bias) | Unclear risk | "The group assignment was revealed to the investigator on the morning of the surgery." "Patients in the control group were given an equal volume of saline. A nurse supplied 3- and 50-mL syringes containing the study drug." "The attending anaesthesiologist was blinded to the patient groups." |
| Blinding of outcome assessment (detection bias) | Low risk | "The postoperative variables, including the VAS pain scores, rescue therapy, and opioid-related complications, were recorded by an investigator who was blinded to the group assignments." |
| Incomplete outcome data (attrition bias) | High Risk | Missing data > 20% At 3 months: 7/32 lost to follow-up Ketamine arm 8/32 lost to follow-up Placebo arm |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Ling 2016**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 12 months. | | |
| **Participants** | 86 patients undergoing general thoracic surgery (bulla resection, lobectomy, or wedge resection) | | |
| **Interventions** | Parecoxib: Intravenous administration of the study drug (40 mg) began 30 minutes before intubation and then administered intravenously every 12 hours and was continued for 60 hours.  Placebo: Placebo (formulation not specified) administered intravenously | | |
| **Outcomes** | Outcomes, measurements, and timing are not very well described a priori. Analgesic efficacy, quality of pain control, intensity and characteristic of residual pain, and safety. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Epidural analgesia. Anesthesia induction was performed with fentanyl, remifentanil, propofol and rocuronium. Anesthesia was maintained with desflurane, propofol, fentanyl and rocuronium. Ropivacaine was used epidurally after induction. Epidural morphine and intravenous tropisetron mesylate were used 30 min before the end of operation.  Post-op: PCEA with bupivacaine, fentanyl, and morphine. Oral oxycodone as rescue analgesia. | | |
| **Source(s) of funding** | This work was supported by the research foundation from The 2nd Oriental Congress of Anesthesiology and Perioperative Medicine for the research on optimizing the intraoperative ventilation strategy in minimal invasive thoracic surgery. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Not reported |
| Allocation concealment (selection bias) | | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | | Unclear risk | Not reported Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | | Unclear risk | Outcomes are not clearly defined a priori. The flowchart indicates the number analyzed at 2 months while Table 6 reports results for 3 months. The dropout rate was <20%. |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Fewer than 50 participants per arm. Chronic pain is not specified as the primary outcome, nor is there any study protocol to verify this. No description of how blinding was created or maintained. Primary and secondary outcomes are not adequately described in the methods. Timing of assessment or instruments used are not clearly described. |

**Malek 2006**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind (patients and outcomes assessor nurse), placebo-controlled trial for 6 months | | |
| **Participants** | 100 women scheduled for total or partial mastectomy | | |
| **Interventions** | Ketamine 1 mg/k/day in IV infusion for 2 days | | |
| **Outcomes** | After 6 months of surgery patients received a questionnaire concerning the presence of chronic pain, its intensity (1 - mild, 2-medium, 3 - strong, 4 - Unbearable), quality (constant vs intermittent), location (in scars, in the whole breast or chest wall, armpit, elsewhere) and nature (using the modified McGill Pain Questionnaire). | | |
| **Notes** | Co-analgesics: preoperative and postoperative meperidine + intraoperative sufentanil | | |
| **Source(s) of funding** | Práca vznikla za finančnej podpory grantu IGA NL7682 | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | Drawing lots |
| Allocation concealment (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | | Unclear risk | Patients were blinded. However, the person that prepared the solutions is unclear if he/she was blinded |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Patient filled out a questionnaire at 6 months. However is unclear if already knew what received during surgery |
| Incomplete outcome data (attrition bias) | | Unclear risk | Insufficient information to permit judgement |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Martin 2008**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicentre (2 centres), randomized, double-blind, 2 arm, placebo controlled, trial, follow-up for 3 months. | |
| **Participants** | 60 patients scheduled for total hip arthroplasty. | |
| **Interventions** | Lidocaine: Patients scheduled to receive lidocaine 10 mg/ml (lidocaine group) were given an intravenous bolus injection of 1.5 mg/kg of lidocaine in 10 min (30 min before surgical incision) followed by a continuous IV infusion of 1.5 mg kg h. The infusion ended 60 min after skin closure.  Placebo: Saline. | |
| **Outcomes** | Primary endpoint: morphine consumption over the initial postoperative 24 h  Other evaluations: visual analog scale pain score at rest and when moving 3 months after the surgery. | |
| **Notes** | Co-analgesia:  Pre-op: Oral hydroxyzine 2 h before anesthesia  Intra-op: General anesthesia was induced with sufentanil followed by thiopental and atracurium to facilitate orotracheal intubation. Patients were ventilated to normocapnia with 50% oxygen and without nitrous oxide. Anesthesia was maintained with sufentanil and sevoflurane. Sufentanil was stopped 30 min before end of surgery.  Post-op: in both groups IV patient controlled morphine. No other co-analgesics were prescribed. Morphine as rescue analgesic. Patient-controlled analgesia was stopped in both  groups at the 48th hour, and further analgesia was provided  by combination of paracetamol, nonsteroidal anti-inflammatory  drugs and subcutaneous morphine as needed. | |
| **Source(s) of funding** | Support was provided solely from institutional and/or departmental sources. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | "a randomization list balanced by center was established and each center enrolled patients and assigned treatments consecutively." |
| Allocation concealment (selection bias) | Unclear risk | "For each patient, an envelope containing the group assignment was prepared, sealed, and sequentially numbered."  The use of assignment envelopes is described, but it remains unclear whether envelopes were opaque |
| Blinding of participants and personnel (performance bias) | Low risk | "On the morning of surgery and before induction of anesthesia, a “blinded” nurse prepared lidocaine or saline solution syringes. None of the other investigators involved in patient management or data collection were aware of the group assignment."… "In the control group, patients were given equal volumes of saline." |
| Blinding of outcome assessment (detection bias) | Low risk | "On the morning of surgery and before induction of anesthesia, a “blinded” nurse prepared lidocaine or saline solution syringes. None of the other investigators involved in patient management or data collection were aware of the group assignment." |
| Incomplete outcome data (attrition bias) | High Risk | “of sixty patients included, two were excluded in the lidocaine group. They decided to leave the study in the PACU because of extreme pain.” Reason for missing outcome data likely to be related to true outcome |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Martinez 2013**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Multicenter (4 centres), randomized, double-blind, 2 arm, placebo-controlled trial, follow-up for 3 months. | | |
| **Participants** | One hundred patients undergoing scheduled standard open lumbar discectomy | | |
| **Interventions** | The minocycline group received 100mg minocycline orally, twice daily, beginning the evening before surgery and continuing for 8days. | | |
| **Outcomes** | The primary outcome was the change in lower limb pain intensity at rest between baseline and 3months. Secondary outcomes were pain intensity on movement, the incidence of persistent pain and chronic neuropathic pain, back pain intensity at rest and on movement, and changes in Neuropathic Pain Symptom Inventory, Brief Pain Inventory, and Roland-Morris scores at 3months. | | |
| **Notes** | Co-analgesia: The anesthetic procedure, postoperative analgesic treatment, and surgical technique were standardized.  Pre-op: Oral hydroxyzine 2 h before anesthesia.  Intra-op: General anesthesia was induced with sufentanil followed by propofol and atracurium, to facilitate intubation. Patients were ventilated with a 1:1 mixture of oxygen–nitrous oxide. Anesthesia maintained with sufentanil and sevoflurane.  Post-op: IV morphine. Oral acetaminophen and morphine pain score >3. No other analgesics were given. A combination of tramadol and paracetamol was prescribed for 1 month after discharge from hospital. | | |
| **Source(s) of funding** | Support was provided solely by institutional and/or departmental sources. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "computer-generated randomization list and a block size of 2" |
| Allocation concealment (selection bias) | | Low risk | "The study drugs were prepared by the pharmacy of Raymond Poincaré Hospital. Minocycline was prepared by over-encapsulating a 100-mg minocycline capsule. The placebo was identical in appearance and consisted of the same large capsule filled with saccharose. The capsules were placed in identical containers marked with the name of the project and patient numbers. These containers were then sent to the pharmacies of the various sites. None of the investigators involved in patient management or data collection were aware of the group to which their patients had been assigned. During the study, the randomization list was held securely at the Raymond Poincaré Hospital pharmacy, from which it was released only after the study had been completed. " |
| Blinding of participants and personnel (performance bias) | | Low risk | "None of the investigators involved in patient management or data collection were aware of the group to which their patients had been assigned." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Low risk | "None of the investigators involved in patient management or data collection were aware of the group to which their patients had been assigned." "The randomization list was held securely at the Raymond Poincaré Hospital pharmacy, from which it was released only after the study had been completed" |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was <20%. Lost to follow-up: 8/51 in the Minocycline group vs. 7/49 placebo group |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | Unclear risk | >50 participants in treatment arm, but <50 in placebo arm. The article states that pain at 3 months was the primary outcome but there is no study protocol in order to verify this: "Our primary outcome was the change in leg pain intensity at rest, between baseline, and 3 months after surgery." |

**Martinez 2014**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicentre (2 centres), randomized, double-blind, 4 arm, placebo controlled trial, follow-up for 3 months (data is reported in the Systematic Review by Martinez et al. 2017). | |
| **Participants** | One hundred and forty-two patients scheduled for total hip arthroplasty | |
| **Interventions** | Pregabalin-alone: oral pre-operative pregabalin 150 mg  Ketamine-alone: 0.5 mg.kg 1 bolus at the time of anaesthesia induction immediately followed by a 3 lg.kg 1.h 1 infusion stopped at skin closure  Pregabalin + Ketamine: intravenous ketamine with a 0.5 mg.kg 1 bolus at the time of anaesthesia induction immediately followed by a 3 lg.kg 1.h 1 infusion stopped at skin closure and oral pre-operative pregabalin 150 mg  Placebo: Placebo pregabalin (lactose) and placebo ketamine (saline 0.9%) | |
| **Outcomes** | Primary outcome measure was morphine consumption after surgery. Our secondary outcome measures were intensity of acute postoperative pain, incidence of opioid- related side-effects and secondary hyperalgesia after total hip arthroplasty. | |
| **Notes** | Co-analgesia:  Pre-op: hydroxyzine orally 2h before.  Intra-op: General anaesthesia induced with sufentanil and propofol.  Post-op: PCIA morphine for 48h. Further analgesia by combination of paracetamol, non-steroidal anti-inflammatory drugs and oral opioid as needed. | |
| **Source(s) of funding** | No external funding or competing interests declared. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Computer-generated randomisation (Excel; Microsoft Office 2007) was based on blocks of four patients." |
| Allocation concealment (selection bias) | Low risk | "Allocations were concealed in sequentially numbered sealed opaque envelopes, which were opened the day before surgery after patients had consented to the trial. Pregabalin was prepared by the Pharmacy Department by over-encapsulating a 150-mg pregabalin capsule. The identically-appearing placebo consisted of the same large capsule filled with lactose. Two syringes were prepared in the operating room by a nurse not involved in the evaluation of the patients. For ketamine, a 5-ml syringe was prepared for an initial bolus of 0.5 ml.kg 1; a 20-ml syringe was prepared for a continuous 0.18 ml.kg 1.h 1 intra-operative infusion. According to the randomisation assignment, these syringes were filled with ketamine solution (1 mg.ml 1) or saline 0.9%." |
| Blinding of participants and personnel (performance bias) | Low risk | "None of the other investigators involved in patient management or data collection was aware of the group assignment." Double-blind study design |
| Blinding of outcome assessment (detection bias) | Unclear risk | "None of the other investigators involved in patient management or data collection was aware of the group assignment." Chronic Pain is not reported as planned outcome and was collected from the authors. It is unclear whether those collecting the 3 Month CP data were still blind to allocation. |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20%. Lost to follow-up: 4/34 Pregabalin and 4/36 Placebo |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. Unable to find the published study protocol on EudraCT (#2009-010859-27). Primary and secondary outcomes stated in the methods do appear to be covered in the results. Chronic pain outcomes do not appear to be planned a priori. |
| Other bias | High risk | Fewer than 50 participants per arm. Data for 3 month CPSP was not a planned outcome and was obtained by the authors of the Martinez et. al. 2017 Systematic Review and Meta-Analysis and reported as unpublished data. It is unclear if investigators were still blind to allocation at the 3 month follow-up. At Baseline, there is a significantly higher number of Males in the Placebo group vs. Ketamine arm 25/38 vs. 11/34 (P<0.005). |

**Mendola 2012**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 6 months. | |
| **Participants** | Sixty-six patients scheduled for elective thoracotomy for various surgeries using muscle-sparing postero-lateral technique | |
| **Interventions** | Thirty-three patients received an i.v. infusion of S (+)-ketamine (Group S(+)K) for 60 hours and 33 patients received i.v. placebo (Group PLAC) | |
| **Outcomes** | Neuropathic Pain Symptom Inventory (NPSI) was evaluated at 1, 3 and 6 months. Quality of analgesia, NRS scores recorded in a personal diary for 6 months after discharge. Clinical evaluation and telephone interview at 1 week, and 1,3, and 6 months to evaluate pain and quality of life. | |
| **Notes** | Co-analgesia:  Pre-op: Midazolam, atropine, and droperidol one hour before anesthesia.  Intra-op: Epidural lidocaine 2% test dose; general anesthesia induced with propofol, remifentanil, and cisatracurium; levobupicaine and sufentanil through the epidural catheter.  Post-op: PCEA levobupivacaine and sufentanil for 60 hours. If NRS >3 paracetamol IV and then ketorolac IV were used as rescue drugs. Finally, the use of morphine was considered. POD 4 oral paracetamol plus codeine was given until discharge. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "The randomization protocol was provided by the Statistic Laboratory of our Institution. SAS software procedure “proc plan” (Release 8.2, by SAS/STAT®, Institute Inc, Cary, NC, USA) was used and a simple randomization assignment of treatments was applied." |
| Allocation concealment (selection bias) | Low risk | "All patients received a continuous i.v. infusion of a solution (prepared by the hospital pharmacy and sent to the operating room with a code blinded to the anesthetist), through an elastomeric pump for the following 60 hours." |
| Blinding of participants and personnel (performance bias) | Low risk | "All patients received a continuous i.v. infusion of a solution (prepared by the hospital pharmacy and sent to the operating room with a code blinded to the anesthetist)". Double-blind study design |
| Blinding of outcome assessment (detection bias) | Unclear risk | Blinding only described for early outcomes: "The quality of analgesia at the thoracotomy side was evaluated by anesthesiologists blinded to the study groups using the NRS after 1, 2, 4, 12, 18, 24 hours (Day0) and every 6 hours on the 1st, 2nd, and 3rd postoperative day (Day1, Day2, Day3), and then twice per day until discharge." "The follow-up was completed with a clinical evaluation and telephonic interview performed by both surgeons and anesthesiologists at 1 week and at 1,3 and 6 months after discharge to evaluate the surgical scar, the presence, intensity and localization of pain, the total amount of analgesics, the quality of life, the need for chemo and radiotherapy." |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20%. Lost to follow-up: 4/32 in Ketamine and 2/30 placebo. |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | High risk | Fewer than 50 participants per arm. There is no study protocol so no way to verify if chronic pain as the primary outcome was pre-specified. |

