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ORIGINAL STUDY

A neuro-anatomically grounded scheme for LIA gives superior analgesia and comfort levels compared to epidural analgesia until seven days after total knee arthroplasty

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LIA is an emerging alternative for patient-controlled epidural analgesia(PCEA) after total knee arthroplasty(TKA). LIA allows faster mobilisation, eliminates the risks of epidural catheters, and can hasten patient turnover. Conversely, PCEA provides reliable pain relief in the first days after this type of surgery. The purpose of this study was to evaluate the quality of antinociception, postoperative nausea & vomiting (PONV), and general comfort until 7 days postoperatively.

40 patients received PCEA and 41 received LIA. Patients were retrospectively asked for pain scores at the day of surgery(=D0), D2, and D7, PONV, and general comfort scores.

Patients in the LIA group reported equal pain scores at D0, significantly better PONV scores and pain scores at D2 and D7.

In addition to faster mobilisation and elimination of the risks and burden of an epidural catheter and PCEA, LIA delivers equal to better analgesia, and better PONV and general comfort scores.

Keywords : Local infiltration analgesia ; patient controlled epidural analgesia ; total knee arthroplasty.

INTRODUCTION

Postoperative pain after total knee arthroplasty (TKA) has a negative impact on patients' early mobilisation and psychological state and can lead to a prolonged hospital stay. In addition, it increases the risk of venous thrombosis and can cause poor wound healing, decrease patient satisfaction and increase the risk of chronic postsurgical pain syndrome (CPSP) *(1,2)*. Adequate pain relief consequently reduces the surgical stress response, thus reducing morbidity, facilitating postoperative recovery and early rehabilitation, shorten hospital stay, and decrease the risk of chronic pain *(1)*. Still, up to half of the patients experience severe postoperative pain after TKA *(1)*. While pain is the most common cause of delayed discharge and a frequent cause of readmission, orthostatic hypotension and muscle

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weakness are also considered important causes of complications, which must be addressed to permit optimised recovery *(1)*. The goal of an optimised analgesic strategy should, therefore, be to provide postoperative analgesia that has a prolonged duration of action, is easy to administer and has minimal adverse side effects. In particular, early rehabilitation within 24 hours after TKA reduces the mean hospital stay and the number of physical therapy sessions required to achieve autonomy and normal gait and balance, as well as the risk for certain postoperative complications such as infection and deep venous thrombosis (DVT) *(1,2)*. Early rehabilitation also reduces knee stiffness, which may be a proxy for arthrofibrosis, which can ultimately require manipulation under anesthesia or revision *(1)*.

Optimal analgesia management must, therefore, permit early mobilisation – yielding beneficial surgical outcome, improved patient satisfaction and economic savings – but must also have a rapid onset giving good operating conditions and good postoperative pain relief, and must have minimal side effects *(1,2)*. As a strategy for optimal postoperative pain relief after TKA, current options are intravenous opiates, Patient Controlled Epidural analgesia (PCEA), femoral or adductor canal block, and local infiltration analgesia (LIA), each involving specific risks and drawbacks.

Enhanced recovery after surgery (ERAS) protocols assert that local anaesthetic should always be included as part of a multi-modal package of analgesia. For this, local anaesthetic can be administered via the neuraxial route, nerve blocks, wound infiltration, or as an intravenous infusion. If adequately applied, the LIA covers both wound infiltration and nerve blockade. While many publications report the benefit of LIA for TKA, the exact location of the multiple injections are rarely described in sufficient detail. A detailed description of the distribution of anesthetics after LIA injection was depicted in a neuroanatomical cadaver study, from which sensible clinical injection sites can be deduced *(1)*. A randomized trial compared PCEA vs LIA and showed no significant difference in pain control over the first three days post-surgery. In this trial however, an indwelling catheter was used for additional LIA boluses until the first post-operative morning *(1)*. Because the exact localisation of the deposition of the multiple injections of local anesthetics is imperative for an optimal antinociceptive effect, the injection technique should be optimized with respect to the neuro-anatomy of the knee. The purpose of this report is to describe such a substantiated scheme with its neuroanatomical annotation, and to describe a comparative study to evaluate its antinociceptive effect compared to epidural analgesia.

