



# **DEPARTMENT OF ANESTHESIOLOGY**

## **JOURNAL CLUB**

**Tuesday October 14, 2014  
1800 HOURS**

**LOCATION:  
The Rivermill  
2 Cataract Street**

**PRESENTING ARTICLES:  
Dr. Andre Schneider & Dr. Karmen Krol**

**SPONSORED BY:  
Abbvie – Penny Reid**

**SUGGESTED GUIDELINES FOR CRITICAL APPRAISAL OF PAPERS**  
**ANESTHESIOLOGY JOURNAL CLUB**  
**QUEEN'S UNIVERSITY**  
**© Joel Parlow, revised 2010**

Two presenters will be assigned to choose and present summaries of their papers. Ideally the two papers will represent similar topics but contrasting research methodologies. The focus remains on critical appraisal of the research and manuscript, more than on the actual contents of the article. Each presenter will then lead an open discussion about the article, based around the guidelines below. The object is to open up the appraisal to wide discussion involving all participants, who will be expected to contribute pending suspension of bar privileges.

**GENERAL**

1. Title of paper: Does it seem like an important problem? Does it reflect the purpose/results?
2. Authors, institution and country of origin

**INTRODUCTION**

1. What is the problem being addressed?
2. What is the current state of knowledge of the problem studied?
3. What is the hypothesis being tested?
4. How does testing the hypothesis help solve the stated problem?

**METHODOLOGY**

1. Study design:
  - a) Clinical trial vs. systematic review/meta-analysis
  - b) Prospective vs. retrospective
  - c) Observational vs. Experimental
  - d) Randomized or not
  - e) Blinded or not
2. Population studied:
  - a) Human, animal, other
  - b) Justification
  - c) Control groups: experimental vs. historical
  - d) Is the sample size/power calculated, and how?
  - e) Is the population similar to your own practice?
  - f) Single vs. multi-centre
3. Is the study ethically sound?
  - a) Clinical equipoise
  - b) Does treatment meet standard of care (esp controls)?
  - c) Appropriate consent and institutional ethics approval
4. Exclusions: what groups are excluded and why?

5. Experimental protocol
  - a) Is it designed to test the hypothesis?
  - b) Is it detailed enough to be reproducible?
  - c) Is the methodology validated?
  - d) Are the drugs/equipment used detailed?
  - e) How does the randomization take place?
6. What are the primary endpoints?
7. Is power sufficient to justify secondary endpoints?
8. Is the protocol clinically relevant?
9. Data collection and analysis
10. Statistical analysis: Is it appropriate? Are results

## **RESULTS**

1. Are the groups comparable?
2. Were any subjects/data eliminated?
3. Analyzed by intent to treat?
4. Are adequate details of results provided? - data, graphs, tables

## **DISCUSSION**

1. What is the main conclusion of the study?
2. Do the results support this conclusion?
3. Do the results address the stated purpose/hypothesis of the study?
4. How do the authors explain the results obtained?
5. Are there any alternative interpretations to the data?
6. Are the results clinically as well statistically relevant?
7. How do the results compare with those of previous studies?
8. What do the results add to the existing literature?
9. What are the limitations of the methods or analysis used?
10. What are the unanswered questions for future work?

## **APPLICABILITY OF THE PAPER**

1. Have you learned something important from reading this paper?
2. Will the results of this study alter your clinical practice?
3. Was the food and wine up to the high standards expected by self-respecting anesthesiologists?

## REVIEW ARTICLE

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

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

*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, Département 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@wvrcsacute.nhs.uk](mailto:barrie.fischer@wvrcsacute.nhs.uk)

Accepted: 16 March 2008

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, anaesthetic\*, '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
Non-pharmacological techniques	Patellar resurfacing vs no resurfacing [72–78]	↓ (OP) [75–78] NS (OP) [74] NS (KS) [72–76, 78]	n/a	n/a
	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] Pre-operative IM morphine [18] IM dextromethorphan [20] IV ketamine [21]  Oral clonidine [22] SI combined femoral-sciatic NB [26, 92] SI combined obturator and femoral NB [32] Continuous lumbar plexus NB [36, 37] Pre-incisional epidural strong opioid [18] Bedside femoral NB [93] Pre-incisional intra-articular bupivacaine [94] Intra-articular bupivacaine bolus [95] Postoperative continuous intra-articular bupivacaine [96]	Strong opioid superior Inconclusive results Inconclusive results NS compared with control (at rest or after mobilisation) NS compared with placebo Inconclusive results NB superior to placebo Inconclusive results Inconclusive results Inconclusive results NS Inconclusive results NS
Comparison of systemic analgesia	Strong opioid vs COX-2-selective inhibitor [14] Diclofenac vs ketoprofen [11] COX-2-selective inhibitor vs conventional NSAID [14]	COX-2-selective inhibitor superior to opioids NS NS
Comparisons of regional analgesia techniques	SI combined obturator and femoral NB vs femoral NB [32] Combined femoral-sciatic NB vs femoral NB (SI [26] or continuous infusion [97]) SI combined obturator and femoral-sciatic NB vs femoral-sciatic NB [98] Continuous lumbar plexus NB vs continuous femoral NB [36] Continuous infusion vs patient-controlled femoral NB [99] Spinal morphine vs SI femoral NB [100] Spinal block with GA vs combined sciatic and femoral 3-in-1 block with GA [101] Spinal LA anaesthesia with IV propofol vs IV fentanyl anaesthesia [102] Lumbar epidural anaesthesia/analgesia vs spinal anaesthesia plus intravenous opioid [103] Lumbar epidural analgesia vs continuous infusion femoral NB [34], vs SI combined femoral and sciatic NB [104], vs SI femoral NB [31] PCEA vs continuous infusion epidural analgesia [105]	Combined obturator and femoral NB superior  Inconclusive results NS NS at rest or during physiotherapy NS NS at rest or on movement Inconclusive results Inconclusive results Epidural superior during ROM, inconclusive at rest Inconclusive results [34], [104] NS [31]
Components of spinal solution	Morphine (with or without clonidine) [39, 41, 106]  Neostigmine [41]	NS Inconclusive results compared with saline, neostigmine and diamorphine Neostigmine superior to saline; inconclusive results compared with morphine
Components of lumbar epidural solution (as adjuncts to local anaesthetics, opioids, or both)	Diamorphine [106] Morphine [18], meperidine [107], fentanyl [107] or tramadol [108]  Ketamine [52, 109] Clonidine [110] Lidocaine [111], bupivacaine [112, 113] or ropivacaine [113]	Inconclusive results compared with morphine 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 Inconclusive results compared with placebo Inconclusive results compared with no clonidine Lidocaine superior to control; NS bupivacaine vs no bupivacaine; inconclusive results for bupivacaine vs ropivacaine
Components of solution via peripheral NB catheter	Clonidine [114]  Adrenaline [115] Ropivacaine [30, 92], bupivacaine [30, 92]	NS at rest or on movement compared with no clonidine NS compared with no adrenaline NS
Timing of administration	Oral and IV conventional NSAID [10]  Lumbar epidural bupivacaine plus opioid [116]  Lumbar epidural lidocaine plus ketamine plus morphine [111] Intra-articular bupivacaine [94]	NS pre- + postoperative vs postoperative administration NS pre- + postoperative vs postoperative administration Inconclusive results pre- vs post-incision 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
Surgical approaches	IV PCA vs IM strong opioid [24]	IM superior for moderate pain scores
	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<sup>-1</sup>; [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 and 48 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).

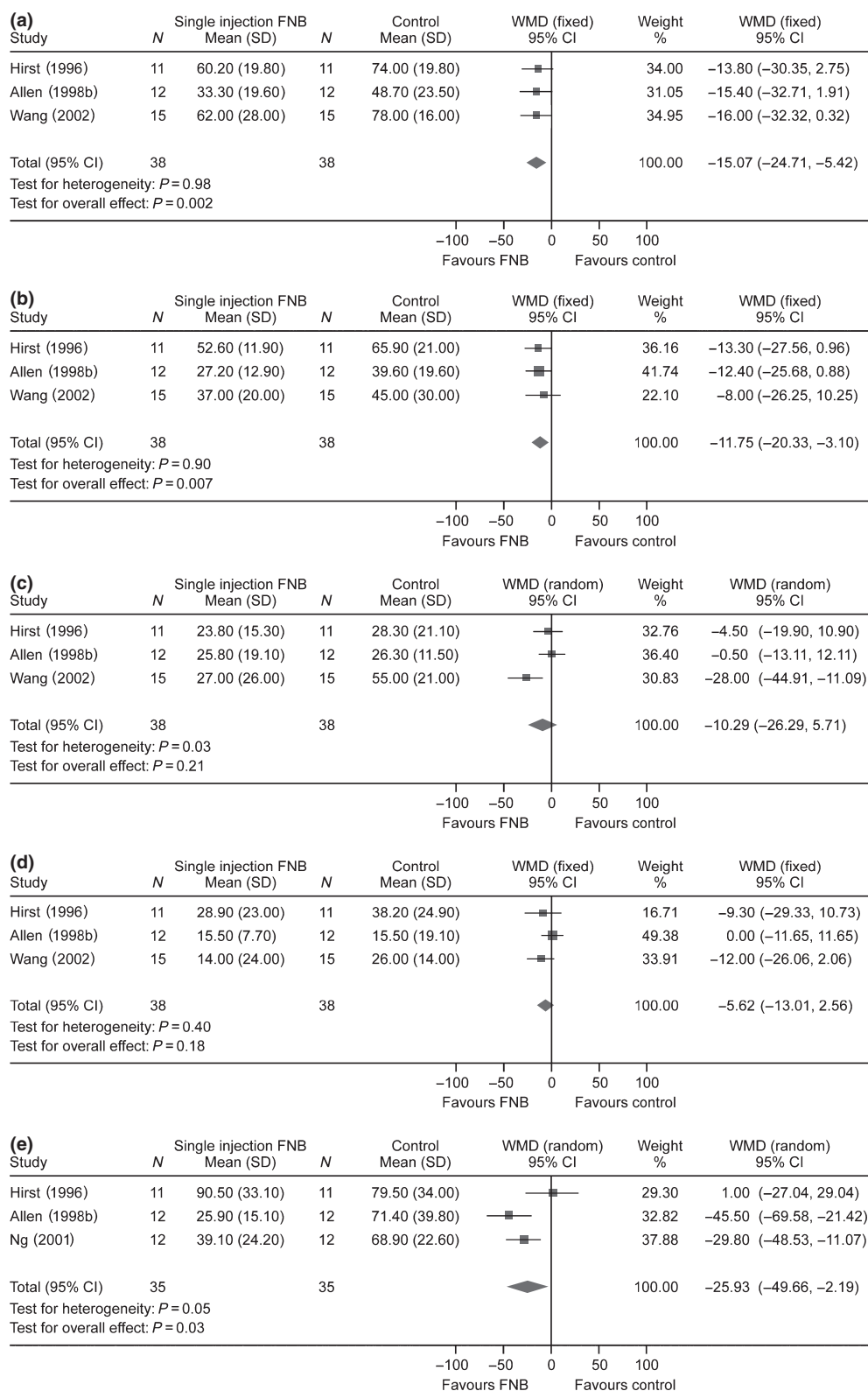
Continuous infusion FNB was associated with significant improvements in some functional outcomes in two out of two studies compared with placebo or no treatment [34, 35], but three out of four studies found that the incidence of PONV was not significantly different between groups [34, 35, 37].

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).

