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REVIEW ARTICLE

A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty

H. B. J. Fischer,[1] C. J. P. Simanski,[2] C. Sharp,[3] F. Bonnet,[4] F. Camu,[5] E. A. M. Neugebauer,[6] N. Rawal,[7] G. P. Joshi,[8] S. A. Schug[9] and H. Kehlet[10]

1 Consultant in Anaesthesia and Pain Management, Department of Anaesthesia, Alexandra Hospital, Redditch, UK
2 Trauma and Orthopaedic Surgeon, Department of Trauma and Orthopaedic Surgery Cologne-Merheim, University of Witten-Herdecke, Cologne, Germany
3 Associate Medical Writer, Choice Pharma, Hertfordshire, UK
4 Chairman, Departement d'Anesthésie Réanimation, Hôpital Tenon, Paris, France
5 Professor Emeritus, Flemish Free University of Brussels, Brussels, Belgium
6 Chairman of Surgical Research, Institute of Research in Operative Medicine, University of Witten-Herdecke, Cologne, Germany
7 Professor, Department of Anaesthesia and Intensive Care, Örebro Medical Center Hospital, Örebro, Sweden
8 Professor of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, USA
9 Professor of Anaesthesiology, School of Medicine and Pharmacology, University of Western Australia, Royal Perth Hospital, Perth, WA, Australia
10 Professor of Perioperative Therapy, Section for Surgical Pathophysiology, The Juliane Marie Centre, Copenhagen, Denmark

Summary

The PROSPECT Working Group, a collaboration of anaesthetists and surgeons, conducts systematic reviews of postoperative pain management for different surgical procedures (http://www.postoppain.org). Evidence-based consensus recommendations for the effective management of postoperative pain are then developed from these systematic reviews, incorporating clinical practice observations, and transferable evidence from other relevant procedures. We present the results of a systematic review of pain and other outcomes following analgesic, anaesthetic and surgical interventions for total knee arthroplasty (TKA). The evidence from this review supports the use of general anaesthesia combined with a femoral nerve block for surgery and postoperative analgesia, or alternatively spinal anaesthesia with local anaesthetic plus spinal morphine. The primary technique, together with cooling and compression techniques, should be supplemented with paracetamol and conventional non-steroidal anti-inflammatory drugs or COX-2-selective inhibitors, plus intravenous strong opioids (high-intensity pain) or weak opioids (moderate- to low-intensity pain).

Correspondence to: Dr H. B. J. Fischer
E-mail: barrie.fischer@worcsacute.nhs.uk
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Total knee arthroplasty (TKA) is a major orthopaedic procedure that is commonly performed in patients with degenerative disease of the knee joint and can relieve disabling joint pain, restore mobility, and improve quality of life. Despite the beneficial long-term effects [1], the procedure is associated with intense early postoperative pain, and effective analgesia is paramount. Patients are usually elderly with comorbid diseases and it is important to choose an anaesthetic and analgesic regimen that will minimise side effects as well as providing suitable pain relief. The impact of surgical and non-pharmacological techniques on postoperative pain and recovery also needs

to be considered. Optimal peri-operative analgesia will enhance functional recovery, including timely recovery of knee mobility, and reduce postoperative morbidity.

This is probably the first comprehensive, systematic review of randomised controlled trials of analgesic, anaesthetic and surgical interventions influencing post-operative pain in adult patients undergoing TKA. The primary outcome measure was postoperative pain, with supplementary analgesic use, functional postoperative recovery and adverse events as secondary outcome measures. The recommendations for pain management are based on the evidence from the systematic review and are also derived, where necessary, from consensus agreements between the members of the Working Group. Complementary data and recommendations are also available online at http://www.postoppain.org [2], together with further details of the individual studies.

Methods

The character, intensity and duration of pain vary between different surgical procedures; thus, the risk vs benefit profile of different analgesic techniques changes depending on the procedure undertaken. A technique may therefore be recommended for some procedures and not for others, and so the PROSPECT Working Group conducts systematic reviews of analgesic techniques on a procedure-specific basis.

Literature search strategy

A systematic review of the literature from 1966 to November 2005 using MEDLINE and EmBASE, was carried out following the protocol of the Cochrane Collaboration, using the following search terms relating to pain and interventions for TKA: pain, analgesia, anaesthe*, 'vas', 'visual analogue', VRS, epidural, neuraxial, intrathecal, spinal, caudal, 'peripheral nerve', 'peripheral block', 'femoral*', '3-in-1 block', 'sciatic nerve', 'psoas compartment', 'lumbar plexus', NSAID, COX-2, paracetamol, acetaminophen, gabapentin, pregabalin, clonidine, opioids, ketamine, corticosteroid, intra-articular, infusion, instillation, injection, unicondylar, bicondylar, 'minimal invasive', 'patella resurfacing', patellofemoral, parapatellar, midvastus, drainage, 'activities of daily living', 'joint mobility', cryoanalgesia, 'cold therapy 'knee replacement', 'knee prosthes*', 'revision prosthes*, 'total knee', 'knee arthroplasty', 'major lower limb surgery'.

Study inclusion criteria

English language randomised studies were included if they had a defined adult population undergoing TKA, and if they assessed postoperative pain scores using a visual analogue scale (VAS), verbal rating scale (VRS) or numerical rating scale (NRS). In studies with mixed surgical procedures (hip and knee arthroplasty), there had to be a defined TKA subgroup, which fulfilled our study criteria for the study to be included.

Study quality assessment

The validity of the systematic review is determined by the quality of the included studies, as this determines the level of evidence and thereby the grades of recommendation [3].

The following criteria were used to assess the quality of the methodology and results that were reported in each cited study:

1 Statistical analyses and patient follow-up assessment: whether statistical analyses were reported and whether patient follow-up was greater or lesser than 80%.
2 Allocation concealment assessment: whether there was adequate prevention of foreknowledge of treatment assignment by those involved in recruitment (A adequate, B unclear, C inadequate, D not used). Concealment of the assignment schedule, performed before randomisation helps to eliminate selection bias; blinding, performed after randomisation, reduces performance and detection biases.
3 Numerical scores (total 1 to 5) for study quality: assigned using the method proposed by Jadad [4], to indicate whether a study reports appropriate randomisation, double-blinding and statements of possible withdrawals. In studies comparing interventional and pharmacological techniques where true double blinding is not possible unless sham interventions are used, allocation concealment is particularly important.
4 Additional study quality assessment: including an assessment of how closely the study report meets the requirements of the CONSORT statement [5, 6].

Outcomes

Summary information for each included study was extracted and recorded in data tables. This information included pain scores, as well as supplementary analgesic use, time to first analgesic request, functional outcomes and adverse effects. Postoperative pain scores were assumed to be recorded at rest, unless otherwise specified in the study report.

