

The Efficacy and Safety of Epidural Infusions of Levobupivacaine With and Without Clonidine for Postoperative Pain Relief in Patients Undergoing Total Hip Replacement

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We assessed the efficacy and tolerability of epidural infusions of levobupivacaine, levobupivacaine plus clonidine, and clonidine for postoperative analgesia in 86 patients undergoing total hip replacement. For each group, an epidural cannula was inserted before surgery and 15 mL of 0.75% plain levobupivacaine was administered. Three hours later, an epidural infusion (6 mL/h) of levobupivacaine 0.125% (L), levobupivacaine 0.125% plus clonidine 8.3 µg/mL (LC) or clonidine alone (8.3 µg/mL) (C) was initiated. Morphine consumption was recorded for the following 24 h as were visual analog pain scores and the degree of sensory and motor blockade. The mean (median) morphine consumption was lowest in the combination

group (LC), 14 (7) mg; higher in the clonidine group (C), 23 (21) mg; and highest in the levobupivacaine group (L), 37 (36) mg ($P = 0.022$). The median times until the first request for analgesia which were 2.9, 5.9, and 12.5 h for Groups L, C, and LC, respectively ($P \leq 0.01$). There were no statistical differences among the groups regarding the maximum degree of postoperative motor blockade. On average, the systolic blood pressure in the two clonidine groups was slightly lower than in those from the levobupivacaine group. We conclude that the epidural administration of a combination of levobupivacaine plus clonidine is well tolerated and gives better analgesia than either drug used alone.

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Bupivacaine is a long-acting, effective local anesthetic that is commonly administered by the epidural route for the relief of postoperative pain. Despite its undoubted efficacy, bupivacaine is associated with cardio- and neurotoxicity, and this has occasionally resulted in death (1). The bupivacaine molecule is a racemate, and in the proprietary solution, two enantiomers, levo-(S[-]) and dex- (R[+]) bupivacaine are present in a 50:50 ratio. Data indicate that, whereas levobupivacaine and racemic bupivacaine have a similar clinical efficacy, levobupivacaine has a reduced potential for producing toxicity (2,3). Clonidine is an α_2 -adrenergic agonist which, when administered by the epidural route, has analgesic properties and potentiates

the effects of local anesthetics (4). The use of clonidine-levobupivacaine mixtures has not been previously described. The aim of this study was to investigate the safety and the analgesic properties of levobupivacaine 0.125% alone and in combination with clonidine when administered as an epidural infusion for the treatment of postoperative pain in patients undergoing total hip replacement.

Methods

The study was approved by The Queen's University of Belfast Research Ethics Committee, and written, informed consent was obtained from all patients. Ninety patients, ASA physical status I-III, between 18 and 80 yr old, weighing 50-110 kg, and presenting for elective primary total hip replacement were recruited. Patients taking medications with adrenergic or psychotropic activity; receiving chronic analgesic therapy other than simple analgesics (acetaminophen/codeine, nonsteroidal antiinflammatories); with a history of neurological or neuromuscular disorders, drug or alcohol

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abuse; or in whom there was a contraindication to regional anesthesia were excluded from the study, as were women of child-bearing potential.

During the preoperative visit, patients were tutored in the use of a 100-mm visual analog scale (VAS) marked "no pain" at one end and "worst pain imaginable" at the other. The use of a patient-controlled analgesia (PCA) system to provide supplementary postoperative analgesia was also explained.

Patients were premedicated orally with temazepam 20 mg and ranitidine 150 mg 1-1.5 h preoperatively. On arrival in the operating room, IV access was established and an infusion of dextran 70 initiated as prophylaxis against deep venous thrombosis. The patients were then placed in the lateral decubitus position. The skin over the proposed epidural site (L2-3 or L3-4) was infiltrated with 3 mL of lidocaine, 1% plain. A 16-gauge epidural catheter was placed 3-5 cm into the epidural space, and, after a negative aspiration, a 3-mL test dose of lidocaine 2% with epinephrine 1:200,000 was injected. Provided there was no evidence of subarachnoid or intravascular injection, three 5-mL increments of levobupivacaine 0.75% were administered at 5-min intervals. At the completion of the final 5-mL injection, sensory levels were assessed every 5 min by using loss of sensation to cold until the sensory block reached T10, at which point surgery proceeded. If this level was not achieved after 30 min, the patient received further 1-mL increments of levobupivacaine 0.75% up to a maximum of 5 mL. If an adequate block was not achieved after a further 15-min period, the patient was withdrawn from the study. In this situation, the patient's study number was reallocated to the next study patient. Motor block was assessed by using a modified Bromage scale (see below) at 0, 10, 20, and 30 min after the completion of the epidural injection until full motor block was achieved or surgery commenced. Patients received IM droperidol 2 mg and cefamandole 2 g IV before surgery as antiemetic and antibiotic prophylaxis, respectively.

