Continuous spinal analgesia with levobupivacaine for postoperative pain management: Comparison of 0.125% versus 0.0625% in elective total knee and hip replacement: A double-blind randomized study

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Abstract

Background and Aims: Continuous spinal anesthesia (CSA) has not been widely used for postoperative analgesia, mainly to avoid complications from the subarachnoid injection. Recently, the introduction of low caliber CSA catheters (Spinocath®), has allowed to decrease anesthetics doses and volumes with good analgesia and reduced complications. The aim of this present study was to compare two concentrations of levobupivacaine administered through CSA for postoperative pain management after major orthopedic surgery. Secondary outcomes were adverse events associated with CSA.

Material and Methods: Thirty-two patients were randomized to receive sufentanil 1 mcg/h plus levobupivacaine 0.125%-1 ml/h (Group $A_{0.125}$) or 0.0625%-2 ml/h (Group $B_{0.0625}$) for postoperative analgesia through CSA catheter, connected to the elastomeric pump over 48 h. The quality of analgesia was assessed based on pain intensity by Visual Analogic Scale (VAS). Sensory and motor function, hemodynamic, and respiratory parameters were recorded for 96 h after surgery, after which the catheter was removed. In addition, joint mobility was assessed, and any side effects were noted.

Results: VAS score was ≤30 mm in 25 patients. Three patients in Group $A_{0.125}$ and 4 in Group $B_{0.0625}$ (NS), received a rescue dose of levobupivacaine. Median VAS in Group $A_{0.125}$ was lower than in Group $B_{0.0625}$ on $T_{1\,h}$ (8 ± 11 vs 16 ± 11; $P < 0.05$), and on $T_{4\,h}$ (11 ± 8 vs 18 ± 1; $P < 0.05$). All patients remained hemodynamically stable. There were no significant differences between groups for postoperative joints mobility.

Conclusion: Levobupivacaine at a dose of 1.25 mg/h administered by CSA provides good quality analgesia independent of concentration and solution volume in patients undergoing total knee and hip replacement.

Key words: Continuous spinal analgesia, levobupivacaine, orthopedic surgery

Introduction

Continuous spinal anesthesia (CSA) is the technique of producing and maintaining spinal anesthesia with small doses of local anesthetics (LA) injected intermittently into the subarachnoid space via an indwelling catheter, while postoperative analgesia can be realized through continuous drug infusion by a pump connected to the catheter. Although widely studied for intraoperative use, CSA is infrequently studied for postoperative pain management, mainly due to the frequent neurological complications such as postdural puncture headache (PDPH) or cauda equina syndrome.[1-9]

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The introduction of catheters (Spinocath®) using 27 gauge Quincke-type spinal needle covered by a 22 gauge nylon catheter that leaves free the needle's tip, limits leakage of cerebrospinal fluid (CSF), and helps overcome these complications.

Continuous spinal anesthesia is a well-established technique with benefits such as high analgesic efficacy, rapid onset, minimal effect on mental status, reduction of blood loss and protection against thromboembolic complications.[5,6] A continuous drug administration modality improves hemodynamic stability compared with a single bolus regimen.[7]

LA have a relatively narrow "therapeutic to toxic window" in the subarachnoid space.[7] Therefore, CSA requires doses and concentrations of LA reduced by 25-33%, from the ones needed with "single shot spinal anesthesia (SSSA).[10,11]

This study was done to evaluate the quality of postoperative analgesia obtained by continuous intrathecal delivering through CSA of low dose of levobupivacaine plus a standard dose of sufentanil for the treatment of postoperative pain after total knee and hip replacement. The endpoint of this study was to compare the same total dose of levobupivacaine solution administered at two different concentrations and volumes to obtain a target Visual Analog Scale (VAS) value ≤30 mm. Secondary outcomes of interest were adverse events and complications by this technique.

Material and Methods

This prospective, randomized, double-blind, controlled study was approved by the Local Institutional Ethics Committee. Written, informed consent was obtained from all patients before surgery.

Exclusion criteria were a need for urgent or emergency surgery, ASA classification >III, coagulation disorders, neurologic diseases, and a history of acute or chronic consumption of any opioids or $\alpha2$-adrenergic agonists.

In the operative room, noninvasive monitoring (electrocardiogram, heart rate [HR], SpO_2, noninvasive arterial blood pressure [NIBP] and hourly urine output) was used.

Patients were randomly allocated into two groups for postoperative analgesia according to a computer-generated list compiled before the start of the study: Group $A_{0.125}$ received levobupivacaine 0.125%-1 ml/h plus sufentanil 1 mcg/h and

Group $B_{0.0625}$ received levobupivacaine 0.0625%-2 ml/h plus sufentanil 1 mcg/h.

