**Table S1.** Summary of key results from studies evaluating systemic analgesics, systemic analgesic adjuncts and regional analgesia used to support the recommended intervention in patients after TKA.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Interventions** | **Pain scores** | **Cumulative opioid dose** | **Analgesic technique** | **Comments** |
| **Acetaminophen Vs placebo** | | | | | |
| O’Neal et al, 201725 | Acetaminophen 1g IV preop (n=57)  Acetaminophen 1g PO preop (n=58)  Placebo preop (n=59) | No difference | No difference | Celecoxib, controlled-release oxycodone, dexamethasone, LIA | Observation until PACU discharge only |
| Murata-Ooiwa et al, 201726 | Acetaminophen 1g IV preop and postop q6h (n=32)  Placebo (n=34) | Reduction at rest and movement at day1 | NA | NSAID IV and PO, LIA | No effect on early rehabilitation (until day 7) |
| **Non-steroidal Anti-inflammatory Drugs (NSAIDs) / Cyclooxygenase-2 Specific Inhibitors Vs placebo** | | | | | |
| Zhu et al, 201429 | Parecoxib 40 mg postop q12h for 3 days (n=50)  Placebo saline (n=50) | Reduction | Reduction | NA | Follow up at 3weeks:no benefit |
| Essex et al, 201830 | Parecoxib 40 mg 1 dose at day1 postop (n=58)  Placebo saline (n=58) | Reduction | Reduction number rescue doses | PCA morphine, IV meperidine | No difference in PONV |
| Gong et al, 201331 | Celecoxib and muscle relaxant for 14 days (n=50)  Placebo and muscle relaxant (n=50) | Reduction at rest and at movement (muscle relaxant) | Reduction (198 mg vs 255 mg) | PCA morphine | No difference in PONV; no difference in blood losses |
| Munteanu et al, 201632 | Etoricoxib 120 mg 1 dose preop (n=55)  Etoricoxib 120 mg 1 dose postop (n=55)  Placebo (n=55) | Increased duration spinal anaesthesia | Reduction 30% for etoricoxib preop and postop | Paracetamol, IV and PO morphine | Follow up limited to 24h  No difference in opioids side effects |
| Reynolds et al, 200333 | Valdecoxib 20 mg/12h for 2 days (n=70)  Valdecoxib 40 mg/12h for 2 days (n=70)  Placebo (n=69) | Reduction maximal pain at day2 | Reduction | PCA morphine | Better effect with 40 mg/12h (for opioid sparing and less fever postop) |
| Meunier et al, 200734 | Celecoxib 200 mg q12h for 3 weeks (n=50)  Placebo (n=50) | Reduction pain scores during 2 weeks | Reduction analgesics use during 3 weeks | Paracetamol, ketobemidone, tramadol for 3 weeks | Follow up 52 weeks  No benefit after 1 month; no difference in blood losses |
| **Glucocorticoids Systemic Vs placebo** | | | | | |
| Lunn et al, 201138 | Methylprednisolone 125mg preop (n=24)  Placebo (n=24) | Reduction at rest and movement | Reduction 50% at 48h | Acetaminophen, celecoxib, gabapentin, LIA, PCA IV morphine | Less PONV, fatigue, CRP up to 48h |
| Koh et al, 201336 | Dexamethasone 10 mg preop (n=134)  Placebo (n=135) | Reduction | Reduction 40% at 24h | Oxycodone, celecoxib, pregabalin, PCA IV fentanyl | Less PONV at 6h |
| Xu B et al, 201839 | Dexamethasone 20 mg preop (n=61)  Dexamethasone 20 mg preop + 10 mg 24h + 10 mg 48h postop (n=60)  Placebo (n=60) | Reduction at movement (repeated doses better effect) | Reduction 70% (repeated doses) | Diclofenac, oxycodone, morphine, LIA | Less PONV, CRP and IL-6 (only versus placebo) |
| Xu H et al, 201837 | Dexamethasone 10 mg preop and postop at 6h (n=54)  Placebo (n=54) | Reduction (minimal effect on movement up to 24h) | Reduction 60% | Diclofenac, oxycodone, pregabalin, LIA | Less PONV, fatigue, CRP and IL-6 |
