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REVIEW ARTICLE

Pain management after total knee arthroplasty

PROcedure SPEcific Postoperative Pain ManagemenT recommendations

Patricia M. Lavand'homme, Henrik Kehlet, Narinder Rawal and Girish P. Joshi, on behalf of the PROSPECT Working Group of the European Society of Regional Anaesthesia and Pain Therapy (ESRA)

BACKGROUND The PROSPECT (PROcedure SPEcific Postoperative Pain ManagemenT) Working Group is a global collaboration of surgeons and anaesthesiologists formulating procedure-specific recommendations for pain management after common operations. Total knee arthroplasty (TKA) is associated with significant postoperative pain that is difficult to treat. Nevertheless, pain control is essential for rehabilitation and to enhance recovery.

OBJECTIVE To evaluate the available literature and develop recommendations for optimal pain management after unilateral primary TKA.

DESIGN A narrative review based on published systematic reviews and meta-analyses, using modified PROSPECT methodology.

DATA SOURCES A literature search was performed in EMBASE, MEDLINE, PubMed and Cochrane Databases, between January 2014 and December 2020, for systematic reviews and meta-analyses evaluating analgesic interventions for pain management in patients undergoing TKA.

ELIGIBILITY CRITERIA Each randomised controlled trial (RCT) included in the selected systematic reviews was critically evaluated and included only if met the PROSPECT requirements. Included studies were evaluated for clinically relevant differences in pain scores, use of nonopioid analgesics, such as paracetamol and nonsteroidal anti-inflammatory drugs and current clinical relevance.

RESULTS A total of 151 systematic reviews were analysed, 106 RCTs met PROSPECT criteria. Paracetamol and nonsteroidal anti-inflammatory or cyclo-oxygenase-2-specific inhibitors are recommended. This should be combined with a single shot adductor canal block and peri-articular local infiltration analgesia together with a single intra-operative dose of intravenous dexamethasone. Intrathecal morphine (100 μg) may be considered in hospitalised patients only in situations when both adductor canal block and local infiltration analgesia are not possible. Opioids should be reserved as rescue analgesics in the postoperative period. Analgesic interventions that could not be recommended were also identified.

CONCLUSION The present review identified an optimal analgesic regimen for unilateral primary TKA. Future studies to evaluate enhanced recovery programs and specific challenging patient groups are needed.

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Introduction

The occurrence of severe knee pain, generally caused by osteoarthritis, has been increasing because of the aging population and an increase in pro-inflammatory conditions, such as obesity. Symptomatic knee pain represents a burden for modern healthcare systems. When conservative treatments, such as physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular steroid, hyaluronic acid injections and peri-articular

From the Department of Anaesthesiology and Perioperative Pain Service, Cliniques Universitaires St Luc, University Catholic of Louvain (UCL), Brussels, Belgium (PML), Section of Surgical Pathophysiology 7621, Rigshospitalet, Copenhagen, Denmark (HK), Department of Anaesthesiology, Orebro University, Orebro, Sweden (NR) and Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, Texas, United States (GPJ)

Correspondence to Patricia M. Lavand'homme, Department of Anaesthesiology and Peri-operative Pain Service, Cliniques Universitaires St Luc, University Catholic of Louvain (UCL), Av Hippocrate 10, 1200, Brussels, Belgium
E-mail: patricia.lavandhomme@saintluc.uclouvain.be

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KEY POINTS

- Total knee arthroplasty (TKA) is associated with significant postoperative pain, and effective pain control affects postoperative rehabilitation and long-term outcomes.
- Several publications provide general opinions and guidelines for pain management after TKA but they often lack critical assessment of included studies.
- Therefore, the optimal combinations of analgesic interventions remain unclear.
- The aim of this review is to provide clinicians with recommendations for pain management after unilateral primary TKA with particular attention to early rehabilitation and mobilisation.
- This approach reports true clinical effectiveness by balancing the invasiveness of the analgesic interventions and the degree of pain after surgery, and also balancing efficacy and adverse effects.

infiltrations of genicular nerves have failed, total knee arthroplasty is considered the most effective treatment.[1] Not surprisingly, the number of TKA performed is constantly increasing.

As TKA is painful, frequently performed and involves a reproducible surgical technique, approaches to the management of peri-operative pain have been extensively studied. There are numerous published systematic reviews and meta-analyses assessing single, individual, analgesic interventions for TKA.[2–6] Furthermore, several publications provide general opinions and guidance for pain management after TKA.[7–9] However, TKA remains a major orthopaedic procedure that is associated with severe postoperative pain and may lead to persistent pain in 15 to 20% of patients.[10,11] Importantly, the best combination of interventions for optimal multimodal analgesia remains unclear.[12]

The PROSPECT (PROcedure SPEcific Postoperative Pain ManagemenT) Working Group is a global collaboration of surgeons and anaesthesiologists formulating procedure-specific recommendations for pain management after common but potentially painful, operations.[13] The PROSPECT approach is unique in that the available evidence is critically assessed for current clinical relevance, balanced with regards to the use of simple non-opioid analgesics, such as paracetamol and NSAIDs. This approach reports true clinical effectiveness by balancing the invasiveness of the analgesic interventions and the degree of pain after surgery, and also balancing efficacy and adverse effects. In addition, attention is paid to early rehabilitation and mobilisation. The aim of the present review was to update the 2009 recommendations using a modified PROSPECT approach for pain management after unilateral primary TKA. This included identifying systematic reviews and meta-analyses evaluating analgesic interventions for TKA, and then critically assessing the individual randomised controlled trials (RCTs) that were already evaluated for risk bias. Only the RCTs that conformed to aforementioned Prospect criteria were then used to develop recommendations.