After prehydration with 500 ml Ringer solution, patients had a 24 gauge spinal catheter (Spinocath Bbraun Melsungen AG, Germany) placed at the L2/L3 or L3/L4 interspace.

To accurately identify the subarachnoid space we used a combination of an epidural and 'catheter over the needle' subarachnoid anesthesia techniques. Once the catheter was inserted 2-3 cm intrathecally, the epidural needle was removed entirely, the luer connector and filter was filled with levobupivacaine 0.25% and was connected to the catheter. Since the density of levobupivacaine decrease at the 37°C, patients were positioned in the lateral position with the surgery side up.[12] Intraoperative anesthesia was obtained in every patient by injecting 7.5 mcg of sufentanil followed by 5 mg of levobupivacaine 0.25% (2 ml) through the catheter in the subarachnoid space. Assessment of sensory block to pinprick were performed bilaterally along the midclavicular line using a short beveled 27 gauge needle at 1, 5, 10, 15 and 20 min after intrathecal injection. Surgery began when a sensory block to pinprick at the T10 dermatome was established.

Sensory level to pinprick was assessed by the Hollmen scale: 0 = Ability to appreciate a pinprick as sharp, 1 = Ability to appreciate a pinprick as less sharp, 2 = Inability to appreciate a pinprick as sharp (analgesia), 3 = Inability to appreciate a pin touching (anesthesia).

The degree of motor block was recorded using the modified Bromage scale: 0 = No residual motor block, 1 = Inability to raise extended legs, 2 = Inability to flex knee and 3 = Inability to flex ankle. If surgical anesthesia (Bromage = 3 and Hollmen = 3 at T10 level) was no achieved within 15 min, additional doses of 2.5 mg of levobupivacaine 0.25% were given every 5 min to obtain the surgical anesthesia. Failure of the technique was considered to have occurred when surgical anesthesia was not achieved after 30 min.

We repeated the same dose of LA intraoperatively every 1 h; at the end of surgery, we connected the elastomeric infusion pump (Hs Hospital Service S.P.A., Italy). Group $A_{0.125}$ received levobupivacaine 0.125%-1 ml/h plus sufentanil 1 mcg/h and Group $B_{0.0625}$ received levobupivacaine 0.0625%-2 ml/h plus sufentanil 1 mcg/h (details of infusion pump required).

After the end of surgery, patients were transferred to the orthopedic ward. Monitoring included pulse oximetry, HR, NIBP. The pain intensity evaluated by VAS-score ranging from 0 to 100 mm (0 = no pain, 100 = unbearable pain), the residual motor and sensory block according to Bromage

and Hollmen scores, hemodynamic, and SpO_2 parameters were recorded at 10 designated times after the last top up: One hour (T_{1h}), 4 h (T_{4h}), 7 h (T_{7h}), 16 h (T_{16h}), 20 h (T_{20h}), 24 h (T_{24h}), 30 h (T_{30h}), 36 h (T_{36h}), 42 h (T_{42h}), 48 h (T_{48h}), 96 h (T_{96h}). CSA was maintained for 48 h, thereafter catheter was removed while complications were recorded during the 96 h after catheter insertion. If patients complained of intolerable pain (resting pain >30 mm and dynamic pain >50 mm using the VAS) then a rescue dose of levobupivacaine 0.25% 2.5 mg (1 ml) was given.[5]

A maximum of three consecutive rescue doses were allowed, thereafter the catheter was removed and patients managed with intravenous analgesia.

An anesthesiologist blinded to group allocation visited the patients and observed for postoperative side effects. All patients were assessed daily. We chose the primary outcome measures to be the pain scores until day 3, and the range of joint movement on postoperative day 7 as a parameter of surgical rehabilitation. Pain scores were recorded for resting pain and dynamic pain experienced during movement or physiotherapy. Joint mobility was evaluated by measuring the range of motion (flexion) of the operated knee, with a difference in flexion defined as a clinically relevant difference in joint movement. Complications were defined as: Hypotension (a decrease in mean BP >30% of the basal preoperative value), bradycardia (HR <60 beats/min), hypoxia (O_2 saturation <90%), PDPH, postoperative nausea and vomiting (PONV), itching, and infection.

Statistical analysis
Based on previous data,[13] we calculated a sample size of 30 (at least 15 per group) was needed to detect a clinically meaningful difference in VAS ≤20% between the two groups ($\alpha = 0.05$, one side, power of 80%).