| Dissanayake et al, 201841 | Dexamethasone 8mg preop and postop at 24h (n=40)  Placebo (n=41) | No difference | Reduction 30% at 24h | Paracetamol, NSAID/coxib, gabapentin oxycodone, LIA | No effect on PONV |
| Li et al, 201940 | Hydrocortisone 100mg preop and postop 8h (n=32)  Hydrocortisone 100mg preop and postop 8h, 16h and 24h (n=36)  Placebo (n=32) | Reduction at movement (better repeated doses) | No difference (even with repeated doses) | Pethidine, celecoxib, LIA | Less PONV, CRP, IL-6  Better sleep quality  Reduced LOS (with 2 and 4 doses) |
| **Intrathecal (IT) Morphine vs IT saline** | | | | | |
| Cole et al, 200073 | IT bupi with morphine 300µg (n=19)  IT bupi (n=19) | Reduction from 4h to 24h during movement | Reduction (20 vs 38 mg) | PCA morphine, diclofenac IM | PONV (60% vs 38%), pruritus (27% vs 14%), no difference hypoxemia |
| Tan et al, 200174 | IT bupi with morphine 300µg (n=20)  IT bupi with neostigmine 50µg (n=20)  IT bupi (n=20) | Reduction up to 24h | NA | Diclofenac IM | PONV (no difference), pruritus (70% vs 0%) |
| Park et al, 200975 | IT bupi with morphine 0 – 50 - 100- 150 or 200 µg (n=20 per group of treatment) | Reduction until day 1 morning | NA | CFNB, diclofenac, butorphanol | PONV (45% vs 10%); pruritus (65-80% vs 0%) Ideal dose: 50 µg IT morphine |
| Lauretti et al, 201376 | IT bupi with morphine 200µg (n=19)  IT bupi (n=19)  IT bupi with ketorolac 2mg (n=19)  IT bupi/morphine 200µg/ketorolac 2mg (n=19) | No difference | Reduction tramadol use | Ketoprofen, tramadol |  |
| Kunopart et al, 201477 | IT bupi with morphine 0 – 100 – 200 or 300 µg (n=15 per group of treatment) | Reduction at day 0 in all morphine groups | Reduction in all morphine groups (8+6 vs 23+11 mg) | SSFNB, PCA morphine | PONV (30% vs 7%),  Pruritus (20% vs 0%) |
| Olive et al, 201578 | IT bupi with morphine 175µg (n=27)  IT bupi and CFNB (n=28)  IT bupi with morphine 175µg and CFNB (n=27) | No difference | Increase use (from 18h to 24h) in IT bupi/morphine groups | Paracetamol, celecoxib, PCA IV morphine | Increased pruritus, no difference PONV |
| Sundarathiti et al, 201679 | IT bupi with morphine 350µg (n=33)  IT bupi (n=35) | Reduction 12 to 24h  Reduction severe pain at 12h (43% vs 70%) | Reduction tramadol use (125 vs 200mg) | CFNB, acetaminophen, tramadol | PONV (40% vs 15%), no difference in pruritus or hypotension |
| Barrington et al, 201780 | IT bupi with morphine 200-250µg (n=40)  IT bupi (n=40) | Reduction 12 to 18h | No difference | LIA (bupi or LipoBupi, epin, ketorolac), Tylenol, oxycontin | Pruritus (38% vs 5%) |
| Biswas et al, 201881 | IT bupi with morphine 100µg (n=64)  IT bupi (n=68) | Reduction at rest and movement at 12h | No difference at 24h (34 vs 45 mg) | SSACB, LIA (ropi, epin, ketorolac), acetaminophen, celecoxib, IV morphine | No difference PONV or pruritus; no functional difference at day2 and 3 months |
| Kaczocha et al, 201882 | IT bupi with morphine 200µg (n=25)  IT bupi (n=17) | Reduction pain at rest at 4h | Reduction at 12h | SSFNB, celecoxib, oxycontin | Reduction endocannabinoids and cortisol levels |
| Miyamoto et al, 201883 | IT bupi with morphine 100µg (n=31)  IT bupi and LIA (n=32)  IT bupi and LIA with morphine 10 mg (n=34) | Reduction pain at rest for 6-12h (max 20h), no difference pain at movement | Reduction until 24h | Pentazocine, diclofenac, flurbiprofen | No difference in side effects; no function difference at 2 weeks |