Methods

Given the impressive number of RCTs that have been published to date regarding pain management after TKA, the PROSPECT group decided to critically assess the published systematic reviews and meta-analyses evaluating individual analgesic interventions for TKA.[14,15] The systematic reviews and meta-analyses included in this review were performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) recommendations including assessments of risk of bias of RCTs using the Cochrane Collaboration tool.[16] The PROSPECT Group decided to capitalise on previous work and not repeat much of the arduous basic work, performing risk bias assessments. This approach is termed Adolopment by the grades of recommendation, assessment, development and evaluation (GRADE) Working Group.[17] This provides advantages of selectively combining adoption, adaptation and de novo development of guidelines recommendations whether updated or new.

A literature search was performed for systematic reviews and meta-analyses evaluating analgesic interventions for pain management in patients undergoing TKA published between January 2014 and December 2020. Although we performed the literature search from January 2014 to December 2020, the RCTs in the included systematic reviews/meta-analyses were those available since the database inception. The EMBASE, MEDLINE, PubMed and Cochrane Databases were queried using the search terms *"knee replacement" OR "knee arthroplasty" AND "postoperative pain" AND "meta-analysis" OR "systematic review"*. Only the publications assessing systemic analgesic interventions [paracetamol, NSAIDs, cyclo-oxygenase (COX)-2 specific inhibitors, gabapentinoids, corticosteroids, ketamine, α_2-adrenergic agonists, opioids and others] and regional techniques [epidural analgesia, spinal opioids, peripheral nerve blocks, local infiltration analgesia (LIA) and others] were considered. Anaesthetic techniques (general anaesthesia and neuraxial anaesthesia), surgical techniques including tourniquet use and nonpharmacological interventions were not reviewed.

Each RCT included in the selected publication was critically evaluated according to the PROSPECT methodology including clinical relevance of the analgesic effects of the intervention according to pain intensity measured by validated pain scales, such as the visual analogue scale (VAS) and numerical rating scale (NRS). Of note, the differences in pain scores should be at least

1/10 cm or 10/100 mm on the VAS or 1/10 point on VAS/NRS. However, risk of bias of individual RCTs was not assessed as it had already been performed by the authors of the systematic reviews and meta-analyses. Particular attention was paid to the added benefits of the co-analgesics (paracetamol and NSAIDs or COX-2 specific inhibitors) in addition to LIA because of their well documented analgesic effects, being simple, inexpensive and safe (NICE guidelines).[18] The primary outcome was the degree of pain as determined by pain scores. The secondary outcome measures included reduction of the side effects of opioids and effects of the treatment on passive knee mobilisation and active rehabilitation, whenever available. In addition, the invasiveness of the analgesic technique and the specific side effects of the treatment itself were considered. Finally, the current clinical relevance of the interventions was considered. Of note, determination of safety of an analgesic intervention was based on all types of studies (RCTs and cohort studies) from all types of procedures.

The proposed recommendations along with the extraction tables that included details of individual RCTs were sent to the PROSPECT Working Group for review and comments and a modified Delphi approach was used to achieve a consensus. Following this, the lead authors drafted the final document that was ultimately approved by the Working Group.

Results

Paracetamol

A total of 6 meta-analyses[19–24] assessing the analgesic effect of oral and intravenous paracetamol were identified with a total of 22 included studies. Of these, only two RCTs[25,26] fulfilled PROSPECT inclusion criteria (Table S1, http://links.lww.com/EJA/A701), other studies being either retrospective cohort studies or mixed TKA and total hip arthroplasty (THA). No side effects related to the treatment were reported. On the basis of the assessments of the included RCTs, paracetamol is recommended preoperatively or intra-operatively and should be continued postoperatively.

Nonsteroidal anti-inflammatory drugs including cyclo-oxygenase-2-specific inhibitors

Two meta-analyses have assessed the efficacy and safety of NSAIDs in the context of TKA. Du and Gu[27] assessed the effects of parecoxib versus saline, whereas Fillingham *et al.*[28] analysed the effects of NSAIDs. From these two meta-analyses, six RCTs of good quality, all assessing peri-operative COX-2-specific inhibitors administration in TKA were considered for analysis (Table S1, http://links.lww.com/EJA/A701).[29–35] In all the included RCTs, COX-2-specific inhibitors reduced postoperative pain scores at rest and during mobilisation and reduced postoperative opioid requirements but without decreasing opioid-related adverse effects like postoperative nausea and vomiting (PONV). It is worth noting that the benefits of COX-2-specific inhibitors, for both their analgesic and opioid-sparing effects, are observed even with concomitant paracetamol administration or LIA. Therefore, NSAIDs or COX-2-specific inhibitors are recommended preoperatively or intra-operatively and should be continued postoperatively.