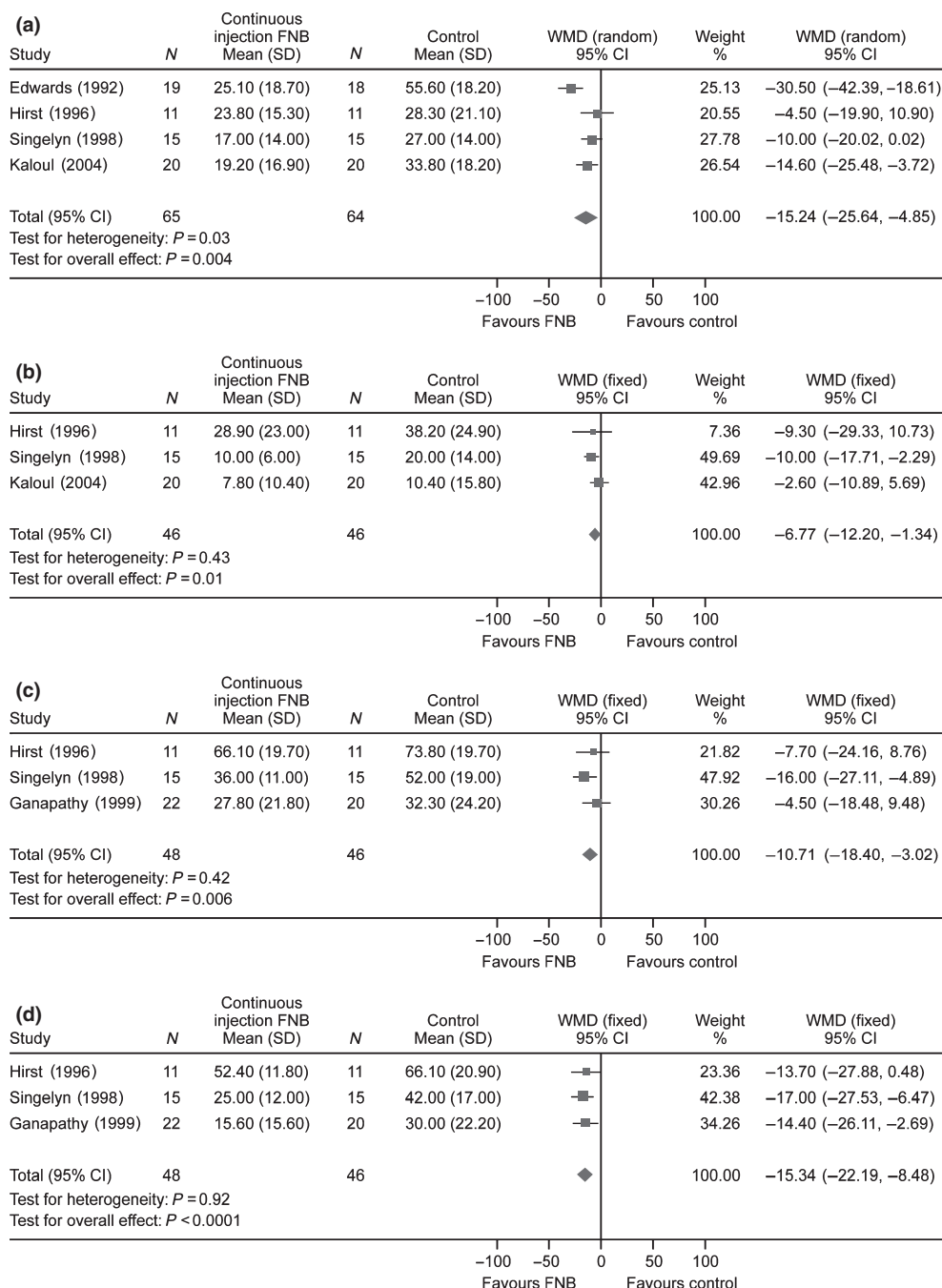
*Spinal techniques*

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 tech-

niques. 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  $\pm$  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.

### Financial support

All authors are members or affiliates of the PROSPECT Working Group, which is supported by an educational grant from Pfizer Inc. New York, NY, USA. Working Group members have been reimbursed by Pfizer Inc. for attending PROSPECT meetings to formulate the consensus recommendations. Caroline Sharp is employed by Choice Pharma which has received funding from Pfizer Inc. to implement PROSPECT activities. This paper makes no specific recommendations about the use of any medical products, drugs or equipment manufactured by Pfizer Inc. or by any of its subsidiaries.

### Acknowledgements

The authors would like to thank Iradj Reza (PhD, Biomedical Information Scientist, Pfizer, Sandwich, UK) for his help and expertise in performing literature searches in EmBASE and MEDLINE; Roseanne Wilkinson (PhD,

Senior Medical Writer, Choice Pharma), Delia Randall (PhD, Medical Writer, Choice Pharma) and James Pickford (BSc, Editorial Director, Choice Pharma) for editorial assistance.

### References

- 1 Rasanen P, Paavolainen P, Sintonen H, et al. Effectiveness of hip or knee replacement surgery in terms of quality-adjusted life years and costs. *Acta Orthopaedica* 2007; **78**: 108–15.
- 2 PROSPECT: Procedure-Specific Postoperative Pain Management. <http://www.postoppain.org> (accessed December 2007).
- 3 Neugebauer EA, Wilkinson RC, Kehlet H, Schug SA. PROSPECT: a practical method for formulating evidence-based expert recommendations for the management of postoperative pain. *Surgical Endoscopy* 2007; **21**: 1047–53.
- 4 Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996; **17**: 1–12.
- 5 Moher D, Schulz KF, Altman D. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials 2001. *Explore (NY)* 2005; **1**: 40–5.
- 6 Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomized controlled trials. The CONSORT statement. *Journal of the American Medical Association* 1996; **276**: 637–9.
- 7 Neugebauer E, Wilkinson R, Kehlet H. Transferable evidence in support of reaching a consensus. *Zeitschrift für Ärztliche Fortbildung und Qualitätssicherung* 2007; **101**: 103–7.
- 8 Dalkey N, Helmer O. An experimental application of the Delphi method to the use of experts. *Management Science* 1963; **9**: 458–67.
- 9 Boeckstyns ME, Backer M, Petersen EM, Hoj I, Albrechtsen H, Andersen HB. Piroxicam spares buprenorphine after total joint replacement. Controlled study of pain treatment in 81 patients. *Acta Orthopaedica Scandinavica* 1992; **63**: 658–60.
- 10 Eggers KA, Jenkins BJ, Power I. Effect of oral and i.v. tenoxicam in postoperative pain after total knee replacement. *British Journal of Anaesthesia* 1999; **83**: 876–81.
- 11 Silvanto M, Lappi M, Rosenberg PH. Comparison of the opioid-sparing efficacy of diclofenac and ketoprofen for 3 days after knee arthroplasty. *Acta Anaesthesiologica Scandinavica* 2002; **46**: 322–8.
- 12 Buvanendran A, Kroin JS, Tuman KJ, et al. Effects of perioperative administration of a selective cyclooxygenase 2 inhibitor on pain management and recovery of function after knee replacement: a randomized controlled trial. *Journal of the American Medical Association* 2003; **290**: 2411–8 (see comment).

- 13 Hubbard RC, Naumann TM, Traylor L, Dhadda S. Parecoxib sodium has opioid-sparing effects in patients undergoing total knee arthroplasty under spinal anaesthesia. *British Journal of Anaesthesia* 2003; **90**: 166–72.
- 14 Rasmussen GL, Steckner K, Hogue C, Torri S, Hubbard RC. Intravenous parecoxib sodium for acute pain after orthopedic knee surgery. *American Journal of Orthopedics (Chatham, NJ)* 2002; **31**: 336–43.
- 15 Reynolds LW, Hoo RK, Brill RJ, North J, Recker DP, Verburg KM. The COX-2 specific inhibitor, valdecoxib, is an effective, opioid-sparing analgesic in patients undergoing total knee arthroplasty. *Journal of Pain and Symptom Management* 2003; **25**: 133–41.
- 16 Ahdieh H, Ma T, Babul N, Lee D. Efficacy of oxymorphone extended release in postsurgical pain: a randomized clinical trial in knee arthroplasty. *Journal of Clinical Pharmacology* 2004; **44**: 767–76.
- 17 Cheville A, Chen A, Oster G, McGarry L, Narcessian E. A randomized trial of controlled-release oxycodone during inpatient rehabilitation following unilateral total knee arthroplasty. [erratum appears in *J Bone Joint Surg Am* 2001 Jun; **83-A**(6):915]. *Journal of Bone and Joint Surgery – American Volume* 2001; **83-A**: 572–6.
- 18 Hendolin H, Nuutinen L, Kokki H, Tuomisto L. Does morphine premedication influence the pain and consumption of postoperative analgesics after total knee arthroplasty? *Acta Anaesthesiologica Scandinavica* 1996; **40**: 81–5.
- 19 Pang WW, Wu HS, Tung CC. Tramadol 2.5 mg  $\times$  kg(-1) appears to be the optimal intraoperative loading dose before patient-controlled analgesia. *Canadian Journal of Anaesthesia* 2003; **50**: 48–51.
- 20 Yeh CC, Ho ST, Kong SS, Wu CT, Wong CS. Absence of the preemptive analgesic effect of dextromethorphan in total knee replacement under epidural anesthesia. *Acta Anaesthesiologica Sinica* 2000; **38**: 187–93 [Erratum appears in *Acta Anaesthesiologica Sinica* 2001 March, **39**(1): inside back cover].
- 21 Adam F, Chauvin M, Du Manoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. *Anesthesia and Analgesia* 2005; **100**: 475–80.
- 22 Park J, Forrest J, Kolesar R, Bhola D, Beattie S, Chu C. Oral clonidine reduces postoperative PCA morphine requirements. *Canadian Journal of Anaesthesia* 1996; **43**: 900–6 [see comment].
- 23 McSwiney M, Cooper J, Karadia S, Campbell M. Intravenous regional analgesia using morphine. The effect on postoperative pain following total knee arthroplasty. *Acta Anaesthesiologica Scandinavica* 1997; **41**: 345–7.
- 24 Ferrante FM, Orav EJ, Rocco AG, Gallo J. A statistical model for pain in patient-controlled analgesia and conventional intramuscular opioid regimens. *Anesthesia and Analgesia* 1988; **67**: 457–61.
- 25 Hirst GC, Lang SA, Dust WN, Cassidy JD, Yip RW. Femoral nerve block. Single injection versus continuous infusion for total knee arthroplasty. *Regional Anesthesia* 1996; **21**: 292–7.
- 26 Allen HW, Liu SS, Ware PD, Nairn CS, Owens BD. Peripheral nerve blocks improve analgesia after total knee replacement surgery. *Anesthesia and Analgesia* 1998; **87**: 93–7.
- 27 Wang H, Boctor B, Verner J. The effect of single-injection femoral nerve block on rehabilitation and length of hospital stay after total knee replacement. *Regional Anesthesia and Pain Medicine* 2002; **27**: 139–44.
- 28 Szczukowski MJ Jr, Hines JA, Snell JA, Sisco TS. Femoral nerve block for total knee arthroplasty patients: a method to control postoperative pain. *Journal of Arthroplasty* 2004; **19**: 720–5.
- 29 YaDeau JT, Cahill JB, Zawadsky MW, et al. The effects of femoral nerve blockade in conjunction with epidural analgesia after total knee arthroplasty. *Anesthesia and Analgesia* 2005; **101**: 891–5.
- 30 Ng HP, Cheong KF, Lim A, Lim J, Puhaindran ME. Intraoperative single-shot ‘3-in-1’ femoral nerve block with ropivacaine 0.25%, ropivacaine 0.5% or bupivacaine 0.25% provides comparable 48-hr analgesia after unilateral total knee replacement. *Canadian Journal of Anaesthesia* 2001; **48**: 1102–8.
- 31 Adams HA, Saatweber P, Schmitz CS, Hecker H. Post-operative pain management in orthopaedic patients: no differences in pain score, but improved stress control by epidural anaesthesia. *European Journal of Anaesthesiology* 2002; **19**: 658–65.
- 32 Macalou D, Trueck S, Meuret P, et al. Postoperative analgesia after total knee replacement: the effect of an obturator nerve block added to the femoral 3-in-1 nerve block. *Anesthesia and Analgesia* 2004; **99**: 251–4.
- 33 Edwards ND, Wright EM. Continuous low-dose 3-in-1 nerve blockade for postoperative pain relief after total knee replacement. *Anesthesia and Analgesia* 1992; **75**: 265–7.
- 34 Singelyn FJ, Deyaert M, Joris D, Penderville E, Gouverneur JM. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. *Anesthesia and Analgesia* 1998; **87**: 88–92 [see comment].
- 35 Ganapathy S, Wasserman RA, Watson JT, et al. Modified continuous femoral three-in-one block for postoperative pain after total knee arthroplasty. *Anesthesia and Analgesia* 1999; **89**: 1197–202 [see comment].
- 36 Kaloul I, Guay J, Cote C, Fallaha M. The posterior lumbar plexus (psoas compartment) block and the three-in-one femoral nerve block provide similar postoperative analgesia after total knee replacement. *Canadian Journal of Anaesthesia* 2004; **51**: 45–51 [Erratum appears in *Can J Anaesth* 2005 January, **52**:119].
- 37 Serpell MG, Millar FA, Thomson MF. Comparison of lumbar plexus block versus conventional opioid analgesia after total knee replacement. *Anaesthesia* 1991; **46**: 275–7 [see comment].
- 38 Cole PJ, Craske DA, Wheatley RG. Efficacy and respiratory effects of low-dose spinal morphine for postoperative