Analyses of outcomes

Studies were stratified according to regimen (analgesic, anaesthetic or operative), mode of delivery (local, systemic, neuraxial) and class of agent. Each outcome was evaluated qualitatively for each intervention by looking at the overall pattern of effectiveness as reported in the study publications.

Meta-analyses

In addition to qualitative analyses, meta-analyses were performed on postoperative outcomes where appropriate using REVIEW MANAGER software (RevMan, version 4.2 for Windows; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2003), which calculates the weighted mean differences (WMD) for continuous data, between active and control groups for each study, with an overall estimate of the pooled effect. The REVIEW MANAGER software performs heterogeneity analyses; data that were not significantly heterogeneous ($p > 0.10$) were analysed using a fixed effects model, and heterogeneous data ($p \leq 0.10$) were analysed using a random effects model. Means and standard deviations were extracted from the text, tables or graphs within the studies. For quantitative analyses, pain scores on VRS or NRS scales were converted to VAS pain scores by adjusting to a standardised 0–100 mm scale. Studies could not be included in the meta-analyses if they did not report mean and standard deviation (SD) or standard error of the mean (SEM), or the number of patients. Overall, few meta-analyses could be performed as there were a limited number of studies of homogeneous design that reported similar outcome measures. Therefore, the majority of the procedure-specific evidence was assessed only qualitatively. In this paper we present only the meta-analyses figures that included data from three or more studies (figures show results for 24 and 48 h measurements only).

Other sources of information used for recommendations

Evidence-based recommendations for clinical practice are based on the systematic review outcomes for TKA-specific evidence, but this evidence is also supplemented by data from studies in other procedures (transferable evidence). Transferable evidence of analgesic efficacy from comparable procedures with similar pain profiles, or evidence of other outcomes such as adverse effects, has been included to support the procedure-specific evidence where this is insufficient to formulate the recommendations [7].

Many studies identified in the literature search included patients undergoing total knee or hip arthroplasty and reported data pooled from all of these patients. Such studies are excluded from the procedure-specific systematic review but have been used as additional transferable evidence where relevant and where additional supporting data are required. Data from other orthopaedic procedures (e.g. anterior cruciate ligament reconstruction, spinal surgery) were not used for transferable evidence of analgesic efficacy because it was considered that the pain profile of these procedures was too different from that of TKA. However, data from studies in a variety of procedures have been used for evidence of adverse-effects, which may occur regardless of the procedure.

Clinical practice information was also taken into account to ensure that the recommendations have clinical validity. The recommendations were formulated using the Delphi method [8] to collate rounds of individual comments on the evidence and draft recommendations, followed by round-table discussion and further Delphi rounds to achieve final consensus [3].

Results

In all, 112 randomised studies were included in the systematic review [9–120] and 135 were excluded, largely because they lacked a defined group of TKA patients within a mixed study population (51 studies) or pain scores were not reported (39 studies). There were 74 studies of pharmacological pain control: allocation concealment was considered adequate in 43 trials and unclear in 31 trials. There were 20 studies of surgical techniques (with allocation concealment deemed adequate in 14 trials and unclear in six trials) and 18 of non-pharmacological (rehabilitation and physical therapy) techniques (allocation concealment was considered adequate in seven trials and unclear in 11 trials). Summaries of these studies can be found in Tables 1 and 2.

Detailed tables and text are available on the http://www.postoppain.org website [2], summarising each included study (number of patients, drug type, dose, route and timing of administration plus outcomes for VAS scores, time to first analgesic request and the use of supplemental analgesics, functional recovery outcomes and adverse effects) and their methodological quality scores (allocation concealment score, Jadad quality score and Level of Evidence). Excluded studies are also tabulated with the reasons for exclusion. Qualitative data were reported for all included studies but few quantitative analyses could be performed because of the limited number of studies of homogeneous design that reported similar outcome measures, which could be pooled for comparison.

In these analyses, Table 1 provides a summary of those interventions that were investigated in three or more studies. As pain scores and analgesic use were often assessed repeatedly during the course of a study, individual assessments in the table indicate whether these parameters decreased at majority of time points (at more than half of the time-points measured), decreased at minority of time points (at fewer than half of the time-points measured), remained unchanged, or increased. In the summarised data in Table 2, interventions that were investigated in

Table 1 Interventions evaluated in three or more studies.

Type of comparison	Intervention studied	Effect on pain scores	Effect on supplemental analgesia	Effect on time to first analgesic request
Treatment vs placebo/sham/no treatment control/systemic analgesia	Systemic conventional NSAID [9–11]	▼ [11] (diclofenac) ↓ [11] (ketoprofen) NS [9, 10]	▼ [9, 10]* ↓ [11] (ketoprofen and diclofenac)	n/a
	COX-2-selective inhibitor [12–15]	▼ [12–15]	▼ [12, 13, 15]	▲ [14]
	Single injection femoral nerve block [25–32]	▼ [26, 29, 30] ↓ [25, 27, 28] NS [31, 32]	▼ [27, 28, 30] ↓ [26] NS [25, 29, 32]	n/a
	Continuous infusion femoral nerve block [25, 33–36]	▼ [33–36] ↓ [25]	▼ [33, 35, 36] NS [25, 34]	n/a
	Pre-operative spinal opioid (spinal LA anaesthesia in both groups) [38–42]	▼ [38–41] NS [42]	▼ [38] ↓ [39] NS [41, 42]	▲ [41, 42]
	Postoperative (± before end of surgery) lumbar epidural opioid [18, 44–46]	▼ [46] ↓ [18] NS [44, 45]	▼ [18, 44, 45]	n/a
	Lumbar epidural LA + opioid (with or without clonidine) [34, 49–51]	▼ [34] ↓ [49, 50] ▲ [51]	▼ [49–51] NS [34]	n/a
	Postoperative (± pre-operative) lumbar epidural LA [31, 47, 48]	▼ [48] NS [31, 47]	▼ [47] ↓ [48]	n/a
	Postoperative (± before end of surgery) lumbar epidural opioid [18, 44–46]	▼ [46] ↓ [18] NS [44, 45]	▼ [18, 44, 45]	n/a
	Postoperative intra-articular LA + morphine [54–56]	▼ [56] ↓ [54] NS [55]	▼ [55, 56]† NS [54]	▲ [56]
	Intra-/postoperative intra-articular morphine (systemic analgesia available to all patients) [45, 54, 55]	↓ [54] NS [45, 55]	▼ [55]† NS [45, 54]	n/a
	Postoperative intra-articular LA bolus [54, 55, 57]	↓ [54] NS [55, 57]	▼ [57] NS [54, 55]	n/a
Comparisons of regional analgesia techniques	Postoperative intra-articular morphine + LA vs intra-articular LA alone [54, 55, 57]	NS [54, 55, 57]	▼ [55]† NS [54, 57]	n/a
	Postoperative intra-articular morphine vs intra-articular LA [54, 55, 57]	NS [54, 55, 57]	▼ [55]† NS [54, 57]	n/a
	Postoperative intra-articular LA + morphine vs morphine alone [54, 55, 57]	NS [54, 55, 57]	NS [54, 55, 57]	n/a
Operative techniques	Drainage vs no drainage [58–60]	NS [58–60]	NS [58]	n/a
	Tourniquet vs no tourniquet [65–67]	↓ [66] NS [67] ▲ [65]	NS [66, 67] ▲ [65]‡	n/a
	Patellar resurfacing vs no resurfacing [72–78]	↓ (OP) [75–78] NS (OP) [74] NS (KS) [72–76, 78]	n/a	n/a
Non-pharmacological techniques	Continuous passive motion machine vs control [79–82]	▼ [81] NS [79, 80, 82]	NS [80, 81]	n/a

