Supplemental Table 1. Characteristics of included studies

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Source | ASA-PS | Age (protocol) | Surgery | Type of anesthesia | Anesthesia agent used | Route of study drug | Bolus dose of study drug | Continuous dose of study drug | Timing of study drug (bolus) | Timing of observation |
| Ulusoy 1995 | 1 - 2 | 30-51 | non-cardiac surgery | General | halothane, N2O | IV | 60 mg · kg-1 |  | Three min before intubation | not clear |
| Tramèr 1996 | 1 - 2 | not defined | abdominal hysterectomy | General | thiopental, fentanyl, vecuronium, N2O, isoflurane, | IV | 3000 mg | 500 mg · h-1 | after induction | postop |
| Kara 2002 | 1 - 2 | 26-65 | abdominal hysterectomy | General | thiopental, fentanyl, vecuronium, N2O, Isoflurane | IV | 30 mg · kg-1 | 500 mg · h-1 | after induction of anesthesia | postop |
| Levaux 2003 | 1 - 2 | adult | lumber arthrodesis | General | propofol, remifentanil, rocuronium, sevoflurane, N2O | IV | 50 mg · kg-1 |  | immediately before induction of anesthesia | at emergence and thereafter |
| Bhatia 2004 | 1 - 2 | not defined | open cholecystectomy | General | thiopental, vecuronium, N2O, halothane | IV | 50 mg · kg-1 | 15 mg · kg-1 · h-1 | 15 min before general anesthesia | postop |
| Tramèr 2007 | not defined | adults | ilioinguinal hernia repair, or varicose vein operation | General | fentanyl, propofol, N2O, isoflurane, 0.5% bupivacaine 20 ml | IV | 4000 mg |  | after anesthetic induction | postop |
| Usmani 2007 | 1 - 2 | 18-50 | surgical procedure of upper abdomen | General | fentanyl, propofol, vecuronium, N2O, | IV | 50 mg · kg-1 | 15 mg · kg-1 · h-1 | 15 min before anesthesia induction | postop |
| Ryu 2008 | 1 - 2 | 30-65 | Total abdominal hysterectomy | General | propofol, remifentanil, rocuronium | IV | 50 mg · kg-1 | 15 mg · kg-1 · h-1 | Immediately before anesthesia induction | postop |
| Lee 2008 | 1 - 2 | not defined | major abdominal surgery | General | propofol, remifentanil, rocuronium, sevoflurane | IV | 50 mg · kg-1 | 10 mg · kg-1 · h-1 | before induction of anesthesia | postop |
| Jang 2009 | 1 - 2 | not defined | major abdominal surgery | General | remifentanil, propofol, rocuronium, sevoflurane | IV | 50 mg · kg-1 | 10 mg · kg-1 · h-1 | intraoperative | postop |
| Abd Elmawgoud 2009 | 1 - 2 | 40-60 | Radical mastectomy | General | Remifentanil, propofol, rocuronium, sevoflurane, | IV | A. 50 mg · kg-1  B. 30 mg · kg-1 | A. 0  B. 10mg · kg-1 · h-1 | Intraoperative | postop |
| Hwang 2010 | 1 - 2 | not defined | hip arthroplasty | Spinal | hyperbaric bupivacaine 0.5%, fentanyl 20μg | IV | 50 mg · kg-1 | 15 mg · kg-1 · h-1 | after spinal anesthesia | postop 30min, 4, 24, 48 h |
| Gozdemir 2010 | 1 - 2 | 40-70 | transurethral resection of prostate | Spinal | 0.5% hyperbaric bupivacaine 3 ml | IV | 80 mg · kg-1 | 2 g · h-1 | just after intrathecal injection | intraop |
| Na 2010 | not reported | 5 - 15 | orthopedic osteotomy (lower extremities) | General | thiopental, rocuronium, sevoflurane, N2O | IV | 50 mg · kg-1 | 15 mg · kg-1 · h-1 | during surgery | postop |