| Schumer et al, 201984 | IT bupi with morphine 100µg (n=65)  IT bupi and LIA bupi (n=64)  IT bupi and LIA lipobupi (n=67) | No difference | Reduction | IV morphine, ketorolac, COX2 inhibitor | PONV (42% vs 22-28%), pruritus (38% vs 11-14%) |
| **Intrathecal (IT) morphine Vs Femoral nerve block (FNB)** | | | | | |
| Tarkkila et al, 199890 | IT bupi with morphine 300µg and CFNB saline (n=18)  IT bupi and CFNB bupi for 24h (n=20) | Reduction until 12h postop in IT morphine group | No difference | Oxycodone iM | IT morphine and CFNB insufficient for pain control |
| Sites et al, 200488 | IT bupi with morphine 250µg and SSFNB saline (n=20)  IT bupi and SSFNB bupi (n=20) | No difference for pain at rest or movement | No difference | Ketorolac, PCA IV morphine | Less side effects with SSFNB bupi |
| Frassanito et al, 201089 | IT bupi with morphine 100µg and SSFNB saline (n=26)  IT bupi and SSFNB ropi 0.75% (n=26) | Reduction in IT morphine group | No difference | PCA IV morphine | Equivalence of treatment |
| Olive et al, 201578 | IT bupi with morphine 175µg (n=27)  IT bupi and CFNB (n=28)  IT bupi with morphine 175µg and CFNB (n=27) | No difference at rest and movement | Increase use (from 18h to 24h) in IT morphine groups | Paracetamol, celecoxib, PCA IV morphine | Increased pruritus, no difference PONV and rehabilitation |
| **Intrathecal (IT) Morphine vs Local Infiltration Analgesia (LIA)** | | | | | |
| Essving et al, 201191 | IT bupi with morphine 100µg and LIA saline (n=25)  IT bupi and LIA (ropi/keto/epin) then 2x intraarticular injection postoperative (n=25) | Increased pain in IT morphine group | Increased opioid use in IT morphine group | PCA IV morphine |  |
| Tammachote et al, 201392 | IT bupi with morphine 200µg and LIA saline (n=28)  IT bupi and LIA (bupi/epin/morphine 5mg) (n=29) | No difference | NA | PCA IV ketorolac |  |
| Zhang et al, 201893 | IT bupi with morphine 100µg and LIA saline (n=50)  IT bupi and LIA (ropi/epin) (n=50) | NA | NA | PCA IV morphine |  |
| McCarthy et al, 201994 | IT bupi with morphine 300µg and LIA saline (n=22)  IT bupi and LIA (levobupi/epin) then 1x intraarticular injection postop (n=21) | Increased pain in IT morphine group | No difference | Paracetamol, diclofenac, PCA IV morphine |  |
| **Adductor Canal Block (ACB) Vs saline ACB Block** | | | | | |
| Jenstrup et al, 2012153 | ACB (ropivacaine 0.75%) repeated bolus (n=34)  ACB (saline) (n=37) | Reduction pain at movement (knee flexion) | Reduction (40+21 vs 56+26 mg) | Acetaminophen, ibuprofen, PCA IV morphine | No difference in PONV, faster mobilisation |
| Jaeger et al, 2012154 | ACB (ropivacaine 0.75%) postop (n=21)  ACB (saline) (n=20) only postop | Reduction pain at knee flexion (for 6h) | No difference | Paracetamol, ibuprofen, PCA IV morphine | ACB used in case of severe postop pain |
| Grevstad et al, 2014155 | ACB (ropivacaine 0.75%) bolus at day2 postop (n=25)  ACB (saline) (n=25) | Reduction of pain at rest and movement (flexion) | NA | Paracetamol, ibuprofen, gabapentin, PCA IV morphine | Severe pain at day2 postop; only 25% response to ACB |
| Hanson et al, 2014156 | ContACB (ropi 0.2%) (n=36)  ContACB (saline) (n=40) | Reduction pain at movement | Reduction | SSFNB, NSAID, acetaminophen, PCA IV hydromorphone, LIA | Increased mobility |
| Zhang et al, 2014157 | ACB (ropivacaine 0.5%) (n=30)  ACB (saline) (n=30) | Reduction pain at movement | No difference | NA |  |