In our hospital, two strategies for postoperative pain control were used : PCEA and LIA. PCEA is unpleasant for the patients and includes some risks, such as nerve damage, epidural hematoma or persisting tenderness of the puncture site. Local infiltration analgesia (LIA) is relatively easy to perform and has few side effects *(1,2)*. It consists of infiltration of a mixture of ropivacaine, ketorolac, and adrenaline into the surrounding tissues of the knee *(13)*.

LIA obviates an epidural catheter or femoral block. It also significantly reduces the need for postoperative opiates, is the cheapest option, has fewer risks and side effects and permits a faster patient turnover at the Post-Anesthesia Care Unit (PACU). Importantly, LIA permits virtually immediate mobilisation owing to preserved muscle strength and proprioception and absence of urinary, epidural or femoral catheters. The absence of an epidural catheter also permits faster removal of the peripheral venous catheter, further increasing mobility. Conversely, PCEA provides reliable pain relief in the first days after TKA. We conducted an observational study to assess the postoperative pain relief and general comfort from the patient's perspective after TKA in both populations. In view of the postulated multitude of advantages of LIA, the aim of this study is to determine whether patient-reported self-assessed comfort scores and analgesic efficacy, nausea & vomiting (PONV) and the general quality of postoperative recovery as experienced from a patient's perspective, is essentially similar or only marginally lower after LIA compared to epidural analgesia.

Given the importance of postoperative pain management, not only in the first two days following

surgery, but also in the period after discharge from the hospital, and the paucity of studies evaluating the longer term effects of LIA on pain experience, pain perception was assessed from day 1 through day 7. In addition, we compared the patient perception of PONV and general comfort after TKA when postoperative analgesia was provided with PCEA versus LIA.

MATERIALS AND METHODS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This study was reviewed and approved (PHB/nm/2015.52) by the Ethics Committee of AZ Maria Middelares, Ghent, Belgium. 124 consecutive patients of ≥ 18 years and scheduled for TKA were assessed for eligibility for this retrospective observational study. Two weeks after discharge from hospital, all eligible patients were sent a questionnaire by mail (Table 1) and asked to rate their perception at different moments during the postoperative period by drawing a vertical line on a visual analogue rating scale (VAS) (Figure 1), and return the questionnaire using the enclosed, pre-addressed envelope.

After collection of the questionnaires and evaluation of completeness, the analogue ratings were quantified and recorded in Excel in a blinded way. No adjustments of the data were made after unblinding.

Table 1. — The questions that were presented to the participants

1. How was your pain experience on the day of surgery?
2. How was your pain experience the first day after surgery?
3. How was your pain experience 7 days after surgery?
4. How was your experience of the preparations in the two hours before surgery?
5. How was your general comfort level the first days after surgery?
6. If you need a second similar operation, how favourable would you be to receive the same pain management, given there are alternative strategies?
7. To what degree did you experience discomfort in urinating one week after surgery?
8. To what degree did you experience dizziness in the first days after surgery?
9. To what degree did you experience nausea the day of surgery?

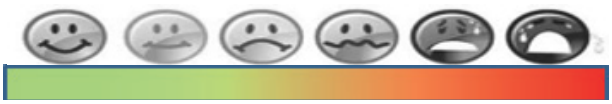

Figure 1. — Visual Analogue Score (VAS) used in the questionnaires. Patients were asked to draw a vertical line on the bar, to indicate the level of (dis)comfort for each of the questions of the questionnaire. The bar on the questionnaire has a width of 100 mm, facilitating quantification of the results.

The primary clinical endpoint was the patient reported pain level on day 7. Secondary endpoints were pain levels at other moments, PONV and patient-reported level of general well-being.

Sample size calculation was based on the pain scores at D7. We considered a mean difference of 15% between both groups to be clinically relevant. A pilot evaluation showed a mean(±SD) pain score of 40(±30) and 25(±20) in an epidural and LIA strategy respectively. A Wilcoxon-Mann-Whitney test, with a α-error probability of 0.05, and a power of 0.80 resulted in a minimal sample size of 39 in each group *(14)*. Taking into account a nonresponse of 35%, 2X60 consecutive patients in each group were approached.

The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Differences between groups were assessed using Student's t-test or Wilcoxon-Mann-Whitney test where appropriate.

Anesthesia and pain management was conducted following a strict protocol. Depending on the preference of the surgeon, either LIA or PCEA was used for postoperative analgesia.

Patients thus received either spinal anesthesia (in the LIA group) or combined spinal-epidural. All patients received a spinal dose of 3ml levobupivacain 0.25% in the LIA group or 0.5% in the PCEA group.