Glucocorticoids

Altogether 12 systematic reviews and meta-analyses were identified, of which 7 focused only on TKA, whereas 5 were combined trials of THA and TKA.[14] From these meta-analyses, six RCTs were included. All RCTs included some form of combination of paracetamol, NSAID/COX-2-specific inhibitors and LIA (Table S1, http://links.lww.com/EJA/A701). The three RCTs assessing a single preoperative dose showed a reduction in pain, postoperative analgesic consumption and PONV.[36–38] There were no safety issues. Similarly, the repeat dosing studies[37,39–41] showed a significant reduction in postoperative pain up to 48 h together with reduction in postoperative opioid requirements and PONV. No safety issues were demonstrated but the total number of glucocorticoid-treated patients was small ($n = 150$). The data do not allow recommendations for a specific dose as no dose-finding studies have been performed but the single preoperative dose regimens have used a dose between 10 to 25 mg of dexamethasone equivalents. The safety of a single preoperative glucocorticoid dose is supported by a large before and after implementation study[42] and a systematic review.[43] However, no such safety studies are available for repeat-dosing regimens. Although several RCTs on local administration of glucocorticoids together with LIA are available,[14] interpretation is hindered by the lack of a systemic dose for control. In summary, single preoperative or intra-operative dose of dexamethasone ($\geq$10 mg, i.v.) is recommended, being simple, safe and effective even with concomitant use of paracetamol, NSAIDs, COX-2 specific inhibitors and LIA.

Gabapentinoids (gabapentin and pregabalin)

A total of six meta-analyses assessed the analgesic effects of gabapentinoids in patients undergoing TKA.[15] Four systematic reviews assessed gabapentin administration,[44–47] which included eight RCTs. Of these eight RCTs, four were included for evaluation (Table S2, http://links.lww.com/EJA/A701).[48–51] There was significant variation in the dose (preoperative ranged from 600 1300 mg and postoperative up to 1300 mg, twice daily), timing of preoperative administration and duration of postoperative administration. The postoperative analgesic regimen included NSAID or COX-2-specific inhibitors $\pm$ paracetamol in only three RCTs, whereas a perineural catheter was used in one RCT. Opioids were used as rescue.

Four systematic reviews/meta-analysis,[47,52–54] including a total of eight RCTs, assessed pregabalin administration, of which six RCTs were included for evaluation (Table S2, http://links.lww.com/EJA/A701).[55–60] There was significant variation in the dose (preoperative: 50 to 300 mg and postoperative: 0 to 300 mg, twice daily), timing of preoperative administration (30 min to 24 h, preoperatively) and duration of postoperative administration (single dose to 6 weeks).[55,56,58,59]

Regional anaesthesia (combined spinal epidural or spinal alone) was used in all included RCTs. Most RCTs ($n = 6$) used regional analgesia, whereas one RCT administered i.v. patient-controlled analgesia (PCA). Supplementary analgesia included intrathecal opioid ($n = 4$; fentanyl, $n = 1$ and morphine, $n = 3$), femoral nerve block (FNB) ($n = 2$) and LIA ($n = 1$). Opioids were used as rescue.

In summary, gabapentinoids are not recommended because of lack of clinically relevant analgesia when combined with paracetamol, NSAID/COX-2 specific inhibitors and LIA and well documented risks of side effects.

Systemic ketamine

Three meta-analyses assessed analgesic effects of perioperative ketamine after TKA[61] or after both TKA and THA.[62,63] Five RCTs assessed intravenous low doses of ketamine after TKA (other studies assessed intra-articular, epidural or only postoperative PCA, or assessed ketamine use in THA). In three RCTs, ketamine was used as a bolus dose ($0.5\,mg\,kg^{-1}$) and a continuous infusion of 4 to $6\,\mu g\,kg^{-1}\,min^{-1}$ until the end of surgery, whereas in two RCTs, a ketamine bolus ($0.5\,mg\,kg^{-1}$) was followed by a continuous infusion of 1.5 to $3.0\,\mu g\,kg^{-1}\,min^{-1}$ over 48 h after surgery (Table S2, http://links.lww.com/EJA/A701). In all these studies, ketamine was compared with placebo, whereas one RCT also included a nefopam group.[64] In two RCTs, ketamine administration displayed significant analgesic effect at rest and during mobilisation independent of the duration of administration but PCA morphine alone was available for postoperative analgesia and nonopioid analgesics were not administered.[64,65] Ketamine was more effective than nefopam in reducing postoperative pain in a single study comparing ketamine to nefopam.[64] When a basic analgesic regimen (NSAID, paracetamol and/or LIA)[66] or continuous FNB[67] was used, systemic ketamine did not significantly reduce postoperative pain intensity. Although opioid-sparing was observed in four of five RCTs,[64,65,67,68] it did not affect opioid side effects (PONV). In two RCTs,[64,67] ketamine was associated with faster passive rehabilitation. Finally, four RCTs[66–69] questioned the long-term benefits of peri-operative ketamine without clear evidence regarding chronic pain development.

In summary, ketamine, intra-operatively and/or postoperatively, is not recommended because of lack of evidence when using a basic analgesia regimen (paracetamol NSAID's/COX-2 specific inhibitors and LIA).