| **Single-Shot Adductor Canal Block (SSACB) Vs Single Shot Femoral Nerve Block (SSFNB)** | | | | | |
| Kim et al, 2014158 | SSACB (ropi 0.5% 15ml) (n=46)  SSFNB (ropi 0.5% 30ml) (n=47) | No difference | No difference | Meloxicam, oxycodone |  |
| Grevstad et al, 2015159 | SSACB (ropi 0.2% 30ml) (n=25) only postop  SSFNB (ropi 0.2% 30ml) (n=25) | No difference | NA | Acetaminophen, celecoxib, gabapentin, morphine, LIA | Postoperative use  Better function with ACB |
| Memtsoudis et al, 2015160 | Bilateral TKA: one side SSACB (bupi 0.25% 15ml) (n=30), other side SSFNB (bupi 0.25% 30ml) (n=29) | ACB less efficient at 24h postop | NA | PCEA, acetaminophen, IV hydromorphone |  |
| Macrinici et al, 2017161 | SSACB (bupi 0.5% 20 ml) (n=46)  SSFNB (bupi 0.5% 20ml) (n=47) | No difference | No difference | Acetaminophen, NSAID, gabapentin, IV morphine, intraarticular infiltration | Better function and ambulation (6-24h) |
| **Single-Shot Adductor Canal Block (SSACB) versus Continuous ACB (CACB)** | | | | | |
| Shah et al, 2015162 | CACB (ropi 0.75% 20ml every 4h) (n=46)  SSACB (ropi 0.75% 30ml) (n=39) | No difference | NA | NA except intraarticular triamcinolone | No effect on LOS |
| Turner et al, 2018163 | CACB (bupi 0.25% 20ml then bupi 0.125% 8ml/h) (n=30)  SSACB (bupi 0.25% with clonidine, dexamethasone, buprenorphine 20ml) (n=30) | No difference | No difference | Acetaminophen, NSAID | Duration effect SSACB mixture = 36h |
| Lee et al, 2018164 | CACB (ropi 0.5% 20m than ropi 0.2% 5ml/h) (n=57)  SSACB (ropi 0.5% 20ml) (n=60) | No difference | No difference | Acetaminophen, ketorolac, morphine IV, LIA | Similar quality of recovery at 48h |
| Elkassabany et al, 2019165 | CACB (bupi 0.25% epin 30ml then ropi 0.2% 8ml/h for 24h or 48h (n=50/51)  SSACB (bupi 0.25% epin 30ml) (n=53) | Reduction severe pain at day2 with CACB (12-14% vs 21% with SSACB) | No difference | Acetaminophen, celecoxib, gabapentin, oxycodone, LIA | No difference in quality of recovery at day2 |
| Zhang et al, 2018166 | CACB (ropi 0.5% 20ml repeated bolus) (n=23)  SSACB (ropi 0.5% 20ml) (n=25) | No difference | No difference | NA | Reduced muscle strength with CACB |
| Lyngeraa et al, 2019167 | CACB (ropi 0.75% 20ml repeated bolus/8h) (n=49)  SSACB (ropi 0.75% 20ml) (n=49) | No difference | No difference | Paracetamol, celecoxib, methylprednisolone |  |
| Canbek et al, 2019168 | CACB (bupi 0.25% 30ml then bupi 0.125% 5ml/h) (n=63)  SSACB (bupi 0.25% 30ml) (n=60) | Reduction pain at rest and movement until 48h | No difference | Paracetamol, diclofenac, tramadol rescue doses | Better mobility with CACB  Similar LOS |
| **Adductor Canal Block bolus Vs intraoperative Local Infiltration Analgesia (LIA)** | | | | | |
| Sawhney et al, 2016169 | ACB (ropi 0.5% 30ml) (n=46)  LIA (ropi, morphine, ketorolac 30ml) (n=49) | Reduction pain at movement with ACB | No difference | Acetaminophen, celecoxib, gabapentin, PCA IV hydromorphone |  |
| Li et al, 201754 | ACB (ropi 0.5%, epin 20ml) (n=24)  MIA\* (ropi 0.25%, epin 70ml) (n=26)  \*Periarticular and intraarticular | ACB inferior to LIA for pain at rest (12h) | Increased use in ACB group | Acetaminophen, NSAID, gabapentin, IV opioids | Decreased LOS with MIA (3.6days vs 4.9 days) |
| Grosso et al, 2018170 | ACB (bupi 0.5% 15ml) (n=53)  LIA (bupi 0.5%, epin 50 ml) (n=51) | No difference | Increased opioid use in ACB group | Acetaminophen, celecoxib, gabapentin, oxycodone | No difference in LOS |