*Supplemental co-dydramol was reduced, but not morphine.
†Supplemental morphine was reduced, but not ketorolac or pethidine.
‡Supplemental IM analgesic use was greater, but not oral analgesic use.
▼, decreased at majority of time points; ↓, decreased at minority of time points; ▲, increased. NS, not significant; n/a, not applicable; KS, Knee Society Pain Scores; OP, other measures of pain; LA, local anaesthesia; NSAID, non-steroidal anti-inflammatory drug.

fewer than three studies are detailed. Studies were individually assessed and results were deemed inconclusive if responses were mixed and neither increased nor decreased at a majority of time points.

Pharmacological agents and techniques

The 74 trials in this section are grouped into two categories: systemic analgesia and regional anaesthesia

Table 2 Interventions evaluated in fewer than three studies.

Type of comparison	Intervention studied	Effect on pain scores
Treatment vs placebo/sham/ no treatment control	Postoperative extended-release strong opioid [16, 17]	Strong opioid superior
	Pre-operative IM morphine [18]	Inconclusive results
	IM dextromethorphan [20]	Inconclusive results
	IV ketamine [21]	NS compared with control (at rest or after mobilisation)
	Oral clonidine [22]	NS compared with placebo
	SI combined femoral-sciatic NB [26, 92]	Inconclusive results
	SI combined obturator and femoral NB [32]	NB superior to placebo
	Continuous lumbar plexus NB [36, 37]	Inconclusive results
	Pre-incisional epidural strong opioid [18]	Inconclusive results
	Bedside femoral NB [93]	Inconclusive results
	Pre-incisional intra-articular bupivacaine [94]	NS
	Intra-articular bupivacaine bolus [95]	Inconclusive results
	Postoperative continuous intra-articular bupivacaine [96]	NS
Comparison of systemic analgesia	Strong opioid vs COX-2-selective inhibitor [14]	COX-2-selective inhibitor superior to opioids
	Diclofenac vs ketoprofen [11]	NS
	COX-2-selective inhibitor vs conventional NSAID [14]	NS
Comparisons of regional analgesia techniques	SI combined obturator and femoral NB vs femoral NB [32]	Combined obturator and femoral NB superior
	Combined femoral-sciatic NB vs femoral NB (SI [26] or continuous infusion [97])	Inconclusive results
	SI combined obturator and femoral-sciatic NB vs femoral-sciatic NB [98]	NS
	Continuous lumbar plexus NB vs continuous femoral NB [36]	NS at rest or during physiotherapy
	Continuous infusion vs patient-controlled femoral NB [99]	NS
	Spinal morphine vs SI femoral NB [100]	NS at rest or on movement
	Spinal block with GA vs combined sciatic and femoral 3-in-1 block with GA [101]	Inconclusive results
	Spinal LA anaesthesia with IV propofol vs IV fentanyl anaesthesia [102]	Inconclusive results
	Lumbar epidural anaesthesia/analgesia vs spinal anaesthesia plus intravenous opioid [103]	Epidural superior during ROM, inconclusive at rest
	Lumbar epidural analgesia vs continuous infusion femoral NB [34], vs SI combined femoral and sciatic NB [104], vs SI femoral NB [31]	Inconclusive results [34], [104] NS [31]
	PCEA vs continuous infusion epidural analgesia [105]	NS
Components of spinal solution	Morphine (with or without clonidine) [39, 41, 106]	Inconclusive results compared with saline, neostigmine and diamorphine
	Neostigmine [41]	Neostigmine superior to saline; inconclusive results compared with morphine
	Diamorphine [106]	Inconclusive results compared with morphine
Components of lumbar epidural solution (as adjuncts to local anaesthetics, opioids, or both)	Morphine [18], meperidine [107], fentanyl [107] or tramadol [108]	Inconclusive results for morphine vs placebo; meperidine but not fentanyl superior to no opioid; morphine superior to tramadol for pain scores at rest and on movement
	Ketamine [52, 109]	Inconclusive results compared with placebo
	Clonidine [110]	Inconclusive results compared with no clonidine
	Lidocaine [111], bupivacaine [112, 113] or ropivacaine [113]	Lidocaine superior to control; NS bupivacaine vs no bupivacaine; inconclusive results for bupivacaine vs ropivacaine
Components of solution via peripheral NB catheter	Clonidine [114]	NS at rest or on movement compared with no clonidine
	Adrenaline [115]	NS compared with no adrenaline
	Ropivacaine [30, 92], bupivacaine [30, 92]	NS
Timing of administration	Oral and IV conventional NSAID [10]	NS pre- + postoperative vs postoperative administration
	Lumbar epidural bupivacaine plus opioid [116]	NS pre- + postoperative vs postoperative administration
	Lumbar epidural lidocaine plus ketamine plus morphine [111]	Inconclusive results pre- vs post-incision
	Intra-articular bupivacaine [94]	NS pre- vs postoperative

Table 2 (*Continued*).