| Song 2011 | 1 - 2 | 20-65 | thyroidectomy | General | thiopental, remifentanil, rocuronium, sevoflurane | IV | 30 mg · kg-1 | 10 mg · kg-1 · h-1 | after induction | postop |
| Singh 2011 | 1 - 2 | 21-50 | elective surgery under general anesthesia | General | propofol, vecuronium, isoflurane, N2O | IV | 2.48mmol |  | before propofol injection | postop |
| Kim 2012 | 1 - 2 | 18-65 | craniotomy for aneurysm clipping  or superficial temporal artery-middle cerebral artery anastomosis | General | valproic acid, rocuronium, propofol | IV | 50 mg · kg-1 | 15 mg · kg-1 · h-1 | after tracheal intubation | postop |
| López 2013 | 1 - 2 | 18-65 | surgery with estimated duration of 60 to 180 min | General | propofol, fentanyl, rocuronium, sevoflurane | IV | 50 mg · kg-1 |  | 10 min prior to ending of surgery | 20 min after study drug |
| Alipour 2013 | 1 | not defined | cesarean section | Spinal | 0.5% hyperbaric bupivacaine 3ml | IV | 30 mg · kg-1 |  | 30 min before spinal anesthesia | intraop (for 90 min after spinal) |
| Piplai 2013 | 1 - 2 | 18-40 | lumbar spinal fixation surgery | General | fentanyl, propofol, N2O | IV | 30 mg · kg-1 | 10 mg · kg-1 · h-1 | immediately before induction of anesthesia | postop |
| Modir 2013 | 1 - 2 | 20-45 | laparotomy | General | propofol, isoflurane, N2O | IV | 80 mg · kg-1 |  | before surgery | postop 0, 10, 20 min |
| Davoudi 2013 | 1 - 2 | not defined | cesarean section | Spinal | 0.5% bupivacaine 3 ml, fentanyl 25 μg | IV | 50 mg · kg-1 | 10 mg · kg-1 · h-1 | 15 min before spinal anesthesia | postop |
| Ibrahim 2014 | 1 - 2 | 18-60 | lower extraperitoneal abdominal or lower limb surgery | Spinal | hyperbaric bupivacaine 20 mg | IV | 50 mg · kg-1 | 2 mg · kg-1 · h-1 | immediately after spinal injection | until after 2 segment regression |
| Bae 2015 | 1 - 2 | 20-70 | laparoscopic gastrectomy | General | propofol, remifentanil, vecuronium | IV | 50 mg · kg-1 | 20 mg · kg-1 · h-1 | before induction of anesthesia | postop |
| Maulik 2015 | 1 - 2 | not defined | cesarean section | Spinal | heavy 0.5% bupivacaine | IV | 40 mg · kg-1 | 10 mg · kg-1 · h-1 | prior to surgery | postop |
| Abdulatif 2015 | 1 - 2 | 18-60 | arthroscopic anterior cruciate ligament reconstruction | General  +regional | 0.25% bupivacaine 20 ml for fem nerve block, propofol, fentanyl, isoflurane | IV IA | 1000 mg |  | at the conclusion of the surgery | postop |
| Argawal 2015 | 1 - 2 | 20-40 | cesarean section | Spinal | 5% hyperbaric lignocaine 1.4 ml | IV | 50 mg · kg-1 |  | 60 min after spinal anesthesia | Intra and postop |
| Elsharnouby 2015 | 1 - 2 | 3-10 | adenotonsillectomy | General | sevoflurane, fentanyl, atracurium | IV | 40 mg · kg-1 | 15 mg · kg-1 · h-1 | after induction of general anesthesia | postop |
| Gomathi 2016 | 1 - 2 | 18-65 | lower abdominal or lower limb surgery | Spinal | hyperbaric bupivacaine 12.5 mg | IV | 2000 mg |  | before spinal anesthesia | intraop |
| Hashemi 2016 | not reported | not defined | abdominal surgery | General |  | IV | 30mg · kg-1 40mg · kg-1 50 mg · kg-1 |  | Before the reverse of anesthesia | At admission to recovery room |