Anesthesia was induced with propofol 2-3mg/kg and sufentanil 10µg, and subsequently administered parecoxib 40mg, paracetamol 1000mg and dexamethasone 5mg. Patients in the PCEA group did not get local anesthesia during surgery, but PCEA (levobupivacain 1.25mg/ml & sufentanil 0.25 µg/ml & clonidine 1.125 µg/ml) was started postoperatively (continuous 3ml/h ; bolus 5ml ; lockout 20min), after the return of motor response.

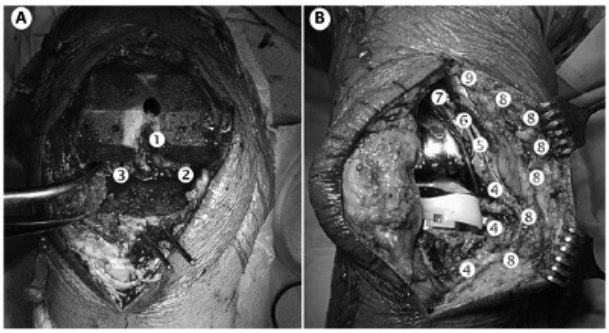

Figure 2. — Location of administration of local anesthetics.

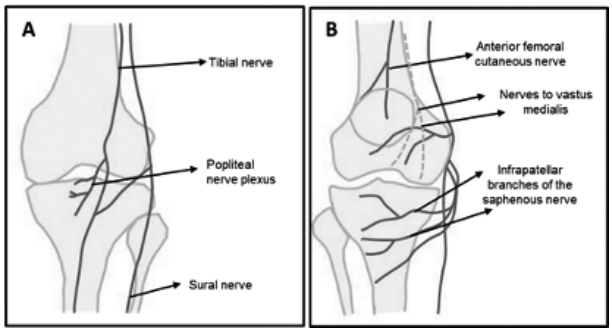

Figure 3. — Posterior (A) and anterior (B) innervation of the knee joint.

The infiltration mixture consisted of 140ml ropivacaine 0.2% (Ropivacaine ; Fresenius Kabi AG, Bad Homburg, Germany), 2.0 mg/mL mixed with 30 mg ketorolac (Taradyl® ; Roche, Penzberg, Germany) and 10 µg/mL adrenaline. Patients with contraindications to the use of Non-Steroidal Anti-Inflammatory Drugs (NSAID's) were excluded from the study. All infiltration was done using 50-mL syringes and 4-cm-long 18-G needles. Injections were done using a "moving needle" technique to avoid depositing large volumes of drug intravascularly.

The injection is made in two stages (Figure 2), as a streamlined procedure, based on the technique described by Kerr *(13)* although our protocol has an advantage of being simpler to administer, and we omit the use of a catheter for a second injection. Importantly, we would also advise not to use adrenaline in the subcutaneous injection because of the risk of necrosis due to extreme vasoconstriction. A relatively large-bore 18 Gauge needle was used for the infiltration of the posterior, proximal and medial structures.

Using a standardised technique, the mixture was injected to ensure uniform delivery to all relevant tissues :

After completion of the bony cuts, a first syringe of 50 ml with a mixture with adrenaline is used to infiltrate the tissues in the back of the knee held by a laminar spreader in 90° of flexion (Figure 2a).

1) Through the posterior capsule in a medial direction along the posterior aspect of the femur : 40ml
2) through the posteromedial capsule : 7 ml
3) through the posterolateral capsule : 3 ml

After cementing the different TKA components (Figure 2b), a second syringe of 50ml with a mixture with adrenaline is used to infiltrate the synovial and muscular tissue in a standardised way :

4) the synovial and capsular structures medially : 3 x 5ml
5) the vastus medialis : 15ml
6) a bolus in the direction of the adductor canal : 15ml
7) the suprapatellar pouch : 5 ml

Followed by a third syringe of 50ml - without adrenaline to prevent cutaneous necrosis :

8) the medial subcutaneous tissues : 6 x 5 ml.
9) the proximal subcutaneous tissue in medial direction : 20ml

The location of each injection was chosen carefully, taking into account the posterolateral (Figure 3a) and anteromedial innervation of the knee (Figure 3b).

The surgical technique for both groups was comparable *(15)*. The surgery was performed through a standard medial parapatellar approach. All components were cemented. A compressive bandage was applied after surgery to produce venous and lymphatic compression to reduce joint and wound swelling. Wound drains were never used.