Type of comparison	Intervention studied	Effect on pain scores
Drug dose response	Parecoxib 40 vs 20 mg [14]	40 mg superior
	Tramadol loading dose [19]	Inconclusive
	Ropivacaine via femoral catheter [117]	NS
	Bupivacaine via femoral catheter [35]	NS
	Spinal diamorphine [42]	NS
	Spinal morphine [43]	NS
	Lumbar epidural ketamine [52]	NS
	Lumbar epidural ropivacaine [50, 53]	Inconclusive
Route and method of drug administration	IV vs IM strong opioid [23]	NS
	IV PCA vs IM strong opioid [24]	IM superior for moderate pain scores
Surgical approaches	Medial trivector approach [61], Subvastus approach [62], vs parapatellar approach	NS
	Posterior cruciate ligament (PCL) surgery during TKA: different surgical approaches [63]	PCL released surgery inferior to other approaches
	Midvastus approach vs medial parapatellar approach [64]	Midvastus superior at rest and on movement
Operative techniques	Mobile-bearing prosthesis vs fixed-bearing prosthesis [69]	Mobile-bearing prosthesis superior
	Uncemented tricompartmental prosthesis: comparison of different designs [70]	NS at rest; Tricon stem design superior during activity at 4 years
	Cemented vs cementless prostheses [71]	NS
Non-pharmacological techniques	Timing of tourniquet release [68]	Release before suturing superior to release after suturing
	Cooling and compression techniques: Cryo/Cuff® vs control [47, 89]	Cryo/Cuff® superior
	Cold compressive dressing vs standard compressive dressing [118]	Inconclusive
	Compression bandaging [119], Robert Jones bandage [120], epidural analgesia [47], vs cryotherapy	NS
	Accelerated/intensive rehabilitation vs control [85, 86]	Inconclusive
	Physiotherapist home visits vs outpatient [88]	NS
	Cardiovascular conditioning [83] or physical therapy [84] vs control	NS
	Continuous passive motion machine vs lower limb mobility board [87]	NS
	TENS, 40 mA vs 14 mA [90]	NS
	Pre-operative pain management and pain communication film vs pain management film only vs standard care [91]	NS

NS, no significant difference; NB, nerve block; SI, single injection.

techniques. The systemic analgesia trials compare active intervention groups of analgesics [paracetamol, conventional non-steroidal anti-inflammatory drugs (NSAID), COX-2-selective inhibitors, weak opioids, and strong opioids] with either a control or placebo group. Trials of NMDA antagonists and clonidine were also included. The regional techniques compared active intervention groups of either central neuraxial blocks (spinal or epidural) or peripheral nerve block techniques (femoral, sciatic, obturator, lumbar plexus) with control groups.

Systemic analgesia

Conventional NSAID

Three studies compared systemic conventional NSAID with placebo (piroxicam [9], tenoxicam [10], ketoprofen and diclofenac [11]). One study showed that conventional NSAID was superior to placebo for reducing pain scores [11], and in all three studies conventional NSAID was superior to placebo for reducing supplemental analgesic use [9–11] (see Table 1).

COX-2-selective inhibitors

Four studies compared COX-2-selective inhibitors with placebo (rofecoxib [12], parecoxib [13, 14], valdecoxib [15]). COX-2-selective inhibitors were superior to placebo for decreasing pain scores in all four studies up to 3 days after surgery; three of three studies demonstrated reduced supplemental analgesic use with COX-2-selective inhibitors [12, 13, 15]. One study also showed that the time to first analgesic request was significantly longer with parecoxib compared with placebo [14] (see Table 1).

Strong opioids
Two studies compared extended release strong opioid with placebo included (oxymorphone [16], oxycodone [17]) and both demonstrated superiority of strong opioid compared with placebo for decreased postoperative pain scores and analgesic use (see Table 2). The effects of pre-operative IM morphine were inconclusive [18].

Weak opioids
One study investigated the effects of tramadol at varying loading doses (1.25, 2.5, 3.75 and 5 $mg.kg^{-1}$; [19] but found no significant differences between groups with regard to pain scores (see Table 2).

NMDA antagonists
Two studies were included, one compared IM dextromethorphan with control [20] the other compared IV ketamine with control [21]. Dextromethorphan demonstrated lower pain scores compared with the control group but only at two of the seven time-points assessed. There were no significant differences in pain scores between ketamine and control in the other study (see Table 2), however, in both studies morphine consumption was reduced.

Clonidine
One study compared oral clonidine with placebo [22], and showed no significant differences in pain scores between groups (see Table 2), but did show a reduction in morphine use.

Timing and route of administration
Three studies in Table 2 showed no effect of the timing of NSAID administration [10] or the route of opioid administration on analgesia [23, 24].

Regional anaesthesia

Peripheral nerve blocks
Six of eight studies demonstrated reduced pain scores with single injection femoral nerve block (FNB) compared with placebo/no treatment/systemic analgesia [25–30]; quantitative analysis of VAS scores showed a significant decrease in VAS scores for single injection FNB vs sham block during motion/physical therapy at 24 h (three studies, WMD −15.07 mm [−24.71, −5.42], p = 0.002) and at 48 h (three studies, WMD −11.75 mm [−20.33, 3.18], p = 0.007; see Fig. 1a,b), but there was no significant effect on VAS pain scores at rest at 24 h (three studies, WMD −10.29 mm [−26.29, 5.71], p = 0.21) or at 48 h (three studies, WMD −5.62 mm [−13.81, 2.56], p = 0.18; see Fig. 1c,d). Four of seven studies showed significantly lower supplemental analgesic use with single injection FNB compared with placebo/no treatment/systemic analgesia [26–28, 30]); quantitative analysis of supplemental post-operative analgesic use (morphine consumption in mg) showed a significant decrease with single injection FNB compared with placebo between 0 and48 h (two studies, WMD −25.93 mg [−49.66, −2.19], p = 0.03; see Fig. 1e).

Single injection FNB was associated with significant improvements in some functional outcomes in two of three studies compared with placebo or no treatment ([27, 29]; the remaining study [28] showed no significant differences between groups), but seven of eight studies found that the incidence of postoperative nausea and vomiting (PONV) was not significantly different between groups [26–32].

Five out of five studies reported reduced pain scores with continuous infusion FNB compared with placebo/no treatment [25, 33–36]; quantitative analysis of VAS scores showed a significant benefit for continuous infusion FNB vs sham block at rest at 24 h (four studies, WMD −14.24 mm [−25.64, −4.85], p = 0.004) and at 48 h (three studies, WMD −6.77 [−12.20, −1.34], p = 0.01), and during motion/physical therapy at 24 h (three studies, WMD −10.71 mm [−18.40, −3.02], p = 0.006) and at 48 h (three studies, WMD −15.34 mm [−22.19, −8.48], p < 0.0001; see Fig. 2a–d). Three out of five studies showed significantly reduced supplemental analgesia use [33, 35, 36] (one arm).

Continuous infusion FNB was associated with significant improvements in some functional outcomes in two out of two studies compared with placebo or no treatment [34, 35], but three out of four studies found that the incidence of PONV was not significantly different between groups [34, 35, 37].

In several studies investigating alternative nerve block techniques (sciatic, femoral, obturator, lumbar plexus), the results for pain scores were not significant or were inconclusive. Addition of different components to the peripheral nerve block solution (ropivacaine or bupivacaine, clonidine or adrenaline) had no significant effect on pain scores (see Table 2).