Systemic α_2-adrenergic agonists

One meta-analysis evaluated the efficacy and safety of intravenous dexmedetomidine in patients undergoing TKA and THA.[70] After exclusion of RCTs where dexmedetomidine was used in THA and those where it was added to local anaesthetic in perineural blocks, two RCTs remained for analysis (Table S2, http://links.lww.com/EJA/A701). A dexmedetomidine bolus dose of 0.5 to $1.0\,\mu g\,kg^{-1}$ followed by a continuous infusion of 0.1 to $0.5\,\mu g\,kg^{-1}\,h^{-1}$ until the end of surgery administered to patients undergoing TKA under spinal anaesthesia was compared either with placebo[71] or to propofol sedation.[72] The primary endpoint of both RCTs was postoperative opioid-sparing effect. Dexmedetomidine significantly decreased postoperative morphine as well as itching (5 versus 30%) and PONV (5 versus 30%) in the study of Chan *et al.*[71] and significantly decreased postoperative fentanyl consumption in the study of Shin *et al.*[72] but without affecting the use of postoperative antiemetics. Although basic analgesics (paracetamol and NSAIDs) were used in both RCTs, dexmedetomidine only reduced pain intensity in one of the two RCTs[72] precluding any conclusion about its analgesic effect. In the later study,[72] patients also received femoral nerve block, LIA, pregabalin and dexamethasone.

In summary, dexmedetomidine is not recommended as it was used for sedation during spinal anaesthesia and because of limited and conflicting evidence and concerns of adverse effects, such as bradycardia and hypotension.

Intrathecal morphine

Intrathecal morphine has been demonstrated to be better than placebo (Table S1, http://links.lww.com/EJA/A701).[73–84] Three meta-analyses including four RCTs compared intrathecal morphine with FNB[85,86] and with LIA.[87] The dose of intrathecal morphine varied between 100 and 300 mcg (Table S1, http://links.lww.com/EJA/A701). Compared with single shot FNB, there was no clinically significant difference in postoperative pain at rest or during mobilisation and no postoperative opioid-sparing effect.[88,89] Similar observations were made for the comparison with continuous FNB.[78,90] Although postoperative opioid consumption was less in the immediate postoperative period (6 to 12 h), Intrathecal morphine increased opioid consumption at 18 to 24 h.[78] In all studies, intrathecal morphine was associated with increased pruritus and decreased patient satisfaction. In a more recent meta-analysis,[87] intrathecal morphine was compared with LIA in both TKA and THA. The four RCTs in TKA patients showed no differences in postoperative analgesia and opioid-sparing with intrathecal

morphine (100 to 300 mcg).[91–94] In two RCTs, intrathecal morphine displayed inferior postoperative analgesia and morphine-sparing effects than LIA followed by repeated postoperative intra-articular injection.[91–94]

In summary, intrathecal morphine (100 mcg) may be considered only for hospitalised patients receiving spinal anaesthesia and whenever regional analgesia (ACB and LIA) is not possible.

Epidural analgesia

Two meta-analyses assessed epidural analgesia after TKA, in comparison to peripheral nerve blocks[95] or to LIA.[96] In the former,[95] 12 RCTs were included, which compared epidural analgesia either with FNB +/- sciatic nerve block (SNB) or with lumbar plexus block. Of these, eight RCTs fulfilled PROSPECT criteria.[97–104] Epidural analgesia included the administration of a local anaesthetic alone or in combination with a lipophilic opioid (fentanyl and sufentanil) and/or epinephrine or clonidine. Almost all the studies (7/8) used basic analgesic treatment like paracetamol and/or NSAID. There was no clinically significant difference in pain scores between epidural analgesia and peripheral nerve blocks at any time point from 0 to 48 h. Only one study among the five RCTs reporting postoperative opioid sparing in favour of epidural analgesia when compared with continuous FNB.[101] Epidural analgesia was associated with significantly higher risk of PONV, hypotension and urinary retention.[95]

The meta-analysis[96] comparing epidural analgesia to LIA included seven RCTs (one RCT was excluded as it was performed in patients undergoing bilateral TKA). In the six included RCTs (Table S2, http://links.lww.com/EJA/A701),[105–110] three reported the administration of high-volume LIA (60 to 100 ml) whereas three mentioned the use of intra-articular injection. In five of six studies, the epidural analgesia included local anaesthetic with or without opioid. Also, five of six studies reported the use of a NSAID as the basic analgesic regimen. Results demonstrated the equivalent analgesic efficacy of epidural analgesia and LIA. Interestingly, epidural analgesia was less effective than LIA in two of six trials.[106,109] There were no differences between epidural analgesia and LIA for postoperative opioid consumption. Epidural analgesia was associated with an increased incidence of PONV and increased length of stay, and was less efficient with regards to mobilisation [lower range of motion (ROM)].

In summary, intra-operative and postoperative epidural analgesia, despite analgesic effects is not recommended because of potential adverse effects (reduced mobility, hypotension, urinary retention) precluding rapid recovery.

Femoral nerve block

A total of 16 systematic reviews and meta-analyses reporting FNB in TKA were identified. Postoperative analgesia and opioid-sparing effects of FNB have been compared with intrathecal morphine[85,86] (two studies, refer to the intrathecal morphine section), epidural analgesia [95] (one study, refer to the Epidural analgesia section), ACB (eight studies, refer to the Adductor Canal Block section)[111–118] and LIA[119–123] (five studies, refer to the Local Infiltration Analgesia section). To summarise, FNB displays similar analgesic efficacy to intrathecal morphine, epidural analgesia ACB and LIA. FNB shows less side effects than intrathecal morphine and epidural analgesia. Importantly, FNB carries an increased risk of quadriceps weakness, particularly when a continuous infusion technique is used.[124] Quadriceps weakness is worse with FNB than ACB.[125] Therefore, FNB (single shot and/or postoperative infusion), despite analgesic effects is not recommended because of reduced mobility from muscle weakness which can preclude rapid recovery.