- analgesia following knee arthroplasty. *British Journal of Anaesthesia* 2000; **85**: 233–7 [see comment].
- 39 Sites BD, Beach M, Biggs R, et al. Intrathecal clonidine added to a bupivacaine-morphine spinal anesthetic improves postoperative analgesia for total knee arthroplasty. *Anesthesia and Analgesia* 2003; **96**: 1083–8.
- 40 Fernandez-Galinski D, Rue M, Moral V, Castells C, Puig MM. Spinal anesthesia with bupivacaine and fentanyl in geriatric patients. *Anesthesia and Analgesia* 1996; **83**: 537–41.
- 41 Tan PH, Chia YY, Lo Y, Liu K, Yang LC, Lee TH. Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement surgery. *Canadian Journal of Anaesthesia* 2001; **48**: 551–6.
- 42 Jacobson L, Kokri MS, Pridie AK. Intrathecal diamorphine: a dose-response study. *Annals of the Royal College of Surgeons of England* 1989; **71**: 289–92 [see comment].
- 43 Bowrey S, Hamer J, Bowler I, Symonds C, Hall JE. A comparison of 0.2 and 0.5 mg intrathecal morphine for postoperative analgesia after total knee replacement. *Anaesthesia* 2005; **60**: 449–52.
- 44 Weller R, Rosenblum M, Conard P, Gross JB. Comparison of epidural and patient-controlled intravenous morphine following joint replacement surgery. *Canadian Journal of Anaesthesia* 1991; **38**: 582–6.
- 45 Klasen JA, Opitz SA, Melzer C, Thiel A, Hempelmann G. Intraarticular, epidural, and intravenous analgesia after total knee arthroplasty. *Acta Anaesthesiologica Scandinavica* 1999; **43**: 1021–6.
- 46 Nielsen PT, Blom H, Nielsen SE. Less pain with epidural morphine after knee arthroplasty. *Acta Orthopaedica Scandinavica* 1989; **60**: 447–8.
- 47 Holmstrom A, Hardin BC. Cryo/Cuff compared to epidural anesthesia after knee unicompartmental arthroplasty: a prospective, randomized and controlled study of 60 patients with a 6-week follow-up. *Journal of Arthroplasty* 2005; **20**: 316–21.
- 48 Pettine KA, Wedel DJ, Cabanela ME, Weeks JL. The use of epidural bupivacaine following total knee arthroplasty. *Orthopaedic Review* 1989; **18**: 894–901.
- 49 Moiniche S, Hjørtso NC, Hansen BL, et al. The effect of balanced analgesia on early convalescence after major orthopaedic surgery. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 328–35.
- 50 Axelsson K, Johanson E, Essving P, Weckstrom J, Ekback G. Postoperative extradural analgesia with morphine and ropivacaine. A double-blind comparison between placebo and ropivacaine 10 mg/h or 16 mg/h. *Acta Anaesthesiologica Scandinavica* 2005; **49**: 1191–9.
- 51 Sharrock NE, Urquhart BL, Ganz S, Williams-Russo PG. Epidural infusions of bupivacaine and fentanyl do not improve rehabilitation following one-stage bilateral total knee arthroplasty. *Annals of the Academy of Medicine, Singapore* 1994; **23** (Suppl.): 3–9.
- 52 Weir PS, Fee JP. Double-blind comparison of extradural block with three bupivacaine-ketamine mixtures in knee arthroplasty. *British Journal of Anaesthesia* 1998; **80**: 299–301.
- 53 Kampe S, Diefenbach C, Kanis B, Auweiler M, Kiencke P, Cranfield K. Epidural combination of ropivacaine with sufentanil for postoperative analgesia after total knee replacement: a pilot study. *European Journal of Anaesthesiology* 2002; **19**: 666–71.
- 54 Mauerhan DR, Campbell M, Miller JS, Mokris JG, Gregory A, Kiebzak GM. Intra-articular morphine and/or bupivacaine in the management of pain after total knee arthroplasty. *Journal of Arthroplasty* 1997; **12**: 546–52.
- 55 Ritter MA, Koehler M, Keating EM, Faris PM, Meding JB. Intra-articular morphine and/or bupivacaine after total knee replacement. *Journal of Bone and Joint Surgery – British Volume* 1999; **81**: 301–3.
- 56 Tanaka N, Sakahashi H, Sato E, Hirose K, Ishii S. The efficacy of intra-articular analgesia after total knee arthroplasty in patients with rheumatoid arthritis and in patients with osteoarthritis. *Journal of Arthroplasty* 2001; **16**: 306–11.
- 57 Badner NH, Bourne RB, Rorabeck CH, Doyle JA. Addition of morphine to intra-articular bupivacaine does not improve analgesia following knee joint replacement. *Regional Anesthesia* 1997; **22**: 347–50 [see comment].
- 58 Confalonieri N, Manzotti A, Pullen C. Is closed-suction drain necessary in unicompartmental knee replacement? A prospective randomised study. *Knee* 2004; **11**: 399–402.
- 59 Esler CN, Blakeway C, Fiddian NJ. The use of a closed-suction drain in total knee arthroplasty. A prospective, randomised study. *Journal of Bone and Joint Surgery – British Volume* 2003; **85**: 215–7 [see comment].
- 60 Jenny JY, Boeri C, Lafare S. No drainage does not increase complication risk after total knee prosthesis implantation: a prospective, comparative, randomized study. *Knee Surgery, Sports Traumatology, Arthroscopy* 2001; **9**: 299–301.
- 61 Fisher DA, Trimble SM, Breedlove K. The medial tri-vector approach in total knee arthroplasty. *Orthopedics* 1998; **21**: 53–6.
- 62 Weinhardt C, Barisic M, Bergmann EG, Heller KD. Early results of subvastus versus medial parapatellar approach in primary total knee arthroplasty. *Archives of Orthopaedic and Trauma Surgery* 2004; **124**: 401–3.
- 63 Straw R, Kulkarni S, Attfield S, Wilton TJ. Posterior cruciate ligament at total knee replacement. Essential, beneficial or a hindrance? *Journal of Bone and Joint Surgery – British Volume* 2003; **85**: 671–4.
- 64 Bathis H, Perlick L, Blum C, Luring C, Perlick C, Grifka J. Midvastus approach in total knee arthroplasty: a randomized, double-blinded study on early rehabilitation. *Knee Surgery, Sports Traumatology, Arthroscopy* 2005; **13**: 545–50.
- 65 Abdel-Salam A, Eyres KS. Effects of tourniquet during total knee arthroplasty. A prospective randomised study. *Journal of Bone and Joint Surgery – British Volume* 1995; **77**: 250–3.
- 66 Vandenbussche E, Duranthon LD, Couturier M, Pidhorz L, Augereau B. The effect of tourniquet use in total knee arthroplasty. *International Orthopaedics* 2002; **26**: 306–9.
- 67 Wakankar HM, Nicholl JE, Koka R, D'Arcy JC. The tourniquet in total knee arthroplasty. A prospective,