Upon arrival at the PACU, patients with PCEA were given a urinary catheter which was removed after cessation of the epidural analgesia. If the patient had pain in the postoperative period, decisions on the administration of additional postoperative analgesics were made following a strict protocol by the nurses, who were unaware of the study. All patients were routinely prescribed paracetamol 1000 mg

IV or PO every 6 hours, and parecoxib 40mg IV every 12 hours for 36h postoperatively, followed by Zaldiar® (tramadol/paracetamol). In patients with PCEA, patient controlled top-up within the PCEA settings was available. In addition, in all patients tramadol 100mg + alizapride 50mg every 6 hours, and piritramide 20mg IM every 6 hours could be administered as rescue medication.

After 36 h, residual pain was managed with oral analgesics : Zaldiar® PO 6-hourly, or paracetamol 1000mg 6-hourly, and diclofenac 75mg PO twice daily. No morphine or gabapentin was used.

Patients were instructed to cease intake of analgesics as soon as the pain had decreased to an acceptable level. In both groups, passive mobilisation of the knee by flexion/extension was performed postoperatively at day D0. At D1, patients in the LIA group were mobilised using walking aids every 2–3 h during the day and were encouraged to walk a minimum of about 30 meters. In the PCEA group, passive mobilisation in bed was sustained, and active mobilisation was initiated at D2.

All patients were under the supervision of a physical therapist and an occupational therapist during their stay in the clinic. At discharge, they all got a prescription for continued physical therapy at home or in an outpatient rehab facility.

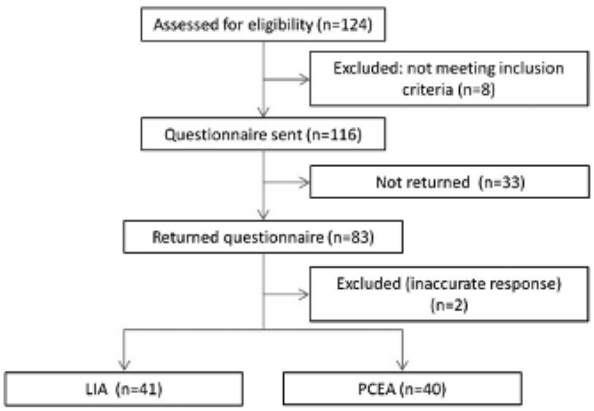

Figure 4. — Flow diagram according to the Consolidated Standards of Reporting Trials (CONSORT) statement.

RESULTS

124 patients were assessed for eligibility, and 8 were ineligible because of the exclusion criteria (6 revisions, 2 partial knee replacements). 116 were contacted. 83 patients returned the questionnaire. 2 responses were rejected due to incorrect data. Of the 81 analysed questionnaires, 41 patients had received LIA, and 40 patients PCEA (Figure 4).

Demographics and reported VAS scores are shown in Table 2.

Table 2. — Demographics and Comfort scores (scale 0-100) of the patients

	CSE Median(IQR) - [min-max]	LIA Median(IQR) - [min-max]	P-value
Number of patients	41	40	
Male/female	31/10	30/10	
Age	63(58-75) - [44-84]	67(53-73) - [40-84]	
Pain at D0	18(0-47) - [0-98]	21(2-41) - [0-100]	0.56
Pain at D2	21(10-65) - [0-100]	20(18-41) - [0-81]	<0.01*
Pain at D7	38(20-59) - [0-100]	18(11-41) - [0-75]	0.01*
Experience during preparations	13(0-32) - [0-100]	21(0-41) - [0-100]	0.66
Comfort score first days	20(18-55) - [0-97]	20(11-36) - [0-77]	0.05
Favour same pain management	17(0-37) - [0-95]	0(0-21) - [0-100]	0.93
Discomfort urinating D7	0(0-17) - [0-100]	0(0-0) - [0-41]	<0.01*
Dizziness first days	0(0-20) - [0-100]	0(0-21) - [0-97]	0.12
Nausea at D0	0(0-35) - [0-100]	0(0-18) - [0-93]	<0.01*

Variables are reported as absolute numbers or as median (interquartile range) - (range). * $P < 0.05$