Sciatic nerve block

Three meta-analyses assessed the analgesic efficacy of SNB in addition to FNB[126–128] and three meta-analyses evaluated benefits of adding either SNB or LIA to a FNB.[121,129,130] Among nine studies included in these meta-analyses, seven RCTs met PROSPECT criteria (Table S2, http://links.lww.com/EJA/A701).[131–137] All the RCTs showed no difference between SNB and LIA in term of postoperative analgesia and opioid consumption. Addition of SNB to the FNB or ACB did not provide any additional clinically relevant analgesic benefits and also no significant decrease of postoperative opioid use. Two studies assessed long-term benefits of SNB, and found no benefits at 3 and 6 weeks.[131,132] Of note, basic analgesics were used consistently in the included studies. An important concern of SNB includes the potential for motor and sensory deficit of the lower leg, with reduction of foot mobility, which may impair early mobilisation and might delay postoperative recovery. Therefore, SNB is not recommended because of concerns of quadriceps weakness and delayed ambulation.

Adductor canal block

A total of 26 systematic reviews and meta-analyses were identified reporting ACB in TKA [ACB versus FNB ($n = 8$),[111–118] ACB versus LIA ($n = 10$),[138–147] and ACB technique ($n = 7$)].[148–152] Five RCTs compared ACB with saline ACB (either bolus or repeated boluses or continuous infusion) (Table S1, http://links.lww.com/EJA/A701).[153–157] Of these, two RCTs evaluated rescue (postoperative) ACB in patients with severe postoperative pain either at 6 h or on postoperative day 2.[154,155] A multimodal analgesic protocol was used in all studies. In all the RCTs, ACB significantly reduced pain associated with knee flexion and mobilisation. However, a decrease in postoperative opioid use was inconsistent with no impact on PONV. When administered in patients enduring severe postoperative pain, ACB provided pain relief at rest and during knee flexion with a duration of up to 6 h.

Four RCTs compared single shot ACB with single shot FNB in terms of postoperative pain relief and quadriceps muscle motor function (Table S1, http://links.lww.com/EJA/A701).[158–161] No differences in analgesic effects and opioid use were found between the two techniques. ACB allowed superior knee function and mobilisation by sparing quadriceps muscle function. Eight RCTs compared continuous ACB with continuous FNB without significant differences in postoperative analgesia and opioids use. Here also, ACB allowed better preservation of knee function than FNB by sparing the quadriceps.[115]

Seven RCTs assessed single shot injection ACB with continuous ACB.[162–168] The majority of the studies also used a multimodal analgesic protocol but rarely LIA. In this setting, no significant benefit of continuous ACB infusion was demonstrated in terms of analgesia and use of rescue opioids (six of seven RCTs). One study questioned the benefit of 48 h ACB infusion over 24 h or single shot.[165] One study also compared ACB bolus and continuous infusion using local anaesthetic alone, with single shot ACB including a mixture of 20 ml bupivacaine 0.25% with clonidine, dexamethasone and buprenorphine.[163] No important differences were found between the groups.

A total of eight RCTs compared ACB with LIA[54,169–175] (six of them included in a recent meta-analysis[142]). In four RCTs, ACB had greater analgesic efficacy than LIA, particularly regarding dynamic pain, whereas in others, ACB was not inferior to LIA.[169,172,174,175] Postoperative opioid consumption was similar between ACB and LIA in four RCTs, whereas in others opioid-sparing was greater but without reduction of opioid-related adverse effects. The majority of the RCTs used multimodal analgesia with paracetamol, COX-2-specific inhibitor, gabapentinoid and systemic opioid. There was a significant variability in the LIA volume (40 and 100 ml, five of eight RCTs) or solution (three of eight RCTs).

Twelve studies evaluated the benefits of combining ACB with LIA in comparison with either technique alone. Among them, five RCTs compared a combination of ACB and LIA to ACB alone.[169–172,176] All studies included a multimodal analgesic regimen. In this setting, ACB alone was equivalent (three of five) or inferior (two of five) to the combination of ACB and LIA in term of analgesia and opioid consumption. Five RCTs compared a combination of ACB and LIA to LIA alone.[169,172,176–178] The combination of ACB and LIA was superior to LIA for pain control only during the first 24 h. All the studies used a multimodal analgesic regimen, except one[177] where patients received only paracetamol and morphine but no NSAIDs. Regarding opioid-sparing effect, the combination of ACB and LIA was not superior to LIA alone (five of five RCTs).

In summary, a single shot ACB is recommended and preferably combined with LIA. Continuous ACB is not recommended because of inconsistent benefits.

Local infiltration analgesia

Most meta-analyses assessing the analgesic efficacy of LIA have compared it with other regional analgesic techniques. All meta-analyses report considerable heterogeneity including variability in types and doses of local anaesthetics used, volumes of injectate, types of analgesic adjuvant (clonidine, ketorolac, morphine and injection sites.