**Moore 2011**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 3 months | | |
| **Participants** | 46 pregnant women 18 years or older, undergoing scheduled cesarean delivery | | |
| **Interventions** | 600 mg of oral gabapentin 1 hour before the surgery | | |
| **Outcomes** | Pain scores, satisfaction with pain management, sedation, supplemental analgesia. At 3 months: sensory abnormalities and pain scores | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Spinal anesthesia was initiated with intrathecal hyperbaric bupivacaine, fentanyl, and morphine. IV fentanyl on request. After cord clamping, cefazolin or clindamycin IV was given, and oxytocin. At the end of the surgery, ketorolac and  acetaminophen was administered.  Post-op: IV morphine on patient request. Oral diclofenac and oral acetaminophen. Morphine as rescue analgesia. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "According to a computer-generated randomization… |
| Allocation concealment (selection bias) | | Low risk | "According to a computer-generated randomization table known only to the pharmacy department, the gabapentin or placebo capsules were then placed in sequentially numbered envelopes". |
| Blinding of participants and personnel (performance bias) | | Low risk | "...identical blue capsule covers". |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Not reported |
| Incomplete outcome data (attrition bias) | | High risk | Missing outcome data balanced across groups; however, the missing outcome data is > 20% |
| Selective reporting (reporting bias) | | Low risk | Protocol was registered and no significant differences were noticed compared with publication |
| Other bias | | High risk | "The study was terminated after 46 patients because a very low recruitment rate led to prolongation of the study". |

**Myhre 2017**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 12 months. | |
| **Participants** | Eighty patients scheduled for elective hand-assisted laparoscopic living donor nephrectomy | |
| **Interventions** | Pregabalin: The study medication, consisting of two capsules 75 mg (totally 150 mg) of pregabalin, was administered 1 h before induction of anesthesia on the day of surgery, in the evening on the day of surgery, as well as in the morning and in the evening on the first postoperative day (Total 600mg).  Placebo: Placebo capsules (formulation not specified) | |
| **Outcomes** | Primary outcome was opioid consumption 0–48 h after surgery.  Secondary outcomes were pain intensity at rest and with movement 0–48 h after surgery using the 0–10 Numeric Rating Scale and incisional hyperalgesia measured 24 h post-surgery and at hospital discharge. Further secondary outcomes were adverse effects. Persistent post-surgical pain was registered 6 weeks, 6 and 12 months after surgery. | |
| **Notes** | Co-analgesia:  Pre-op: All patients were premedicated with oral diazepam.  Intra-op: General anesthesia was induced and maintained by the use of infusion pumps delivering propofol and remifentanil as total intravenous anesthesia (TIVA). Thirty minutes before the anticipated end of surgery, an intravenous bolus of IV fentanyl was administered in addition to paracetamol. After closure of the surgical incision bupivacaine + epinephrine 5 was infiltrated in the wound area.  Post-op: Standard multimodal postoperative analgesic regimen comprising local anesthetic wound infiltration, dexamethasone IV, paracetamol and opioids as required. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "A person not involved in the treatment or follow-up randomized the patients in sex-stratified blocks of 4–6 to one of two groups (1:1 ratio), using a computerized randomization program (DatInf RandListversion 1.2, DatInf GmbH, T€ubingen, Germany). Block size and randomization code were unknown to all investigators (LR, AS, MM)" |
| Allocation concealment (selection bias) | Low risk | "Block size and randomization code were unknown to all investigators (LR, AS, MM), and the treatment allocation was concealed in opaque, sealed and sequentially numbered envelopes for use in potential emergencies only (no envelopes opened). The participants were assigned to the next consecutive participant number and given study medication marked with the corresponding number." |
| Blinding of participants and personnel (performance bias) | Low risk | "The study drug consisting of pregabalin 75 mg capsules and placebo capsules of identical appearance were produced by Oslo University Hospital Pharmacy, and pre-packed in sequentially numbered and identical containers according to the randomization list and labeled with identical study information. Patients and healthcare providers involved in the treatment of the patients were all blinded to the test drug, and the randomization code was not revealed to the investigators before all measurements were registered and entered into a database." |
| Blinding of outcome assessment (detection bias) | Low risk | "Patients and healthcare providers involved in the treatment of the patients were all blinded to the test drug, and the randomization code was not revealed to the investigators before all measurements were registered and entered into a database." |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20% |
| Selective reporting (reporting bias) | High Risk | One or more reported secondary outcomes were not pre-specified. According to ClinicalTrials.gov, there is no mention of outcomes for persistent post-surgical pain. |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Na 2016**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 3 months. | | |
| **Participants** | Ninety-four patients scheduled to undergo lumpectomy with axillary lymph nodes dissection (ALND) or sentinel lymph node biopsy (SLNB) | | |
| **Interventions** | Nefopam: 20 mg of nefopam in 100 mL of normal saline administered intravenously over 15 minutes during skin preparation and surgical draping  Placebo: Normal saline 100ml | | |
| **Outcomes** | Primary outcomes were NRS for pain and rescue analgesic drugs. Pain NRS was evaluated at 10days and 3 months.  Secondary outcomes were adjuvant chemo, radiation, hormone therapy, complication of surgery. | | |
| **Notes** | Co-analgesia:  Pre-op: IV midazolam  Intra-op: Alfentanil, propofol, and rocuronium were used for the induction of general anesthesia. Sevoflurane. At the end of the  procedure, IV ketorolac was given to all patients.  Post-op: Fentanyl if NRS=>5 in PACU. IV ketorolac if NRS =>5 in the general ward. Oral meloxicam, was prescribed to all patients as soon as they started eating at postoperative 6h taken daily for the next 5 days. | | |
| **Source(s) of funding** | No funding | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "According to the computer-generated randomization table, each patient was assigned to either the nefopam group or the control group." |
| Allocation concealment (selection bias) | | Low risk | "One anesthesiologist who did not take anesthetic care of patients was in charge of the randomization and the preparation of the nefopam. According to the computer-generated randomization table, each patient was assigned to either the nefopam group or the control group. The anesthesiologist prepared 20mg of nefopam in 100 mL of normal saline or 100 mL of normal saline alone for the nefopam or the control group, respectively. Both solutions were clear; thus, the other anesthesiologist who took care of patients in the operating room could not distinguish them." |
| Blinding of participants and personnel (performance bias) | | Low risk | "Both solutions were clear; thus, the other anesthesiologist who took care of patients in the operating room could not distinguish them." "Double-blind" is stated in title. |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Not reported. According to ClinicalTrials.gov masking was Double (Participant, Outcomes Assessor) |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was <20%. Lost to follow-up: 6/47 in the Nefopam group vs. 5/47 in the placebo group |
| Selective reporting (reporting bias) | | Unclear risk | The study protocol is available and several outcomes specified in the article were not pre-specified. According to ClinicalTrials.gov the primary outcome was "The change of pain numerical rating score from postoperative 30 min until postoperative 3 month [ Time Frame: Postoperative 30 min, postoperative 1 day, postoperative 1 week, postoperative 3 month]" and Secondary outcome was "The dose of ketorolac administered to the patient. [ Time Frame: postoperative 1 day]". In the article, the following is described "The primary outcomes were the NRS for pain and the administration of rescue analgesic drugs. The NRS was recorded at the PACU, and postoperative 6 and 24 h during the hospitalization period. The number of times each patient received the rescue analgesic drug in each time frame was also recorded. On postoperative 10 days and at 3 months, the NRS was evaluated in an outpatient clinic. As secondary outcomes, we investigated the following factors: the implementation of postoperative adjuvant chemotherapy, radiotherapy (RT), or hormone therapy, and any complication following the breast surgery, such as lymphedema, infection, seroma, hematoma, and axillary web syndrome." |
| Other bias | | Unclear risk | Fewer than 50 participants per arm. Pain at 3 months was specified as a primary outcome according to ClinicalTrials.gov |

**Nielsen 2015**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 3 months. | | |
| **Participants** | One hundred and sixty patients scheduled for 1-level or 2-level primary lumbar discectomy | | |
| **Interventions** | Dexamethasone: Immediately after induction of anesthesia, patients received 4 ampules with a total IV dexamethasone 16 mg (4 mL)  Placebo: Isotonic sodium chloride 9mg/ml | | |
| **Outcomes** | The primary outcome was pain during mobilization 2 to 24 hours postoperatively.  Secondary outcomes included pain at rest, total morphine consumption (0-24 hours and 24-48 hours), pain at rest and during mobilization 48 hours postoperatively, morphine-related adverse effects, and quality of sleep 24 hours postoperatively. Outcomes for the 3-month follow-up included back and leg pain (VAS 0-100 mm), use of analgesics, postoperative complications, walking distance, duration of sick leave, working capability, and contentment with the results of the operation. | | |
| **Notes** | Co-analgesia:  Pre-op: Oral paracetamol and ibuprofen 1h before surgery.  Intra-op: General anesthesia was induced and maintained with propofol and remifentanil. Rocuronium was used to facilitate intubation. IV sufentanil 20 min before end of surgery.  Post-op: Oral paracetamol and ibuprofen and PCA morphine for 24h. Morphine as rescue analgesia. The PCA was discontinued after 24h, oral morphine PRN in addition to paracetamol and ibuprofen, for the next 24-48h. No other analgesics, antiemetics, or sedative drugs were administered in the 48-hour study period. | | |
| **Source(s) of funding** | The study was supported by the Department of Anaesthesiology, Glostrup University Hospital, Denmark. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Randomization was performed by the pharmacy according to a computer-generated block randomization list (each block containing 10 numbers), in a 1:1 ratio." |
| Allocation concealment (selection bias) | | Low risk | "Information about treatment was concealed in consecutively numbered, sealed, opaque envelopes to enable unblinding in case of acute complications." |
| Blinding of participants and personnel (performance bias) | | Low risk | "Study medication was prepacked by the pharmacy in consecutively numbered boxes according to the computer- generated randomization list, containing identical 1 mL ampules of either dexamethasone 4 mg/mL or isotonic sodium chloride 9 mg/ mL. After inclusion, patients were given the treatment corresponding to their randomization number and the corresponding box. The intervention was blinded to patients, investigators, surgeons, and clinical personnel." |
| Blinding of outcome assessment (detection bias) | | Low risk | "Before breaking the randomization code, enrollment of all patients and the 3 months follow-up had ended; the data had been computed twice and afterward double-checked in Microsoft Excel, exclusion of patients was decided, and statistical handling of the data was completed." |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups for 3-month follow-up. Lost to follow-up: 3/80 Dexamethasone group and 4/80 Placebo group. |
| Selective reporting (reporting bias) | | High risk | One or more reported outcomes were not pre-specified. There is no mention of a 3-month or 12-month follow-up on ClinicalTrials.gov. The longest time period mentioned after surgery for outcomes is 48 hours. |
| Other bias | | High risk | "Our study contains exploratory secondary outcomes from an original trial. Thus, the sample size calculation was not performed with regards to these secondary outcomes." Also, there is a discrepancy between the response rates for the 3-month follow-up reported in the text versus Table 3. In the text: 62/77 in the dex group and 50/76 in the placebo group. 62/77=81%, but 82% reported in Table 3. 50/76=66%, but 69% reported in Table 3. |

**Nielson 2016**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 6 months. | |
| **Participants** | One hundred and sixty patients scheduled for 1-level or 2-level primary lumbar discectomy | |
| **Interventions** | Dexamethasone: Immediately after induction of anesthesia, patients received 4 ampules with a total IV dexamethasone 16 mg (4 mL)  Placebo: Isotonic sodium chloride 9mg/ml | |
| **Outcomes** | The primary outcome of the original trial was pain  during mobilization 2 to 24 h postoperatively calculated  as a ‘weighted average level’ area under the curve (AUC)  (in mm) (Nielsen 2015).  Secondary outcomes included pain at rest (AUC, 2–  24 h), total morphine consumption 0–24 h postoperatively,  and 3- and 12-months follow-up (for further information, see Nielsen 2015).  The 1-year follow-up was performed by a written questionnaire that consists of demographic data, back and leg pain (VAS 0–100 mm), duration of sick leave, working capability and contentment with the results of the operation. Further it contains the following questionnaires: Short form 36 survey (SF-36), EuroQol 5D (EQ-5D) and OSWESTRY Low Back Pain Questionnaire. | |
| **Notes** | Co-analgesia:  Pre-op: Oral paracetamol and ibuprofen 1h before surgery.  Intra-op: General anesthesia was induced and maintained with propofol and remifentanil. Rocuronium was used to facilitate intubation. IV sufentanil 20 min before end of surgery.  Post-op: Oral paracetamol and ibuprofen and PCA morphine for 24h. Morphine as rescue analgesia. The PCA was discontinued after 24h, oral morphine PRN in addition to paracetamol and ibuprofen, for the next 24-48h. No other analgesics, antiemetics, or sedative drugs were administered in the 48-hour study period. | |
| **Source(s) of funding** | The study was supported by the Department of Anaesthesiology, Glostrup University Hospital, Denmark. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Randomization was performed by the pharmacy according to a computer-generated block randomization list (each block containing 10 numbers), in a 1:1 ratio." |
| Allocation concealment (selection bias) | Low risk | "Information about treatment was concealed in consecutively numbered, sealed, opaque envelopes to enable unblinding in case of acute complications." |
| Blinding of participants and personnel (performance bias) | Low risk | "Study medication was prepacked by the pharmacy in consecutively numbered boxes according to the computer- generated randomization list, containing identical 1 mL ampules of either dexamethasone 4 mg/mL or isotonic sodium chloride 9 mg/ mL. After inclusion, patients were given the treatment corresponding to their randomization number and the corresponding box. The intervention was blinded to patients, investigators, surgeons, and clinical personnel." |
| Blinding of outcome assessment (detection bias) | Unclear risk | "Before breaking the randomization code, enrollment of all patients and the 3 months follow-up had ended; the data had been computed twice and afterward double-checked in Microsoft Excel, exclusion of patients was decided, and statistical handling of the data was completed." The randomization code was broken prior to the 1-year follow-up study. |
| Incomplete outcome data (attrition bias) | High risk | For the 1-year follow-up there is a high rate (38%) of loss to follow-up: 25/80 Dexamethasone group and 36/80 Placebo group |
| Selective reporting (reporting bias) | High risk | One or more reported primary outcomes were not pre-specified. There is no mention of a 3-month or 12-month follow-up on ClinicalTrials.gov. The longest time period mentioned after surgery for outcomes is 48 hours. |
| Other bias | High risk | There is no mention of a 1-year follow-up as a planned outcome in the first paper. Also given they broke the randomization codes after the 3-month follow-up, this outcome was not planned a priori. In the 2nd paper they describe this as a limitation: "Our study contains exploratory secondary outcomes from an original trial. Thus, the sample size calculation was not performed with regards to these secondary outcomes." |