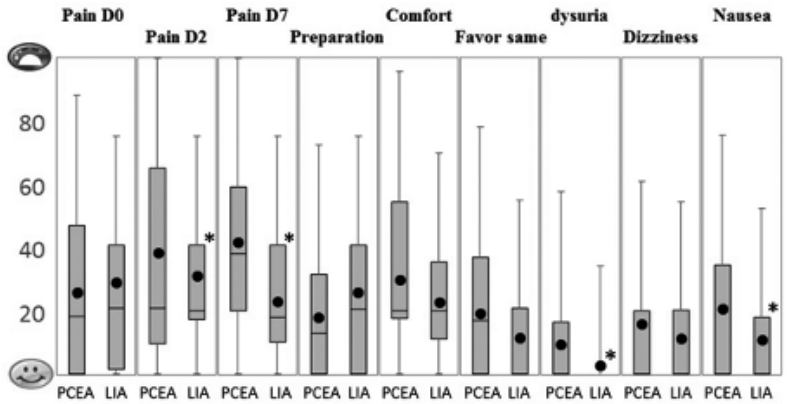

Figure 5. — Boxplot of the main findings. The boxplots show minimum value, lower quartile, median value, upper quartile, maximum, and average (●) value. * indicates statistically significant difference between PCEA and LIA (P<0.05).

Figure 5 visualises the main findings. At D0, no significant difference in pain scores was reported. Pain scores at D2 and D7 and PONV scores were significantly better in the LIA group. General comfort was not significantly different (P=0.054), although there was a clear tendency towards better scores in the LIA group. In addition to significantly better mean scores in the LIA group, a remarkably favourable 75th percentile for most questions indicates a much lower incidence of the most intense discomfort in this group.

DISCUSSION

The most important finding of this study is an equal analgesic performance between the two techniques at D0, but a significantly better analgesic effect of LIA at D2. At D7 – long after LIA and PCEA would intuitively be expected to have little residual effect – a remarkably better pain score is observed in the LIA group.

For postoperative pain relief after TKA, LIA is an emerging alternative for PCEA. A comprehensive review to identify the main outcome determinants after orthopedic surgery identified 12 principal outcome parameters : mortality, length of stay, time to surgery, complications, readmission rate, mobility, quality of life, pain, activities of daily living, medication use, place of residence and costs *(16)*. Postoperative analgesia management should optimise these where possible.

The cornerstone of peri-operative pain management therefore consists of a multimodal balanced analgesia minimising the risk of complications, fasten recovery and prevent evolution to chronic pain at a minimal cost. The concept of preventive analgesia involves any perioperative analgesic and anti-hyperalgesic treatment aimed to control central nervous system sensitization to reduce the development of immediate and persistent postsurgical pain *(17)*. This led to the recognition of the importance of pre-emptive analgesia to anticipate central sensitization, which is most efficiently achieved by spinal anesthesia administered before surgical incision.

In addition to paracetamol and NSAID's, several analgesic strategies exist to manage postoperative pain. Amongst these, systemic opiates, femoral nerve block, adductor canal block, epidural analgesia and LIA are most frequently used. While opiates have a unique immediate analgesic efficacy, several adverse effects such as respiratory depression, urinary retention, nausea and vomiting, ileus, constipation, pruritus, confusion and excessive somnolence have a very high incidence and mandate that they are only used when potential benefits outweigh these risks *(18)*. Opiates may also induce "opiate-induced postoperative hyperalgesia" and acute tolerance, enhancing postoperative pain *(17)*.

Epidural anaesthesia provides reliable analgesia following TKA, but can be technically demanding

and time-consuming. In addition, serious neurologic complications such as epidural hematoma or abscesses occur more frequently than used to be thought, mandating a proper assessment of the risk-benefit ratio and consideration of alternatives *(19,20,21)*. In addition to the risk of rare but severe neurological complications, epidural analgesia has innate disadvantages such as bladder dysfunction requiring a urinary catheter with its particular risks and drawbacks, spinal headache, decreased mobility, orthostatic hypotension, motor weakness and hemodynamic instability due to the sympathectomy.