| Zhou et al, 2018171 | ACB (ropi 0.375% 30ml) (n=20)  LIA\* (ropi 0,2% 100ml) (n=20)  \*posterior capsular infiltration | No difference | No difference | Acetaminophen, oxycodone, tramadol | No difference in PONV and LOS |
| Kampitak et al, 2018172 | ACB (levobupi 0.5% 20ml) (n=29)  LIA (levobupi 0.5%, epin 40ml) (n=28) | Reduction at rest (18h) and movement(24-48h) in ACB group | Reduction in ACB group | Acetaminophen, parecoxib, pregabalin, dexamethasone 10mg, PCA IV morphine | No difference in PONV and LOS  No difference at 1y outcomes |
| Tong et al, 2018173 | ACB (ropi 0.5% 30ml) (n=20)  LIA (ropi, epin, morphine, ketorolac 75ml) (n=20) | No difference | Reduction in ACB group | Paracetamol, PCA IV morphine | No difference in PONV, sedation and LOS |
| Nader et al, 2016174 | ACB (bupi 0.5% 20ml) (n=20)  LIA (ropi 0.2%, epin, ketorolac, morphine, clonidine 50ml) (n=20) | Reduction pain at movement (36h) in ACB group | Reduction | Acetaminophen, ketorolac, hydrocodone | No difference in pain and opioids use at 3weeks |
| Cicekci et al, 2019175 | ACB (levobupi 0.25% 20ml) (n=40)  LIA (levobupi 0.125% 40ml) (n=39) | Reduction pain at rest and movement | Reduction | Paracetamol, dexketoprofen, PCA IV morphine | Better 48h postop mobility but no difference at 3-6weeks |
| **ACB bolus Vs ACB bolus added to LIA** | | | | | |
| Sawhney et al, 2016169 | ACB (ropi 0,5% 30 ml) (n=46)  ACB/LIA (ropi, morph, ketorolac 30 ml) (n=40) | Increased pain in ACB group | No difference | Acetaminophen, celecoxib, gabapentin, PCA IV hydromorphone |  |
| Grosso et al, 2018170 | ACB (bupi 0,5% 15 ml) (n=53)  ACB/LIA (bupi epin 50ml) (n=51) | Increased pain in ACB group | Increased opioid use in ACB group | Acetaminophen, celecoxib, gabapentin, IV morphine | No difference in LOS |
| Kampitak et al, 2018172 | ACB (levobupi 0,5% 20 ml) (n=30)  ACB/LIA (bupi morphine epin 40ml) (n=30) | No difference | No difference | Acetaminophen, celecoxib, gabapentin, PCA IV morphine | No difference in PONV and LOS  No difference at 1y outcomes |
| Zhou et al, 2018171 | ACB (ropi 0,375% 30 ml) (n=20)  ACB/LIA\* (ropi 0,2% 100 ml) (n=20)  \*posterior capsular infiltration | No difference | No difference | Acetaminophen, oxycodone, tramadol | No difference in PONV and LOS |
| Goytizolo et al, 2019176 | ACB (bupi 0,25% 15 ml) (n=56)  ACB/LIA (bupi 0,5% morph epin methylpred 30 ml) (n=55) | No difference (up to 24h) | No difference | Acetaminophen, meloxicam/ketorolac, dexamethasone, hydromorphone | No difference in LOS |
| **ACB bolus added to LIA Vs LIA alone** | | | | | |
| Andersen et al, 2013177 | CACB (ropi 0,75% repeated bolus)/LIA (ropi 0,2% epin) (n=20)  LIA (n=16) | Reduction pain in ACB/LIA (24h) | No difference | Paracetamol, PCA IV morphine | No difference LOS |
| Gudmundsdottir et al, 2017178 | CACB (ropi 0,2% CI) /LIA (ropi 0,2%, epin, ketorolac) (n=34)  LIA (n=35) | No difference | No difference | Acetaminophen, parecoxib, oxycodone, dexamethasone |  |
| Goytizolo et al, 2019176 | ACB (bupi 0,25% 15 ml)/ LIA (n=56)  LIA (bupi 0,5%, morph, epin, methylpredni 30 ml) (n=55) | Reduction pain in ACB/LIA (24h) | No difference | Acetaminophen, meloxicam/ketoprofen, dexamethasone, hydromorphone | No difference PONV and LOS |