**Nielsen 2017**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 6 months. | | |
| **Participants** | One hundred and fifty patients scheduled for lumbar fusion surgery | | |
| **Interventions** | Ketamine: S-ketamine bolus 0.5 mg/kg immediately after induction of anesthesia followed by infusion of S-ketamine 0.25 mg·kg21·h21  Placebo: Isotonic sodium chloride 9mg/mL | | |
| **Outcomes** | The primary outcome was total PCA morphine consumption 0 to 24 hours postoperatively. Secondary outcomes included pain during mobilization 2 to 24 hours postoperatively, pain at rest, morphine-related adverse events, and persistent pain 6 months postoperatively. | | |
| **Notes** | Co-analgesia:  Pre-op: opioids and oral paracetamol.  Intra-op: General anesthesia induced and maintained with propofol and remifentanil. Forty-five minutes before end of surgery, morphine IV. unacceptable pain on awakening IV sufentanil was administered.  Post-op: oral paracetamol every 6 hours, starting 2 hours postoperatively for 24 hours and the patients’ usual opioid  treatment. In addition, all patients received PCIA morphine. Rescue medication IV morphine administered by a nurse for the first postoperative hour in case the PCA was insufficient. After 24 hours, the PCA was discontinued and all patients were treated according to the department’s standard regime. | | |
| **Source(s) of funding** | The study was funded by the Department of Neuroanesthesiology Rigshospitalet-Glostrup, Copenhagen University Hospital. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Randomization was performed by the Capital Region Pharmacy according to a computer-generated block randomization list (each block containing 10 numbers) in a 1:1 ratio. " |
| Allocation concealment (selection bias) | | Low risk | " Information about treatment was concealed in consecutively numbered, sealed, opaque envelopes to enable unblinding in case of acute complications." |
| Blinding of participants and personnel (performance bias) | | Low risk | "Study medication and placebo were produced in identical ampules and pre-packed by the pharmacy in consecutively numbered boxes according to the computer-generated randomization list, containing identical 2 mL ampules of either S-ketamine (25 mg/mL) (Pfizer ApS, Denmark), or isotonic sodium chloride (NaCl) 9 mg/mL. The intervention was blinded to all patients, investigators, surgeons, and clinical personnel. " |
| Blinding of outcome assessment (detection bias) | | Low risk | "Before breaking the randomization code, enrolment of all patients and the 6-month follow-up period had ended; the data had been computed twice and afterwards double-checked in Microsoft Excel; exclusion of patients was decided, and statistical handling of the data was completed." |
| Incomplete outcome data (attrition bias) | | High risk | There is a large number of participants lost to follow-up for the 6-month outcome with only 43/75 and 52/73 who responded to the follow-up questionnaire (~36% missing data). This is not addressed in the article. |
| Selective reporting (reporting bias) | | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Nielsen 2019**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 12 months. | |
| **Participants** | One hundred and fifty patients scheduled for lumbar fusion surgery | |
| **Interventions** | Ketamine: S-ketamine bolus 0.5 mg/kg immediately after induction of anesthesia followed by infusion of S-ketamine 0.25 mg·kg21·h21  Placebo: Isotonic sodium chloride 9mg/mL | |
| **Outcomes** | The primary outcome: Total PCA morphine 0–24 hr  postoperatively, and secondary outcomes: Acute pain, adverse  events and 6-month follow-up are previously published (Nielsen et al., 2017).  The 1-year follow-up is reported here and includes five  questionnaires all validated for spine surgery patients: (a) The Dane Spine Questionnaire including patient-reported analgesics, (b) The Oswestry Low Back Pain (c) EuroQol 5D-3L, (d) The Douleur Neuropathique 4, and (e) Short form 36 survey (SF-36). | |
| **Notes** | Co-analgesia:  Pre-op: opioids and oral paracetamol.  Intra-op: General anesthesia induced and maintained with propofol and remifentanil. Forty-five minutes before end of surgery, morphine IV. unacceptable pain on awakening IV sufentanil was administered.  Post-op: oral paracetamol every 6 hours, starting 2 hours postoperatively for 24 hours and the patients’ usual opioid  treatment. In addition, all patients received PCIA morphine. Rescue medication IV morphine administered by a nurse for the first postoperative hour in case the PCA was insufficient. After 24 hours, the PCA was discontinued and all patients were treated according to the department’s standard regime. | |
| **Source(s) of funding** | The study was funded by the Department of Neuroanesthesiology Rigshospitalet-Glostrup, Copenhagen University Hospital. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Randomization was performed by the Capital Region Pharmacy according to a computer-generated block randomization list (each block containing 10 numbers) in a 1:1 ratio." (See primary article Nielsen 2017) "The pharmacy generated randomization code…" (Nielsen 2019) |
| Allocation concealment (selection bias) | Low risk | " Information about treatment was concealed in consecutively numbered, sealed, opaque envelopes to enable unblinding in case of acute complications." (Nielsen 2017) |
| Blinding of participants and personnel (performance bias) | Low risk | "Study medication and placebo were produced in identical ampules and pre-packed by the pharmacy in consecutively numbered boxes according to the computer-generated randomization list, containing identical 2 mL ampules of either S-ketamine (25 mg/mL) (Pfizer ApS, Denmark), or isotonic sodium chloride (NaCl) 9 mg/mL. The intervention was blinded to all patients, investigators, surgeons, and clinical personnel. " (Nielsen 2017) "The intervention was blinded to patients, investigators and all staff." (Nielsen 2019) |
| Blinding of outcome assessment (detection bias) | High risk | "The pharmacy generated randomization code was disclosed after 6-month follow-up for statistical analyses but prior to 1-year follow-up. Patients remained blinded at 1-year follow-up." (Nielsen 2019) |
| Incomplete outcome data (attrition bias) | High Risk | Missing data > 20%: Ketamine: 27/74; Placebo: 22/73 (Nielsen 2019) |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way (Nielsen 2019) |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. (Nielsen 2019) |

**Nikolajsen 2006**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 3 and 6 months | | |
| **Participants** | 46 adults undergoing lower limb amputation because of peripheral vascular disease | | |
| **Interventions** | Patients received one capsule (300 mg gabapentin or placebo) on the first postoperative day, 3 capsules (900 mg) on days 2–4, 4 capsules (1,200 mg) on days 5 and 6, 5 capsules (1,500 mg) on days 7 and 8, 6 capsules (1,800 mg) on days 9 and 10, seven (2,100 mg) capsules on days 11 and 12, and eight capsules (2,400 mg) on days 13–30. Patients with a creatinine clearance 30 ml/min but 60 ml/min received a maximum dose of 1,200 mg. If patients experienced intolerable side effects before the maximum dose of 1,200/2,400 mg was reached, they were allowed to stay on a lower dose for the rest of the study period. Patients who did not tolerate a minimum dose of 900 mg were withdrawn from the study. | | |
| **Outcomes** | Phantom limb and stump pain scores, McGill pain questionnaire, guessing about treatment | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Epidural infusion of bupivacaine combined with spinal or general anesthesia. Patients who did not receive an epidural catheter had either general or spinal anesthesia  Post-op: Epidural infusion of bupivacaine for 2-3 days, paracetamol, opioids | | |
| **Source(s) of funding** | Supported by a grant from Pfizer, Ballerup, Denmark. Pfizer supplied the study drugs (gabapentin and placebo) and paid approximately US $20,000 (salary to a research nurse). | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "….using a computer-generated randomization list in block sizes of 8 and 10". |
| Allocation concealment (selection bias) | | Low risk | "During the study, the randomization list was held securely at the hospital pharmacy and released only after study completion". |
| Blinding of participants and personnel (performance bias) | | Low risk | "After 30 days of treatment, 10/39 patients correctly identified the treatment given". |
| Blinding of outcome assessment (detection bias) | | Low risk | In 5 cases, the investigator correctly identified the treatment given: gabapentin: side effects (n =  3); placebo: lack of effect (n  = 2). In 8 cases, the answers were incorrect, and in 26 cases the treatment could not be identified |
| Incomplete outcome data (attrition bias) | | High risk | Significant number of drop outs (26.1%) and incomplete treatments |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Small sample size, pain intensity was low in both treatment groups; fewer than 50 pts per arm |

**Ok 2016**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 3 months. | | |
| **Participants** | Eighty patients scheduled for percutaneous endoscopic lumbar discectomy (PELD). | | |
| **Interventions** | Nefopam: 180 mg of nefopam mixed with 15 mg of morphine and 270 mg of ketorolac using a using a postoperative intravenous PCA infusion device. The PCA was programmed as a total volume of 100 ml with a basal infusion rate of 1 ml/h, a bolus infusion volume of 1 ml, and a lockout interval of 1 hour without a 4 hour volume limit, for 3 days  Placebo: Saline (mixed with 15 mg of morphine and 270 mg of ketorolac using a using a postoperative intravenous PCA infusion device) | | |
| **Outcomes** | Number of bolus infusions, neuropathic pain symptom inventory scores (NPSI), and adverse reactions. | | |
| **Notes** | Co-analgesia:  Pre-op: They had already taken oral medications, including a  mixture of codeine, acetaminophen, ibuprofen, gabapentin, and nortriptyline, 3 times in a day at least 1 week before PELD. A lidocaine patch was applied on the skin of the back, covering the anticipated path of the working channel 1h before surgery.  Intra-op: PCA morphine and ketorolac, with or without the study drug or placebo. Continuous infusion of dexmedetomidine and a local infiltration of 10 ml of 1% lidocaine into the skin.  Post-op: PCA morphine and ketorolac, with study drug or placebo for 3 days | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Using a computer-generated random allocations sequence, 80 patients who underwent PELD at L4-L5 were randomized and assigned into 2 equal groups: an NFP group and a normal saline (NS) group." |
| Allocation concealment (selection bias) | | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | | Low risk | "The mixture of analgesics with or without NFP was made by the same researcher. The operator and another researcher who started the patient-controlled analgesia (PCA) infusion pump, and checked the NPSI score during the study, did not know whether NFP was included or not. Both the participants and the care providers did not know whether the intravenous drugs contained NFP or not." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias) | | Unclear risk | No missing data or participants lost to follow-up reported. States: "There were no drop-out patients who stopped taking medicine or receiving intravenous NFP due to ADRs." |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Fewer than 50 participants per study arm. No protocol to verify whether chronic pain was a primary outcome. Number screened not reported. Number of completers/ drop-outs prior to day 90 not reported, only that there were no drop-outs due to ADRs. |

**Perrin 2009**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 1, 2; long term FU: 6 months after surgery | | |
| **Participants** | 12 patients booked for elective unilateral total knee arthroplasty (2 or 3 compartment) with an ASA I to III | | |
| **Interventions** | A programmed syringe delivered ketamine 0.5 mg/kg bolus followed by 4 μg/kg/min infusion, or equivalent volumes of the saline solution. The infusion commenced before surgical incision and continued until the surgical wound was bandaged or the syringe was empty. | | |
| **Outcomes** | Numerical rating scale pain scores at rest and movement (pressure care turning) were collected at 4, eight, 12, 16 and 20 hours post intrathecal injection and averaged to give a first 24-hour pain ‘score’ with a denominator of 10. The next 5 pain enquiries from 24 to 40 hours were poorly recorded and are not presented. 48 h morphine request; Primary outcome measures 1. Incidence of pain at 6 months equal to or worse than that preoperatively using WPS; 2. Incidence of zero pain in operated knee at 6 months using WPS; 3. Presence of pain not meeting the above criteria, arbitrarily labelled mild/moderate. | | |
| **Notes** | Co-analgesia:  Pre-op: None administered.  Intra-op: Intrathecal injection of bupivacaine and morphine. General anaesthesia induced within the following parameters; airway management as appropriate to patient requirements and end-tidal volatile ≥0.5 MAC or propofol infusion with appropriate anaesthetic depth monitoring.  Post-op: Midazolam IV for psychomimetic effects if present. Paracetamol 750 mg 24h, PCA morphine, Nurse-initiated morphine rescue for severe pain, ibuprofen 800 mg PRN | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Allocation concealment (selection bias) | | Low risk | The sealed syringe code was stored in our pharmacy department |
| Blinding of participants and personnel (performance bias) | | Low risk | The publication states that the study is triple blind |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Insufficient information to permit judgement |
| Incomplete outcome data (attrition bias) | | High risk | Significant number of drop outs (25%) and incomplete treatments |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Pesonen 2011**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for one and 3 months | | |
| **Participants** | Seventy patients, aged 75 yr or older and undergoing primary elective coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) or single valve repair or replacement with CPB, were initially included in the study. | | |
| **Interventions** | Beginning on the first postoperative morning, patients received 75 mg pregabalin or placebo twice daily until the fifth postoperative day. | | |
| **Outcomes** | Pain scores, Richmond Agitation, Sedation Score, oxycodone consumption, ICU stay, paracetamol requirement | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Anaesthesia was induced with fentanyl followed by propofol or etomidate. Rocuronium was used for muscular relaxation. Continuous infusion of fentanyl was maintained  until skin closure.  Post-op: Paracetamol, oxycodone | | |
| **Source(s) of funding** | This work was supported by Helsinki University Hospital Research Fund and Finska La¨karesa¨ llskapet, Finland. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "pharmacy performed the randomization using a computer generated randomization schedule" |
| Allocation concealment (selection bias) | | Low risk | "Each consenting patient received the study drug according to a consecutive randomization number, which was labelled to opaque plastic containers containing the study drugs". |
| Blinding of participants and personnel (performance bias) | | Low risk | "The pharmacy also prepared the study medication by packing pregabalin or placebo into identical capsules for blinding". |
| Blinding of outcome assessment (detection bias) | | Low risk | "The Verbal Rating pain score at rest and during movement and the analgesics consumed were recorded in a telephone interview by a blinded interviewer 1 and 3 months after the surgery". |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups and < 20% |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Peyton 2017**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicentre (3 centres), randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 6 months. | |
| **Participants** | Eighty patients undergoing abdominal or thoracic surgery (including video-assisted thoracic surgery), breast surgery, or inguinal herniorrhaphy | |
| **Interventions** | Ketamine: Intraoperative infusion was delivered by syringe driver, as a solution of ketamine (200 mg in 40 ml). A bolus of 0.5 mg/kg was given after induction of anaesthesia and before surgical incision, followed by 0.25 mg/kg/hour intraoperatively until commencement of skin closure. In the PACU, an infusion of ketamine at 0.1 mg/kg/hour or equivalent rate of normal saline was commenced and continued for 24 hours on the postoperative ward, or until hospital discharge  Placebo: Saline | |
| **Outcomes** | Primary endpoint (CPSP) defined as the presence of pain in the area of the surgery in the preceding month reported by the patient at the six-month follow-up contact on an intention-to-treat basis  Secondary endpoints included the incidence of CPSP allowing for any loss to follow-up, the effect of IV ketamine on acute and chronic pain severity and character (NRS, modified Brief Pain Inventory, NPQ), QoR-15, quality of life assessment (WHODAS, K-10, PCS), change in WHODAS and K-10 from preoperative baseline, cumulative morphine equivalents consumption over the first 72 hours, cumulative NRS pain scores over the first 72 hours, side-effects and safety data. | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Relaxant general anaesthesia was induced and maintained with the attending anaesthetist’s choice of drugs, except that the use of gabapentin, pregabalin, nitrous oxide, and open label ketamine was prohibited. Regional blockade or use of local anaesthetic infiltration was permitted only at the end of surgery.  Post-op: Opioids delivered as bolus doses or via patient-controlled analgesia. Ancillary analgesia (including non-steroidal anti-inflammatories, cyclooxygenase inhibitors and paracetamol) could be administered according to standard practice. | |
| **Source(s) of funding** | Funding was provided by a Project Grant from the Australian and New Zealand College of Anaesthetists and a Pilot Grant from the Australian and New Zealand College of Anaesthetists Clinical Trials Network. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Unclear risk | "Patients were randomised using pre-prepared sealed envelopes"  Insufficient information to permit judgement |
| Allocation concealment (selection bias) | Unclear risk | "Patients were randomised using pre-prepared sealed envelopes to receive a double-blind IV infusion of ketamine (treatment group) or normal saline (control group). The active drug was prepared by a research staff member such that the attending anaesthetist, operating room and postanaesthesia care unit (PACU) staff, and staff collecting all intraoperative and postoperative data were blinded to treatment allocation." The use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, and sealed. |
| Blinding of participants and personnel (performance bias) | Low risk | "double-blind IV infusion of ketamine (treatment group) or normal saline (control group). The active drug was prepared by a research staff member such that the attending anaesthetist, operating room and postanaesthesia care unit (PACU) staff, and staff collecting all intraoperative and postoperative data were blinded to treatment allocation." |
| Blinding of outcome assessment (detection bias) | Low risk | "...the attending anaesthetist, operating room and postanaesthesia care unit (PACU) staff, and staff collecting all intraoperative and postoperative data were blinded to treatment allocation." |
| Incomplete outcome data (attrition bias) | Unclear risk | Insufficient information to permit judgement |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | Unclear risk | Number screened not reported. Numbers lost to follow-up in each study arm unclear. |