Spinal techniques
Four out of five studies reported significantly lower pain scores up to 24 h with pre-operative spinal opioid vs control [38–41]; two out of four studies showed a decrease in rescue analgesic use [38, 39] and two out of two studies reported an increase in the time to first analgesic request [41, 42] with spinal opioid compared with control (see Table 1). Four out of five studies that reported PONV found that the incidence was not significantly different between spinal opioid and control [38, 39, 41, 42].

Comparisons of spinal opioid with other regional analgesia techniques in several studies were either not

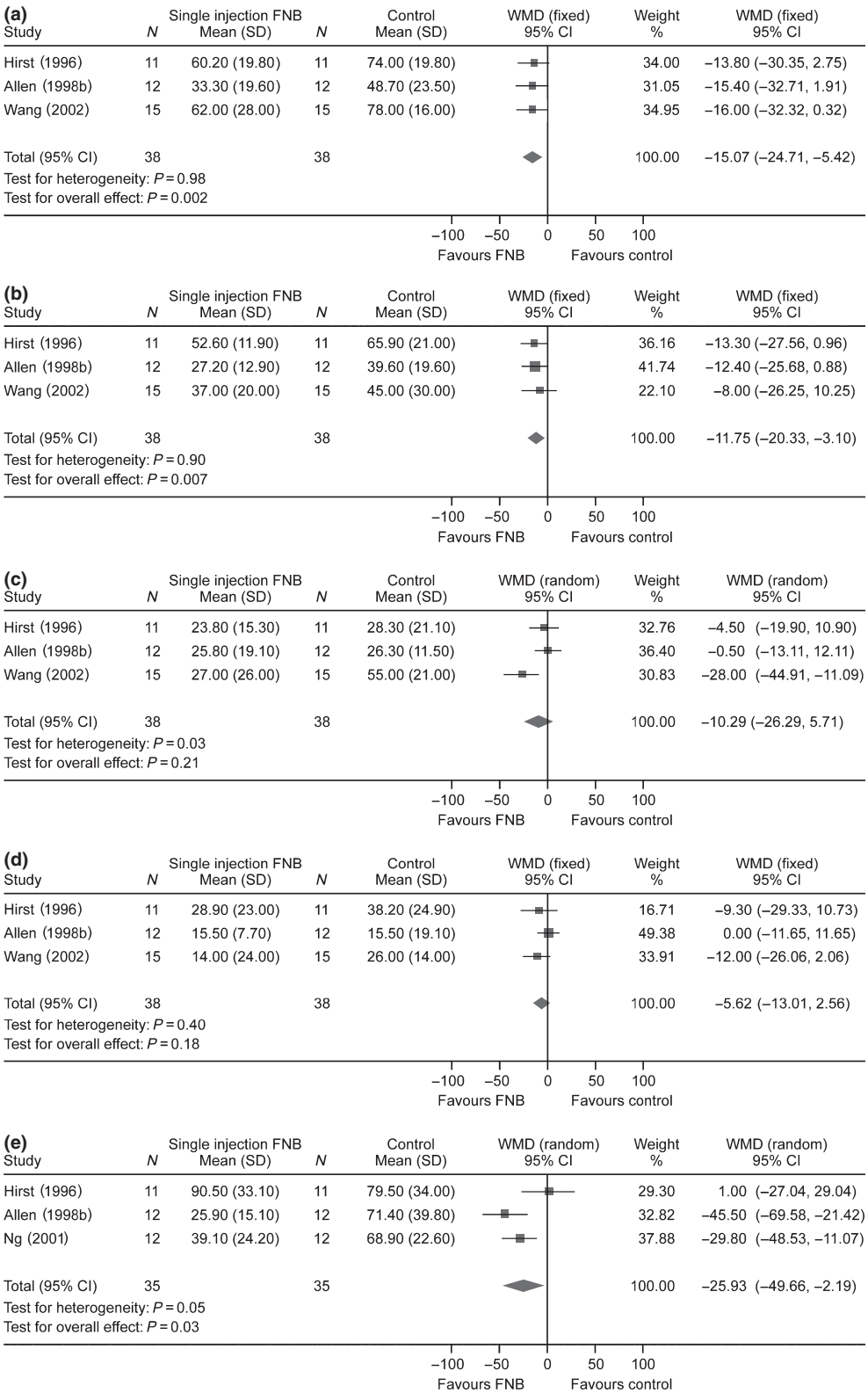

Figure 1 The effect of single injection femoral nerve block (FNB) vs sham block (control) on (a) VAS pain scores (mm) during motion/physical therapy at 24 h (b) VAS pain scores (mm) during motion/physical therapy at 48 h (c) VAS pain scores (mm) at rest at 24 h (d) VAS pain scores (mm) at rest at 48 h (e) the use of supplemental analgesia from 0 to 48 h.