Five meta-analyses considered efficacy of LIA versus no injection or placebo.[179–183] In a systematic review by Seangleulur *et al.*,[181] peri-articular but not intra-articular injection reduced pain at rest at 24 and 48 h and increased range of motion ($n = 7$ RCTs). Twenty meta-analyses[111,112,114–116,118–120,123,125–127,129,130,146,184–188] compared the analgesic benefits of LIA with various peripheral nerve blocks.[4] The RCTs comparing LIA with ACB have been reported above. There were 11 meta-analyses compared LIA with FNB with mixed results.[5,119,120,123,188,189] Placement of intra-articular catheter ($n = 10$ RCTs) and subcutaneously ($n = 1$ RCT) was associated with reduced pain and opioid requirements up to 72 h postoperatively.[179,181] However, deep knee infection was reported in 3 out of 735 patients receiving a catheter included in the meta-analysis of Seangleulur *et al.*[181] Similar conclusions were drawn by Zhang *et al.* who included seven RCTs in their meta-analyses[183] and by Sun *et al.*[190] who included 10 RCTS in their meta-analyses. Another meta-analysis[191] found that the use of continuous peripheral nerve blocks (FNB or ACB) does not provide superior analgesic benefit over single shot LIA. The potential benefits of using liposomal bupivacaine has been evaluated in six meta-analyses[125,192–197] and a Cochrane review.[198] The role of liposomal bupivacaine in LIA for TKA remains unclear because of conflicting evidence.

Overall, the included RCTs showed improved pain relief and reduced opioid requirements with LIA. In addition, LIA allowed earlier functional recovery, range of motion, time to straight leg raise and 90° knee flexion but influence on hospital length of stay was inconsistent. Compared with control group, the catheter LIA technique was associated with reduced pain and opioid requirements up to 72 h postoperatively but there are concerns of infection. Of note, cost-effectiveness of LIA has been supported by the NICE guidelines.[18]

In summary, peri-articular LIA is recommended. However, continuous LIA or continuous intra-articular local anaesthetic infusion are not recommended because of inconsistent benefits and concerns of potential infection. The optimal site and volume for peri-articular administration of drugs remains unclear because of heterogeneity between the studies.

Discussion

This review examined the effects of analgesic interventions for the management of pain after unilateral, primary

TKA. The selected RCTs were critically assessed according to the PROSPECT methodology, which goes beyond evaluating the statistical differences in pain scores and opioid use.[13] Considerable attention was given to the use of basic analgesics (paracetamol and NSAIDs), the balance of analgesic efficacy and adverse effects of the intervention and current clinical relevance.

The use of NSAIDs or COX-2-specific inhibitors administered either preoperatively or intra-operatively, and continued postoperatively is recommended. This is in agreement with the strong recommendation made in a recent meta-analysis by Fillingham *et al.*[28] Both NSAIDs and COX-2 specific inhibitors have been reported to control pain and promote rehabilitation for 3 to 6 weeks after TKA.[34,199] In a large population-based study involving 1 028 069 knee arthroplasties, NSAIDs and COX-2-specific inhibitors were found to be the most effective means of improving peri-operative outcomes and reducing resource utilisation (19% fewer respiratory and 26% fewer gastro-intestinal complications, up to 18.5% reduction in opioid prescriptions and 12.1% reduction in hospital length of stay).[200,201] Of note, COX-2-specific inhibitors possess similar analgesic efficacy to NSAIDs but with no effects on platelet function, and thus, could be administered preoperatively. A recent meta-analysis including a large number of patients receiving various types of NSAIDs and undergoing a variety of surgical procedures found that NSAIDs are unlikely to be the cause of postoperative bleeding complications.[202] To date, no safety concerns have been reported but prescribers need to remain vigilant as the typical older TKA population may be at a higher risk of adverse effects.[28] Although paracetamol alone has limited analgesic and opioid-sparing efficacy, moderate evidence supports its use for peri-operative pain management after TKA.[24] It is a low-cost and low-risk option and more importantly, it demonstrates an interesting opioid-sparing effect when combined to NSAIDs.[203,204]

Glucocorticoids for a long time have been considered as the 'ultimate anti-inflammatory drugs', and there has been increased attention given to their peri-operative use to provide PONV prophylaxis, analgesia and fatigue reduction.[14] Glucocorticoid administration was beneficial both in terms of pain relief and opioid-sparing effects even when used as a component of multimodal analgesic regimen. Therefore, a single intra-operative intravenous dexamethasone dose is recommended, being simple, safe and effective with concomitant use of basic analgesics and LIA.[14] It is worth noting that glucocorticoids represent a highly valuable alternative for some patients who have contraindications to NSAIDs and COX-2-specific inhibitors. However, the safety of repeated doses of glucocorticoids to improve postoperative recovery remains questionable. The optimal dose of preoperative dexamethasone still remains undetermined as the dose used in the different RCTs varied significantly from 10 to 25 mg.[14] However, a previous meta-analysis in a mixed surgical population has reported that dexamethasone greater than 0.1 mg kg^{-1} was an effective adjunct to multimodal strategies.[205] In the TKA setting, a recent study reported a significant reduction of postoperative pain from 12 to 21 h when a preoperative dose of 0.15 mg kg^{-1} dexamethasone was used.[206] Although side effects of wound healing and infections are of potential concern, these have so far not been demonstrated, although more data are required in diabetic patients.[42,43]

Gabapentinoids have been reported to reduce postoperative pain scores and opioid consumption. However, a critical analysis of the published literature shows major flaws that limit the interpretation for the recommended use of peri-operative gabapentinoids in TKA.[15] Furthermore, there are several concerns of potential adverse effects of gabapentinoids, such as sedation, dizziness and visual disturbances that might interfere with early ambulation. These concerns are of even greater importance when gabapentinoids are combined with opioids,[207,208] which are typically necessary after TKA despite use of nonopioid analgesic strategies. Therefore, gabapentinoids are not recommended for TKA.