| Modanlou Jubari 2016 | not reported | 15-36 | orthognathic surgery | General | propofol, remifentanil, N2O | IV | 30 mg · kg-1 | 10 mg · kg-1 · h-1 | unclear | postop |
| El Shal 2017 | 1 - 2 | 20-60 | arthroscopic knee surgery requiring thigh tourniquet | Epidural | 0.5% bupivacaine | IV | 30 mg · kg-1 | 10 mg · kg-1 · h-1 | before insertion of epidural catheter | postop |
| Goyal 2017 | 1 - 2 | 18-50 | craniotomy for nonvascular ICSOL | General | N2O, isoflurane | IV | 30 mg · kg-1 |  | after skin closure | postop |
| El Sayed 2017 | 1 - 2 | 18- | diagnostic or therapeutic knee arthroscopy | Spinal | 0.5% bupivacaine 15 mg | IV IT IA | A. 30 +10 mg · kg-1 B. 50 mg C. 800 mg |  | A. 10 min after intrathecal injection B. with spinal injection C. 10 min before the end of surgery | postop |
| Hirmanpour 2017 | 1 - 2 | not defined | cesarean section | Spinal | 0.5 ml Sufentanil, 0.2 ml of 0.5% hyper-thin Marcaine | IV | 40 mg · kg-1 | 15 mg · kg-1 · h-1 | before spinal anesthesia | not defined |
| Ghatak 2010 | 1 - 2 | 18-60 | lower abdominal or lower limb surgery | Epidural | 0.5% bupivacaine 19 ml | ED | 50mg |  | with initial epidural injection | intra and postop |
| Yousef 2010 | 1 - 2 | 18-40 | cesarean section | spinal +epidural | 0.5% hyperbaric bupivacaine 2 ml, bupivacaine, fentanyl | ED | 500 mg |  | after spinal injection | intra and postop |
| Sun 2012 | 1 - 2 | -35 | cesarean section | spinal +epidural | 0.5% isobaric bupivacaine, 0.1% bupivacaine10 ml, (morphine 1.5mg) | ED | 500 mg |  | after delivery of fetus | postop |
| Shahi 2014 | 1 - 2 | not defined | lower limb surgery | Epidural | 0.5% bupivacaine 14ml | ED | 50 mg |  | with epidural anesthesia | For 1-2 h of drug administration |
| Yousef 2014 | 1 - 2 | 1-6 | inguinal hernia repair | General  +epidural | ropivacaine 0.15%  1.5　ml · kg-1, N2O  sevoflurane, | ED | 50 mg |  | with caudal block | postop |
| Roy 2015 | 1 - 2 | 18-60 | subumbilical surgery | Epidural | 0.5% bupivacaine 19ml | ED | 50 mg |  | at the same time of epidural injection | Not defined |
| Lakra 2015 | 1 - 2 | 18-60 | lower limb surgery | Epidural | 0.5% bupivacaine 19ml | ED | 50 mg |  | with epidural anesthesia | postop |
| Mohammad 2015 | 1 - 3 | 20-60 | unilateral thoracic surgery | General  +epidural | propofol, fentanyl, rocuronium, isoflurane, bupivacaine | ED | 50 mg |  | approximately 20 min prior to anticipated extubation | PACU to postop 24h |
| Shruthi 2016 | 1 - 2 | 18-50 | elective infraumbilical surgery (orthopedic, gynecologic) | Epidural | 0.5% bupivacaine 15 ml | ED | 50 mg |  | with epidural injection | postop |
| Kogler 2016 | 1 - 3 | not defined | thoracic surgery | General  +epidural | 0.5% levobupivacaine, sufentanil, midazolam, rocuronium, propofol | ED | 50 mg | 10mg · h-1 during surgery  postop 1mg · h-1 | 15 min before general anesthesia induction | postop (48 h) |
| Rashmi 2016 | 1 - 2 | 35-45 | lower limb orthopedic surgery | Spinal | hyperbaric bupivacaine 0.5% 2.5 ml,  fentanyl 50 μg | ED | 50mg |  | after regression of sensory block to L1 | postop |
| Nagre 2017 | 3 | 40-65 | femoral popliteal bypass | Epidural | 0.25% bupivacaine 10 ml, fentanyl 50 μg, | ED | 100 mg |  | With inititial epidural bolus | postop |