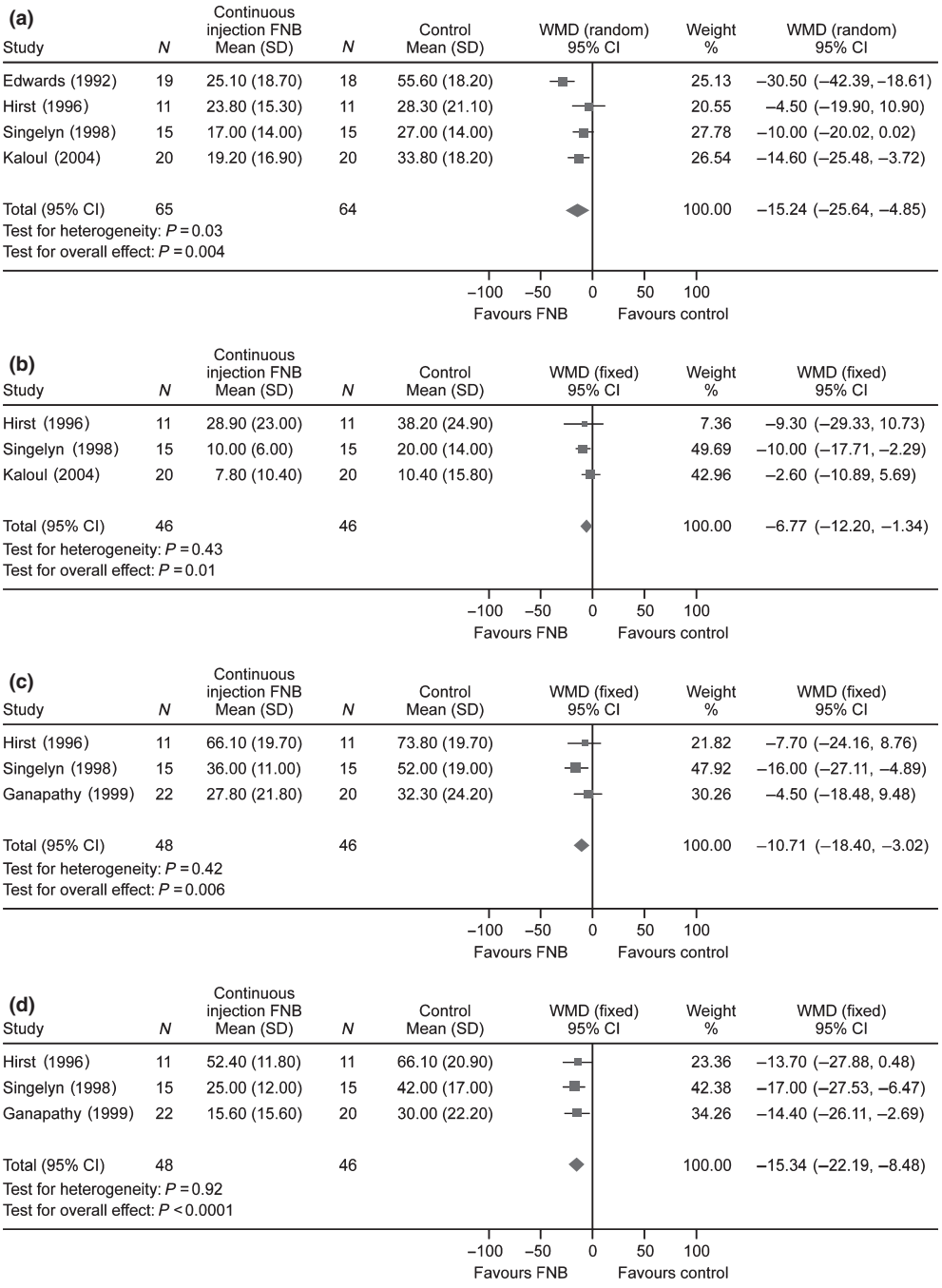

Figure 2 The effect of continuous infusion femoral nerve block (FNB) vs sham block/no treatment (control) on (a) VAS pain scores (mm) at rest at 24 h (b) VAS pain scores (mm) at rest at 48 h (c) VAS pain scores (mm) during motion/physical therapy at 24 h (d) VAS pain scores during motion/physical therapy at 48 h.

significant or inconclusive (see Table 2). Addition of different components to the spinal solution demonstrated mixed results for pain scores. Dose-response studies with diamorphine [42] and morphine [43] showed no significant differences between doses in terms of pain scores (see Table 2).

Epidural techniques

Three studies out of three showed that rescue analgesic consumption was lower with lumbar epidural opioid compared with placebo/systemic analgesia ([18, 44, 45]; although the Klasen study did not report a p value), but effects on pain scores were mixed in four studies

[18, 44–46]). In four out of four studies, the incidence of PONV was similar with lumbar epidural morphine and placebo/systemic analgesia.

Two studies out of two showed that rescue analgesic use was lower with lumbar epidural local anaesthetic (LA) compared with placebo/systemic analgesia [47, 48], but effects on pain scores were not conclusive in three studies [31, 47, 48]. In two out of two studies [47, 48], functional outcomes and the incidence of complications were similar between groups.

Three out of four studies demonstrated superior pain scores with lumbar epidural LA + opioid (with or without clonidine) [34, 49, 50] and three out of four studies reported reduced supplemental analgesic use [49–51], compared with systemic analgesia. Two out of three studies showed no improvement in functional outcomes in the lumbar epidural LA + opioid group compared with the systemic analgesia group [34, 49, 51].

Addition of different components to the epidural solution (as adjuncts to local anaesthetics, opioids, or both) had inconclusive effects on pain scores (see Table 2). Lumbar epidural dose response studies showed no significant differences in pain scores for ketamine [52] and inconclusive results with different doses of ropivacaine [50, 53] (see Table 2).

Intra-articular techniques

Three studies of intra-articular LA + morphine [54–56], three studies of intra-articular morphine [45, 54, 55], and three studies of intra-articular LA bolus [54, 55, 57] showed mixed results for pain scores and rescue analgesic use compared with placebo.

The three studies [54, 55, 57], which compared intra-articular LA + morphine vs intra-articular LA alone, intra-articular morphine vs intra-articular LA and intra-articular LA + morphine vs intra-articular morphine alone [54, 55, 57], showed no significant differences in pain scores and rescue analgesic use (see Table 1).

Non-pharmacological methods

There were 20 trials of surgical techniques and equipment (wound drain, surgical approach, tourniquet, type of prosthesis, patellar resurfacing) and 18 trials of physical therapies (rehabilitation techniques) and non-pharmacological analgesic treatment (cooling and compression techniques, transcutaneous nerve stimulation (TENS)). Many of the studies have limited or no effect on postoperative pain relief (see Tables 1 and 2).

Operative techniques

Drains

Three studies were included. The use of wound drains showed no benefit for pain scores or analgesic use compared with no drains in three out of three studies ([58–60]; see Table 1).

Surgical approach

Four studies were included that compared different surgical approaches for TKA surgery [61–64], but the results were inconclusive in terms of pain scores (see Table 2) given the limited number of studies for each technique.

Tourniquets

Three studies were included that compared the use of tourniquet vs no tourniquet (see Table 1), but effects on pain scores were mixed [65–67]. In one study [68], release of the tourniquet before suturing and bandaging was significantly superior to release after suturing and bandaging for reducing pain scores (see Table 2).

Prostheses

Three studies compared different types of prosthesis for knee replacement surgery [69–71], but they provided only limited data on the influence of the prosthesis on pain scores (see Table 2).

Patellar resurfacing

In seven studies of patellar resurfacing vs no resurfacing [72–78], six studies reported no significant difference in Knee Society Pain Scores at follow-up between patients with resurfaced patella compared with those with non-resurfaced patella. Four out of five studies showed that resurfacing was associated with superior pain control for other measures of pain, such as anterior knee pain [75–78].

Physical therapies and non-pharmacological techniques

Rehabilitation techniques

Four studies compared continuous passive motion (CPM) treatment with control [79–82]; three out of four studies reported no significant differences in pain scores between groups [79, 80, 82], and two out of two studies demonstrated no significant difference in supplemental analgesic use [80, 81] (see Table 1). Three studies measuring various functional outcomes reported superiority with CPM compared with control [80–82]. Studies reporting on the impact of different rehabilitation techniques [83–88] showed no significant differences between groups for pain scores (see Table 2).

Cooling and compression techniques

Two studies demonstrated lower morphine consumption with cooling and compression techniques vs control [47, 89], although only one study showed reduced pain compared with control [89] (see Table 2).

TENS

One study was included; TENS showed no significant effect on either postoperative pain management or functional improvement [90] (see Table 2).

Patient education

One study of pre-operative pain management and a pain management film vs a pain management film only vs standard care only showed no significant differences between groups [91].