- randomised study. *Journal of Bone and Joint Surgery – British Volume* 1999; **81**: 30–3 [see comment].
- 68 Barwell J, Anderson G, Hassan A, Rawlings I. The effects of early tourniquet release during total knee arthroplasty: a prospective randomized double-blind study. *Journal of Bone and Joint Surgery – British Volume* 1997; **79**: 265–8 [see comment; erratum appears in *J Bone Joint Surg Br* 1997 Jul;**79**(4):693 Note: Barwell NJ (corrected to Barwell J)].
  - 69 Price AJ, Rees JL, Beard D, et al. A mobile-bearing total knee prosthesis compared with a fixed-bearing prosthesis. A multicentre single-blind randomised controlled trial. *Journal of Bone and Joint Surgery – British Volume* 2003; **85**: 62–7.
  - 70 Hilding MB, Backbro B, Ryd L. Quality of life after knee arthroplasty. A randomized study of 3 designs in 42 patients, compared after 4 years. *Acta Orthopaedica Scandinavica* 1997; **68**: 156–60.
  - 71 McCaskie AW, Deehan DJ, Green TP, et al. Randomised, prospective study comparing cemented and cementless total knee replacement: results of press-fit condylar total knee replacement at five years. *Journal of Bone and Joint Surgery – British Volume* 1998; **80**: 971–5.
  - 72 Barrack RL, Bertot AJ, Wolfe MW, Waldman DA, Milicic M, Myers L. Patellar resurfacing in total knee arthroplasty. A prospective, randomized, double-blind study with five to seven years of follow-up. *Journal of Bone and Joint Surgery – American Volume* 2001; **83-A**: 1376–81.
  - 73 Barrack RL, Wolfe MW, Waldman DA, Milicic AM, Bertot AJ, Myers L. Resurfacing of the patella in total knee arthroplasty. *Journal of Bone and Joint Surgery American* 1997; **79**: 1121–31.
  - 74 Burnett RS, Haydon CM, Rorabeck CH, Bourne RB. Patella resurfacing versus nonresurfacing in total knee arthroplasty: results of a randomized controlled clinical trial at a minimum of 10 years' followup. *Clinical Orthopaedics and Related Research* 2004; **428**: 12–25.
  - 75 Mayman D, Bourne RB, Rorabeck CH, Vaz M, Kramer J. Resurfacing versus not resurfacing the patella in total knee arthroplasty: 8- to 10-year results. *Journal of Arthroplasty* 2003; **18**: 541–5.
  - 76 Partio E, Wirta J. Comparison of patellar resurfacing and nonresurfacing in total knee arthroplasty: a prospective randomized study. *Journal of Orthopaedic Rheumatology* 1995; **8**: 69–74.
  - 77 Waters TS, Bentley G. Patellar resurfacing in total knee arthroplasty. A prospective, randomized study. *Journal of Bone and Joint Surgery – American Volume* 2003; **85**: 212–17 [see comment].
  - 78 Wood DJ, Smith AJ, Collopy D, White B, Brankov B, Bulsara MK. Patellar resurfacing in total knee arthroplasty: a prospective, randomized trial. *Journal of Bone and Joint Surgery – American Volume* 2002; **84**: 187–93.
  - 79 Can F, Alpaslan M. Continuous passive motion on pain management in patients with total knee arthroplasty. *The Pain Clinic* 2003; **15**: 479–85.
  - 80 Harms M, Engstrom B. Continuous passive motion as an adjunct to treatment in the physiotherapy management of the total knee arthroplasty patient. *Physiotherapy* 1991; **77**: 301–7.
  - 81 McInnes J, Larson MG, Daltroy LH, et al. A controlled evaluation of continuous passive motion in patients undergoing total knee arthroplasty. *JAMA* 1992; **268**: 1423–8.
  - 82 Montgomery F, Eliasson M. Continuous passive motion compared to active physical therapy after knee arthroplasty: similar hospitalization times in a randomized study of 68 patients. *Acta Orthopaedica Scandinavica* 1996; **67**: 7–9.
  - 83 Beaupre LA, Lier D, Davies DM, Johnston DB. The effect of a preoperative exercise and education program on functional recovery, health related quality of life, and health service utilization following primary total knee arthroplasty. *Journal of Rheumatology* 2004; **31**: 1166–73.
  - 84 D'Lima DD, Colwell CW Jr, Morris BA, Hardwick ME, Kozin F. The effect of preoperative exercise on total knee replacement outcomes. *Clinical Orthopaedics and Related Research Issue* 1996; **326**: 174–82.
  - 85 Frost H, Lamb SE, Robertson S. A randomized controlled trial of exercise to improve mobility and function after elective knee arthroplasty. Feasibility, results and methodological difficulties. *Clinical Rehabilitation* 2002; **16**: 200–9.
  - 86 Moffet H, Collet JP, Shapiro SH, Paradis G, Marquis F, Roy L. Effectiveness of intensive rehabilitation on functional ability and quality of life after first total knee arthroplasty: a single-blind randomized controlled trial. *Archives of Physical Medicine and Rehabilitation* 2004; **85**: 546–56.
  - 87 May LA, Busse W, Zayac D, Whitridge MR. Comparison of continuous passive motion (CPM) machines and lower limb mobility boards (LLiMB) in the rehabilitation of patients with total knee arthroplasty. *Canadian Journal of Rehabilitation* 1999; **12**: 257–63.
  - 88 Mitchell C, Walker J, Walters S, Morgan AB, Binns T, Mathers N. Costs and effectiveness of pre- and post-operative home physiotherapy for total knee replacement: randomized controlled trial. *Journal of Evaluation in Clinical Practice* 2005; **11**: 283–92.
  - 89 Webb JM, Williams D, Ivory JP, Day S, Williamson DM. The use of cold compression dressings after total knee replacement: a randomized controlled trial. *Orthopedics* 1998; **21**: 59–61.
  - 90 Angulo DL, Colwell CW Jr. Use of postoperative TENS and continuous passive motion following total knee replacement. *Journal of Orthopaedic and Sports Physical Therapy* 1990; **11**: 599–604.
  - 91 McDonald DD, Molony SL. Postoperative pain communication skills for older adults. *Western Journal of Nursing Research* 2004; **26**: 836–52; Discussion 53–9.
  - 92 McNamee DA, Convery PN, Milligan KR. Total knee replacement: a comparison of ropivacaine and bupivacaine in combined femoral and sciatic block. *Acta Anaesthesiologica Scandinavica* 2001; **45**: 477–81.
  - 93 Niskanen RO, Strandberg N. Bedside femoral block performed on the first postoperative day after unilateral

- total knee arthroplasty: a randomized study of 49 patients. *The Journal of Knee Surgery* 2005; **18**: 192–6.
- 94 Badner NH, Bourne RB, Rorabeck CH, MacDonald SJ, Doyle JA. Intra-articular injection of bupivacaine in knee-replacement operations. Results of use for analgesia and for preemptive blockade. *Journal of Bone and Joint Surgery – American Volume* 1996; **78**: 734–8.
- 95 Browne C, Copp S, Reden L, Pulido P, Colwell C Jr. Bupivacaine bolus injection versus placebo for pain management following total knee arthroplasty. *Journal of Arthroplasty* 2004; **19**: 377–80.
- 96 Nechleba J, Rogers V, Cortina G, Cooney T. Continuous intra-articular infusion of bupivacaine for postoperative pain following total knee arthroplasty. *The Journal of Knee Surgery* 2005; **18**: 197–202.
- 97 Dang CP, Gautheron E, Guille J, et al. The value of adding sciatic block to continuous femoral block for analgesia after total knee replacement. *Regional Anesthesia and Pain Medicine* 2005; **30**: 128–33.
- 98 McNamee DA, Parks L, Milligan KR. Post-operative analgesia following total knee replacement: an evaluation of the addition of an obturator nerve block to combined femoral and sciatic nerve block. *Acta Anaesthesiologica Scandinavica* 2002; **46**: 95–9.
- 99 Singelyn FJ, Gouverneur JM. Extended 'three-in-one' block after total knee arthroplasty: continuous versus patient-controlled techniques. *Anesthesia and Analgesia* 2000; **91**: 176–80.
- 100 Sites BD, Beach M, Gallagher JD, Jarrett RA, Sparks MB, Lundberg CJ. A single injection ultrasound-assisted femoral nerve block provides side effect-sparing analgesia when compared with intrathecal morphine in patients undergoing total knee arthroplasty. *Anesthesia and Analgesia* 2004; **99**: 1539–43.
- 101 Allen JG, Denny NM, Oakman N. Postoperative analgesia following total knee arthroplasty: a study comparing spinal anesthesia and combined sciatic femoral 3-in-1 block. *Regional Anesthesia and Pain Medicine* 1998; **23**: 142–6 [see comment].
- 102 Kudoh A, Takase H, Takazawa T. A comparison of anesthetic quality in propofol-spinal anesthesia and propofol-fentanyl anesthesia for total knee arthroplasty in elderly patients. *Journal of Clinical Anesthesia* 2004; **16**: 405–10.
- 103 Farag E, Dilger J, Brooks P, Tetzlaff JE. Epidural analgesia improves early rehabilitation after total knee replacement. *Journal of Clinical Anesthesia* 2005; **17**: 281–5.
- 104 Davies AF, Segar EP, Murdoch J, Wright DE, Wilson IH. Epidural infusion or combined femoral and sciatic nerve blocks as perioperative analgesia for knee arthroplasty. *British Journal of Anaesthesia* 2004; **93**: 368–74 [see comment].
- 105 Silvasti M, Pitkanen M. Patient-controlled epidural analgesia versus continuous epidural analgesia after total knee arthroplasty. *Acta Anaesthesiologica Scandinavica* 2001; **45**: 471–6.
- 106 Riad T, Williams B, Musson J, Wheatley B. Intrathecal morphine compared with diamorphine for postoperative analgesia following unilateral knee arthroplasty. *Acute Pain* 2002; **4**: 5–8.
- 107 Ferrante FM, Fanciullo GJ, Grichnik KP, Vaisman J, Sacks GM, Concepcion MA. Regression of sensory anesthesia during continuous epidural infusions of bupivacaine and opioid for total knee replacement. *Anesthesia and Analgesia* 1993; **77**: 1179–84.
- 108 Grace D, Fee JP. Ineffective analgesia after extradural tramadol hydrochloride in patients undergoing total knee replacement. *Anaesthesia* 1995; **50**: 555–8.
- 109 Himmelseher S, Ziegler-Pithamitsis D, Argiriadou H, Martin J, Jelen-Esselborn S, Kochs E. Small-dose S(+)-ketamine reduces postoperative pain when applied with ropivacaine in epidural anesthesia for total knee arthroplasty. *Anesthesia and Analgesia* 2001; **92**: 1290–5.
- 110 Forster JG, Rosenberg PH. Small dose of clonidine mixed with low-dose ropivacaine and fentanyl for epidural analgesia after total knee arthroplasty. *British Journal of Anaesthesia* 2004; **93**: 670–7.
- 111 Wong CS, Lu CC, Cherng CH, Ho ST. Pre-emptive analgesia with ketamine, morphine and epidural lidocaine prior to total knee replacement. *Canadian Journal of Anaesthesia* 1997; **44**: 31–7.
- 112 Badner NH, Reimer EJ, Komar WE, Moote CA. Low-dose bupivacaine does not improve postoperative epidural fentanyl analgesia in orthopedic patients. *Anesthesia and Analgesia* 1991; **72**: 337–41 [see comment; erratum appears in *Anesth Analg* 1991 May; **72**(5):718].
- 113 Muldoon T, Milligan K, Quinn P, Connolly DC, Nilsson K. Comparison between extradural infusion of ropivacaine or bupivacaine for the prevention of postoperative pain after total knee arthroplasty. *British Journal of Anaesthesia* 1998; **80**: 680–1.
- 114 Casati A, Vinciguerra F, Cappelleri G, et al. Adding clonidine to the induction bolus and postoperative infusion during continuous femoral nerve block delays recovery of motor function after total knee arthroplasty. *Anesthesia and Analgesia* 2005; **100**: 866–72.
- 115 Weber A, Fournier R, Van Gessel E, Riand N, Gamulin Z. Epinephrine does not prolong the analgesia of 20 mL ropivacaine 0.5% or 0.2% in a femoral three-in-one block. *Anesthesia and Analgesia* 2001; **93**: 1327–31.
- 116 Dahl JB, Dagaard JJ, Rasmussen B, Egebo K, Carlsson P, Kehlet H. Immediate and prolonged effects of pre- versus postoperative epidural analgesia with bupivacaine and morphine on pain at rest and during mobilisation after total knee arthroplasty. *Acta Anaesthesiologica Scandinavica* 1994; **38**: 557–61.
- 117 Weber A, Fournier R, Riand N, Gamulin Z. Duration of analgesia is similar when 15, 20, 25 and 30 mL of ropivacaine 0.5% are administered via a femoral catheter. *Canadian Journal of Anaesthesia* 2005; **52**: 390–6.
- 118 Levy AS, Marmar E. The role of cold compression dressings in the postoperative treatment of total knee arthroplasty. *Clinical Orthopaedics and Related Research* 1993; **297**: 174–8.