Demographics between the groups were compared with χ^2 — or Fisher exact test for categorical data, nonpaired, two-tailed Student's *t*-test for continuous data, and with Mann–Whitney test U-test for nonparametric data. The effect of treatment and time on the level of pain (expressed as VAS) was assessed by two-way ANOVA, the effect of treatment and time on the degree of motor block (Bromage scale) and the level of the sensory block (Hollmen scale) were assessed with nonparametric, two-way Friedman tests. Changes in Bromage and Hollmen scores, over time within each group were statistically analyzed using individual repeated-measures design Friedman tests. Subsequent intragroup comparisons, when appropriate, were performed pair-wise using paired Wilcoxon's signed ranks tests. For intergroup comparisons, the

Bromage and Hollmen values were compared between groups at each time point with Mann–Whitney tests. A $P < 0.05$ was considered as statistically significant. All statistical calculation were performing using STATISTICA (data analysis software system), version 8.0, (Statistica StatSoft, Inc. [2007], Tulsa, OK, USA).

Results

Thirty-two patients of 40 initially evaluated for enrolment were included in the study. The enrolment flow-diagram has been shown in Figure 1.

According to demographic characteristics, there were no significant differences between the two groups [Table 1].

There were no catheter dislodgements and all patients retained their elastomeric infusion pumps for 48 h. There were no mechanical pump failures.

The incidence of PDPH and PONV in 32 patients was 6.2% and 9.3% respectively. The headache resolved within 10 days. The PONV was treated with Ondansetron 0.05 mg/kg. No other important complication was recorded [Table 1]. All patients showed hemodynamic stability, without significant within- or between-group variations of HR and NIBP throughout the study period. Spo_2 remained stable throughout the observation period.
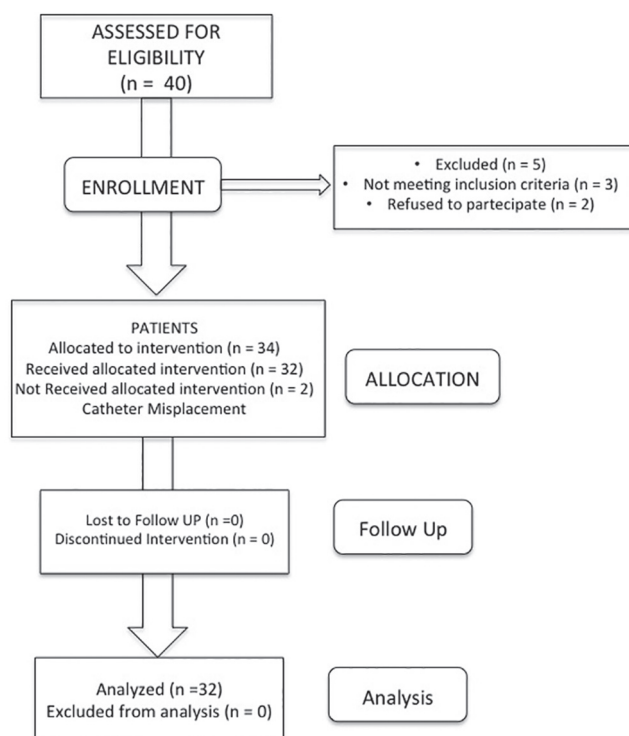

Figure 1: Flow diagram of the progress through the phases of the trial

The maximum levels of sensory block (median values) reached throughout the study period in every patient was T7, no difference was observed between the two groups [Table 1].

All median pain scores for resting and dynamic pain were below the threshold recommended for intervention. The levels of postoperative pain assessed by VAS has been shown in Figure 2: Mean VAS was below 30 mm in both groups at all study times. We found significant differences among the VAS value in the two groups, with regard to the effect of the type of treatment and to the effect of time. Intragroup comparison of VAS over time showed significant differences within the

Group $A_{0.125}$: VAS value was significantly lower on $T_{1\,h}$ (VAS 8 ± 11) versus all time points $\geq T_{10\,h}$ ($P < 0.01$); on the contrary in Group $B_{0.0625}$, intragroup VAS did not differ during the study period. Intergroup comparison showed a mean VAS value significantly lower in Group $A_{0.125}$ than Group $B_{0.0625}$ on $T_{1\,h}$ (8 ± 11 vs. 16 ± 11; $P < 0.05$), and on $T_{4\,h}$ (11 ± 8 vs. 18 ± 1; $P < 0.05$). In Group $A_{0.125}$, 3 patients needed a rescue doses: in pt#1 at $T_{10\,h}$ and $T_{36\,h}$; in pt#3 at $T_{24\,h}$ and in pt#5 at $T_{30\,h}$. In Group $B_{0.0625}$, 4 patients needed rescue doses: pt#1 at $T_{7\,h}$, $T_{24\,h}$, $T_{30\,h}$; pt#2 at $T_{10\,h}$; pt#3 at $T_{10\,h}$ and $T_{24\,h}$ and pt#5 at $T_{30\,h}$. In these 7 patients, the spinal catheter had been located into L3-4 interspaces because of anatomical features. Before the injection of supplementary dose, the location of catheter was checked for possible misplacement. In all cases, the VAS value recorded was never higher than 30 mm.