Discussion

Total knee arthroplasty is a common procedure, but there is currently no evidence-based national or international consensus on overall pain management following TKA surgery. Early postoperative recovery and mobilisation is improved by effective pain control, but postoperative pain management can be influenced at an institutional level by factors such as local experience and skills (particularly for regional techniques), custom and practice, as well as cultural and social preferences. Over 59 000 TKA procedures were carried out in England and Wales in 2005 [121], and approximately 478 000 operations were performed in the USA in 2004 [122]. Despite the large number of TKA operations performed annually, relatively few of the studies initially identified were eligible for inclusion in this systematic review and the quality of these studies points towards a need for future improvements in study design, data analysis and reporting. A recent systematic review of epidural analgesia and peripheral nerve blocks for TKA also noted the lack of suitable publications for inclusion, finding only eight studies which fulfilled their review criteria [123].

Since the strength of a systematic review depends entirely on the quality of the published studies, it may be considered too rigid for determining clinically useful advice. The interventions, drugs, doses or routes of administration in published studies may no longer be appropriate in current practice; alternatively, some pain management techniques may have been introduced into current clinical practice without being subjected to a rigorous comparative study, thus decreasing the clinical relevance of the review. By combining procedure-specific evidence, transferable evidence from other appropriate surgical procedures, and current clinical best practice, this review has produced clinically relevant, evidence-based recommendations for postoperative pain management in TKA.

Recommendations for postoperative analgesia in TKA

The recommendations below are graded A–D according to the overall level of evidence (LoE), which is determined by the quality of studies cited, the consistency of evidence and the source of evidence. Transferable evidence is cited at http://www.postoppain.org [2] and the overall recommendations are summarised in Table 3.

- Postoperative conventional NSAID are recommended (grade A) for their analgesic and opioid-sparing effect (procedure-specific, LoE 1; transferable evidence, LoE1). They are recommended in combination with strong opioids for high-intensity pain (grade D, LoE 4), or with weak opioids for moderate- or low-intensity pain (grade D, LoE 4), and/or with paracetamol (grade D, LoE 4). No recommendations can be made at this time about combining postoperative conventional NSAID with regional analgesia techniques because of a lack of data. The use of conventional NSAID should depend upon assessment of individual patient risks (grade B), including bleeding complications, actual or recent gastroduodenal ulcer history (transferable evidence, LoE 1), cardiovascular morbidity (LoE 4), aspirin-sensitive asthma, renal function and hepatic function (transferable evidence, LoE 3). Limited data show that conventional NSAID may have dose- and duration-dependent detrimental effects on bone healing (transferable evidence, LoE 1; [124, 125]).

Table 3 Overall PROSPECT recommendations for total knee arthroplasty. The columns show the anaesthetic technique, systemic analgesia and non-drug interventions recommended for each of the situations shown in the rows.

	Anaesthesia/regional analgesia		Systemic analgesia	Non-pharmacological techniques
Pre-/intra-operative	GA + femoral nerve block	Spinal LA + morphine (but not as the first choice)		
Postoperative high-intensity pain	Continuing femoral nerve block (or spinal/spinal morphine) effect		Conventional NSAID/COX-2-selective inhibitors + strong opioids, titrated to effect + paracetamol	Cooling and compression techniques
Postoperative low-intensity pain	Residual femoral nerve block (or spinal morphine) effect		Conventional NSAID/COX-2-selective inhibitors ± weak opioids, titrated to effect + paracetamol	Cooling and compression techniques

- Postoperative COX-2-selective inhibitors are recommended (grade A) based on their reduction in pain scores and supplemental analgesic requirements (procedure-specific evidence, LoE 1). They are recommended in combination with strong opioids for high-intensity pain (grade D, LoE 4), or with weak opioids for moderate- or low-intensity pain (grade D, LoE 4), and/or with paracetamol (grade D, LoE 4). Currently, no recommendations can be made about combining postoperative COX-2-selective inhibitors with regional analgesia techniques because of insufficient data. It is recommended that the use of COX-2-selective inhibitors should depend upon assessment of individual patient risks (grade B), cardiovascular morbidity (transferable evidence, LoE 1), renal function and hepatic function (transferable evidence, LoE 3) or actual or recent gastroduodenal ulcer history (LoE 4). Although there is concern about impairment of bone-healing with COX-2-selective inhibitors, limited evidence shows that they have no detrimental effects (transferable evidence, LoE 1; [124, 125]).
- Postoperative systemic strong opioids are recommended (grade A) in combination with non-opioid analgesia (grade D, LoE 4) for high-intensity pain (procedure-specific evidence, LoE 1). IV PCA is recommended in preference to other analgesic administration regimens (grade B) because of improved pain control and higher patient satisfaction (transferable evidence, LoE 1). IM administration is not recommended (grade B) because of unfavourable pharmacokinetics, injection-associated pain (LoE 4) and patient dissatisfaction (transferable evidence, LoE 1).
- Weak opioids are not recommended for high-intensity pain (grade D, LoE 4). They are recommended (grade B) for moderate- or low-intensity pain, if non-opioid analgesia is insufficient or contra-indicated (transferable evidence, LoE 1). Weak opioids are recommended (grade B) in combination with non-opioid analgesics (transferable evidence, LoE 1).
- Paracetamol is recommended, in combination with other analgesics (grade B), as it reduces supplemental analgesic use in orthopaedic procedures (transferable evidence, LoE 1). It is not recommended as a sole agent for high- or moderate-intensity pain (grade D, LoE 4).
- Femoral nerve block is recommended (grade A) based on evidence for a reduction in pain scores and supplemental analgesia (procedure-specific evidence, LoE 1). No recommendation can be made concerning continuous femoral infusion techniques vs a single bolus because of heterogeneity in study design and inconsistency of procedure-specific data (LoE 4). Only one study [126], published after the cut-off date for the literature search, directly compared continuous and single bolus techniques. This study shows a benefit of continuous FNB for reducing pain scores and analgesic use compared with single injection FNB, although no difference in functional recovery (LoE 1). Meta-analyses showed that single injection and continuous infusion FNB have prolonged effects on pain up to 48 h, with the most pronounced effect observed on pain on movement, though the number of studies (and therefore the number of patients) included was small (see Figs 1 and 2). Although no recommendations can be made with regard to selecting one method of administration over the other, the analgesic benefits of continuous infusion may not be sufficient to justify the placement of catheters on a routine basis, and the balance of risks and complexity vs analgesic benefits needs to be studied further.
- Spinal LA + opioid is recommended (grade A, LoE 1) but not as the first choice of analgesic technique because of a greater potential for adverse events (e.g. nausea and vomiting [127]) compared with FNB (transferable evidence, LoE 3). Morphine is recommended as the opioid in the spinal LA + opioid combination based on procedure-specific evidence for a longer duration of analgesic effect than lipid-soluble opioids.
- Cooling and compression techniques are recommended (grade B) for postoperative analgesia, based on limited procedure-specific evidence for a reduction in pain scores (LoE 2) and analgesic use (LoE 1). This is supported by studies in other orthopaedic procedures [128–131].
- Continuous passive motion (grade A) and intensive rehabilitation (grade D) are recommended for reasons other than analgesia (procedure-specific evidence, LoE 1 and 2 respectively). These physical therapies showed no significant pain-reducing effect, but may be used for improvements in other outcomes (e.g. increased range of movement [80], reduced number of days taken to achieve 70° range of movement [82], superior active flexion [81]).