- 119 Smith J, Stevens J, Taylor M, Tibbey J. A randomized, controlled trial comparing compression bandaging and cold therapy in postoperative total knee replacement surgery. *Orthopaedic Nursing* 2002; **21**: 61–6.
- 120 Gibbons CE, Solan MC, Ricketts DM, Patterson M. Cryotherapy compared with Robert Jones bandage after total knee replacement: a prospective randomized trial. *International Orthopaedics* 2001; **25**: 250–2.
- 121 National Joint Registry for England and Wales. *3rd Annual Clinical Report 2005*. <http://www.njrcentre.org.uk> (accessed December 2007).
- 122 National Hospital Discharge Survey. *US Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for Health Statistics 1991–2005*. [http://www.cdc.gov/nchs/data/series/sr\\_13/sr13\\_162.pdf](http://www.cdc.gov/nchs/data/series/sr_13/sr13_162.pdf) (accessed December 2007).
- 123 Fowler SJ, Symons J, Sabato S, Myles PS. Epidural analgesia compared with peripheral nerve blockade after major knee surgery: a systematic review and meta-analysis of randomized trials. *British Journal of Anaesthesia* 2008; **100**: 154–64.
- 124 Reuben SS, Ablett D, Kaye R. High dose nonsteroidal anti-inflammatory drugs compromise spinal fusion. *Canadian Journal of Anaesthesia* 2005; **52**: 506–12.
- 125 Reuben SS, Ekman EF. The effect of cyclooxygenase-2 inhibition on analgesia and spinal fusion. *Journal of Bone and Joint Surgery – American Volume* 2005; **87**: 536–42.
- 126 Salinas FV, Liu SS, Mulroy MF. The effect of single-injection femoral nerve block versus continuous femoral nerve block after total knee arthroplasty on hospital length of stay and long-term functional recovery within an established clinical pathway. *Anesthesia and Analgesia* 2006; **102**: 1234–9.
- 127 Reay BA, Semple AJ, Macrae WA, MacKenzie N, Grant IS. Low-dose intrathecal diamorphine analgesia following major orthopaedic surgery. *British Journal of Anaesthesia* 1989; **62**: 248–52.
- 128 Saito N, Horiuchi H, Kobayashi S, Nawata M, Takaoka K. Continuous local cooling for pain relief following total hip arthroplasty. *Journal of Arthroplasty* 2004; **19**: 334–7.
- 129 Singh H, Osbahr DC, Holovacs TF, Cawley PW, Speer KP. The efficacy of continuous cryotherapy on the postoperative shoulder: a prospective, randomized investigation. *Journal of Shoulder and Elbow Surgery* 2001; **10**: 522–5.
- 130 Brandner B, Munro B, Bromby LM, Hetreed M. Evaluation of the contribution to postoperative analgesia by local cooling of the wound. *Anaesthesia* 1996; **51**: 1021–5.
- 131 Fountas KN, Kapsalaki EZ, Johnston KW, Smisson HF III, Vogel RL, Robinson JS Jr. Postoperative lumbar micro-discectomy pain. Minimalization by irrigation and cooling. *Spine* 1999; **24**: 1958–60.
- 132 Moïniche S, Kehlet H, Dahl JB. A qualitative and quantitative systematic review of preemptive analgesia for postoperative pain relief: the role of timing of analgesia. *Anesthesiology* 2002; **96**: 725–41.
- 133 Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesthesia and Analgesia* 2005; **100**: 757–73.
- 134 Rostlund T, Kehlet H. High-dose local infiltration analgesia after hip and knee replacement – what is it, why does it work, and what are the future challenges? *Acta Orthopaedica* 2007; **78**: 159–61.
- 135 Busch CA, Shore BJ, Bhandari R, et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty. A randomized trial. *Journal of Bone and Joint Surgery – American Volume* 2006; **88**: 959–63.
- 136 Vendittoli PA, Makinen P, Drolet P, et al. A multimodal analgesia protocol for total knee arthroplasty. A randomized, controlled study. *Journal of Bone and Joint Surgery – American Volume* 2006; **88**: 282–9.
- 137 Biboulet P, Morau D, Aubas P, Bringuier-Branchereau S, Capdevila X. Postoperative analgesia after total-hip arthroplasty: comparison of intravenous patient-controlled analgesia with morphine and single injection of femoral nerve or psoas compartment block. A prospective, randomized, double-blind study. *Regional Anesthesia and Pain Medicine* 2004; **29**: 102–9.

# Recovery after total intravenous general anaesthesia or spinal anaesthesia for total knee arthroplasty: a randomized trial†

A. Harsten<sup>1\*</sup>, H. Kehlet<sup>2,3</sup> and S. Toksvig-Larsen<sup>4</sup>

<sup>1</sup>Department of Anaesthesiology, Håssleholm Hospital and Lund University, Box 351, 281 25 Håssleholm, Sweden

<sup>2</sup>Lundbeck Centre for Fast-track Hip and Knee Arthroplasty, Rigshospitalet, Denmark

<sup>3</sup>Department of Surgical Pathophysiology, Rigshospitalet, Copenhagen University, Blegdamsvej 9, DK-2100 Rigshospitalet, Denmark

<sup>4</sup>Department of Orthopedic Surgery, Håssleholm Hospital and Lund University, Box 351, 281 25 Håssleholm, Sweden

\* Corresponding author. Email: andreas.harsten@skane.se

## Editor's key points

- Regional anaesthesia is often recommended for total knee arthroplasty (TKA).
- General anaesthesia (GA) and spinal anaesthesia (SA) were compared in a study of short term recovery parameters.
- The GA group had higher immediate pain scores, but shorter length of hospital stay, and reduced postoperative nausea and vomiting, pain and morphine consumption.
- GA has a more favourable recovery profile than SA in a fast-track protocol.

**Background.** This study was undertaken to compare the effects of general anaesthesia (GA) and spinal anaesthesia (SA) on the need for postoperative hospitalization and early postoperative comfort in patients undergoing fast-track total knee arthroplasty (TKA).

**Methods.** One hundred and twenty subjects were randomly allocated to receive either intrathecal bupivacaine (SA group) or GA with target controlled infusion of propofol and remifentanyl (GA group). Primary outcome was length of hospital stay (LOS) defined as time from end of surgery until the subject met the hospital discharge criteria. Secondary outcome parameters included actual time of discharge, postoperative pain, intraoperative blood loss, length of stay in the Post Anaesthesia Care Unit, dizziness, postoperative nausea and vomiting, need for urinary catheterization and subject satisfaction.

**Results.** GA resulted in shorter LOS (46 vs 52 h,  $P<0.001$ ), and less nausea and vomiting (4 vs 15,  $P<0.05$ ) and dizziness (VAS 0 mm vs 20 mm,  $P<0.05$ ) compared with SA. During the first 2 postoperative hours, GA patients had higher pain scores ( $P<0.001$ ), but after 6 h the SA group had significantly higher pain scores ( $P<0.001$ ). Subjects in the GA group used fewer patient-controlled analgesia doses and less morphine ( $P<0.01$ ), and were able to walk earlier compared with the SA group ( $P<0.001$ ). Subjects receiving SA would request a change in the method of anaesthesia in the event of a subsequent operation more often than the GA subjects ( $P<0.05$ ).

**Conclusion.** GA had more favourable recovery effects after TKA compared with SA.

**Keywords:** anaesthetic techniques; i.v.; outcome; subarachnoid

Accepted for publication: 26 February 2013

Total knee arthroplasty (TKA) is a common and painful procedure. Pain is not only unpleasant for the patient but the intensity of early postoperative pain is a strong risk factor for developing persistent pain. The operation is usually performed under regional anaesthesia (RA) or general (GA), and previous data have shown better outcome effect after RA.<sup>1</sup> Consequently, RA with the intrathecal technique has been recommended.<sup>2</sup> However, RA has not often been compared with modern GA techniques with multimodal non-opioid analgesia and a fast-track approach. RA produces good pain control in the first couple of postoperative hours, but the question is whether this advantage remains for the first 1–2 postoperative days or whether a modern GA technique would be preferable in a fast-track set-up. Therefore, we conducted a prospective, randomized trial to compare the effect of spinal anaesthesia (SA) and GA on length of hospital stay (LOS), postoperative pain,

opioid requirements and other patient comfort factors in patients undergoing TKA.

## Methods

This study was approved by the Research Ethics Committee at Lund University (no. 2011/180) and was carried out at Håssleholm Hospital, Sweden. It was registered with ClinicalTrials.gov under the US National Library of Medicine (reg. no. NCT01312298). Written informed consent was obtained from all subjects.

## Study design

The study design was consecutive and randomized. Patients with osteoarthritis undergoing TKA at the Department of Orthopaedic Surgery, Håssleholm Hospital, Sweden, were

† This article is accompanied by Editorial IV.



eligible for participation in the study. One hundred and twenty-four consecutive patients were assessed by two orthopaedic surgeons between September 2011 and June 2012, and 120 subjects were enrolled after the preoperative visit to the anaesthetist. Inclusion criteria were ASA I–III, able to understand the given information, age >45 yr and <85 yr and having signed the informed consent. Exclusion criteria were previous major knee surgery to the same knee, obesity (BMI >35), rheumatoid arthritis, immunological depression, and allergy to any of the drugs used in this study. Patients were also excluded if they were taking opioids or steroids or if they had a history of stroke or psychiatric disease that could affect the perception of pain.

### Randomization and blinding procedure

Randomization was performed by an employee not involved in the study, who prepared non-transparent, sealed envelopes each containing a slip of paper with a computer generated description of whether the patient should receive GA or SA. On the day of surgery a nurse, likewise not involved in the study, opened the appropriate envelope and prepared the procedures accordingly. Subjects and investigating doctors were blinded to treatment group until 1 h before surgery. After that, both subjects and personnel in the operation theatre were, for obvious reasons, aware of the method of anaesthesia being used. Once subjects left the operating theatre, staff responsible for monitoring and assessing home readiness were blinded as to treatment group.

### Anaesthesia and perioperative care

Approximately 1 h before surgery all subjects received oral celecoxib 400 mg and acetaminophen 1 g, and thereafter 12-hourly (celecoxib 200 mg) and 6-hourly (acetaminophen 1 g). No subjects received an indwelling urinary catheter before surgery, and a thigh tourniquet was not used. No drains were used.

A low-volume fluid regimen was used with 2000 ml of Ringer's solution (Fresenius-Kabi AB, Uppsala, Sweden) during the first 24 h. All subjects received 1 g of tranexamic acid i.v.

Subjects in the SA group received intrathecal (L<sub>4</sub>–L<sub>5</sub>) administration (using a 25 G Quinke needle, Spinocan®, B.Braun AG, Germany) consisting of bupivacaine 0.5%, 3 ml. They were also given an infusion of propofol 10 mg ml<sup>-1</sup> to induce light sedation during surgery, breathing spontaneously with supplemental oxygen 2 litre min<sup>-1</sup>.

Subjects in the GA group were anaesthetized using target controlled infusion (TCI) with propofol and remifentanyl.<sup>3 4</sup> Rocuronium bromide 0.6 mg kg<sup>-1</sup> was given to facilitate intubation. Ventilation was with oxygen/air targeting an end-tidal CO<sub>2</sub> of 4.5 kPa. At the end of surgery glycopyrronium 0.5 mg and neostigmine 2.5 mg was given i.v., with i.v. bolus dose of oxycodone 10 mg 20 min before the end of surgery.

All subjects received cloxacillin 2 g i.v. (or clindamycin 600 mg i.v. if penicillin allergy) before surgical incision. The

preoperative fasting period was 6 or 2 h before surgery for solid food or clear fluids, respectively.<sup>5</sup>

Towards the end of surgery, all subjects received infiltration of local anaesthetic in the perisurgical area<sup>6</sup> consisting of 150 ml of ropivacaine (0.2%) with epinephrine (10 µg ml<sup>-1</sup>) (i.e. 148.5 ml ropivacaine 2 µg ml<sup>-1</sup>+1.5 ml epinephrine 1 µg ml<sup>-1</sup>). The mixture was injected using a systematic technique to ensure uniform delivery of local anaesthetic to all tissues incised, handled or instrumented during the procedure. The first 50 ml were injected into the posterior joint capsule and both collateral ligaments after the bone cuts had been performed. After insertion of the prosthesis, 50 ml were injected along the borders of and into the capsule and cut quadriceps tendon, infra-patellar ligament, possible remnants of the fat pad, cruciate ligaments and soft tissues surrounding the joint. Another 50 ml were infiltrated into the subcutaneous tissues before wound closure.<sup>6</sup> A Cryo-bandage (Iceband, Nordic Medical Supply A/S, Denmark) was applied directly after surgery and remained in place for 24 h.