In Figure 3, motor block expressed in Bromage scale mean values observed postoperatively during the levobupivacaine/sufentanil solution infusion by the elastomeric pump are reported.

Table 1: Demographic data of 32 patients that received continuous spinal postoperative analgesia

Variables	Group $A_{0.125}$	Group $B_{0.0625}$	P value
Number of patients randomized	16	16	
Age (years)	78.4±8.5	72.4±9.9	0.71
Sex (female/male)	10/6	7/9	0.78
Height (cm)	162.2±7.3	161.4±6	0.69
Weight (kg)	73±14	76.3±13.3	0.75
ASA class II/III	5/11	10/6	#
Duration of surgery (min)	125±23	115±43	0.75
Highest sensory block (median [minimum–maximum])	T10 (T7-T12)	T10 (T7-T10)	0.89
Hip/knee replacement (n/tot)	13/16	11/16	#
Complications in the postoperative period (n)	1 PDPH, 1 PONV	2 PONV, 1 PDPH	0.87
Patients needing rescue doses (n/tot)	3/16	4/16	0.80
Rescue doses (mg/pat)	3.3±1.4	5.8±2.9	*

ASA = American society of anesthesiologists, PDPH = Postdural puncture headache, PONV = Postoperative nausea and vomiting, *p < 0.05, #p < 0.01
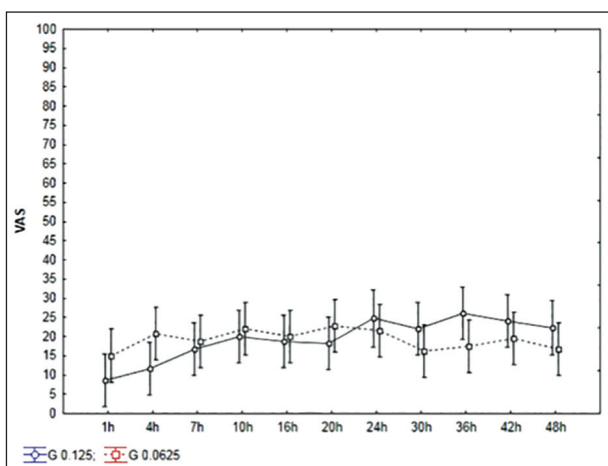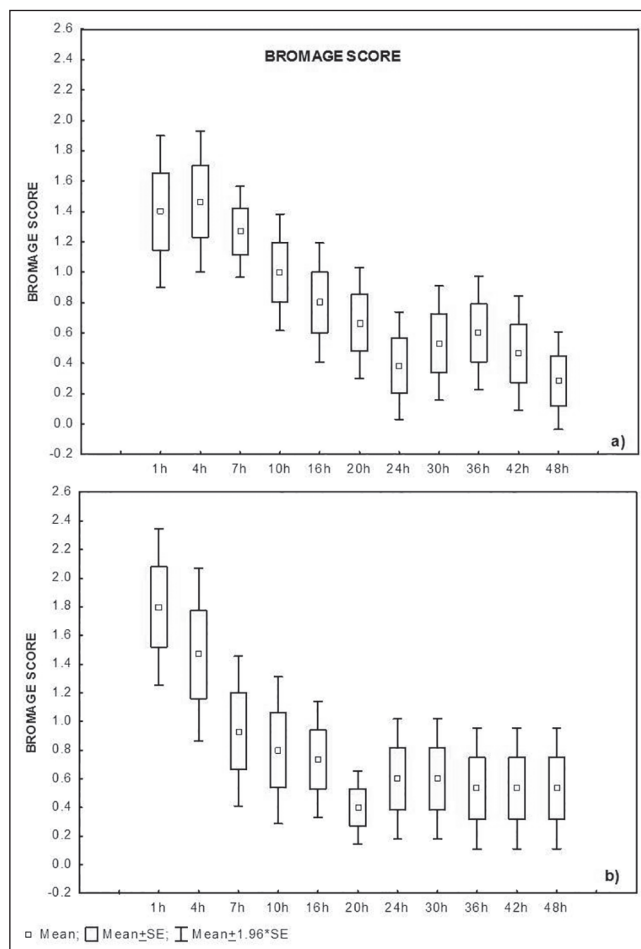

Figure 2: Postoperative pain assessed by Visual Analogical Scale (VAS score). Solid line indicate the VAS threshold of 30 mm; *P < 0.05 Group $A_{0.125}$ vs Group $B_{0.0625}$; #P < 0.01 Group $A_{0.125}$ vs Group $B_{0.0625}$