**Quail 2017**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 24 months | |
| **Participants** | One hundred patients scheduled for inguinal hernia repairs | |
| **Interventions** | Gabapentin: 300 mg before surgery, then three times daily for 6 total doses  Placebo: Placebo pill (formulation not specified) | |
| **Outcomes** | The primary outcomes were pain and health-related QoL. Pain was assessed preoperatively and at 1, 6, 12, and 24 months postoperatively using a VAS. | |
| **Notes** | Co-analgesia:  Pre-op: IV midazolam  Intra-op: General anesthesia consisted of fentanyl, lidocaine, and propofol. If intubated, rocuronium or succinylcholine was used. Before skin incision, local anesthesia was given using lidocaine + bupivacaine with epinephrine During emergence, toradol was used after confirmation with surgeon and ondansetron was administered.  Post-op: Fentanyl and ondansetron were administered in the recovery room. Postoperative pain medications were provided at the discretion of the attending surgeon. No ketamine or dexamethasone was administered during the perioperative period. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "The inpatient research pharmacist performed the randomization using a random numbers table…" |
| Allocation concealment (selection bias) | Low risk | "The inpatient research pharmacist performed the randomization…" "Anesthesia, nursing, and surgical staff were blinded to the group assignment." Central allocation |
| Blinding of participants and personnel (performance bias) | Unclear risk | "Anesthesia, nursing, and surgical staff were blinded to the group assignment." Identical matching of placebo capsules is not explicitly described |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias) | High Risk | Missing data > 20% |
| Selective reporting (reporting bias) | High Risk | The study started in August 2011 but was not registered until April 2014, therefore unable to verify whether the primary outcome of chronic pain at 1, 6, 12, and 24 months was pre-specified. |
| Other bias | High Risk | Fewer than 50 participants per study arm. Study protocol registered after study start, so no way to verify if chronic pain was a pre-specified primary outcome. |

**Remerand 2009**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 1, 14, 30, 90 and 6 months after surgery | | |
| **Participants** | 154 adult patients scheduled for a total hip arthroplasty using lateral approach | | |
| **Interventions** | Patients received an IV bolus of 0.5 mg/kg ketamine (maximum 50 mg) from the first blinded 5-mL syringe, followed by a 24-h infusion using the second study syringe at 2 mL/h (equivalent to 2 mcg/Kg/min). | | |
| **Outcomes** | "Morphine consumption during the first 24 postoperative hours was our primary outcome". | | |
| **Notes** | Co-analgesia:  Pre-op: hydroxyzine or alprazolam 1h before anesthesia.  Intra-op: General anesthesia was induced with propofol and sufentanil. Patients’ lungs were mechanically ventilated with 40%–50% oxygen with nitrous oxide and sevoflurane.  Post-op: IV paracetamol and ketoprofen every 6h for 24 h. Morphine as rescue analgesic. PCA morphine plus droperidol for 48h. Oral morphine (day 2-4) on patient request. Preoperative chronic analgesics (NSAIDs, tramadol, and dextropropoxyphene) could be reinstated on patient request. | | |
| **Source(s) of funding** | Supported by institutional and/or departmental sources. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | " as part of a computer generated randomization process".... |
| Allocation concealment (selection bias) | | Low risk | "160 identical white envelopes were prepared, numbered, and sealed by a person external to our clinical unit. Each envelope contained detailed instructions of the preparation of 2 syringes (ketamine or saline). On the morning of the THA, a nurse prepared 2 syringes as described in the instructions, left them in a sterile box, and had no further clinical or research involvement". |
| Blinding of participants and personnel (performance bias) | | Low risk | "Nurses, anesthesiologists, and surgeons were unaware of the group assignment until the end of the study". |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "Patients were interviewed by phone on Days 30, 90, and 180 for pain location and intensity (at rest and while walking), need for help when walking, and analgesic consumption, by 1 of the 2 first authors". Insufficient information to permit judgement. |
| Incomplete outcome data (attrition bias) | | Low risk | "The study size was then set at 80 patients per group, to compensate for possible dropout patients and the fact that randomization was not created in blocks. In case of incomplete follow-up, missing data were excluded from analysis, but the remaining data (before any missing phone interview) were analyzed". |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Reyad 2019**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 6 months | |
| **Participants** | Two hundred patients scheduled for elective breast cancer surgery (either modified radical mastectomy or conservative breast surgery) combined with axillary dissection | |
| **Interventions** | Pregabalin: 75 mg one hour before induction of anesthesia and repeated 12 hourly for seven days  Placebo: Placebo capsules (formulation not specified) | |
| **Outcomes** | The primary outcome measure was the proportion of patients who developed neuropathic PMPS at different follow-up times. We defined postmastectomy neuropathic pain as pain involving the anterior aspect of the chest, axilla, and/or upper arm with the classical features of neuropathic pain including numbness,  tingling, burning, shooting, stinging, or stabbing pains, and hyperesthesia. Neuropathic pain was evaluated according to the Grading System for Neuropathic Pain (GSNP).  Secondary outcome measures: VAS Scores... Weeks 2, 3, 4, 12, and 24, Average daily drug consumption, frequency of side effects | |
| **Notes** | Co-analgesia:  Pre-op: IV midazolam.  Intra-op: Propofol, fentanyl, and atracurium were given for induction of general anesthesia. All patients received paracetamol, ketorolac, and morphine sulfate. Anesthesia was maintained by sevoflurane in O2/air mixture with reinjection of atracurium every 30 minutes.  Post-op: Postoperative analgesia was scheduled to keep VAS <40 mm using PCA morphine, ondansetron, and ketorolac. Additional morphine doses of were available for all patients to ensure good analgesia (VAS < 40 mm). On discharge, pain killers in form of oral/parenteral paracetamol, NSAIDs, and tramadol HCl were prescribed according to patient preference and drugs availability for the rest of the first postoperative week. | |
| **Source(s) of funding** | This research received no specific funding/grant from any funding agency in the public, commercial, or not-for-profit sectors; as all patients were treated under total governmental coverage (in the National Cancer Institute, Cairo University), no funding or grants were accepted from any public or commercial funding agents. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "A computer-generated random numbers list was used for the allocation of the participants. Block randomization with a block size of 4 was used with 1:1 ratio of pregabalin and control groups." |
| Allocation concealment (selection bias) | Low risk | "The allocation sequence was concealed from the researchers enrolling and assessing participants." The control group received placebo capsules at the same time points with the same steps. Both pregabalin and placebo capsules were supplied to patients by nurses blinded to the study. Neither the researcher allocating the participants nor the assessing person knew the decoding of the groups in its relation to the allocation sequence." |
| Blinding of participants and personnel (performance bias) | Unclear risk | "The allocation sequence was concealed from the researchers enrolling and assessing participants." "Both pregabalin and placebo capsules were supplied to patients by nurses blinded to the study. Neither the researcher allocating the participants nor the assessing person knew the decoding of the groups in its relation to the allocation sequence. Data were collected by a junior pain resident blinded to the study protocol." Identical matching of placebo capsules is not explicitly described |
| Blinding of outcome assessment (detection bias) | Low risk | "The average VAS values at the end of Weeks 2, 3, 4, 12, and 24 were assessed by a junior pain physician who was blinded to the study design." |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20% |
| Selective reporting (reporting bias) | High Risk | Retrospective registration: The study was conducted between December 2015 to March 2017 and registered in May 2017. Therefore unable to verify whether the primary outcome of chronic post-mastectomy pain syndrome was pre-specified |
| Other bias | Low risk | Unable to find additional potential bias. >50 participants per study arm. |

**Romundstad 2006**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, 3 arms, placebo-controlled trial with follow-up for days 6 weeks and 1 year after surgery | | |
| **Participants** | 219 patients (20-45) underwent breast augmentation surgery | | |
| **Interventions** | Single i.v. preoperative dose of methylprednisolone 125 mg, parecoxib 40 mg or saline | | |
| **Outcomes** | The primary outcome variable was prevalence of pain at rest. Secondary outcome variables were prevalence of evoked pain, and sensory changes. | | |
| **Notes** | Co-analgesia:  Pre-op: Before the start of surgery, the patients were sedated.  Intra-op: Surgery was performed under local anesthesia (intercostal lidocaine + adrenaline) combined with propofol/fentanyl sedation.  Post-op: acetaminophen 500 mg/codeine 30mg | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "A person not involved in the treatment and follow-up of patients randomized the patients in blocks of nine to 1 of 3 groups of equal size using a list of random numbers, according to the Moses-Oakford algorithm". |
| Allocation concealment (selection bias) | | Low risk | "Block size and randomization code were not revealed to the investigators until all measurements and calculations had been entered into the database". |
| Blinding of participants and personnel (performance bias) | | Low risk | "Methylprednisolone (Solu-Medrol) 125 mg, parecoxib 40 mg, and placebo (NaCl) were prepared at Rikshospitalet University Hospital by a doctor not in contact with the observers or patients. Test drugs were diluted with saline to fill a 10-mL syringe, marked with patient number and the possible test drugs, and appeared identical for all persons involved in the trial". |
| Blinding of outcome assessment (detection bias) | | Low risk | "Neither the person conducting the interview nor the patients were aware of the group to which the patients were assigned". |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced in numbers across intervention groups |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Sadatsune 2016**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 6 months. | |
| **Participants** | Forty patients scheduled for open carpal tunnel release surgery | |
| **Interventions** | Gabapentin: 600mg 1 hour prior to surgery  Placebo: Placebo pill (formulation not specified) | |
| **Outcomes** | Primary outcome was pain intensity according to a NRS prior to procedure, at time 0, 30 min, 1 h, 2 h, 2 weeks, 1 month, 3 months and 6 months after the procedure.  Secondary outcomes included: total dose of lidocaine supplementation; need for and dose of midazolam; post- operative need for and total dose of paracetamol and/or codeine; development of neuropathic pain and/or complex regional pain syndrome. | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Intravenous regional anesthesia (IVRA) with lidocaine using two tourniquets. Local infiltration of 1% lidocaine PRN. Midazolam PRN.  Post-op: Paracetamol PRN for up to 6 months post-surgery. Codeine was given if paracetamol was insufficient. The use of other drugs was not allowed for pain control during the  follow-up period. | |
| **Source(s) of funding** | Funding sources: Departmental, hospital-based, institutional | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "The patients were randomly assigned to one of two parallel groups in a 1:1 ratio, through using the computer program Randomizer. " |
| Allocation concealment (selection bias) | Low risk | "Opaque envelopes were prepared in accordance with the computer randomization and were numbered and sealed by a researcher who was not involved in patient assessment." |
| Blinding of participants and personnel (performance bias) | Low risk | "Each envelope contained either a gabapentin or a placebo tablet and was stored at the research hospital, to be given to the research physician prior to each surgery. The gabapentin and placebo tablets were identical in order to maintain patients and researchers blinded to the randomization group. None of the participating physicians or the researchers involved in data collection were aware of the patient study-group randomization. " Double-blind study design |
| Blinding of outcome assessment (detection bias) | Low risk | "None of the participating physicians or the researchers involved in data collection were aware of the patient study-group randomization" |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20%. Lost to follow-up: 2/20 Gabapentin group and 1/20 Placebo group |
| Selective reporting (reporting bias) | Unclear risk | The study protocol is available and several outcomes specified in the article were not pre-specified. In the article secondary outcomes included: total dose of lidocaine supplementation; need for and dose of midazolam; post- operative need for and total dose of paracetamol and/or codeine; development of neuropathic pain and/or complex regional pain syndrome. According to ClinicalTrials.gov the secondary outcome was: "Chronic Pain [ Time Frame: 6 months ] Numerical score from 0 to 10; zero means no pain and 10 is the more intense pain" |
| Other bias | Unclear risk | Fewer than 50 participants per arm. Pain at 3 months was specified as a primary outcome according to ClinicalTrials.gov |

**Schley 2007**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with a long term FU up to 6 months | | |
| **Participants** | 19 patients scheduled for traumatic amputation of the upper extremity | | |
| **Interventions** | Memantine: First week: 10 mg/day; second week: 20 mg/day; Week 3 and 4th: 30 mg/day versus placebo matched pills | | |
| **Outcomes** | Primary outcome variable was intensity of Phantom Limb Pain (PLP). Secondary outcome parameters were prevalence PLP, intensity of stump pain, phantom sensation and stump sensation. Intensity of these sensations was recorded via visual analogue scale (VAS 1–100) upon (1) admission; (2) before primary block; (3) 30 min after primary block; (4) twice daily during hospitalization; (5) 4 weeks after end of memantine treatment; (6) 6 and 12 months after end of memantine treatment. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: In all patients, surgery was performed under brachial plexus blockade. Two patients of the memantine group and four patients of the placebo group required additional general anesthesia, which was induced with thiopentone, sufentanil and vecuronium to facilitate intubation. Anesthesia was maintained with nitrous oxide, oxygen and isoflurane and incremental doses of sufentanil, if necessary.  Post-op: Continuous brachial plexus analgesia (CBPB) for one week after the amputation. In case of recurring pain (VAS > 30),  treatment was reinitiated with ropivacaine bolus and infusion. | | |
| **Source(s) of funding** | Supported, in part, by grants of the Deutsche Forschungsgemeinschaft, the Federal Ministry of Education, Science, Research and Technology, the Interdisciplinary Center of Clinical Research (IZKF) Tubingen, and the Fortune Program of the Medical Faculty of the University of Tubingen. Akatinol Memantine was provided free of charge by Merz & Co, Frankfurt. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Allocation concealment (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | | Low risk | "Patients and treating physicians were blinded for the medication". |
| Blinding of outcome assessment (detection bias) | | Low risk | …..Also data acquisition and processing were performed in a blinded fashion |
| Incomplete outcome data (attrition bias) | | Unclear risk | 9/30 patients patients redraw their agreement briefly after beginning of the treatment. Reasons are not stated |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | Unclear risk | Before the beginning of treatment (admission) 11 of 19 patients (58%) had developed PLP: 6 patients (60%) in memantine group and 6 patients in the control group. |