All subjects were before operation familiarized with a patient controlled analgesia (PCA) device for postoperative pain medication during the first postoperative 24 h. The PCA pump (Abbott GemStar™ PCA Pump) delivered i.v. morphine in doses of 20 µg kg<sup>-1</sup> and with a lock out time of 10 min.<sup>6</sup> After 24 h the PCA device was disconnected and subjects received slow-release oxycodone (OxyContin®) 10 mg orally twice daily. After 24 h oxycodone (OxyNorm®) 10 mg orally was used as rescue medication. The PCA device was fitted to subjects as they left the operating theatre, and was removed 24 h later and the amount of morphine administered registered. The number of requested and administered PCA doses were registered along with the time at which these doses were requested.

In order to prevent overdistension of the bladder ultrasound bladder scans were performed at least every third hour until subjects could control their urinary bladder and the following rules were observed:

- (1) bladder volume <300 ml, repeat bladder scan within 3 h;
- (2) 300–399 ml, repeat bladder scan within 2 h;
- (3) 400–499 ml, repeat bladder scan within 1 h;
- (4) ≥500 ml, do intermittent catheterization. This can be repeated twice after which an indwelling urinary bladder catheter is used.

### Assessments

All subjects were familiarized with a horizontal visual analogue scale (VAS, 100 mm) used for assessment of pain (0=no pain, 100=worst imaginable pain), postoperative nausea and vomiting (PONV), and dizziness (0=no symptoms, 100=worst symptoms possible).

Pain was registered before operation, on arrival to Post Anaesthesia Care Unit (PACU), after 2, 4, 6 and 10 h. The first and second day after surgery pain was assessed at 08:00 and 14:00 h. Pain was registered at rest, with 45° knee



flexion, with the knee straight and 45° hip flexion, and after walking 5 m.<sup>7</sup>

Dizziness (and at the same time blood pressure) was recorded twice per day by asking the patient to score his/her dizziness on a 100 mm VAS anchored with 'no dizziness' and 'worst possible dizziness'. Dizziness and blood pressure were monitored in supine and upright standing position. Blood pressure (systolic and diastolic, mmHg) was also measured after standing, with the measurement of blood pressure commencing within 60 s. When analysing the data, mean arterial blood pressure (MAP) was used. Orthostatic function was defined as being able to walk 5 m at 6, 10, 24 and 48 h after operation.

Discharge criteria from PACU to the ward were assessed every 15 min until obtained by a nurse blinded to treatment group. Discharge criteria from PACU were: (i) sufficient level of consciousness (aroused by verbal stimuli), (ii) able to maintain a free airway, (iii) adequate breathing with  $SpO_2 > 94\%$  when administering a maximum of 5 litre  $O_2$  min<sup>-1</sup> nasally, (iv) mild or no PONV (<30 mm), (v) pain control adequate (VAS ≤ 30 mm at rest).

LOS was defined as the time from the end of surgery until the subject met the discharge criteria from the ward: (i) able to get in and out of bed, (ii) able to get dressed, (iii) able to sit down in a chair and get up again, (iv) able to walk 50 m with or without walking aids (crutches, etc.), (v) able to flex the knee to ≥ 70°, (vi) able to walk stairs, (vii) pain manageable with oral analgesics, (viii) acceptance to be discharged.

Discharge criteria were checked twice daily, at 08:00 and again at 14:00 h by a nurse blinded to treatment group. The actual time at which the subject was discharged from the ward was noted and compared with LOS.

PONV was monitored using a 100 mm VAS for nausea anchored with 'no nausea' and 'worst possible nausea'. The number of vomiting occasions was recorded. PONV was monitored twice daily.

Intraoperative blood loss was calculated by weighing gauze and draping sheets together with the content in the surgical suction bottle corrected for irrigation fluid volume.

Six months after operation, subjects were interviewed via telephone by an employee blinded to assigned treatment. They were asked to assess the anaesthesia they had received 6 months earlier on a 100 mm scale where 0 = worst imaginable experience and 100 = best possible experience. They were also asked what type of anaesthesia they would like to have in case of a subsequent TKA (SA or GA).

## Surgery

Surgeries were performed via a ventral incision with a parapatellar medial entrance to the joint. The patella was everted. A cemented single radius cruciate retaining (CR) total knee was used [the Triathlon™ Knee System (Stryker, Mahwah, New Jersey, USA)] for all subjects. Appropriate guide instruments were used according to the surgical technique manual supplied with the knee system.

## Statistical analyses

Power and sample size calculation was done with <http://biostat.mc.vanderbilt.edu/wiki/bin/view/Main/PowerSampleSize>.

We planned a study of a continuous response variable from independent control and experimental subjects with 1 control per experimental subject. In a previous pilot study at Håssleholm Hospital, the response within each subject group was 72 h with standard deviation of 42. If the true difference between experimental and control means was 24 h, we would need to study 49 experimental subjects and 49 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.8. The Type I error probability associated with testing of this null hypothesis is 0.05. To compensate for drop outs we decided to include 124 subjects.

Data analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL, USA). Data distribution was tested for normality with Shapiro–Wilks test and residual plots. According to data distribution either Student *t*-test or Mann–Whitney *U*-test for unpaired data was used. Chi-square test was used for binary data. Data are presented as mean (sd) or median 25–75% interquartile range (IQR).  $P < 0.05$  was assigned statistical significance.

## Results

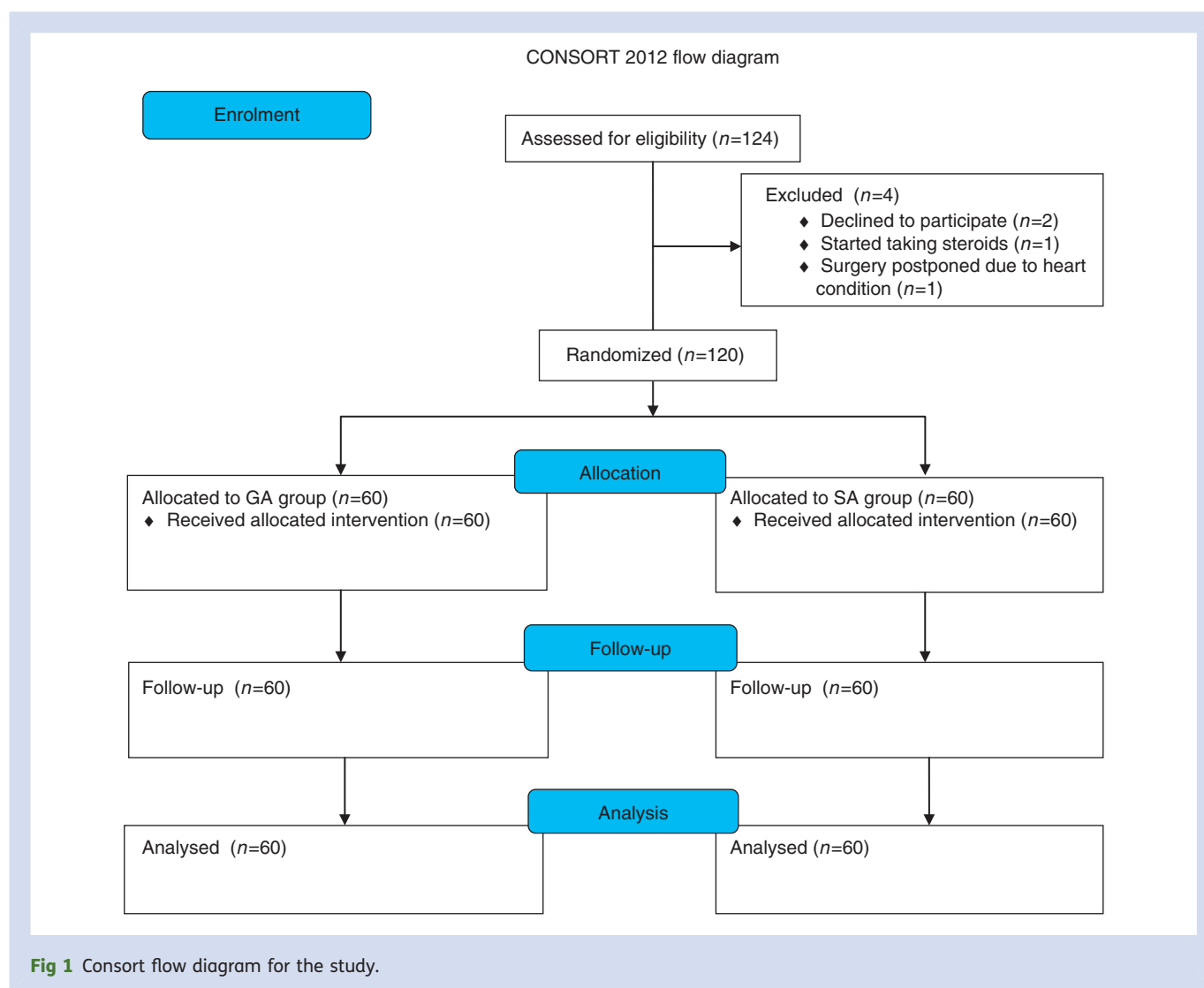
Patients were recruited between September 2011 and June 2012. One hundred and twenty-four consecutive patients were assessed for eligibility by 2 orthopaedic surgeons and 120 were included after the preoperative visit by the anaesthetist [Fig. 1 (CONSORT flow diagram)]. The 6-month follow-up was completed in December 2012. There were no differences in subject characteristics or surgical data (Table 1).

Sixty-six per cent of subjects were ready to be discharged from PACU upon arrival without statistical differences between the groups (Mann–Whitney).

LOS (fulfilling discharge criteria) was shorter in the GA group (46 h) compared with the SA group (52 h,  $P < 0.001$ ), but without difference between groups in actual day of discharge [ $\chi^2$ -test Table 2]. The reasons for not being discharged in spite of meeting discharge criteria were organizational (39 patients), general weakness (2), dizziness (3), and pain (5).

Preoperatively, there were no differences in pain scores between GA and SA. In the early phase of the postoperative period, subjects in the GA group had higher pain scores, but from 6 h onwards the SA patients had higher pain scores (Fig. 2).

The median (IQR) 24 h postoperative consumption of morphine was 19 mg (11–28) in the GA group and 54 mg (37–78) in the SA group ( $P < 0.001$ ). The median number (IQR) of administered PCA doses was 12 (10–22) in the GA group and 30 (20–41) in the SA group ( $P < 0.001$ ). The median (IQR) number of requested, but not administered, PCA doses was 2 (0–7) in the GA group and 9 (1–26) in the