Figure 3: Motor block assessed with a modified Bromage scale in Group $A_{0.125}$ [Figure 2a] and Group $B_{0.0625}$ [Figure 2b]. Box plot shows mean ± standard error (SE) and mean ± 1.96*SE. *P < 0.01 $T_{1\,h}$ and $T_{4\,h}$ versus all study steps $\geq T_{7\,h}$ in Group $A_{0.125}$ and Group $B_{0.0625}$

Intragroup comparison showed that residual motor block was present both in Group $A_{0.125}$ and in Group $B_{0.0625}$ $T_{1 h}$ and $T_{4 h}$ after surgery (Bromage mean scores 1.23 ± 0.93 on $T_{1 h}$ and 1.38 ± 0.87 on $T_{4 h}$ in Group $A_{0.125}$ [NS], 2 ± 1 on $T_{1 h}$ and 1.61 ± 1.19 on $T_{4 h}$ in Group $B_{0.0625}$ [NS]): 3 patients in Group $A_{0.125}$ and 5 patients in Group $B_{0.0625}$ (NS), showed a Bromage value of 3 on $T_{1 h}$; on $T_{4 h}$ Bromage of 3 was still recorded in the same 3 patients in Group $A_{0.125}$ while in Group $B_{0.0625}$ no patient showed Bromage of 3. In both groups mean Bromage score significantly reduced on $T_{7 h}$ and remained stable thereafter ($P < 0.01$ $T_{7 h}$ vs. $T_{1 h}$ and $T_{4 h}$, with the clinical resolution of motor block in every patient and a residual weakness of lower limbs. The comparison between groups showed that there were no significant differences in mean Bromage score at any time during the study. In Figure 4, sensory block expressed in Hollmen scale mean values are reported. The Hollmen score was higher in Group $A_{0.125}$ when compared to Group $B_{0.0625}$ in all study steps except for at $T_{1 h}$ ($P < 0.02$). Intragroup comparison showed that

residual sensory block was present both in Group $A_{0.125}$ and in Group $B_{0.0625}$ $T_{1 h}$ and $T_{4 h}$ after surgery (Hollmen mean scores 1.5 ± 0.82 on $T_{1 h}$ and 1.31 ± 0.79 on $T_{4 h}$ in Group $A_{0.125}$ [NS] and 1.69 ± 0.95 on $T_{1 h}$ and 1.19 ± 0.91 on $T_{4 h}$ in Group $B_{0.0625}$ [NS]): on $T_{1 h}$ 3 patients in Group $A_{0.125}$ and 4 patients in Group $B_{0.0625}$ (NS) had an Hollmen score of 3, complete sensory block, on $T_{4 h}$ no patients had an Hollmen score of 3. In both groups, Hollmen score significantly reduced over time with a clinical resolution of sensory block even though with a good analgesia: in Group $A_{0.125}$, mean Hollmen score decreased from $T_{1 h}$ and $T_{4 h}$ versus every time point $\geq T_{20 h}$ ($P < 0.001$), and in Group $B_{0.0625}$ it decreased from $T_{1 h}$ and $T_{4 h}$ versus every time point $\geq T_{7 h}$ ($P < 0.001$). A joint movement based on range of motion was similar in both the groups.

Discussion

The present study showed that CSA spinal catheter (22-24 gauge) system connected to elastomeric pump delivering 1.25 mg/h levobupivacaine plus 1 mcg/h sufentanil provided adequate postoperative pain relief over 48 h, independently from the concentration used, with hemodynamic stability and without complications.

The advantages of CSA over SSSA are rapid onset, titration to the desired level of anesthesia with a minimum amount of anesthetic,[14] top ups to extend and control block duration, better control of anesthesia level,[15] less risk of circulatory/respiratory depression,[16] possibility to give anesthetic agent with patients already in operative position and shorter recovery period.[7,9,14]

Continuous spinal anesthesia was in disfavor for several years, because microcatheters, together with hyperbaric lidocaine solution, were considered responsible for several neurological complications,[6,8,15-18] since they perforated the dura thus causing loss of CSF, notwithstanding their small diameter (<28 gauge).[8,19] These complications were overcome by the introduction of new catheters system (Spinocath®)[16,17] that consists of a 22-24 gauge catheter covering a 27-29 gauge spinal Quincke needle. The "over the needle" design eliminates leakage of CSF because the catheter immediately seals the dural puncture hole reducing the loss of CSF.