**Schroer 2011**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double-blind, 2 arm, placebo-controlled trial, follow-up for 12 months. | | |
| **Participants** | One hundred and seven patients scheduled for unilateral total knee arthroplasty | | |
| **Interventions** | Celecoxib: 200 mg to be taken twice daily for 6 weeks after hospital discharge  Placebo: Placebo (formulation not specified) | | |
| **Outcomes** | The primary end point of this study was narcotic use.  Secondary measures included: Knee range of motion, The Knee Society Score pain score and function score, Short-Form 12 (SF-12), and a standardized visual analog scale (VAS) pain score was determined based on a patient questionnaire to measure pain at rest, with activity, and at night. | | |
| **Notes** | Co-analgesia:  Pre-op: Celecoxib 400 mg was given to each patient before surgery and daily throughout hospitalization. All patients had access to PCA morphine on the night of surgery.  Intra-op: Spinal anesthesia  Post-op: A standardized postoperative clinical care pathway was  followed. All patients were placed on oral narcotics the morning after surgery. At the time of hospital discharge, all patients were instructed to take an enteric-coated aspirin twice daily. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Hospital pharmacy staff sequentially assigned patients to either the study or control regimen based on a randomization table provided by an outside statistician." |
| Allocation concealment (selection bias) | | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | | Low risk | "Patients, surgeon, nurses, and office staff were blinded to study randomization." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "Patients, surgeon, nurses, and office staff were blinded to study randomization." The article does not specify whether outcomes assessors were blinded. |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was <20%. 3 Months: 1/53 Celecoxib and 0/54 Placebo; 6 Months: 5/53 Celecoxib and 6/54 Placebo; 12 Months: 1/53 Celecoxib and 5/54 Placebo |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Participants were provided the treatment or placebo pills upon discharge and therefore it was self-administered. There is no guarantee that participants adhered to their allocated treatment. There is no mention of this as a possible limitation. |

**Sen 2009**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 3 and 6 months | | |
| **Participants** | Sixty male patients – aged 20–40 years, ASA I – who were scheduled for unilateral elective indirect inguinal herniorrhaphy under spinal anaesthesia using Lichtenstein technique | | |
| **Interventions** | In the gabapentin group, a single dose of 1.2 g oral gabapentin was given to patients 1 h before surgery; in the placebo group, a placebo capsule was given 1 h before surgery. | | |
| **Outcomes** | Pain scores, side effects, sedation, nausea, vomiting | | |
| **Notes** | Co-analgesia:  Pre-op: All patients received premedication with midazolam and atropine intramuscularly 45 min before surgery.  Intra-op: Spinal anaesthesia with bupivacaine  Post-op: Tramadol in PCA for 24 h. Rescue analgesia with IM diclofenac | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "randomly allocated into 2 groups (according to computer-generated randomization)". |
| Allocation concealment (selection bias) | | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | | Low risk | "All measurements were recorded by the same anaesthesiologist who was blinded to the study groups". |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "Assessment of postoperative pain at 1, 3 and 6 months was carried out – via telephone – with an 11-point numerical rating scale (NRS); 0 indicating ‘no pain’ and 10 indicating ‘worst pain imaginable’". |
| Incomplete outcome data (attrition bias) | | Low risk | Minimum missing outcome data |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Sen 2009a**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for 3 and 6 months | | |
| **Participants** | Sixty women scheduled for abdominal hysterectomy using Pfannenstiel incision with salpingo-oophorectomy | | |
| **Interventions** | The patients were assigned to 1 of the 3 treatment groups. The control group received oral placebo capsules and bolus plus infusion of saline; the ketamine group received oral placebo capsules and, before incision, 0.3 mg/kg IV bolus and 0.05 mgkg1h1 infusion of ketamine until the end of surgery11; and the gabapentin group received oral gabapentin 1.2 g and bolus plus infusion of saline. The initial dose of the study medication was administered 1 h before surgery. | | |
| **Outcomes** | Pain scores, sedation scale, morphine requirement, recovery of bowel function, patient satisfaction | | |
| **Notes** | Co-analgesia:  Pre-op: Midazolam 45 min before the procedure  Intra-op: General anesthesia was induced with propofol and atracurium and maintained with sevoflurane and nitrous oxide 50% in oxygen. Fentanyl, was administered 3–5 min before the surgical incision. Morphine IV administered immediately before discontinuing sevoflurane and nitrous oxide. At the start of skin closure, residual neuromuscular blockade was antagonized with neostigmine and atropine.  Post-op: PCA morphine. Oral analgesia using acetaminophen and codeine PRN. | | |
| **Source(s) of funding** | Supported by institutional and departmental sources at GATA Haydarpasa Eg˘itim Hastanesi. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "The patients were randomly assigned to 1 of the 3 treatment groups using a computer-generated table". |
| Allocation concealment (selection bias) | | Low risk | "All study drugs were prepared by the hospital pharmacy, and an appropriate code number was assigned to each patient". |
| Blinding of participants and personnel (performance bias) | | Low risk | "The same label was used for all the infusions for blinding purposes". |
| Blinding of outcome assessment (detection bias) | | Low risk | "All measurements were recorded by a research assistant who was blinded to the study medication. Patients were also contacted by one of the investigators at 1, 3, and 6 months after discharge to inquire as to when they were able to resume normal activities of daily living (i.e., return to work) and if they had any residual postoperative (incisional) pain". |
| Incomplete outcome data (attrition bias) | | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Shimony 2016**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double-blind, 2 arm, placebo controlled trial, follow-up for 3 months. | |
| **Participants** | One hundred patients undergoing intracranial surgery for brain tumor resection under general anesthesia | |
| **Interventions** | Pregabalin: 150 mg at 8:00 pm the night before surgery and 1.5 hours before undergoing surgery the next day. Postoperatively, they continued to receive their allocated capsules 2 hours after surgery, and then twice daily for the next 72 hours.  Placebo: Placebo pill 500 mg (starch). | |
| **Outcomes** | Pain intensity; Opioid consumption; Postoperative rates of drug usage, including analgesics and antiemetics; Length of stay (LOS) in the hospital; overall satisfaction rate (by telephone survey); overall satisfaction rate (by telephone survey); (NRS) pain scores and analgesics usage at 2 weeks and 1 and 3 months following surgery (by telephone survey, whenever obtainable); anxiety; quality of sleep | |
| **Notes** | Co-analgesia:  Pre-op: No other premedication drugs were given to the patients preoperatively.  Intra-op: General anesthesia consisted of propofol and a muscle relaxant, fentanyl boluses, or remifentanil by infusion, as deemed adequate by the anesthesiologist, as hemodynamically permitted, and as surgically required. Oxygen and isoflurane (infrequent) were provided, while no nitrous oxide was administered. Prior to surgical incision, lidocaine plus bupivacaine was injected into the subcutaneous and deeper areas at the surgical site. In the cases of awake surgery (i.e., monitored anesthesia care), propofol, fentanyl, or remifentanil was used to maintain minimal hypnosis and analgesia and avoid apnea, permitting the patient’s cooperation at intervals either for motor or speech tasks (such as verb generation, free speech, or naming) that were performed by a dedicated advanced neuropsychologist.  Post-op: Boluses of morphine and propofol were available to the patient, as deemed necessary by the attending anesthesiologist. Upon the demand for analgesia, IV paracetamol or dipyrone was administered. Further requests for pain relief were satisfied with intramuscular 75 mg diclofenac or 100 mg tramadol by slow intravenous infusion. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Randomization was accomplished using the institution’s pharmacy prepared patient list and RANDOM.org’s software model (Randomness and Integrity Services Ltd.)." |
| Allocation concealment (selection bias) | Low risk | "Randomization was accomplished using the institution’s pharmacy prepared patient list…" (central allocation: pharmacy controlled) |
| Blinding of participants and personnel (performance bias) | Low risk | "Patients in the placebo group were given identical capsules…" (identical appearance of active and control medications) |
| Blinding of outcome assessment (detection bias) | Unclear risk | "Various parameters were assessed perioperatively by the attending nurses." (unclear - does not specifically state they were blinded to allocation) |
| Incomplete outcome data (attrition bias) | High Risk | Missing data > 20% Only 27/50 participants in each arm were analyzed at 3 months. |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. |

**Short 2012**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 3 arm, placebo controlled trial, follow-up for 3 months. | |
| **Participants** | One hundred and thirty-two women undergoing elective cesarean delivery | |
| **Interventions** | Participants were randomized into 3 groups to receive 300 or 600 mg oral gabapentin, or placebo, 1 hour before surgery. | |
| **Outcomes** | The primary outcome was pain on movement at 24 hours. Secondary outcomes included satisfaction with analgesia, supplemental opioid consumption, lactation difficulties, neonatal outcomes, maternal sedation, and other adverse effects. Three months after delivery, patients were contacted for assessment of chronic pain. | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Spinal anesthesia with bupivacaine, fentanyl, and morphine. IV fentanyl PRN. Oxytocin infusion over 8 hours after umbilical cord clamping. At the end of the operation, ketorolac and PR acetaminophen.  Post-op: IV morphine PRN. Oral diclofenac and acetaminophen for 72h. Subcutaneous morphine for breakthrough pain. Subcutaneous nalbuphine for pruritus PRN. | |
| **Source(s) of funding** | Funding: Departmental resources. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "...according to a computer-generated randomization table. The randomization was done in blocks of 6" |
| Allocation concealment (selection bias) | Low risk | "Hospital pharmacists, who were not otherwise involved in the study, placed doses of 300 mg gabapentin or lactose placebo in identical blue capsule covers. Two capsules were placed in sequentially numbered envelopes" |
| Blinding of participants and personnel (performance bias) | Low risk | "each woman was assigned an ascending sequential study number, and given the study medication..." "The medication was administered by the study personnel, who also performed the subsequent assessments. Study personnel were blinded to group assignment until all women had been recruited and assessments were completed." Double-blind study design |
| Blinding of outcome assessment (detection bias) | Low risk | "The medication was administered by the study personnel, who also performed the subsequent assessments. Study personnel were blinded to group assignment until all women had been recruited and assessments were completed." |
| Incomplete outcome data (attrition bias) | Unclear risk | The number lost to follow-up by group is not reported. Only the total lost to follow-up for the whole sample (20/132 lost to follow-up at 3-Months) |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | High risk | Fewer than 50 participants per study arm. Total lost to follow-up reported for full study sample, not broken down by study arm. According to the methods they collected a variety of pain outcomes (i.e. pain intensity, whether it affected activities or daily living, and taking analgesics for pain) at 3 months yet there is minimal reporting in the results and discussion. |

**Sidiropoulou 2016**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 3 arm, placebo controlled trial, follow-up 3 months. | | |
| **Participants** | Forty-five patients scheduled for elective thoracotomy. | | |
| **Interventions** | Pregabalin-alone: 75mg every 12 hours, starting the afternoon before surgery (8.00 pm) and continuing for the first 5 postoperative days.  Pregabalin + Ropivacaine Wound Infusion: 75mg every 12 hours, starting the afternoon before surgery (8.00 pm) and continuing for the first 5 postoperative days plus ropivacaine 0.75% for the first 48 hours postoperatively with a low rate of 5 ml/hr.  Placebo: Placebo pill (formulation not specified) and Normal Saline | | |
| **Outcomes** | Primary endpoint: baseline pain intensity using VAS scale to for a mean difference of 2 among treatment groups. Secondary endpoints included opioid consumption, sedation rate, incidence of side effects, patient satisfaction, and persistence of post-thoracotomy pain and neuropathic pain at 1 and 3 months postoperatively (verbal rating score, DN4). | | |
| **Notes** | Co-analgesia:  Pre-op: Patients were not pre-medicated.  Intra-op: Anaesthesia was induced with propofol and fentanyl and tracheal intubation was facilitated with cis-atracurium. Anaesthesia was maintained with sevoflurane in an O2/air. Thirty minutes before the end of surgery all patients received ondansetron and paracetamol intravenously.  Post-op: PCA morphine for 48h, IV paracetamol, paracetamol and codeine PRN. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Subsequently they were randomly allocated (with a computer generated list of random numbers) in one of three groups" |
| Allocation concealment (selection bias) | | Low risk | "The medication (drug or placebo) was packed in sealed envelopes where only the patient number was visible and the name of the study." |
| Blinding of participants and personnel (performance bias) | | Low risk | "The placebo drug was manufactured identical in size and colour to pregabalin in our hospital pharmacy. A hospital nurse, in charge of the study randomisation administered the medication to the patients. The same person prepared the postoperative wound infusions (normal saline or local anaesthetic) and was not otherwise involved in the study." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | According to the clinicaltrials.gov record the study was Triple Blind (Participant, Investigator, Outcomes Assessor). Blinding for outcome assessment not explicitly stated in the manuscript. |
| Incomplete outcome data (attrition bias) | | Low risk | Missing outcome data balanced across groups. The dropout rate was <20%. 0 lost to follow-up in Pregabalin and Placebo Groups |
| Selective reporting (reporting bias) | | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | | High risk | Fewer than 50 participants per study arm and chronic pain was not the primary outcome. |