| Kampitak et al, 2018172 | ACB (levobupi 0,5% 20 ml)/LIA (n=30)  LIA (levobupi 0,25% morph epin) (n=30) | No difference | No difference | Acetaminophen, PCA IV morphine | No difference PONV and pruritus  No difference at 1y outcomes |
| Sawhney et al, 2016169 | ACB (ropi 0,5% 30 ml) /LIA (n=49)  LIA (ropi, morph, ketorolac 30 ml) (n=46) | Reduction pain in ACB/LIA (24h) | No difference | Acetaminophen, celecoxib, gabapentin, PCA IV hydromorphone | No difference PONV and LOS |

**Table S2. Summary of key results from studies evaluating systemic analgesics, systemic analgesic adjuncts and regional analgesia used to support interventions that are not recommended for analgesic benefit in patients having TKA.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Study** | **Interventions** | **Pain scores** | **Cumulative opioid dose** | **Analgesic technique** | **Comments** |
| **Gabapentin (GBP) Vs Placebo** | | | | | |
| Clarke et al, 200948 | GBP 600mg preop and postop (n=7)  GBP 600mg preop and postop 100mg q 8h (4days) (n=7)  GBP 600mg preop and postop 200mg q 8h (4day) (n=8)  Placebo (n=7) | No difference | Reduction | SSFNB and SS sciatic block, celecoxib, PCA IV morphine | Improved knee flexion with GBP |
| Clarke et al, 201449 | GBP 600 mg preop and postop 200mg q 8h (4 days)  Placebo and PGB postop 200mg q 8h (4 days) | No difference | Reduction | SSFNB and SS sciatic block, celecoxib, PCA IV morphine | Improved ROM  No benefit at 6 weeks |
| Paul et al, 201350 | GBP 600mg preop and postop 200mg q 8h (3 days)  Placebo | No difference | No difference | Paracetamol, ketorolac, PCA IV morphine |  |
| Lunn et al, 201551 | GBP 900mg preop and postop 400mg/900mg daily (7days)  GBP 600mg preop and postop 600mg/300mg daily (7days)  Placebo | No difference | No difference | Paracetamol, celecoxib, PCA IV morphine | Better sleep quality, higher dizziness with high GBP doses.  Unconventional dosing – twice a day rather than three times a day |
| **Pregabalin (PGB) Vs Placebo** | | | | | |
| Buvanendran et al, 201055 | PGB 300mg preop then decreasing doses postop (150, 75, 50mg) q 12h until day14 (n=120)  Placebo (n=120) | NA | No difference in PCEA use (n.s.) | Celecoxib and PCEA for 3days | Outcome: pain at 3 and 6 months |
| Jain et al, 201256 | PGB 150mg preop then q 12h (2days) (n=20)  Placebo (n=20) | No difference | No difference in PCEA use (n.s.) | PCEA |  |
| Lee et al, 201557 | PGB 150mg preop (n=20)  Placebo (n=21) | No difference | Reduction until 12h | Celecoxib, PCA IV morphine, LIA |  |
| Singla et al, 201558 | PGB 300mg preop and 150mg postop q 12h for 6 weeks (n=98)  PGB 150mg preop and postop 75mg q 12h for 6 weeks (n=90)  Placebo (n=98) | No difference | NA | CFNB for 2days,  opioids (?) | Variable postop pain management |
| Yadeau et al, 201259 | PGB 300mg preop and postop 150mg q 12h (16days) (n=30)  PGB 150mg preop and postop 75mg q 12h (16days) (n=30)  PGB 100mg preop and postop 50mg q 12h (16days) (n=30) | No difference | No difference in PCEA use | CFNB and PCEA | Increased sedation (dose related effect) |
| Yik et al, 201960 | PGB 75mg preop and postop 1x (2days) (n=45)  Placebo (n=42) | No difference | No difference | SSFNB, paracetamol, etoricoxib, IV opioids | No difference in functional outcome at 6 months |
| **Ketamine Vs placebo** | | | | | |