| Özalevli 2005 | 1 - 2 | not defined | lower extremity surgery | Spinal | 0.5% bupivacaine 10 mg, fentanyl 25 μg | IT | 50mg |  | immediately following intrathecal injection | postop |
| Said-Ahmed, 2008 | 1 - 2 | adult | repair of femur fracture | Spinal | 0.75% ropivacaine 2ml, sufentanil 5μg | IT | 50 mg |  | with spinal anesthesia | not clear |
| El Samahy 2008 | 1 - 2 | not defined | transurethral prostatectomy | Spinal | 0.5% bupivacaine 2 ml, fentanyl 25μg | IT | 50mg |  | immediately before intrathecal injection | Throughout periop period |
| Unlugenc 2009 | 1 - 2 | not defined | cesarean section | spinal +epidural | 0.5% isobaric bupivacaine 2 ml | IT | 50mg |  | immediately after intrathecal bupivacaine | intra and postop |
| Okojie 2012 | 1 - 2 | not defined | transurethral resection of prostate | Spinal | 0.5% hyperbaric bupivacaine 3ml | IT | 100mg |  | with spinal anesthesia | intraop |
| Nath 2012 | 1 - 2 | 18-60 | total abdominal hysterectomy | Spinal | 0.5% hyperbaric bupivacaine 2.5ml, fentanyl 25μg | IT | 100mg |  | with spinal anesthesia | postop |
| Ahmed Sayed 2012 | 1 - 2 | 18-50 | cesarean section | Spinal | 0.5% hyperbaric bupivacaine 2ml, fentanyl 25μg | IT | 50mg 100mg |  | with spinal anesthesia | intraop and postop (24 h) |
| Jabalameli 2012 | 1 - 2 | 18-45 | cesarean section | Spinal | 0.5% hyperbaric bupivacaine 2.5 ml | IT | A 50 mg B 75 mg C 100 mg |  | with spinal anesthesia | postop |
| Jaiswal 2013 | 1 - 2 | 20-60 | lower limb orthopedic surgery | Spinal | 0.5% hyperbaric bupivacaine 2.5ml | IT | A 50mg  B 100mg |  | with spinal anesthesia | postop |
| Faiz 2013 | 1 - 2 | 18-37 | cesarean section | Spinal | 0.5% bupivacaine 2ml | IT | 25 mg |  | with spinal anesthesia | 90 min after spinal anesthesia. |
| Joshi-Khadke 2015 | 1 - 2 | 20-60 | gynecological surgery | Spinal | hyperbaric bupivacaine 17.5mg | IT | 50 mg |  | with spinal anesthesia | postop |
| Xiao 2016 | not reported | not defined | cesarean section | Spinal | 0.5% bupivacaine 1.2 ml, sufentanil 2.5μg | IT | 50 mg |  | with spinal anesthesia | intraop and postop (24 h) |
| Vasure 2016 | 1 - 2 | 20-50 | Lower limb orthopedic surgery | Spinal | 0.5% bupivacaine 2.5 ml, fentanyl 25 μg | IT | 50 mg |  | with spinal anesthesia | postop |
| Xiao 2017 | 1 - 2 | not defined | cesarean section | spinal +epidural | 0.5% bupivacaine, sufentanil 5 μg | IT | 50 mg |  | with spinal anesthesia | intraop and postop (24 h) |
| Khandelwal 2017 | 1 - 2 | 20-60 | lower abdominal surgery | Spinal | 0.5% hyperbaric bupivacaine 3 ml | IT | 50 mg |  | with spinal anesthesia | postop (24 h) |
| Lee 2011 | 1 - 2 | not defined | robot-assisted laparoscopic prostatectomy | General | desflurane, remifentanil, rocuronium, | infiltration | 80 mg · kg-1 |  | after pneumoperitoneum | postop |
| Sun 2017 | not reported | 50-70 | toe amputation | regional | 0.25% ropivacaine 15ml | perineural | 200 mg |  | popliteal sciatic nerve block | intraop and postop (48h) |

IV, intravenous; IA, intra-articular; ED, epidural; IT, intrathecal.