As TKA may be performed under spinal anaesthesia, intrathecal morphine might seem to be a good choice for control of early (first 12 to 24 h) postoperative pain. It is easier to perform compared with regional blocks like FNB or ACB, which require skill and training and may be time consuming. However, intrathecal morphine carries bothersome side effects (pruritus, nausea, urinary retention), which interfere with postoperative recovery.[85,86] Also, the administration of intrathecal morphine does not seem to provide superior benefit to LIA.[87] The interpretation of intrathecal morphine studies is hindered by the fact that most studies did not use LIA and had a variable use of basic analgesics. Although intrathecal morphine has been demonstrated to be more beneficial than placebo, it has not been shown to be superior to regional analgesic techniques (peripheral nerve blocks and LIA). Also, intrathecal morphine was associated with a rebound increase in postoperative opioid use at 18 to 24 h.[78] Furthermore, although intrathecal morphine 100 μg is safe with respect to respiratory depression,[209,210] it is associated with bothersome side effects like PONV, pruritus and urinary retention. These potential adverse effects may delay ambulation and oral intake, and influence patient satisfaction. Given that sufficient pain relief may be achieved with the combination of paracetamol, NSAIDs, dexamethasone and LIA, and also the possibility of bothersome adverse effects, the use of intrathecal morphine remains controversial. Of note, intrathecal morphine is not suitable for ambulatory TKA because of potential concerns of respiratory depression, albeit remote. Therefore, low-dose intrathecal morphine (100 mcg) may only be considered in hospitalised patients when the surgery is performed under spinal anaesthesia

and in the situation wherein both ACB and LIA are not possible.

Although epidural analgesia provides effective pain relief, and was once considered a standard of care for managing pain after TKA, it suffers several limitations, particularly delayed time to ambulation.[211,212] Several RCTs found no significant differences between epidural analgesia and peripheral nerve blocks at any time point until 48 h after surgery. Also, RCTs comparing epidural analgesia and LIA favoured the use of LIA, as it provides similar pain relief and does not negatively affect early rehabilitation. Therefore, epidural analgesia is not recommended for management of pain after TKA. The analysis of the RCTs using PROSPECT criteria is in agreement with the conclusions of the published meta-analysis and systematic reviews.[95,96]

FNB was widely used to control postoperative pain and opioid consumption after TKA,[3,5] although it only covers pain from the antero-medial part of the knee, leaving the posterior knee uncovered. However, FNB induces quadriceps weakness, which, combined with the muscle loss after knee surgery, may impair postoperative mobilisation.[115] Also, continuous blocks have been incriminated in the risk of falls.[213] Therefore, it has been replaced with ACB, which demonstrates similar analgesic efficacy to FNB but seems to better preserve quadriceps function.[214] Single shot ACB has been used as a rescue block to control pain on the first or second postoperative day when it reduced pain at rest (92% success) but less so during active flexion (22% success).[155] As ACB have analgesic effects limited to the anteromedial aspect of the knee, leaving the lateral and posterior compartments untargeted, the use of complementary blocks, such as LIA is recommended.

Since its first description in 2008 by Kerr and Kohan,[215] LIA has demonstrated consistent benefits in terms of postoperative analgesia and opioid-sparing effect, allowing faster mobilisation and in some case earlier discharge when compared with 'older' analgesic techniques like intrathecal morphine and epidural analgesia. Of note, unlike other analgesic interventions, in which we used assessment of individual RCTs to determine the recommendation, the conclusions of meta-analyses were accepted as most included RCTs conformed to Prospect inclusion criteria. The NICE expert group reviewed evidence for best anaesthesia and analgesia techniques for knee replacement including costs involved with these techniques and recommends LIA and peripheral nerve blocks.[18] Also, LIA was considered cost-effective whereas nerve blocks were cost-effective only if administered by an experienced anaesthesiologist.[18] Overall, LIA is an effective, simple and minimally invasive analgesic technique, which should be considered as 'basic' analgesia in combination with paracetamol and NSIADs/COX-2-specific inhibitors. Of note, there was no additional analgesic benefit of adding posterior capsular infiltration to LIA,[216] particularly as it is not without risk of intravascular and neurological injury.

LIA generally includes infiltration of different knee compartments with a cocktail consisting of local anaesthetic (typically, bupivacaine or ropivacaine) and one or more drugs, such as epinephrine, ketorolac, clonidine, glucocorticoids and morphine. The addition of ketorolac, which was part of the original mixture described by Kerr and Kohan,[215] was claimed to provide further reduction of early postoperative pain scores, on top of NSAIDs and paracetamol,[217,218] but this is debatable when compared with concomitant use of a systemic dose of NSAID.[107,179] Similarly, the need for epinephrine in LIA is questionable.[219] The addition of glucocorticoids to local anaesthetic mixture has also been studied without definitive conclusion and without direct comparison with the systemic administration of the drug.[14,220] The use of liposomal bupivacaine has been evaluated in several RCTs but it did not demonstrate benefits over plain bupivacaine with regards to analgesic efficacy[221] or postoperative analgesic outcomes, functional outcomes and safety.[222] The risk of local anaesthetic systemic toxicity with LIA has been evaluated in several studies but not reported to be a problem. These studies used high-dose ropivacaine (300 to 400 mg), and reported free plasma levels of ropivacaine ranging from 0.37 to 1.35 $\mu g\,ml^{-1}$, which are lower than the toxicity threshold concentration of 1.5 $\mu g\,ml^{-1}$.[223]