**Singla 2015 (Post-HRT Trial NCT00468845)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Multicenter, randomized, double blind, 3 arm, placebo-controlled trial, follow-up for 6 months. | | |
| **Participants** | Five hundred and one patients scheduled for elective abdominal hysterectomy using a transverse incision with or without bilateral salpingo-oophorectomy under general anesthesia. | | |
| **Interventions** | Pregabalin: 150 mg/d (75 mg bid).  Pregabalin: 300 mg/d (150 mg bid)  Placebo (bid)  Patients received two preoperative treatment doses at 12 hours and 2 hours before surgery and continued treatment (bid dosing) for 4 weeks post surgery | | |
| **Outcomes** | Primary measure mean worst pain past 24 hours, assessed 24 hours post HRT. Secondary measures worst and current pain intensity assessed 72 hours post-HRT and severity of movement-related pain assessed up to 72 hours postsurgery. Continued pain in the area of surgery was assessed 3 and 6 months post-HRT. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: General anesthesia. Supplemental analgesia with parenteral morphine by PCA pump and bolus injections of opioids.  Post-op: PCA morphine and bolus injections of opioids. NSAID (naproxen, ibuprofen, diclofenac, ketorolac, or ketoprofen) and/or  acetaminophen was added or substituted as appropriate. | | |
| **Source(s) of funding** | These studies were sponsored by Pfizer Inc. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomized via a computer-generated 1:1:1 ratio to one of three arms." |
| Allocation concealment (selection bias) | | Low risk | Investigators used the sponsor’s inter- active response technology system (via phone or Internet) to screen, randomize, and assign treatment to patients in a double-blinded manner. |
| Blinding of participants and personnel (performance bias) | | Low risk | Pregabalin and placebo were administered as gray capsules identical in appearance. Patients were assigned a subject identification number at screening and a separate number at randomization to identify which treatment was to be received. Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | According to the clinicaltrials.gov record the study masking was Double (Participant, Investigator). Blinding for outcome assessment not explicitly stated in the manuscript. |
| Incomplete outcome data (attrition bias) | | Unclear risk | Numbers analyzed and lost to follow-up in each group at the 3 and 6-month assessment time points is not reported. |
| Selective reporting (reporting bias) | | High risk | One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis. The study report fails to include results for a key outcome that would be expected to have been reported for such a study. According to ClinicalTrials.gov, the following was a pre-specified secondary outcome "The Incidence of Chronic Post-operative Pain [Time Frame: 3 and 6 Months PS]". However, the incidence of pain at 3 and 6 months for the 150mg/d arm is not reported. |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Singla 2015 (Post-IHR Trial NCT00551135)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Multicenter, randomized, double blind, 4 arm, placebo-controlled trial, follow-up for 6 months. | | |
| **Participants** | Four hundred and twenty-five patients scheduled for primary, elective, open, unilateral inguinal herniorrhaphy using Lichtenstein mesh repair under general anesthesia | | |
| **Interventions** | Pregabalin: 50 mg/d (25 mg bid)  Pregabalin: 150 mg/d (75 mg bid)  Pregabalin: 300 mg/d (150 mg bid)  Placebo (bid)  Patients received two preoperative treatment doses at 12 hours and 2 hours before surgery and continued treatment (bid dosing) for 1 week post-IHR | | |
| **Outcomes** | Primary measure mean worst pain past 24 hours, assessed 24 hours post-IHR. Secondary measures worst, average, and current pain intensity 72 hours post-IHR, severity of movement-induced pain assessed at 1, 2, and 48 hours post-IHR. Continued pain in the area of surgery was assessed 1, 3, and 6 months post-IHR. | | |
| **Notes** | Co-analgesia:  Pre-op: Premedication with midazolam or temazepam.  Intra-op: General anesthesia was induced with propofol and sevoflurane, isoflurane, or desflurane. Intraoperative analgesia was managed with fentanyl or sufentanil. Muscle relaxants were allowed during the surgical procedure.  Post-op: Local infiltration of the surgical site with bupivacaine. Standard analgesic medication consisted naproxen (bid) for 3 days and then as needed. If inadequate, tramadol and acetaminophen. If still inadequate, oxycodone and acetaminophen. | | |
| **Source(s) of funding** | These studies were sponsored by Pfizer Inc. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomized via a computer-generated 1:1:1:1 ratio to one of four arms" |
| Allocation concealment (selection bias) | | Low risk | Investigators used the sponsor’s inter- active response technology system (via phone or Internet) to screen, randomize, and assign treatment to patients in a double-blinded manner. |
| Blinding of participants and personnel (performance bias) | | Low risk | Pregabalin and placebo were administered as gray capsules identical in appearance. Patients were assigned a subject identification number at screening and a separate number at randomization to identify which treatment was to be received. Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | According to the clinicaltrials.gov record the study masking was Double (Participant, Investigator). Blinding for outcome assessment not explicitly stated in the manuscript. |
| Incomplete outcome data (attrition bias) | | Unclear risk | Numbers analyzed and lost to follow-up in each group at the 3 and 6-month assessment time points is not reported. |
| Selective reporting (reporting bias) | | High risk | One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis. The study report fails to include results for a key outcome that would be expected to have been reported for such a study. According to ClinicalTrials.gov, the following was a pre-specified secondary outcome "Participants With Chronic Postoperative Pain [ Time Frame: 1, 3, and 6 months (mo) post surgery (PS)] Number of participants who reported surgery-related pain at assessment (by answering 'yes' to a single question: "In the last 24 hours, have you had pain in the area affected by your surgery?"). Vague reporting of pain at 3 and 6 months post-surgery. "Fewer patients reported continued pain at 3 months post-IHR, and by 6 months post-IHR, only 1 participant in each of the pregabalin groups reported continued pain compared with 0 in the placebo group." |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Singla 2015 (Post-TKA Trial NCT00442546)**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Multicenter, randomized, double blind, 3 arm, placebo-controlled trial, follow-up for 6 months. | | |
| **Participants** | Three hundred and seven patients with osteoarthritis undergoing elective total knee arthroplasty | | |
| **Interventions** | Pregabalin: 150 mg/d (75 mg bid)  Pregabalin: 300 mg/d (150 mg bid)  Placebo (bid)  Patients received two preoperative treatment doses at 12 hours and 2 hours before surgery and continued treatment (bid dosing) for 6 weeks post-TKA | | |
| **Outcomes** | Primary measure mean worst pain past 24 hours, assessed 48 hours post-TKA. Secondary measures worst, average, and current pain intensity assessed 72 hours post-TKA. Passive and active flexion range of motion (ROM) of the operated knee were measured at baseline, and at weeks 2, 4, and 6 (or early termination) post-TKA. Continued pain in the area of surgery was assessed at 3 and 6 months post-TKA. | | |
| **Notes** | Co-analgesia:  Pre-op: Sedation with midazolam or propofol. PCA/PCEA.  Intra-op: Anesthesia was provided by epidural, spinal, or combined spinal/epidural analgesia with local anesthetic and hydromorphone or fentanyl.  Post-op: Peripheral nerve block allowed for the first 36h. Oral hydrocodone/acetaminophen tablets; or oxycodone/acetaminophen and/or intravenous opioid PCA  (morphine, hydromorphone, fentanyl). PCA/PCEA was used to maintain pain at rest at 4 on the 11-point NRS. | | |
| **Source(s) of funding** | These studies were sponsored by Pfizer Inc. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were randomized via a computer-generated 1:1:1 ratio to one of three arms." |
| Allocation concealment (selection bias) | | Low risk | Investigators used the sponsor’s inter- active response technology system (via phone or Internet) to screen, randomize, and assign treatment to patients in a double-blinded manner. |
| Blinding of participants and personnel (performance bias) | | Low risk | Pregabalin and placebo were administered as gray capsules identical in appearance. Patients were assigned a subject identification number at screening and a separate number at randomization to identify which treatment was to be received. Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | According to the clinicaltrials.gov record the study masking was Double (Participant, Investigator). Blinding for outcome assessment not explicitly stated in the manuscript. |
| Incomplete outcome data (attrition bias) | | Unclear risk | Only numbers analyzed at 3 and 6 months for the 300mg arm are reported in the results. Number analyzed in 150mg arm not reported. |
| Selective reporting (reporting bias) | | High risk | One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis. The study report fails to include results for a key outcome that would be expected to have been reported for such a study. According to ClinicalTrials.gov, the following was a pre-specified secondary outcome: "Number of Subjects With Persistent Pain Based on 11-Point Verbal Rating Scale (VRS) [ Time Frame: Month 3, Month 6 (phone call)]. The presence of persistent pain was evaluated on the 11-point VRS. The subject answered the question: how much pain did you experience in the last 24 hours in your operated knee? A zero score of VRS was the only number considered as a "no." Any positive score (1-10) of VRS was consider as "yes."" However, the incidence of pain at 3 and 6 months for the 150mg/d arms are not reported. |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Spreng 2010**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with scheduled follow ups at 7 and 90 days after surgery | | |
| **Participants** | 77 patients > 18, ASA I-II scheduled for day-care elective hemorrhoidectomy | | |
| **Interventions** | Approximately 1 h before surgery all patients received oral paracetamol 1-2 grams. Total Intravenous Anesthesia (remifentanil +propofol) was the anesthesia technique. During operation all patients received intravenous 8mg dexamethasone and 30mg ketorolac. After surgery, the surgeon injected 10–20 ml bupivacaine 2.5mg/ml + epinephrine in the surgical field. After insertion of laryngeal mask, but before start of surgery, patients in the (S)-ketamine group received an intravenous bolus dose of 0.35mgkg (S)-ketamine (Pfizer, 2.5mgml−1) followed by continuous infusion of 5gkg−1 min−1 (S)-ketamine. Patients in the placebo group received an equivalent volume of isotonic saline (bolus and infusion). Rescue pain medication was fentanyl 0.05–0.1mg IV during 0–30 min after end of surgery and paracetamol + codeine (500mg+ 30mg) orally later on; and was given when VAS > 30, NRS > 3 or upon patient request. | | |
| **Outcomes** | VAS (0-100) pain scores and numerical rating scales (0-10). At 30 min after the end of surgery the patients completed the trail making test for evaluation of (S)-ketamine psychotomimetic side-effects: patient is asked to connect randomly distributed numbers (from 1 to 25) as fast as possible. At discharge from the PACU patients’ grade of satisfaction was registered (satisfied–indifferent–not satisfied) and need of rescue analgesics in the PACU was documented. The patients were interviewed by phone on postoperative day 1, day 7 and 3 months after surgery; assessing pain intensity, need for analgesics, grade of satisfaction and side-effects (nausea, hallucinations, double and/or abnormal colour vision). | | |
| **Notes** | Co-analgesia:  Pre-op: Oral paracetamol 1h before surgery.  Intra-op: Total intravenous anaesthesia (TIVA) induced with a bolus dose of propofol and remifentanil followed by continuous infusion. Dexamethasone 8mg and ketorolac 30mg. After completion of surgery the surgeon injected local anaesthesia (bupivacaine + epinephrine) in the surgical field. TIVA was stopped when surgery was finished.  Post-op: Rescue pain medication was fentanyl 0–30 min after end of surgery and paracetamol + codeine orally later on; and was given when VAS > 30, NRS > 3 or upon patient request.  Dexamethasone was administered at analgesic range + local analgesia infiltration, which increases the external validity of the results. | | |
| **Source(s) of funding** | The study has been financed by institutional means. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Unclear risk | The method of sequence generation is not stated |
| Allocation concealment (selection bias) | | Low risk | "Permuted block randomization, blinding and packing of the study medication were performed by the hospital pharmacy. The randomization codes were provided in sealed envelopes". |
| Blinding of participants and personnel (performance bias) | | Low risk | Patients in the placebo group received an equivalent volume of isotonic saline (bolus and infusion) |
| Blinding of outcome assessment (detection bias) | | Low risk | ...."They were observed and evaluated by nursing staff which were blinded to the treatment. Pain intensity was assessed after 15, 30, 60 min and before discharge from PACU using visual analog scale (VAS, 0–100) and numeric rating scale (NRS, 0–10) for pain". |
| Incomplete outcome data (attrition bias) | | Unclear risk | Compensating for missing data a total of 80 patients was planned for this study. However, It is unclear what proportion of patients was effectively contacted at the 3 months follow-up |
| Selective reporting (reporting bias) | | Low risk | The protocol was registered and the primary outcome fits with the primary outcome of the publication |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Sun 2013**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 12 months | | |
| **Participants** | Sixty patients who underwent surgery for unilateral primary breast cancer and axillary lymph nodes dissection (ALND) | | |
| **Interventions** | Flurbiprofen axetil: Intravenous injection of 5 mL of flurbiprofen axetil (50 mg) at 15 minutes before surgical incision and 6 hours later  Placebo: Placebo (intralipid) | | |
| **Outcomes** | Chronic pain assessments were conducted by telephone at 2, 4, 6 and 12 months after the surgery. Included the following: included the following reports: 1) the location, intensity, nature and duration of pain, aggravating or mitigating factors; 2) use of medications or nonpharmacologic means for the control of pain; 3) any additional treatments administered for their cancer, such as chemotherapy or radiotherapy. | | |
| **Notes** | Co-analgesia:  Pre-op: No premedication was given.  Intra-op: General intravenous anesthesia was induced with midazolam, fentanyl, and vecuronium. Propofol and remifentanil  to maintain anesthesia.  Post-op: PCIA fentanyl for 48 h | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Using computer-generated random number, 60 patients were randomly divided into 2 groups, each group of 30 patients." |
| Allocation concealment (selection bias) | | Unclear risk | Not reported "Randomization and anesthesia procedure was done by an anesthesiologist" |
| Blinding of participants and personnel (performance bias) | | Low risk | "Randomization and anesthesia procedure was done by an anesthesiologist, and the follow up and evaluation after the surgery was done by another anesthesiologist blinded to group allocation." Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Low risk | "Telephone interviews by a blinded anesthesiologist…" |
| Incomplete outcome data (attrition bias) | | Low risk | There does not appear to be any missing outcome data. |
| Selective reporting (reporting bias) | | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | | High risk | Fewer than 50 participants per arm and there is no study protocol to verify whether chronic pain was pre-specifed as a primary outcome. Methods indicate only the anesthesiologist conducting the telephone interviews was blinded to allocation. The number screened to obtain a sample of 60 is not described. |

**Suzuki 2006**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 1, 2, 30, 90 and 180 days after surgery | | |
| **Participants** | 50 patients who were scheduled to undergo open thoracotomy with 15cm incision including rib and muscle reconstruction | | |
| **Interventions** | Before Anesthesia induction, an epidural inserted and confirmed with ropivacaine. After tracheal intubation, an intravenous infusion of 0.05 mg/kg/h ketamine or placebo at the same volume was started. The infusion rate of ketamine was determined by simulation in a target-controlled infusion program to maintain a blood concentration of 20 ng/ml. After surgery, all patients received a continuous epidural infusion of 0.05 mg/ml morphine and 0.15% ropivacaine at an initial rate of 3 ml/h or by an infusion pump. Epidural infusion was continued for 48 h. All patients continued to receive infusion of ketamine or placebo for 72 h after surgery. If the patient requested additional analgesia within 24 h of surgery, 50 mg intravenous flurbiprofen was administered. | | |
| **Outcomes** | The primary endpoint of the study was the number of patients who felt baseline pain at 3 months after thoracotomy. In a long term, the outcomes were the number of patients who felt usual pain at 1, 3, and 6 months after surgery; the number of patients who were taking pain medication 1, 3, and 6 months after surgery; the number of patients who felt an unpleasant sensation on the surgical wound; and the number of patients who felt inconvenienced by the wound. | | |
| **Notes** | Co-analgesia:  Pre-op: Intramuscular injection of atropine sulfate and hydroxyzine 30 min before induction of anesthesia.  Intra-op: Epidural analgesia (ropivacaine every 90 min). Propofol was administered intravenously to induce anesthesia. General anesthesia was maintained with isoflurane and a mixture of 50–60% oxygen with nitrous oxide. At the end of skin closure, morphine sulfate + ropivacaine administered epidurally.  Post-op: Morphine and ropivacaine epidural infusion for 48h. Intravenous flurbiprofen within 24h and oral loxoprofen 24-48h if patient requested. | | |
| **Source(s) of funding** | Supported by Hisamitsu Pharmaceutical Company, Tokyo, Japan. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Patients were assigned to one of 2 groups using a computer-generated randomization schedule". |
| Allocation concealment (selection bias) | | Unclear risk | Insufficient information to permit judgement |
| Blinding of participants and personnel (performance bias) | | Low risk | The study drug, ketamine or placebo, was prepared and placed in the infusion pump by an investigator who did not participate in the administration of anesthesia or the evaluation of postoperative pain. |
| Blinding of outcome assessment (detection bias) | | Low risk | At 1, 3, and 6 months after surgery, one of the investigators, who did not know the group assignment, called each patient’s home and administered the same questionnaire that had been given on day 7. |
| Incomplete outcome data (attrition bias) | | Low risk | Minimum missing outcome data (12% only) |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**Sveticic 2008**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up for days 1, 2, 90 and 180  after surgery | | |
| **Participants** | 352 patients undergoing major elective orthopedic surgery (spine, hip, knee, shoulder, other) | | |
| **Interventions** | Morphine PCA + ketamine (1mg:1mg). Boluses of 1.5 mg of each drug, max. 6 per 4 | | |
| **Outcomes** | Primary outcome: rate of unsatisfactory treatment; secondary outcomes: mean pain scores at rest and movement-evoked; analgesic consumption; side effects profile; and incidence of pain at 3 months and 6 months | | |
| **Notes** | Co-analgesia:  Pre-op: Midazolam 20–30 min before anesthesia.  Intra-op: Either general or regional anesthesia. General anesthesia induced with IV fentanyl; thiopental or propofol or etomidate; vecuronium or atracurium. After tracheal  intubation, a mixture of oxygen + nitrous oxide was administered,  supplemented by either isoflurane or propofol. Regional anesthesia mepivacaine for nerve blockade or bupivacaine for spinal anesthesia.  Post-op: IV propacetamol + morphine PCA and ketorolac | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "Randomization was performed by drawing lots immediately before administering the solution". |
| Allocation concealment (selection bias) | | Unclear risk | "Patients were randomly allocated to receive PCA consisting of either morphine 1.5 mg (Group M) or morphine with ketamine 1.5 mg of each"…..Insufficient information to permit judgment |
| Blinding of participants and personnel (performance bias) | | Low risk | "The patients, nurses who cared for patients, anesthesiologists who performed the anesthesia were not aware of the PCA drug used". |
| Blinding of outcome assessment (detection bias) | | Low risk | "The investigators who gathered the data were not aware of the PCA drug used". |
| Incomplete outcome data (attrition bias) | | High risk | Only 25.9% and 10.2% of all patients returned our chronic pain questionnaire 3 and 6 mo after the surgery, respectively |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | Low risk | No other potential sources of bias were detected |