The first key point of interest of the present study in our opinion is the prolongation of CSA analgesia using elastomeric pump over 48 h in the orthopedic ward. In fact, in literature[1-7] to our knowledge all patients submitted to CSA for postoperative pain management have been monitored in an Intensive Care Unit[1,2] or in an Intermediate Care Unit.[3,5] The inability to
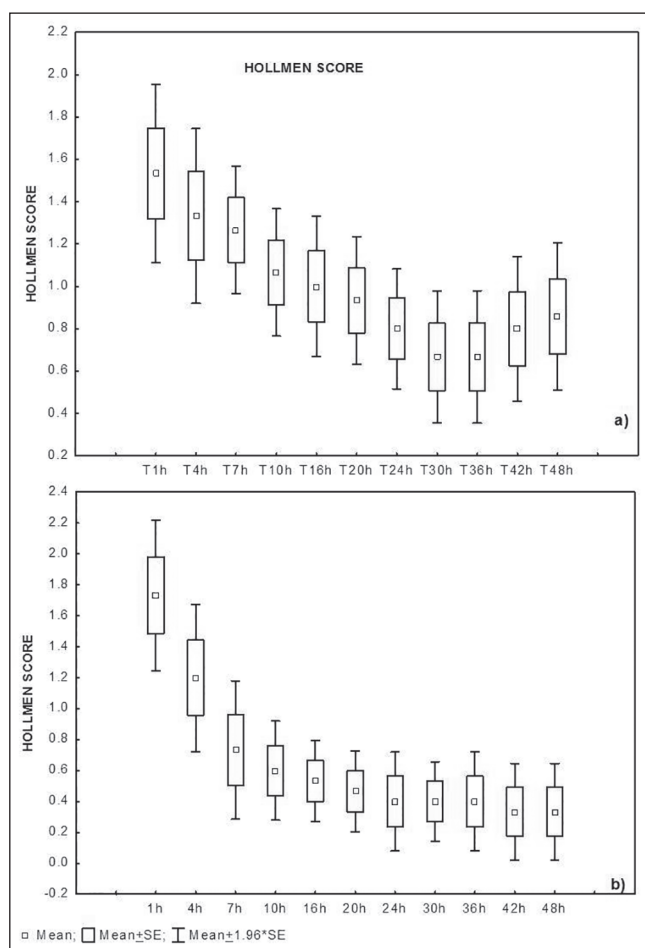

Figure 4: Sensory block assessed with Hollmen scale in Group $A_{0.125}$ [Figure 4a] and Group $B_{0.0625}$ [Figure 4b]. Box plot shows mean ± standard error (SE) and mean ± 1.96SE. *$P < 0.001$ $T_{1 h}$ and $T_{4 h}$ versus all study steps $\geq T_{20 h}$ in Group $A_{0.125}$; #$P < 0.001$ $T_{1 h}$ and $T_{4 h}$ versus all study steps $\geq T_{7 h}$ in Group $B_{0.0625}$; §$P < 0.02$ Group $A_{0.125}$ versus Group $B_{0.0625}$; in all study steps $\leq T_{1 h}$

adequately monitor patients in ward may be one of the reason why this technique was not frequently used for postoperative pain relief thus far. In our study, we prolonged analgesia using portable, safe, and user friendly elastomeric infusion pump connected to the spinal catheter until 48 h after the surgery, even if patients were transferred in a ward. Furthermore, the use of low dose and low concentration of LA and opioid did reduce the possibility of hemodynamic impairment/respiratory depression.[5]

The synergism between LA and opioids[9-11,19] allows the reduction of the total dose of each drug.[10,11,21-24] Actually, CSA requires small doses of LA to achieve anaesthesia and analgesia.[24,25] Given that SSSA doses are approximately $1/10^{th}$ the amount of LA used in the epidural space, CSA doses can be further reduced by 25-33%:[24,26] When smaller amounts of LA do not produce the expected levels of anesthesia or analgesia, we can re-dose the same medication until the achievement of the required anesthesia/analgesia.

The concentration of LA is important as well as these drugs have a relatively narrow "therapeutic to toxic window" in the subarachnoid space. The concentration of LA also influences the motor block, and in the postoperative period motor block should be avoided, then LA concentration could be reduced while monitoring pain level and sensory block.

In our patients, we performed CSA with 1.25 mg/h of levobupivacaine at two different concentrations of 0.125 mg/ml and 0.0625 mg/ml and obtained a good control of pain: mean VAS was <30 mm, the threshold indicated in international guidelines on postoperative pain as safe for pain management,[27] without any important complications; moreover, differential block was excellent given that from $T_{10\,h}$ on wards Bromage score was 0-1 and Hollmen score 1-2 in every patient.

This means that both the concentrations of levobupivacaine associated with a standard dose of sufentanil used in the present study were able to control pain without inducing residual motor block.

All patient in this study received thromboprophylaxis with low molecular weight heparin, and we did not observe any deep venous thrombosis or pulmonary embolism clinically in cases during or after surgery.