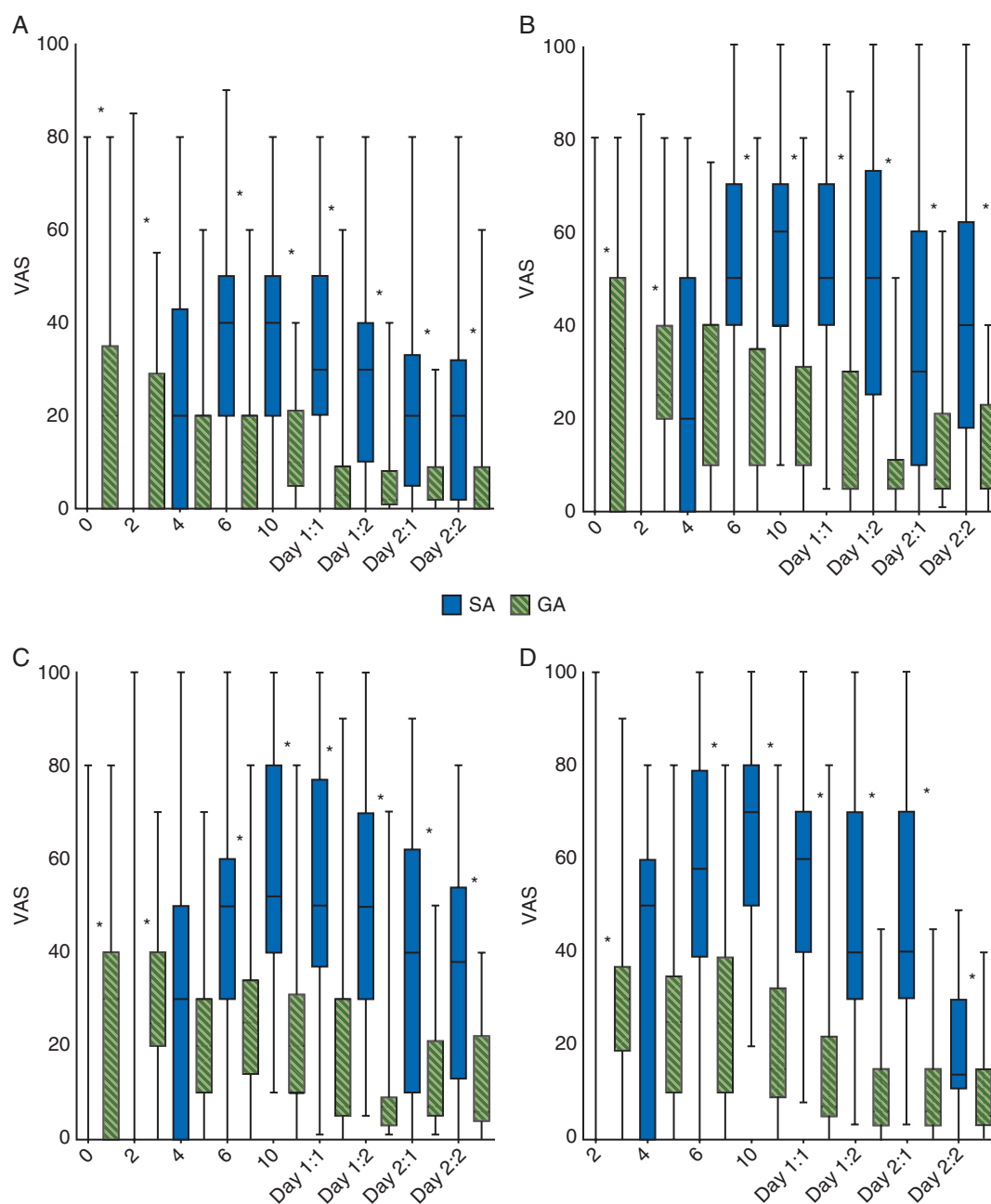


**Table 1** Weight, height, age, and duration of surgery presented as mean (sd). Operative bleeding presented as median (IQR). Gender and ASA status presented as numbers

Subject characteristics and surgical data		
	GA group n=60	SA group n=60
Weight (kg)	82 (11)	83 (16)
Height (cm)	172 (8)	170 (9)
Male/Female	31/29	28/32
Age (yr)	68 (7)	67 (7)
ASA physical status		
I	18	11
II	35	39
III	7	10
Duration of surgery (min)	44 (11)	49 (7)
Operative bleeding (ml)	208 (145–267)	218 (132–293)

**Table 2** Cumulative number of subjects meeting discharge criteria from the ward at different postoperative times and the actual number of subjects that in fact were discharged ( $\chi^2$ -test, GA group vs SA group). Day 1 is the day after the day of surgery

Discharge from the ward	According to criteria			Actual discharge		
	GA group n=60	SA group n=60	P-value	GA group n=60	SA group n=60	P-value
Day 1, 08:00	0	0	n.s.	0	0	n.s.
Day 1, 14:00	16	3	<0.01	1	1	n.s.
Day 2, 08:00	38	17	<0.01	1	1	n.s.
Day 2, 14:00	54	43	n.s.	23	25	n.s.
Day 3				49	44	n.s.
Day 4				56	53	n.s.



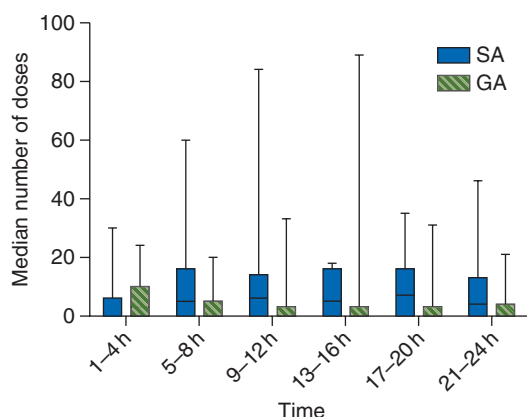
**Fig 2** Pain (VAS 0–100 mm) at (A) rest, (B) during knee flexion, (C) with the knee straight and hip flexion and (D) when walking. Green bars=GA and blue bars=SA. A line within the boxes indicates a median and the boxes indicate 25–75% IQR. Whiskers indicate range. \* $P < 0.001$ . Numbers indicate the hours after surgery. Day 1:1 and 1:2 is the day after the day of surgery at 08:00 and 14:00. Day 2:1 and 2:2 are the same times but the second postoperative day.

SA group ( $P < 0.001$ ). The distribution of the median (IQR) number of requested and administered PCA doses during the first 24 h after operation hours are shown in Figure 3.

Subjects in the SA group had higher dizziness scores ( $P < 0.05$ ) (Fig. 4). Orthostatic function was less affected in the GA group ( $\chi^2$ -test) as 57 subjects in the GA group and 18 in the SA group were able to walk 5 m after 6 h ( $P < 0.001$ ). After 10 h and 24 h the same figures were 59

and 60 subjects in the GA group and 40 and 59 in the SA group ( $P < 0.01$  at 10 h and n.s. at 24 h). There were no differences in MAP between the groups except on the first postoperative day at 14:00 h where MAP was significantly higher in the SA group when standing up [96 (10) mm Hg vs 90 (12) mm Hg, Student  $t$ -test,  $P < 0.05$ ].

PONV scores and number of subjects that vomited are given in Table 3; both were higher in the SA group. The



**Fig 3** Median number of administered, and requested but not administered PCA doses during the first 24 h after surgery. A line within the boxes indicates median and boxes indicate 25–75% IQR. Whiskers indicate range.  $P < 0.001$  at all times.

median (IQR) number of redressings were 2 (0–3) in the GA group and 1 (0–3) in the SA group (n.s. Mann–Whitney).

Forty-two subjects in the GA group and 36 in the SA group were managed without bladder catheterization. Sixteen subjects in the GA group and 23 in the SA group had to have one or two intermittent catheterizations [ $P > 0.05$  between groups ( $\chi^2$ -test)].

There was no difference between groups in total anaesthesia satisfaction score. However, significantly more subjects in the SA group indicated that they would like to change the method of anaesthesia for a subsequent operation (14 vs 2,  $\chi^2$ -test,  $P < 0.05$ ).

There were no deaths during this study but a pulmonary embolus was diagnosed in two subjects, one in each group. No other pulmonary or cardiac complications were diagnosed.

## Discussion

TKA is an effective treatment for end-stage knee osteoarthritis, and on a global scale this procedure is increasing. For example, 550 000 TKAs were performed in 2007 in the USA.<sup>8</sup> A major challenge for the future will be to perform such a large number of operations not only with good medical outcome but also with acceptable economical and logistical quality.

In this standardized study in TKA, subjects receiving GA had shorter LOS (time to reach discharge criteria), less dizziness and PONV, and better early orthostatic function compared with SA. Also, pain scores were lower after 6 h with an opioid-sparing effect in the GA group compared with the SA group. Furthermore, patients in the GA group were more likely to favour the same type of anaesthesia if they had to have surgery again. No differences were found in length of PACU stay, blood loss and need for urinary catheterization between the groups.

At 14:00 h on the second day after the day of surgery, 79% of subjects met or had met the discharge criteria from the

ward, which is in line with previous findings.<sup>9</sup> More interesting is that the GA subjects seemed to be ready for discharge earlier than the SA subjects (36 vs 48 h), probably explained by reduced PONV and dizziness. In a systematic study by Liu and Wu<sup>10</sup> the effect of anaesthesia technique on pain and outcome was investigated. They found that RA resulted in a modest reduction in pain scores accompanied by an increase in side-effects that was not perceived as an improvement.

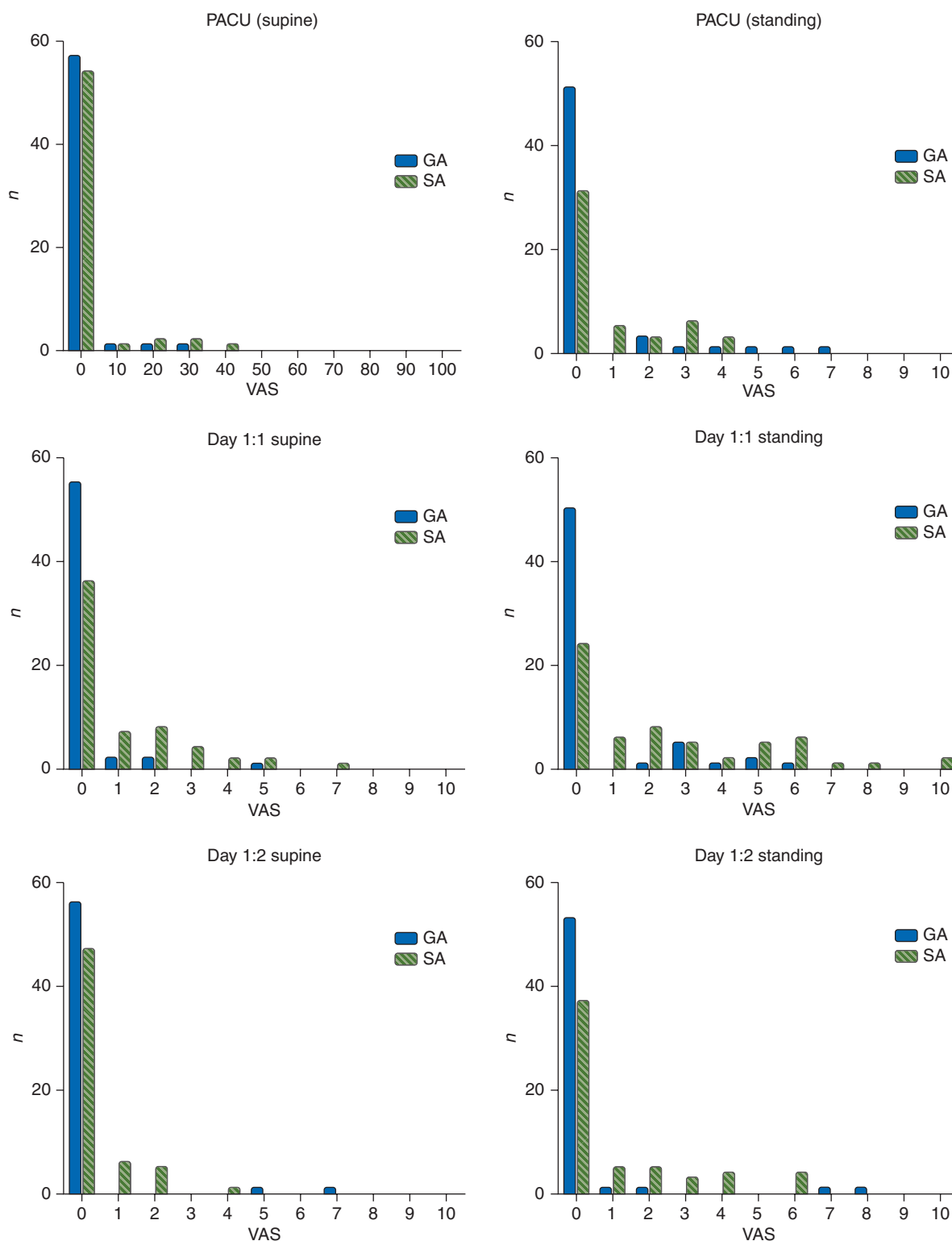
The main reasons for still being in hospital in spite of meeting discharge criteria in our study were exudation from the surgical wound and organizational causes. None of the subjects in our study had a tourniquet during surgery, which might have contributed to less pain but also to the increased postoperative wound exudation.<sup>11</sup> We refrained from the use of a thigh tourniquet due to its association with intraoperative, ischaemic nociception.<sup>11</sup>

A review by Macfarlane and colleagues<sup>12</sup> reported reduced postoperative pain and morphine consumption among patients receiving RA compared with GA. However, most of the studies included in this review were done before the introduction of the high-volume local infiltration technique (LIA),<sup>13</sup> which has been widely used since 2008 in connection with TKA and which is more simple compared with many other regional anaesthetic techniques.<sup>13 14</sup> In our study, both groups received the same type of LIA. Other differences compared with older studies are that we used TCI as the GA method as TCI is well tolerated with rapid and clear headed emergence.<sup>15</sup> Finally, all subjects received standardized opioid-sparing analgesia with cyclo-oxygenase-2 inhibitor and acetaminophen.