**Tena 2014**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 3 arm, placebo controlled trial, follow-up 6 months. | |
| **Participants** | One hundred and twenty-five patients scheduled for pulmonary resection through posterolateral thoracotomy. | |
| **Interventions** | Ketamine IV (Kiv): 0.5mg/kg of ketamine plus an epidural bolus of saline before surgical incision, and then, postoperatively, 0.25 mg/kg/h ketamine in the IV elastomeric pump and saline in the epidural pump.  Ketamine epidural (Kep): 0.5mg/kg ketamine plus an IV bolus of saline before surgical incision, and then, postoperatively, 0.25mg/kg/h ketamine in the epidural PCA pump (equivalent to 3.6 mg/ mL for a 60-kg patient) and a continuous infusion of saline in the IV elastomeric pump.  Placebo: Saline | |
| **Outcomes** | VAS was completed at rest 2 hours, 4 hours, 24 hours, 72 hours, 7 days, 3 months, and 6 months after surgery; NPSI was administered the day before surgery and 7 days, 3 months, and 6 months after surgery; Catastrophizing Scale, which measures distress reactions to pain stimulation, was completed the day before surgery and 7 days and 3 months after surgery; QST performed at 72 hours, 7 days, 3 months, and 6 months after surgery | |
| **Notes** | Co-analgesia:  Pre-op: Sublingual diazepam the night before and 1 hour before.  Intra-op: Anesthesia consisted of IV midazolam, fentanyl, propofol, and cisatracurium. Anesthesia was maintained with desflurane 4% to 6% in O2/air 60%, remifentanil, and cisatracurium. Remifentanil and desflurane were discontinued at the end of chest closure.  Post-op: Epidural ropivacaine bolus, epidural PCA ropivacaine and fentanyl for 48h. TEA was supplemented with paracetamol. Metamizol administered if additional analgesia was requested. After 48 hours, following TEA withdrawal, analgesia was maintained with IV metamizol and paracetamol, along with methadone subcutaneously as rescue analgesia if necessary. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Patients were randomized to one of 3 double-blinded groups using a computer-generated randomization procedure (GraphPad Statmate 1.0 software)." |
| Allocation concealment (selection bias) | Low risk | "To mask the groups, the apparent instrumentation of the 3 groups was the same: every patient received a 5-mL bolus, both epidural and IV (either racemic preservative-free ketamine or saline), 15 minutes before surgical incision, as well as a continuous epidural infusion by PCA electronic pump and a continuous IV infusion by elastomeric pump of 300 mL at a rate of 5 mL/h (Baxter) for 48 hours postoperatively." "All study solutions were prepared by a trained nurse who was not involved in patient care. All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated." |
| Blinding of participants and personnel (performance bias) | Low risk | "All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated." Double-blind study design |
| Blinding of outcome assessment (detection bias) | Low risk | "All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated." |
| Incomplete outcome data (attrition bias) | Unclear risk | Insufficient reporting. There were 125 patients randomized, 21 withdrawn after randomization, and 104 analyzed. Numbers excluded/withdrawn are not reported by study arm. The dropout rate was <20% |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | High risk | Fewer than 50 participants per study arm. The number randomized to each group is not reported, only the numbers analyzed in each group. |

**Terkawi 2015**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 6 months. | | |
| **Participants** | Eighty patients scheduled for simple or modified radical mastectomy with or without axillary dissection | | |
| **Interventions** | Lidocaine: 2 mg/kg/hr (to a maximum upper limit of 200 mg/hr)  Placebo: Saline. | | |
| **Outcomes** | The primary outcome for this analysis was whether the use of perioperative lidocaine infusion reduced the incidence of CPSP after breast surgery. | | |
| **Notes** | Co-analgesia:  Pre-op: All patients received lidocaine as a bolus prior to anesthetic induction.  Intra-op: The use of pre-medication, choice of induction drug, and muscle relaxant were left to the discretion of the attending anesthesiologist. Sevoflurane in air/oxygen was used for maintenance. Intraoperative analgesia was limited to fentanyl IV  Post-op: Fentanyl or morphine PRN. Postoperative analgesia was not standardized. We requested the use of morphine patient-controlled analgesia to allow easier comparison between groups, but postoperative analgesia was at the discretion of the surgical team responsible for the patient. | | |
| **Source(s) of funding** | Supported by the Department of Anesthesiology, University of Virginia Health System, Charlottesville, VA. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "The patients were randomized at 1:1 ratio to receive either lidocaine or placebo."... "A website random number generator was used (www.randomization.com)." |
| Allocation concealment (selection bias) | | Unclear risk | "Numbers were concealed in opaque sealed envelopes and the patient was asked to select one envelope on the morning of surgery." |
| Blinding of participants and personnel (performance bias) | | Low risk | "Both the patients and research team remained blinded until after all data were analyzed." ... "either lidocaine (prepared blinded by our investigational pharmacy as 8 mg/mL) or placebo (0.9% NaCl)" Double-blind study design |
| Blinding of outcome assessment (detection bias) | | Low risk | "A research associate, who was blinded to treatment group and management, conducted a telephone interview with the patients 6 months after surgery." |
| Incomplete outcome data (attrition bias) | | Unclear risk | More participants lost to follow up in the Placebo group: 13/40 (33%) vs. treatment group 6/40 (15%). This is addressed under Limitations: "The large difference in dropout rates between the groups may have affected our results as well. Given the small sample size, if the dropout had been comparable between groups, our results might have been different." Dropout rate >20%. |
| Selective reporting (reporting bias) | | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. |

**Turan 2015**

|  |  |  |
| --- | --- | --- |
| **Methods** | Multicenter (8 centres in 4 countries), randomized, double-blind, 2 arm, placebo-controlled trial, follow-up for 6 months. | |
| **Participants** | One thousand and forty-three patients scheduled for cardiopulmonary bypass for cardiac surgery via a median sternotomy | |
| **Interventions** | Methylprednisolone: 500 mg of methylprednisolone divided into two intravenous doses of 250mg each, one during anesthetic induction and the other on cardiopulmonary bypass initiation  Placebo: Placebo solution | |
| **Outcomes** | Primary outcomes were incisional pain assessed at 30 days and 6 months after surgery using an 11-point verbal response scale. | |
| **Notes** | Co-analgesia:  Intraoperative and postoperative clinical care was per institutions’ guidelines and practices, including postoperative analgesic management. | |
| **Source(s) of funding** | Supported by the Canadian Institutes of Health Research, Ottawa, Ontario, Canada. The sponsor was not involved in study design, data analysis, or manuscript preparation. None of the authors has a personal financial interest related to this research. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "By using a computerized randomization phone service or interactive web randomization system, patients were allocated…" |
| Allocation concealment (selection bias) | Low risk | "Based on randomization, the unblinded pharmacist prepared the methylprednisolone or matching placebo and provided the study drug to the blinded surgical staff" |
| Blinding of participants and personnel (performance bias) | Low risk | "All clinicians and investigators were thus fully blinded to allocation." |
| Blinding of outcome assessment (detection bias) | Low risk | "Blinded investigators evaluated patients for persistent surgical pain..." |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20% |
| Selective reporting (reporting bias) | High risk | One or more reported primary outcomes were not pre-specified. According to ClinicalTrials.gov the primary outcome was Mortality at 30 days and Composite (Time Frame: 30 days post-randomization Incidence of the composite outcome of death, myocardial infarction, stroke, renal failure (KDIGO Stage III acute kidney injury, 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines), or respiratory failure within 30 days). Secondary outcomes included MI or Mortality, Mortality at 6 months, Atrial Fibrillation, Transfusion Requirements, Chest Tube Output, ICU and Hospital Length of Stay, Infection, Delirium, Wound Complication, GI Hemorrhage, Insulin Use, Peak Blood Glucose. There is no mention of pain as an outcome. |
| Other bias | Low risk | Unable to find additional potential bias. >50 participants per study arm. |

**Turan 2017**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 3 months | |
| **Participants** | One hundred and fifty patients scheduled for elective cardiac surgery performed via a median sternotomy | |
| **Interventions** | Acetaminophen: Patients were given 4 doses of 1g of IV acetaminophen over 15 minutes every 6hours for 24hours  Placebo: Saline | |
| **Outcomes** | Primary analyses. We assessed the effectiveness of IV acetaminophen (vs placebo) on pain management, measured by cumulative opioid consumption and pain intensity scores within the first 24 hours after surgery (Negmeldeen 2016)  Follow-up study: Study participants were assessed by phone for incisional pain severity 30 and 90 days after surgery | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: Standard anesthesia care included routine American Society of Anesthesiologists recommended monitors, invasive arterial pressure, central venous pressure, transesophageal echocardiography, and bladder temperature monitoring.  Post-op: PCA fentanyl or hydromorphone if allergy to fentanyl. Rescue analgesia included IV fentanyl or hydromorphone boluses or oral oxycodone if inadequately controlled with PCA. IV meperidine was given as needed for shivering. Other analgesics were not permitted, such as topical lidocaine patches and nonsteroidal anti-inflammatory drugs, and neither were drugs containing acetaminophen such as Percocet (acetaminophen and oxycodone) and Vicodin (acetaminophen and hydrocodone) to avoid exceeding the maximum allowable dose of acetaminophen. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Patients were randomized (1:1) without stratification…" "Randomization codes were computer generated using the PLAN procedure in SAS statistical software (SAS Institute, Cary, NC)" |
| Allocation concealment (selection bias) | Low risk | "Allocations were concealed by a password-protected website." "The randomization was accessed shortly before induction of anesthesia to conceal allocation as long as practical." "All the drugs were prepared by pharmacy staff, and investigators blinded to drug allocation performed the evaluations." |
| Blinding of participants and personnel (performance bias) | Low risk | "All the drugs were prepared by pharmacy staff, and investigators blinded to drug allocation performed the evaluations." |
| Blinding of outcome assessment (detection bias) | Low risk | "...investigators blinded to drug allocation performed the evaluations." |
| Incomplete outcome data (attrition bias) | High Risk | Missing data > 20% At 3 months: 25/75 lost to follow-up Acetaminophen arm 20/75 lost to follow-up Placebo arm |
| Selective reporting (reporting bias) | High Risk | One or more reported primary outcomes were not pre-specified. According to ClinicalTrials.gov there is no mention of any outcomes planned for 30 or 90 days after surgery. |
| Other bias | Low risk | Unable to find additional potential bias. >50 participants per study arm. |

**Ucak 2011**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial for one, 3 and 6 months | | |
| **Participants** | 40 patients (34 men and 6 women) who were less than 80 years of age and undergoing elective CABG surgery with cardiopulmonary bypass (CPB) were enrolled. | | |
| **Interventions** | The gabapentin group received orally 1.2 g/d 1 h before and 2 days after surgery, and the placebo group received a placebo capsule instead. | | |
| **Outcomes** | Pain scores, tramadol request, side effects, and pop morbidities | | |
| **Notes** | Co-analgesia:  Pre-op: IM diazepam 45 minutes before surgery.  Intra-op: General anesthesia was induced using midazolam, fentanyl, vecuronium, and propofol. Maintenance was provided with fentanyl, midazolam, sevoflurane, and a 50% mixture of air and oxygen. Additional bolus doses of fentanyl were given PRN.  Post-op: IV tramadol if VAS ≥4 during first 24h. After 24h until POD2, oral tramadol and paracetamol (acetaminophen) for all patients. IV tramadol as rescue analgesia. After the first 72h paracetamol every 8 hours. | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "The patients were assigned randomly into 2 groups (using a computer- generated table)". |
| Allocation concealment (selection bias) | | Unclear risk | Not reported |
| Blinding of participants and personnel (performance bias) | | Low risk | "A single nurse who was blinded to the study protocol prepared the placebo capsules and administered them to the patients. The doctors and nurses in the operating room, intensive care unit, and ward were blinded to the study protocol". |
| Blinding of outcome assessment (detection bias) | | Unclear risk | "All patients completed a 1- and 3-month follow-up. The assessment of postoperative pain at 1 month was performed at the outpatient visits, and at 3 months it was carried out via telephone with a 10 point numeric rating scale". |
| Incomplete outcome data (attrition bias) | | Low risk | No missing outcome data |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | Fewer than 50 patients per arm |

**van Helmond 2016**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 12 months. | |
| **Participants** | One hundred and thirty-eight patients scheduled for lumpectomy, total simple mastectomy or modified radical  mastectomy with or without axillary lymph node dissection | |
| **Interventions** | Parecoxib: 40 mg i.v. 30 minutes before surgery start. This injection was repeated 6 hours later. The postoperative morning, patients started celecoxib 200mg, continued to the morning of day five postoperatively.  Placebo: Placebo injections and tablets according to same regime as study drug | |
| **Outcomes** | Primary study outcomes are change in electric and pressure SOT after surgery vs. baseline values. Secondary outcomes are VAS pain and EORTC symptom, functional and QOL sum scores. | |
| **Notes** | Co-analgesia:  Pre-op: Oral midazolam premedication morning of surgery.  Intra-op: Paravertebral blockade with ropivacaine. Patients received standardized general anaesthesia (propofol, fentanyl, rocuronium, air/oxygen (40%), sevoflurane). Fentanyl supplementation for surgeries >45min.  Post-op: In recovery, piritramide as soon as patients complained of pain. Thereafter, standard postoperative analgesia acetaminophen with on-demand tramadol up to POD5. | |
| **Source(s) of funding** | This study was supported by a grant from Pfizer. They had no role in study design, data  collection and analysis, decision to publish, or preparation of the manuscript. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "eligible patients were randomized in a one-to-one ratio" "A pseudo-random code was computer generated for the randomization blocks that had a size of six. Stratified random sampling ensured equal distribution of axillary lymph node dissections over groups." |
| Allocation concealment (selection bias) | Low risk | "The hospital pharmacy held the randomization scheme for the trial and supplied parecoxib and celecoxib (active treatment) or placebo in blinded packages." |
| Blinding of participants and personnel (performance bias) | Low risk | "Medication was blinded, neither observers nor persons involved in patient management were aware of patient assignment." Double-blind study design |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20% |
| Selective reporting (reporting bias) | High risk | The study report fails to include results for a key outcome that would be expected to have been reported for such a study. According to the Netherlands Trial Register, secondary outcomes were 1. Neuroplasticity at other time points after surgery; 2. Acute and chronic clinical pain measures (pain scores, analgesic consumption, pain questionnaires); 3. Other pain outcome measures (incidence of phantom pain, pain maps, analgesia complications); 4. Surgical outcome measures (complications); 5. Patient satisfaction and well-being (including nausea and vomiting, opioids symptom distress score SDS).  According to the article methods, the secondary outcomes were: "VAS pain and EORTC symptom, functional and QOL sum scores." There is no mention of why the other pre-specified outcomes (e.g. Patient Satisfaction and well-being) were not included in the article. |
| Other bias | High risk | Fewer than 50 participants per study arm. |