| Adam et al, 200567 | Ketamine 0.5mg/kg then 1.5-3.0 µg/kg/min for 48h (n=20)  Placebo saline infusion (n=20) | No difference (rest or movement) | Reduction (45+20 vs 69+30 mg) | CFNB for48h, PCA morphine  Only after 48h: paracetamol, ketoprofen, dextropropoxyphen | Faster mobilization in ketamine infusion group; no ketamine side effects  No benefits at 6 weeks or 3 months |
| Aveline et al, 200964 | Ketamine 0.2 mg/kg then 60-120 µg/kg/h for 48h (n=25)  Nefopam (n=24)  Placebo saline (n=24) | Reduction of pain at rest and movement (ketamine > nefopam) | Reduction in ketamine (similar in nefopam) 50+7 vs 70+10 mg | PCA morphine  Only after 48h: paracetamol, ketoprofen | Faster mobility recovery in ketamine |
| Perrin et al, 200968 | Ketamine 0.5 mg/kg then 4 µg/kg/min until end surgery (n=5)  Placebo saline (n=7) | No difference (rest, movement) | Reduction at 48h (28+19 vs 43+25 mg) | Spinal morphine 100µg, PCA morphine, paracetamol, ibuprofen | Pilot study  Less chronic pain at 6 months with ketamine (60% no pain vs 29%) |
| Cengiz et al, 201465 | Ketamine 6µg/kg/min until end of surgery (n=30)  Placebo saline (n=30) | Reduction pain at rest and movement for 24h | Reduction for 24h | PCA morphine | No ketamine side effects |
| Tan et al, 201966 | Ketamine 6µg/kg/min until end of surgery (n=48)  Placebo saline (n=43) | Reduction average pain at day1 and day4 with ketamine; no difference worse pain | No significant difference after day0 | Oxycodone, acetaminophen, celecoxib, LIA (liposomal bupi) | Follow up at day 14 and at 6 months: no difference in narcotic use |
| **Alpha-2 adrenergic agonists vs placebo** | | | | | |
| Chan et al, 201671 | Dexmedetomidine 0.5 µg/kg then 0.5 µg/kg/h until end of surgery for sedation (n=20)  Placebo saline (n=20) | No difference | Reduction (29+11 vs 61+17 mg) | PCA morphine, acetaminophen, naproxen | Hypotension, bradycardia  Reduction in PONV (5 vs 35%) and itching (5 vs 30%) |
| Shin et al, 201972 | Dexmedetomidine 1 µg/kg then 0.1-0.5 µg/kg/h for sedation (n=24)  Propofol sedation (n=24) | Reduction until 48h | Reduction PCA fentanyl use at all time points (135 vs 360 µg) | PCA fentanyl, CFNB, acetaminophen, celecoxib, pregabalin, dexamethasone, LIA | Hypotension, bradycardia  No reduction PONV |
| **Epidural (EPID) Vs Peripheral Nerve Block (PNB)** | | | | | |
| Singelyn et al, 199897 | ContEPID (bupivacaine, sufenta, epin) (n=15)  CFNB (bupivacaine, clonidine) (n=15)  PCA IV morphine (n=15) | No difference | NA | Paracetamol, piritramide | More urinary retention with EPID  No difference in function and late outcomes (6 weeks, 3 months) |
| Capdevila et al, 199998 | ContEPID (lidocaine, morph, clo) (n=17)  CFNB (lido, morph, clo) (n=20)  PCA IV morphine (n=19) | No difference | NA | Paracetamol, ketoprofen, morphine IV | More urinary retention with EPID  No difference at 3 months |
| Adams et al, 200299 | ContEPID (bupivacaine) (n=21)  CFNB (bupi) (n=21)  PCA IV morphine (n=21) | No difference | No difference | Diclofenac, PCA IV piritramide | Follow up only 3h  Endocrine stress response better controlled with EPID |
| Davies et al, 2004100 | ContEPID (bupivacaine) (n=30)  SSFNB and SS sciatic block (bupi) (n=30) | Increased pain at 24h at movement in EPID | No difference | PCA IV morphine | More urinary retention with EPID  Hypotension at 24h (37% vs 27%) |
| Barrington et al, 2005101 | ContEPID (bupivacaine) (n=54)  CFNB (bupi) (n=54) | No difference | Increased in CFNB (21+15 vs 13+12 mg) | Rofecoxib, oxycodone PO, IV morphine | Less PONV with CFNB, less quadriceps strength with CFNB but better mobilisation |