A femoral block is often considered the gold standard following TKA and mainly affects the infrapatellar branch of the saphenous nerve, the nerves to the vastus medialis and the medial femoral cutaneous nerve *(22,23)*. However, the procedure is time-consuming, may fail, and can cause nerve injury. Most importantly, the motor blockade often causes quadriceps weakness, increasing the risk of falling and it may prevent early mobilisation thereby extending the length of stay *(24,25)*. The adductor canal block has recently been proposed as a valuable alternative for the femoral block, since it does not cause quadriceps weakness and has a comparable analgesic effect by anesthetizing the saphenous nerve and retinacular nerves to the vastus medialis *(22,26,27)*. Figure 3B demonstrates that these same nerves are reached during the LIA by carefully injecting the mixture in the direction of the adductor canal (Figure 2b, nr. 6) and in the suprapatellar pouch (Figure 2b, nr. 7). An important disadvantage of the adductor canal block is that it does not cover pain derived from the popliteal nerve branches, which is the main reason why an additional ultrasounded infiltration of the interspace between the popliteal artery and the capsule of the posterior knee has been proposed *(28)*. Of particular advantage is that LIA also can eliminate pain from the popliteal plexus when the mixture is carefully injected through the posterior capsule, along the posteromedial aspect of the femur (Figure 2a and Figure 3a).

LIA allows faster mobilisation – with beneficial orthopedic results – and potentially faster discharge from hospital ; it obviates epidural and urinary catheters, therefore eliminating several complication risks, and in addition brings important cost savings and improves mobility and patient turnover. Early mobilisation and shorter hospital stay additionally reduce the risk of nosocomial infections and deep vein thrombosis *(29)*. Conversely, PCEA is acknowledged to provide reliable pain relief in the first days after this type of surgery.

Few studies have thus far been published comparing LIA with continuous epidural analgesia in TKA, and all but few only cover the first 2-3 days after surgery *(12,11)*. Our data mostly show a similar efficacy on D0 and a moderate superiority of LIA on D2. The most remarkable finding, however, was a very significantly superior pain score in the LIA group at D7. Even more important than the difference in mean pain score in the LIA group is our observation that the 75th percentile was 59 in the PCEA group versus 41 in the LIA group. This indicates that after one week, 25% of the patients reported a score of 61 or higher in the PCEA group, while in the LIA group, the worst 25% of the patients experienced a score of only 41 or higher.

From a patient perspective, PONV is a major issue for the general feeling of wellbeing in the postoperative period. Remarkably, the patients in the LIA group also experienced a significantly better score on PONV than in the PCEA group. This might be explained by a lower tendency to use opiates in the LIA group, or by less vasomotor disturbance.

The general comfort level in the first postoperative week also shows that the mean and 75th percentile in the LIA group were significantly more favourable than in the PCEA group. An important concern in the perioperative care of the elderly population is the prevention of postoperative cognitive disorders (POD). While POD is the result of a complex interplay of predisposing and precipitating factors, many confirmed precipitating factors – such as bladder catheters, use of opiates, delayed mobilisation, and decreased self-care can be avoided or significantly improved by making use of LIA instead of epidural analgesia *(30,31)*. This is also reflected in the advice for targeted prevention of specific risk factors, such as immobility and bladder catheters to reduce the risk of cognitive and functional decline in older hospitalised patients *(32)*. As such, since epidural analgesia brings about a significant risks for POD, but optimal pain control is also a key target for

the prevention of POD, the use of LIA shows very promising for optimising analgesia in this regard. From a managerial perspective, LIA permits a higher efficiency in patient flow, cost savings, improved safety, reduction in complications and improved patient satisfaction.

The present study has limitations that deserve comment. This retrospective review was not controlled or randomised. However, since every effort was made to prevent bias, we are confident these results reflect the genuine patient perception of the enquired comfort scores. While the surgery was performed by two different surgeons, the surgical technique was the same in all measurable aspects.

Secondly, the numerical values of the VAS scores may seem rather high, compared with conventional reporting. However, quantification of internal experiences as "pain", and "general comfort" is highly dependent on the enquiry method and support and interaction with the interrogator. The interpretation of these numerical values must therefore be made relatively between the two groups. Importantly, this methodology was chosen in order to permit performing this kind of study in a double-blinded fashion and to minimise the risk of bias.

Thirdly, the retrospective nature of enquiring the experiences of the patient several weeks after the procedure differs from the general research method in this domain. Although this complicates comparison with previous studies, it gives a more relevant reflection of the experience by the patient in a patient-centred care perspective and permits optimising the perioperative experience by prioritising patient concerns.

CONCLUSIONS

In addition to faster mobilisation of the patients and elimination of the risks, costs and burden of an epidural catheter and PCEA, LIA delivers equal to better analgesia, and better PONV and general comfort scores at a very low cost.

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