In the PACU, 73% of the SA and 59% of the GA patients met the PACU discharge criteria on arrival. Thus, many TKA patients can bypass PACU and go directly to the ward. Lunn and colleagues<sup>16</sup> found in a recent study that 85% of the patients met PACU discharge criteria within 15 min, but their study and ours had slightly different discharge criteria compared with standard recommendations<sup>7</sup> in that motor function was not taken into consideration. This change did not cause any complication on the ward in terms of respiratory or cardiovascular instability, decreases due to motor weakness or other organ dysfunctions<sup>16</sup> and therefore calls for further large-scale studies.

In the SA group, intrathecal morphine was not used despite being recommended,<sup>1</sup> which may slightly have influenced our results. However, the analgesic effects of intrathecal morphine are rather small, and in elderly patients the side-effects from intrathecal opioids can be undesirable for early recovery. Furthermore, we used a rather comprehensive multimodal non-opioid analgesic programme, which we thought would reduce the need for intrathecal morphine. The GA group received intraoperative oxycodone at the end of surgery due to the shortlasting analgesic effects of the GA technique. In contrast, we found routine intraoperative oxycodone inappropriate in the SA group, receiving a combination of opioid-sparing intrathecal local anaesthetics and the LIA technique.

We found that subjects in the SA group had significantly more dizziness compared with those in the GA group. As



**Fig 4** Number of subjects having different levels of dizziness (VAS 0–100 mm) when in a supine or standing up position. Measurements made at PACU, the day after the day of surgery at 08:00 h (Day 1:1) and at 14:00 h (Day 1:2). Area under the curve analysed for PACU–Day 1:1 and Day 1:1–Day 1:2 using Mann–Whitney test. Statistically significant differences (more subjects having higher scores in SA group).  $P < 0.05$ , at both intervals.

**Table 3** Postoperative nausea and vomiting. Median (IQR) [range] score for postoperative nausea (Mann–Whitney). Number of subjects vomiting each day ( $\chi^2$ -test). Day 1 is the day after the day of surgery

	VAS score for nausea			Number of subjects vomiting		
	GA group n = 60	SA group n = 60	P-value	GA group n = 60	SA group n = 60	P-value
PACU	0 (0) [0–30]	0 (0–20) [0–100]	<0.01			
Day 1, 08:00 h	0 (0) [0–63]	17 (0–44) [0–90]	<0.001			
Day 1, 14:00 h	0 (0) [0–50]	0 (0–16) [0–100]	<0.01	4	15	<0.05
Day 2, 08:00 h	0 (0) [0–50]	0 (0–10) [0–50]	<0.05			
Day 2, 14:00 h	0 (0) [0–50]	0 (0) [0–50]	n.s.	1	5	n.s.

dizziness and muscle weakness are two of the major reasons for delayed discharge,<sup>9</sup> it might be possible to reduce these complaints by using GA instead of SA. However, the increase in dizziness among the SA subjects could not be explained by orthostatic dysfunction,<sup>17</sup> because we only found differences in MAP at 14:00 h the first day after the day of surgery, which was higher in the SA group.

Lumbar SA might have more profound effect on urinary bladder dysfunction, but 68% in both groups managed without having their bladder catheterized. Provided that bladder scans are done regularly it might be an advantage to avoid urinary catheters as they are associated with a number of serious complications such as urinary tract infections and subsequently deep wound infections.<sup>18 19</sup>

We found no difference between groups in bleeding during surgery, as suggested before.<sup>2</sup> Furthermore, blood loss was limited in both groups in spite of the fact that tourniquet was not used. This is, in contrast, with a recent publications by Stundner and colleagues<sup>20</sup> where neuraxial anaesthesia was associated with reduced blood transfusions. However, their study was retrospective and in one-third of the cases analysed, method of anaesthesia could not be determined.

When anaesthetists were asked if they would like GA or RA themselves in a hypothetical situation of requiring surgery for a lower extremity orthopaedic problem they preferred RA.<sup>21</sup> It is, therefore, interesting that we found no differences in satisfaction scores between groups, although more subjects in the SA group would prefer GA in the case of a future operation.

A limitation of our study was that from 1 h before the start of surgery until reaching the PACU, subjects and caregivers were, for obvious reasons, not blinded to which anaesthetic technique was being used. However, all nurses and doctors involved in monitoring and registration were otherwise unaware of treatment allocation. Another limitation was that this study looked solely at comfort factors and not serious morbidity or mortality which will require a sufficiently powered prospective randomized trial to compare RA and GA, although differences are probably being minimal.<sup>22</sup> Major complications after RA are rare but sometimes serious (vertebral canal abscess or haematoma, meningitis, nerve injury, and cardiovascular collapse).<sup>23</sup> Other serious complications

such as deep vein thrombosis, pulmonary embolism, pneumonia, and respiratory depression were reported as less frequent when using RA in a large systematic review.<sup>2</sup> However, their conclusions were based on studies performed in the 1980s and 1990s. Today, a fast-track regimen including early mobilization and effective treatment of pain has reduced those outcomes.<sup>24</sup>

In conclusion, in TKA GA resulted in earlier recovery, less pain, dizziness and nausea and earlier ability to walk compared with SA. In addition, subjects preferred GA over SA in the event of another TKA.

## Authors' contributions

A.H. participated in the design of the study, did preoperative evaluation, enrolled patients, administered anaesthesia, performed statistical analyses and wrote the manuscript. H.K. and S.T.-L. designed and coordinated the study and participated in writing the manuscript.

## Acknowledgements

We thank the staff at the Department of Anaesthesiology and the Department of Orthopedic Surgery, Hässeholm Hospital, Sweden, for helpful assistance.

## Declaration of interest

None declared.

## Funding

The study was supported with institutional grants.

## References

- 1 Fischer HB, Simanski CJ, Sharp C, et al. A procedure-specific systematic review and consensus recommendations for postoperative analgesia following total knee arthroplasty. *Anaesthesia* 2008; **63**: 1105–23
- 2 Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *Br Med J* 2000; **321**: 1493
- 3 Marsh BJ, Morton NS, White M, Kenny GN. A computer controlled infusion of propofol for induction and maintenance of anaesthesia in children. *Can J Anaesth* 1990; **37**: S97



- 4 Minto CF, Schnider TW, Shafer SL. Pharmacokinetics and pharmacodynamics of remifentanyl. II. Model application. *Anesthesiology* 1997; **86**: 24–33
- 5 American Society of Anesthesiologists Committee. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. *Anesthesiology* 2001; **114**: 495–511
- 6 Andersen LO, Husted H, Otte KS, Kristensen BB, Kehlet H. High-volume infiltration analgesia in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. *Acta Anaesthesiol Scand* 2008; **52**: 1331–5
- 7 Lunn TH, Kristensen BB, Andersen LO, et al. Effect of high-dose preoperative methylprednisolone on pain and recovery after total knee arthroplasty: a randomized, placebo-controlled trial. *Br J Anaesth* 2011; **106**: 230–8
- 8 Buvanendran A, Kroin JS, Della Valle CJ, Kari M, Moric M, Tuman KJ. Perioperative oral pregabalin reduces chronic pain after total knee arthroplasty: a prospective, randomized, controlled trial. *Anesth Analg* 2010; **110**: 199–207
- 9 Husted H, Lunn TH, Troelsen A, Gaarn-Larsen L, Kristensen BB, Kehlet H. Why still in hospital after fast-track hip and knee arthroplasty? *Acta Orthop* 2011; **82**: 679–84
- 10 Liu SS, Wu CL. The effect of analgesic technique on postoperative patient-reported outcomes including analgesia: a systematic review. *Anesth Analg* 2007; **105**: 789–808
- 11 Estebe JP, Davies JM, Richebe P. The pneumatic tourniquet: mechanical, ischaemia-reperfusion and systemic effects. *Eur J Anaesthesiol* 2011; **28**: 404–11
- 12 Macfarlane AJ, Prasad GA, Chan VW, Brull R. Does regional anesthesia improve outcome after total knee arthroplasty? *Clin Orthop Relat Res* 2009; **467**: 2379–402
- 13 Kerr DR, Kohan L. Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery: a case study of 325 patients. *Acta Orthop* 2008; **79**: 174–83
- 14 Kehlet H, Andersen LO. Local infiltration analgesia in joint replacement: the evidence and recommendations for clinical practice. *Acta Anaesthesiol Scand* 2011; **55**: 778–84
- 15 Wang Y, Yan M, He JG, et al. A randomized comparison of target-controlled infusion of remifentanyl and propofol with desflurane and fentanyl for laryngeal surgery. *ORL J Otorhinolaryngol Relat Spec* 2011; **73**: 47–52
- 16 Lunn TH, Kristensen BB, Gaarn-Larsen L, Husted H, Kehlet H. Post-anaesthesia care unit stay after total hip and knee arthroplasty under spinal anaesthesia. *Acta Anaesthesiol Scand* 2012; **56**: 1139–45
- 17 Jans O, Bundgaard-Nielsen M, Solgaard S, Johansson PI, Kehlet H. Orthostatic intolerance during early mobilization after fast-track hip arthroplasty. *Br J Anaesth* 2012; **108**: 436–43
- 18 Balderi T, Carli F. Urinary retention after total hip and knee arthroplasty. *Minerva Anestesiol* 2010; **76**: 120–30
- 19 Hameed A, Chinegwundoh F, Thwaini A. Prevention of catheter-related urinary tract infections. *Br J Hosp Med (Lond)* 2010; **71**: 148–50, 51–2
- 20 Stundner O, Chiu YL, Sun X, et al. Comparative perioperative outcomes associated with neuraxial versus general anesthesia for simultaneous bilateral total knee arthroplasty. *Reg Anesth Pain Med* 2012; **37**: 638–44
- 21 Roy RC. Choosing general versus regional anesthesia for the elderly. *Anesthesiol Clin N Am* 2000; **18**: 91–104, vii
- 22 Kettner SC, Willschke H, Marhofer P. Does regional anaesthesia really improve outcome? *Br J Anaesth* 2011; **107**(Suppl. 1): i90–5
- 23 Cook TM, Counsell D, Wildsmith JA. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. *Br J Anaesth* 2009; **102**: 179–90
- 24 Husted H, Otte KS, Kristensen BB, Orsnes T, Wong C, Kehlet H. Low risk of thromboembolic complications after fast-track hip and knee arthroplasty. *Acta Orthop* 2010; **81**: 599–605

Handling editor: H. C. Hemmings