| Zaric et al, 2006102 | ContEPID (ropivacaine, sufenta) (n=30)  CFNB and SS sciatic block (ropi, suf) (n=30) | No difference | No difference | Rofecoxib, sustained morphine release PO, PCA IV morphine | More urinary retention and limb weakness with EPID, lateralized EPID (n=6), no difference in pain at 6 weeks |
| Campbell et al, 2008103 | ContEPID (levobupivacaine, clonidine) (n=30)  ContLumbar plexus block (levobupi, clo) (n=26) | No difference for pain at rest and movement | No difference | Paracetamol, tramadol, PCA IV morphine | More urinary retention with EPID  No difference in function |
| Sakai et al, 2013104 | ContEPID (ropivacaine) (n=33)  CFNB with SS tibial nerve block (ropivacaine) (n=33) | Increased pain at movement with EPID | NA | Diclofenac, pentazocine, PCA IV fentanyl | Earlier increased ROM with CFNB (8 days vs 15 days)  Less knee and calf edema with CFNB |
| **Epidural (EPID) Vs Local Infiltration Analgesia (LIA)** | | | | | |
| Klasen et al, 1999105 | EPID morphine (n=10)  LIA with intra articular (morphine)  (n=10) | No difference | No difference | PCA IV morphine |  |
| Andersen et al, 2010106 | ContEPID (ropivacaine) (n=19)  LIA with intraarticular (ropi, ketorolac) (n=21) | Increased pain in EPID group | No difference | Ketorolac, PCA IV morphine |  |
| Spreng et al, 2010107 | ContEPID (ropivacaine) (n=33)  LIA (ropivacaine) (n=33)  LIA (morphine) (n=33) | No difference | No difference | Ketorolac, PCA IV morphine |  |
| Binici Bedir et al, 2014108 | ContEPID (bupivacaine) (n=15)  ContLIA (bupivacaine) (n=15) | No difference | NA | Diclofenac IV |  |
| Tsukada et al, 2014109 | ContEPID (ropivacaine, morphine) (n=61)  LIA (ropi, morphine, ketoprofen, epin, prednisolone) (n=50) | No difference | NA | Flurbiprofen, diclofenac |  |
| Kasture et al, 2015110 | ContEPID (bupivacaine, fentanyl) (n=35)  Intraarticular (bupivacaine, ketorolac) (n=40) | No difference | NA | Diclofenac, tramadol |  |
| **Sciatic nerve block (SNB) Added to FNB vs LIA added to FNB** | | | | | |
| Gi et al, 2014133 | SNB/ FNB (n=24)  LIA (LA, epin)/ FNB (n=25) | Increased pain (12-24h) in SNB/FNB group; no difference in flexion | NA | Loxoprofen, diclofenac | More posterior knee pain in SNB (8.7% vs 4.3%) for 36h |
| Nagafuchi et al, 2015136 | SNB/ CFNB (n=17)  LIA (LA, epin)/ CFNB (n=17) | No difference (rest, flexion) | No difference | Diclofenac, pentazocine IM |  |
| Safa et al, 2014131 | SNB/ FNB (n=32)  \*posterior capsular infiltration (LA, epin)/ FNB (n=33)  Placebo saline/ FNB (n=35) | No difference at rest and movement for 48h | No difference | Acetaminophen, celecoxib, gabapentin, PCA IV hydromorphone | No difference PONV  No difference in recovery at 6 weeks |
| Tanikawa et al, 2014132 | SNB/ CFNB (n=23)  LIA (LA, epin)/ CFNB (n=23) | No difference (rest, flexion) | NA | diclofenac | No difference in recovery at 3 weeks |
| Mahadevan et al, 2012134 | SNB/ FNB (n=26)  LIA (LA,epin)/ FNB (n=26) | No difference (rest, movement) | No difference | Paracetamol, diclofenac, PCA IV morphine | No difference PONV and LOS |
| Uesugi et al, 2014135 | SNB/ FNB (n=105)  LIA\*/ FNB (n=105)  \*ropi, epin, morphine, dexamethasone | Less pain with LIA (not significant) 24-48h | NA | NA |  |
| Spangehl et al, 2015137 | SNB/ FNB (n=79)  LIA\*/ FNB (n=81)  \*ropi, epin, ketorolac, morphine | No difference | No difference | Paracetamol, diclofenac, PCA IV morphine |  |