**Vig 2019**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single center, randomized, double blind, 2 arm, placebo controlled trial, follow up for 3 months. | |
| **Participants** | Eighty patients with carcinoma breast posted for modified radical mastectomy | |
| **Interventions** | Pregabalin: Pregabalin 75 mg twice a day starting from the morning of surgery and continued for 1 week  Placebo: Placebo capsule (formulation not specified) | |
| **Outcomes** | Primary outcome: to evaluate the effect of perioperative oral pregabalin on the incidence of chronic postmastectomy pain (at 3 months postoperatively).  Secondary outcomes: (1) the assessment of the severity of chronic postmastectomy pain, (2) the evaluation of the effect of perioperative pregabalin on acute postoperative pain and analgesic requirements and; and (3) the assessment of adverse effects such as dizziness, somnolence, nausea, and vomiting due to pregabalin use. | |
| **Notes** | Co-analgesia:  Pre-op: No anxiolytic premedication was used in either group. Premedication with dexamethasone was given to each patient to prevent postoperative nausea and vomiting.  Intra-op: The technique of general anesthesia was standardized in all patients. Anesthesia was induced with fentanyl, propofol, and atracurium. After induction IV paracetamol was given and thereafter repeated every 6 h until the patient was allowed oral intake. Anesthesia was maintained with oxygen, air, and desflurane. Fentanyl was given if heart rate or arterial blood pressure increased by >20% of the baseline values.  Post-op: Paracetamol was the standard analgesic in all cases every 6 h. Rescue analgesia with diclofenac was given if NRS ≥4.  Analgesics were converted to oral doses to be taken for 1 week. | |
| **Source(s) of funding** | No funding. | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "Patients were randomly allocated in one of the two groups using a computer-generated random number table in 1:1 ratio." |
| Allocation concealment (selection bias) | Unclear risk | "The numbers were concealed in an opaque envelope, to be opened after recruitment. " The use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, and sealed. |
| Blinding of participants and personnel (performance bias) | Unclear risk | "Group 2 received placebo capsules at identical time intervals. " "The technique of general anesthesia was standardized in all patients and the anesthesiologist performing the general anesthesia was blinded to the group allocation."  Identical matching of placebo capsules is not explicitly described |
| Blinding of outcome assessment (detection bias) | Low risk | "This parallel group double-blind, randomized pilot trial..." "In the postoperative period pain, assessment and data collection were done by an independent anesthesiologist blinded to group allotment and not involved in the intraoperative management of the patient. " |
| Incomplete outcome data (attrition bias) | Low risk | Missing outcome data balanced across groups. The dropout rate was <20% |
| Selective reporting (reporting bias) | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | Unclear risk | Reasons for lost to follow-up not reported. |

**Weis 2006**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single center, randomized, double-blind, placebo-controlled trial with follow-up to 6 months after surgery | | |
| **Participants** | 36 high-risk patients undergoing cardiac surgery with cardiopulmonary bypass | | |
| **Interventions** | Hydrocortisone: loading dose (IV 100 mg) before induction, followed by infusion of 10 mg/h for 24 hours, which was reduced to 5 mg/h POD 2 and then tapered to 3X20 mg IV on POD 3 and 3  X 10 mg IV on day 4 | | |
| **Outcomes** | Acute period: Inotropic agents use and acute phase reactants. At 6 months the patients were contacted by telephone and received a detailed re-explanation of the purpose of the study. The authors measured SF-36, traumatic memories and chronic stress symptoms. | | |
| **Notes** | Co-analgesia is not stated | | |
| **Source(s) of funding** | Not reported | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | The patients were randomly assigned to one of 2 treatment groups with the use of a computer-generated randomization list |
| Allocation concealment (selection bias) | | Unclear risk | Insufficient information to permit judgment |
| Blinding of participants and personnel (performance bias) | | Low risk | ….received normal saline in identical vials in a double-blind fashion. The vials were prepared by a study nurse who was not involved in the care of patients participating in the trial. |
| Blinding of outcome assessment (detection bias) | | Low risk | Patients returned questionnaires to the authors…. |
| Incomplete outcome data (attrition bias) | | High risk | Missing data > 20% |
| Selective reporting (reporting bias) | | Low risk | Outcomes reported are clinically meaningful and validated |
| Other bias | | High risk | The paper is unclear about the number of patients with any pain at 6 months. Fewer than 50 patients per arm |

**YaDeau 2015**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 4 arm, placebo controlled trial, follow-up for 3 months. | | |
| **Participants** | One hundred and twenty patients scheduled for total knee arthroplasty | | |
| **Interventions** | Pregabalin: Total daily dose of 100mg. Two 50mg capsules were given ∼30 min before transfer to the operating room. Patients received one capsule twice a day until POD14 (total daily dose of 100mg pregabalin) then one capsule at bedtime on POD15 and POD16.  Pregabalin: Total daily dose of 200mg. Two 100mg capsules were given ∼30 min before transfer to the operating room. Patients received one capsule twice a day until POD14 (total daily dose of 200mg pregabalin) then one capsule at bedtime on POD15 and POD16.  Pregabalin: Total daily dose of 300mg. Two 150mg capsules were given ∼30 min before transfer to the operating room. Patients received one capsule twice a day until POD14 (total daily dose of 300mg pregabalin) then one capsule at bedtime on POD15 and POD16.  Placebo: Placebo pill (formulation not specified) | | |
| **Outcomes** | Primary outcome was pain with flexion (POD14). At 3 months after surgery, opioid usage and neuropathic pain were assessed. Neuropathic pain was evaluated as a binary outcome [using a cut-off of 12 on the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)] and by comparison of LANSS scores as a continuum. | | |
| **Notes** | Co-analgesia:  Pre-op: Oral meloxicam and dexamethasone  Intra-op: Ultrasound-guided femoral nerve block (bupivacaine) with adrenaline, followed by a combined spinal and epidural. Sedation consisted of midazolam and propofol.  Post-op: PCEA bupivacaine plus hydromorphone. Meloxicam and oxycodone–paracetamol PRN | | |
| **Source(s) of funding** | Hospital for Special Surgery Anesthesiology Department, New York, NY, USA (Research and Education Fund); the REDCap electronic data capture tools are funded by the CTSC grant  (grant number UL1 TR000457-06) from the National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, USA. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "The computer-generated randomization table was prepared by a research assistant not otherwise involved in the study" |
| Allocation concealment (selection bias) | | Low risk | "The hospital pharmacy prepared indistinguishable capsules." |
| Blinding of participants and personnel (performance bias) | | Low risk | "No other study personnel were aware of group assignment." |
| Blinding of outcome assessment (detection bias) | | Low risk | "No other study personnel were aware of group assignment." According to ClinicalTrials.gov masking was Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |
| Incomplete outcome data (attrition bias) | | Unclear risk | Number lost to follow-up after post-operative day 14 is not reported. It is unclear how many participants in each arm were analyzed at 3 months |
| Selective reporting (reporting bias) | | Low risk | The study protocol is available and all of the study’s pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way |
| Other bias | | High risk | Fewer than 50 participants per arm and chronic pain was not the pre-specified primary outcome. |

**YaDeau 2016**

|  |  |  |  |
| --- | --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up for 3 months | | |
| **Participants** | One hundred and six patients scheduled for total knee arthroplasty | | |
| **Interventions** | Duloxetine: 60mg approximately 30 min. prior to surgery and one capsule per day up until and including POD14  Placebo: Placebo pill (formulation not specified) | | |
| **Outcomes** | The VAS was used to estimate the patients’ degree of pain at 0, 2, 4, 6, 12, and 24 hours, and then at 1, 2, 3, 4, 5, and 6 months after surgery. | | |
| **Notes** | Co-analgesia:  Pre-op: None reported  Intra-op: Patients received a standardized anesthetic and multimodal analgesic protocol. This included a combined spinal epidural anesthetic (bupivacaine spinal); adductor canal block (ultrasound guided in mid-thigh, bupivacaine with dexamethasone); IV sedation with midazolam and propofol; IV dexamethasone; and IV ketorolac.  Post-op: PCEA (bupivacaine/hydromorphone until 5 PM on POD1), meloxicam and oxycodone/acetaminophen. Patients were discharged with meloxicam and oxycodone/acetaminophen.  Patients provided journal to track opioid and study drug intake. | | |
| **Source(s) of funding** | Supported by Hospital for Special Surgery Anesthesiology Department Research and Education Fund, New York, New York. The REDCap electronic data capture tools are funded by the Weill Cornell Clinical and Translational Science Center grant (No. UL1 TR000457-06) from the National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, Maryland. | | |
|  | | | |
| **Risk of Bias table** | | | |
| **Bias** | | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | | Low risk | "a computer-generated randomization table was provided to the hospital pharmacy. "… "Patients were randomized (1:1)" |
| Allocation concealment (selection bias) | | Low risk | "...randomization table was provided to the hospital pharmacy." "The hospital pharmacy prepared indistinguishable capsules containing either duloxetine or placebo, which were used for the study." |
| Blinding of participants and personnel (performance bias) | | Low risk | "Group assignment was concealed from the patients, the treating physicians, and the statistician." Triple-blind study design |
| Blinding of outcome assessment (detection bias) | | Unclear risk | Not reported. |
| Incomplete outcome data (attrition bias) | | Unclear risk | Number lost to follow-up after post-operative day 14 is not reported. According to data received from the authors, numbers analyzed at 3 months was 47/53 and 49/53 |
| Selective reporting (reporting bias) | | High risk | One or more reported secondary outcomes were not pre-specified. According to ClinicalTrials.gov follow-up was for 6-weeks. Numeric Rating Scale (NRS) Pain Scores at Rest, during Ambulation and while Bending Knee [ Time Frame: Preoperative, postoperative day (POD) 1, POD 3, POD 14, POD 18-20, 6 weeks after surgery ] There is no mention of a 3 month follow-up. |
| Other bias | | Unclear risk | According to the methods the following were collected at 3 months, yet there is very little reported for these outcomes: Pain at rest, pain with knee flexion, opioid consumption, pain severity at other time points (NRS) and the PainOUT Questionnaire, side effects. Delayed (3-month) outcomes included analgesic use, PainOUT (including pain severity), and incidence of manipulations. >50 participants per study arm. |

**Yazdani 2016**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 2 arm, placebo controlled trial, follow-up 6 months. | |
| **Participants** | Sixty patients undergoing open reduction and internal fixation (ORIF) of a recent mandibular unilateral body fracture | |
| **Interventions** | Amantadine: 100mg capsule 1 hour before surgery  Placebo: Placebo pill (lactose) | |
| **Outcomes** | The VAS was used to estimate the patients’ degree of pain at 0, 2, 4, 6, 12, and 24 hours, and then at 1, 2, 3, 4, 5, and 6 months after surgery. | |
| **Notes** | Co-analgesia:  Pre-op: None reported.  Intra-op: All patients were given general anesthesia. The same general anesthetic technique was used for all patients (fentanyl, midazolam, propofol and cisatracurium besylate. All  patients were intubated, and propofol was used for the maintenance of anesthesia.  Post-op: Analgesic drugs PRN. All patients received a bolus dose of morphine sulfate through a PCA pump. If necessary, pain management at 1, 2, 3, 4, 5, and 6 months after surgery was achieved with ibuprofen 400mg. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "We used simple randomization to allocate subjects to each group due to homogenous disease severity. Randomization based on a single sequence of random assignments was performed using computer- generated random numbers." |
| Allocation concealment (selection bias) | Unclear risk | "To avoid bias, subject allocation was concealed to the two groups." |
| Blinding of participants and personnel (performance bias) | Low risk | "The study was double-blinded, so that all patients and personnel involved in patient care, data collection, scoring, and entry were unaware of the group to which each patient had been assigned." Double-blind study design |
| Blinding of outcome assessment (detection bias) | Low risk | "The study was double-blinded, so that all patients and personnel involved in patient care, data collection, scoring, and entry were unaware of the group to which each patient had been assigned." |
| Incomplete outcome data (attrition bias) | Unclear risk | Numbers lost to follow up or analyzed at each follow-up timepoint is not reported. |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | High risk | Fewer than 50 participants per study arm. No study protocol, so no way to verify if chronic pain was a pre-specified primary outcome. Number screened not reported, 60 enrolled, number analyzed at each follow-up time-point not reported. |

**Zarei 2016**

|  |  |  |
| --- | --- | --- |
| **Methods** | Single centre, randomized, double blind, 3 arm, placebo controlled trial, follow-up for 12 months | |
| **Participants** | One hundred and five patients scheduled for lumbar surgery (bilateral foramenotomy and interlaminar discectomy) | |
| **Interventions** | Pregabalin 1: 300 mg 8 h preoperatively and 150 mg 12 and 24 h postoperatively and for the rest of the 13 days received placebo.  Pregabalin 14: 300 mg eight hours preoperatively and 150 mg every 12 h postoperatively for 14 days  Placebo: Placebo pill (formulation not specified) | |
| **Outcomes** | At two weeks postoperatively (first visit after surgery) the three main outcome measurements were pain scores, radiculopathy and treatment side effects. At 3 months and 12 months postoperatively all the patients were asked to complete Oswestry low back pain disability questionnaire and Euro-QOL form. | |
| **Notes** | Co-analgesia:  Pre-op: Dexamethasone and ranitidine IV.  Intra-op: Anesthesia was induced with phentanyl and propofol followed by Atracurium to facilitate tracheal intubation and ventilation. Anesthesia was maintained using N2O/O2 and isoflurane. The subcutaneous tissue was infiltrated with bupivacaine and epinephrine just before skin incision.  Post-op: PCA morphine, IV morphine as needed. | |
| **Source(s) of funding** | Not reported | |
|  | | |
| **Risk of Bias table** | | |
| **Bias** | **Authors' judgement** | **Support for judgement** |
| Random sequence generation (selection bias) | Low risk | "patients were randomized to 1 of 3 groups using computer-generated random number table" |
| Allocation concealment (selection bias) | Unclear risk | "Medication was prepared and available in 3 same boxes, but the contents were different."… "All the pills were labeled as D1 to D30 to prevent making mistake especially in that 1 day Pregabalin group." Insufficient information to permit judgement. |
| Blinding of participants and personnel (performance bias) | Low risk | "In this study none of the patients, investigators, surgeons and health care providers were informed about randomization during the study." Triple-blind study design |
| Blinding of outcome assessment (detection bias) | Low risk | "Oswestry low back pain disability index (ODI) questionnaire is completed by an investigator who had not been informed about randomization." |
| Incomplete outcome data (attrition bias) | Unclear risk | Numbers analyzed and lost to follow-up not reported. |
| Selective reporting (reporting bias) | Unclear risk | Unable to assess. There is no mention of a Registered Clinical Trial number or published protocol. |
| Other bias | High risk | Fewer than 50 participants per study arm and chronic pain was not specified as the primary outcome. Side effects were described as one of the 3 main outcome measures at 2 weeks post-surgery yet there is no mention of side-effects in the results or discussion. The Euro-Qol was collected but there is no mention of this data in the results. |