A previous systematic review of pre-emptive analgesia for postoperative pain relief in a variety of surgical procedures (orthopaedic, dental, gynaecological and abdominal) has concluded that there is no benefit of pre-operative over postoperative administration of analgesic drugs [132]. A meta-analysis of studies comparing similar pre- and postoperative interventions in various procedures found that pre-operative epidural analgesia resulted in improvements in pain scores and analgesic use, whereas pre-operative NSAID and local anaesthetic wound infiltration improved analgesic use but not pain scores, compared with postoperative analgesia. Evidence did not support an improvement in postoperative analgesia following administration of pre-operative NMDA antagonists and opioids [133]. In the absence of firm data

supporting the clinical value of pre-emptive analgesia, analgesic medication should be initiated in time to ensure an adequate analgesic effect in the immediate postoperative period. This may necessitate administration prior to the postoperative period.

Interventions with no recommendations for postoperative analgesia in TKA

Due to insufficient studies, limited or inconclusive evidence of benefit, heterogeneity of study design, methodological weakness, or an adverse risk-benefit ratio, it is not possible to recommend some interventions in current clinical use for TKA. These include:

- *Intra-articular techniques*: LA and/or morphine are not recommended, on current data, because of inconsistent analgesic efficacy in procedure-specific and transferable evidence. Intra-articular NSAID, neostigmine, clonidine and corticosteroids are not recommended, because there is inconsistent transferable evidence.
- *Combined intra-articular + incisional techniques:* After the completion of this review, several randomised trials have been performed with a high-volume local infiltration technique in both TKA and THA [134–136]. Preliminary evidence is promising but the technique requires further evaluation before the current recommendations are revised.
- *Alternative peripheral nerve blocks*: a combination of femoral and sciatic nerve blocks cannot be recommended because of limited and inconsistent procedure-specific evidence. While FNB does not guarantee analgesia of the posterior aspect of the knee joint, the combination of a sciatic nerve block with FNB to improve postoperative analgesia cannot be recommended as there is no evidence at this time that this option is better than a combination of FNB and systemic analgesia [123]. A combination of femoral and obturator nerve blocks cannot be recommended because of limited procedure-specific evidence. Lumbar plexus block (posterior approach) is not recommended because FNB is equally effective and is associated with fewer complications [137]. Adjuvant peripheral nerve drugs such as alpha-2-adrenoceptor agonists (clonidine, epinephrine) are not recommended because of lack of efficacy in procedure-specific studies.
- *Central neuraxial techniques*: spinal clonidine is not recommended because of limited and inconsistent procedure-specific evidence; similarly spinal neostigmine is not recommended because of limited procedure-specific evidence and because of side effects. Epidural LA ± opioid is not recommended because of an increased risk of serious adverse events and no better analgesia compared with FNB in procedure-specific studies [123]. Epidural ketamine is not recommended because of sedative side effects and inconclusive analgesic effects in TKA. Epidural tramadol is not recommended because of insufficient analgesia (procedure-specific evidence).

On the basis of procedure-specific studies and transferable data, drains are not recommended, as they do not provide analgesic or other recovery benefits, and are associated with pain on removal. No recommendations could be made regarding the type of surgical approach, the use of tourniquets, or patella resurfacing vs non-resurfacing, as these depend on individual patient factors and surgical/anatomical requirements, rather than pain. The type of prosthesis used is chosen according to the patient's joint requirements rather than for pain-reducing benefits, and there are only limited data showing that the type of prosthesis can influence pain scores.

Conclusions

Evidence from this systematic review supports the use of FNB for postoperative analgesia for primary TKA. Alternatively, there is good evidence to support the use of a spinal injection of local anaesthetic and morphine. The primary anaesthesia/analgesia technique, together with cooling and compression techniques should be supplemented with paracetamol and conventional NSAID or COX-2-selective inhibitors, plus intravenous strong opioids for break-through high-intensity pain, or weak opioids for moderate- to low-intensity pain.

Although the review is concerned primarily with the effective management of postoperative pain in TKA, the choice of anaesthetic technique is also determined by patient comorbidities and the overall requirements of the surgery. Therefore, optimal postoperative pain management should account for the choice of anaesthetic technique by offering different clinical pathways. Where GA is inappropriate, spinal LA plus morphine may be used (see Table 3).

The review has identified several areas for future research where the current data for both pain management and secondary outcomes (e.g. adverse events and functional recovery) is insufficient, inadequate or conflicting. A number of regional anaesthesia techniques are in common use, particularly continuous femoral nerve infusions and a combination of femoral and sciatic nerve blocks (both single injection and continuous infusion techniques). Although these techniques may be popular in current practice, there are insufficient data from randomised comparative studies that evaluate both the benefits and risks of these techniques [123] to recommend

them in preference to single-injection FNB. Further comparative studies are necessary as a priority, to properly evaluate the addition of a sciatic single injection technique to a single injection femoral nerve block, looking at functional recovery as well as pain scores. The role of continuous infusions needs to be critically evaluated against single injection techniques – pain scores, morphine sparing effect, duration of infusion, dose-response effect of differing infusate concentrations, impact on mobilisation and reaching rehabilitation goals. The objective assessment of pain is currently unsatisfactory with different end points making comparison between trials difficult. Future studies should formally measure serial pain scores at rest and during a preset dynamic range of movement, say to 90° over a set time period of, for example, 72 h. Evaluation of the effects of different analgesic regimens on patient rehabilitation goals and length of hospital stay is also required. More research into the dose- and duration-dependent effects of conventional NSAID and COX-2-selective inhibitors on bone healing is also required.

A number of other analgesic treatments have potential utility in TKA but procedure-specific data were not available at the time of the review, therefore they cannot currently be recommended. These include alpha-2-delta subunit ligands (gabapentinoids), peri-operative ketamine, pre-operative corticosteroids and high volume intra-articular/incisional techniques. With more data about these techniques becoming available together with better data from the research suggestions above it may be possible to better define our current recommendations for TKA analgesia in the future.

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