The present review suffers from the limitations inherent in the included studies just like any other meta-analysis or systematic review. Also, these recommendations do not address pain management in patients undergoing re-operation or associated secondary surgical procedures. Neither did this review addresses one of the key goals of peri-operative pain management, patient stratification.[224] Also, several sub-groups of patients still experience severe acute postoperative pain despite standardised postoperative analgesia, such as those with preoperative chronic pain conditions, and those taking preoperative opioids.[225,226] Unfortunately, those patients remain excluded from most RCTs, so studies aiming to assess the benefit of specific intervention are too scarce. In addition, a modified methodology was utilised when the literature search was performed for systematic reviews and meta-analyses that evaluate analgesic interventions rather than searching individual RCTs. Thus, it is possible that some of the RCTs evaluating newer regional analgesia techniques for TKA (iPACK block, cryoneurolysis, genicular nerve block, saphenous nerve block methocarbamol and others) may not be included. However, based on the PROSPECT methodology, these analgesic interventions could not have been recommended because of limited evidence. A novel block, 'iPACK', which targets the interspace between the popliteal artery and the capsule of the posterior knee, has

promise as a good compromise between posterior knee analgesia and knee function.[227] However, unlike LIA, which is easy to perform and has proven to be very safe and effective, iPACK uses ultrasound techniques that requires some expertise and is time consuming. A recent MRI and cadaveric study seems to show that saphenous nerve block is feasible from within the knee, and thus could be performed by the surgeon.[228]

It was observed that administration of basic analgesics (NSAIDs or COX-2-specific inhibitors combined with paracetamol) was missing in a significant number of RCTs, which precludes an objective evaluation of the benefits of the analgesic intervention studied.[229] There was considerable heterogeneity between studies with regards to anaesthetic and analgesic techniques as well as variability in outcomes assessed. TKA patients represent a specific group of patients presenting with factors, which adversely influence postoperative pain, like long-lasting preoperative pain and opioid use (~28% of the patients filled an opioid prescription 1 month before their surgery).[230] However, studies evaluating analgesic interventions in this challenging group with chronic pain states, chronic opioid use, and psychiatric disorders are lacking.[225,231] It is possible that analgesic interventions not recommended because of limited analgesic efficacy and/or concerns of adverse effects, may be appropriate in patients at high risk of postoperative pain or in situations where the currently recommended interventions are not possible. Also, studies assessing the effects of analgesic interventions on functional outcomes, which is mandatory for rehabilitation, hospital length of stay, persistent postoperative pain and patient-related outcomes, are lacking. Although enhanced recovery pathways are increasingly implemented, none of the included studies reported use of such protocols,[232] and there are no high-quality studies to assess the relative importance of the different analgesic techniques to facilitate an outpatient TKA facility. Recent reviews on the effect of peripheral nerve blocks on postoperative outcomes in TKA have supported their use,[233] but it is noteworthy that this evidence is not built on studies with a short 1 to 2 days or an outpatient TKA facility, thereby limiting conclusions for current practice in many places.

Conclusion

The present review identified an optimal analgesic regimen for unilateral, primary TKA (Table 1). Analgesic interventions that could not be recommended were also identified (Table 2). Future well designed studies should evaluate the analgesic interventions in comparison with the use of co-analgesics (paracetamol, NSAIDs, local infiltration analgesia and glucocorticoid) instead of being placebo-controlled studies.[14,234] Furthermore, these studies should focus on enhanced recovery programs[232] with regards to early ambulation and patient-related outcomes. Also, studies assessing analgesic techniques in specific challenging patient groups are urgently needed.

Table 1 Overall recommendations for pain management following primary total knee arthroplasty

Preoperative and intra-operative
Paracetamol and nonsteroidal anti-inflammatory drugs or cyclo-oxygenase-2 specific inhibitors, administered either preoperatively or intra-operatively
Single shot adductor canal block administered preoperatively and peri-articular local infiltration analgesia administered intra-operatively. Combination of these two techniques is preferred
Dexamethasone (≥10 mg, i.v.) administered intra-operatively
Intrathecal morphine (100 μg) may only be considered only in hospitalised patients when surgery is performed under spinal anaesthesia and in the situation wherein both adductor canal block and local infiltration analgesia are not possible
Postoperative
Paracetamol and nonsteroidal anti-inflammatory drug or cyclo-oxygenase-2 specific inhibitors
Opioids should be reserved as rescue analgesics

i.v., intravenously.

Table 2 Analgesic interventions that are not recommended for pain management following primary total knee arthroplasty

Intervention	Reason for not recommending
Gabapentinoids	Minimal analgesic and opioid-sparing effects and concerns of potential adverse effects, particularly when combined with postoperative opioids, which are typically high for total knee arthroplasty
Ketamine	Conflicting evidence
Dexmedetomidine	Inconsistent evidence
Epidural analgesia	Potential adverse effects precluding rapid recovery
Femoral nerve block	Negative impact on functional recovery
Sciatic nerve block	Negative impact on functional recovery

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