Another key point of our study is the use of levobupivacaine as the LA. Levobupivacaine recently emerged as a safer alternative in regional anesthesia than its racemic parent.[7,20] It demonstrated less affinity and strength of depressant effects onto myocardial and central nervous vital centers in

pharmacodynamic studies, and a superior pharmacokinetic profile. Clinically, levobupivacaine is well-tolerated in a variety of regional anesthesia techniques both after bolus administration and continuous postoperative infusion. Limited data is available in literature, to our knowledge about the use of levobupivacaine during CSA in postoperative pain management.[28,29] In this study, levobupivacaine was effective for the management of postoperative pain at a dosage of 1.25 mg/h. No significant differences between groups were observed with regard to the quality and duration of pain relief and the need of additional analgesia; patients were hemodynamically stable throughout the whole study period and without complications.

Despite recognition of the potential advantages of CSA, the latter is a technique that should be reserved for the clinician with extensive experience of both single-dose spinal anesthesia and other catheter techniques.

The use of large needles and catheters for CSA was found to be associated with PDPH, ranging from very low to over 30%.[30-32] In this study, 6.2% patients experienced PDPH. When the occurrence of PDPH, the reported symptoms are generally mild, and it can be difficult to distinguish posture-dependent headache from other forms of headache.

In major orthopedic surgery, CSA and combined spinal epidural anesthesia (CSE) are safe and reliable anesthesia techniques. In major orthopedic surgery, Imbelloni *et al.* concluded that both CSA and CSE provided good surgical conditions with low incidence of complications.[18]

The safe use of CSA for postoperative analgesia without complications allows the patients to be monitored in wards.

Conclusion

Although further data based on large population are necessary, in our patients CSA followed by postoperative infusion with 1.25 mg/h levobupivacaine plus sufentanil demonstrated a useful system to control postoperative pain up to 48 h independently from the LA concentration used, without hemodynamic impairment or side effects.

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Conflicts of interest
There are no conflicts of interest.

References

1. Niemi L, Pitkänen MT, Tuominen MK, Rosenberg PH. Comparison of intrathecal fentanyl infusion with intrathecal morphine infusion or bolus for postoperative pain relief after hip arthroplasty. Anesth Analg 1993;77:126-30.

2. Niemi L, Pitkänen M, Tuominen M, Rosenberg PH. Technical problems and side effects associated with continuous intrathecal or epidural post-operative analgesia in patients undergoing hip arthroplasty. Eur J Anaesthesiol 1994;11:469-74.

3. Niemi L, Pitkänen M, Dunkel P, Laakso E, Rosenberg PH. Evaluation of the usefulness of intrathecal bupivacaine infusion for analgesia after hip and knee arthroplasty. Br J Anaesth 1996;77:544-5.

4. Puolakka R, Haasio J, Pitkänen MT, Kallio M, Rosenberg PH. Technical aspects and postoperative sequelae of spinal and epidural anesthesia: A prospective study of 3,230 orthopedic patients. Reg Anesth Pain Med 2000;25:488-97.

5. Förster JG, Rosenberg PH, Niemi TT. Continuous spinal microcatheter (28 gauge) technique for arterial bypass surgery of the lower extremities and comparison of ropivacaine with or without morphine for postoperative analgesia. Br J Anaesth 2006;97:393-400.

6. Maurer K, Bonvini JM, Ekatodramis G, Serena S, Borgeat A. Continuous spinal anesthesia/analgesia vs. single-shot spinal anesthesia with patient-controlled analgesia for elective hip arthroplasty. Acta Anaesthesiol Scand 2003;47:878-83.

7. Burlacu CL, Buggy DJ. Update on local anesthetics: Focus on levobupivacaine. Ther Clin Risk Manag 2008;4:381-92.

8. Bevacqua BK, Slucky AV, Cleary WF. Is postoperative intrathecal catheter use associated with central nervous system infection? Anesthesiology 1994;80:1234-40.

9. Reuben SS, Dunn SM, Duprat KM, O'Sullivan P. An intrathecal fentanyl dose-response study in lower extremity revascularization procedures. Anesthesiology 1994;81:1371-5.

10. Pöyhiä R, Kalso EA. Antinociceptive effects and central nervous system depression caused by oxycodone and morphine in rats. Pharmacol Toxicol 1992;70:125-30.

11. Kalso E. Effects of intrathecal morphine, injected with bupivacaine, on pain after orthopaedic surgery. Br J Anaesth 1983;55:415-22.

12. McLeod GA. Density of spinal anaesthetic solutions of bupivacaine, levobupivacaine, and ropivacaine with and without dextrose. Br J Anaesth 2004;92:547-51.

13. Cacciapaglia M, Cinnella G, Schiraldi R, Cormio L, Vetuschi P, Cotoia A, et al. Combined sequential spinal epidural anesthesia: A prospective study. J Anesth Clin Res 2012;3:8.

14. Michaloudis D, Petrou A, Bakos P, Chatzimichali A, Kafkalaki K, Papaioannou A, et al. Continuous spinal anaesthesia/analgesia for the perioperative management of high-risk patients. Eur J Anaesthesiol 2000;17:239-47.

15. Bevacqua BK. Continuous spinal anaesthesia: What's new and what's not. Best Pract Res Clin Anaesthesiol 2003;17:393-406.

16. Favarel-Garrigues JF, Sztark F, Petitjean ME, Thicoïpé M, Lassié P, Dabadie P. Hemodynamic effects of spinal anesthesia in the elderly: Single dose versus titration through a catheter. Anesth Analg 1996;82:312-6.

17. Silvanto M, Pitkänen M, Tuominen M, Rosenberg PH. Technical problems associated with the use of 32-gauge and 22-gauge spinal catheters. Acta Anaesthesiol Scand 1992;36:295-9.

18. Imbelloni LE, Gouveia MA, Cordeiro JA. Continuous spinal anesthesia versus combined spinal epidural block for major orthopedic surgery: Prospective randomized study. Sao Paulo Med J 2009;127:7-11.

19. Standl T, Eckert S, Schulte am Esch J. Microcatheter continuous spinal anaesthesia in the post-operative period: A prospective study of its effectiveness and complications. Eur J Anaesthesiol 1995;12:273-9.

20. Wenk M, Pöpping DM. Feasibility of infusion pumps for continuous spinal administration of local anesthetics in post-operative pain therapy. Acta Anaesthesiol Scand 2009;53:634-40.

21. Vercauteren MP, Geernaert K, Hoffmann VL, Dohmen D, Adriaensen HA. Postoperative intrathecal patient-controlled analgesia with bupivacaine, sufentanil or a mixture of both. Anaesthesia 1998;53:1022-7.

22. Camann WR, Denney RA, Holby ED, Datta S. A comparison of intrathecal, epidural, and intravenous sufentanil for labor analgesia. Anesthesiology 1992;77:884-7.

23. Standl TG, Horn E, Luckmann M, Burmeister M, Wilhelm S, Schulte am Esch J. Subarachnoid sufentanil for early postoperative pain management in orthopedic patients: A placebo-controlled, double-blind study using spinal microcatheters. Anesthesiology 2001;94:230-8.

24. Breivik H. Epidural opioids: current use. Curr Opin Anesthesiol 1992;5:61-665.

25. Krämer S, Wenk M, Fischer G, Möllmann M, Pöpping DM. Continuous spinal anesthesia versus continuous femoral nerve block for elective total knee replacement. Minerva Anestesiol 2011;77:394-400.

26. Aksoy M, Dostbil A, Ince I, Ahiskalioglu A, Alici HA, Aydin A, et al. Continuous spinal anaesthesia versus ultrasound-guided combined psoas compartment-sciatic nerve block for hip replacement surgery in elderly high-risk patients: A prospective randomised study. BMC Anesthesiol 2014;14:99.

27. Rosenquist RW, Rosenberg J, United States Veterans Administration. Postoperative pain guidelines. Reg Anesth Pain Med 2003;28:279-88.

28. Baydilek Y, Yurtlu BS, Hanci V, Ayoglu H, Okyay RD, Kayhan GE, et al. The comparison of levobupivacaine in continuous or single dose spinal anesthesia for transurethral resection of prostate surgery. Braz J Anesthesiol 2014;64:89-97.

29. Sell A, Olkkola KT, Jalonen J, Aantaa R. Minimum effective local anaesthetic dose of isobaric levobupivacaine and ropivacaine administered via a spinal catheter for hip replacement surgery. Br J Anaesth 2005;94:239-42.

30. Mahisekar UL, Winnie AP, Vasireddy AR, Masters RW. Continuous spinal anesthesia and post dural puncture headache: A retrospective study. Reg Anesth 1991;16:107-11.

31. Horlocker TT, McGregor DG, Matsushige DK, Chantigian RC, Schroeder DR, Besse JA. Neurologic complications of 603 consecutive continuous spinal anesthetics using macrocatheter and microcatheter techniques. Perioperative Outcomes Group. Anesth Analg 1997;84:1063-70.

32. Lux EA, Althaus A. Is there a difference in postdural puncture headache after continuous spinal anesthesia with 28G microcatheters compared with punctures with 22G Quincke or Sprotte spinal needles? Local Reg Anesth 2014;7:63-7.