Routine monitoring consisted of electrocardiogram and noninvasive blood pressure monitoring. Respiratory rate and pulse oximetry was done on all patients. Intraoperative sedation was provided by a propofol infusion, titrated to effect, the patients being drowsy but arousable. Supplemental oxygen was provided via a face mask. Blood and fluids were replaced as clinically indicated, and hypotension, defined as a decrease of more than 30% of baseline systolic pressure, was treated with IV fluids and ephedrine as necessary.

Postoperatively patients were connected to a PCA programmed to deliver morphine 1 mg IV on demand, with a 5-min lockout. The time to the first demand for analgesia, the total morphine consumption, and the number of requests for analgesia were recorded.

Three hours after the completion of the final epidural injection, the patients were randomly allocated

Table 1. Patient Characteristics

	Levobupivacaine	Levobupivacaine/ clonidine	Clonidine
Sex (M/F)	13/17	6/24	13/17
Age (yr)	65 ± 10	65 ± 9	65 ± 9
Weight (kg)	75 ± 12	73 ± 14	73 ± 12
Height (cm)	164 ± 8	160 ± 8	164 ± 9

Values are mean ± SD.

to one of three study groups, all of whom received an epidural infusion which ran at 6 mL/h for 24 h. These were: levobupivacaine 0.125% (Group L); levobupivacaine 0.125% plus clonidine 8.3 µg/mL (Group LC); or clonidine alone 8.3 µg/mL (Group C). The solutions were prepared in the pharmacy department, and the patient and the medical/nursing attendants were not aware of which solution the patient was receiving. VAS scores were recorded hourly for the first 12 h after the start of the infusion and every 2 h thereafter up to 24 h. Recordings were taken both at rest and on passive movement of the operated leg. Sensory and motor block were assessed hourly for 24 h. Motor block was assessed on the nonoperated leg by using a modified Bromage scale where 0 = no paralysis, full flexion of the knee and ankle; 1 = inability to raise extended leg, able to move knee; 2 = inability to flex knee, able to flex ankle; and 3 = inability to move lower limb.

All patients received routine postoperative clinical monitoring and all adverse events were recorded.

Statistical analysis of the data was carried out by using the SAS-PC-Windows package (Version 6.10; Chiroscience, Cambridge, UK). The time until the first request for analgesia was analyzed by using the Wilcoxon test using survival analysis techniques, and the number of requests for analgesia was analyzed by using the Wilcoxon two-sample test on the basis that data were nonnormal. Motor block was analyzed by using logistical regression. A *P* value <0.05 was considered significant.

In a previous study (5), the mean dose of morphine delivered to patients receiving an infusion of 50 µg/mL clonidine was 10.5 mg with a standard deviation of 6.0 mg. Based on these estimates, $\alpha = 0.017$ (i.e., adjusting for multiple comparisons) and $\beta = 0.2$, the number of patients required to detect a difference of 50% from the clonidine mean was 30 patients per group.

Results

Surgery and follow up were successfully completed for 86 of the 90 patients: 27 from Group L, 30 from Group LC and 29 from Group C. The groups were similar in terms of the patient characteristics except for

Table 2. Time to First Request for Morphine, Total Morphine Consumption, and Total Morphine Requests

	Levobupivacaine (n = 27)	Levobupivacaine/ clonidine (n = 30)	Clonidine (n = 29)
Time to first morphine (h)	5.0 ± 5.6*	13.0 ± 8.3†	7.2 ± 5.9
Total morphine consumption (mg)	34.9 ± 22.7*	13.9 ± 17.3‡	21.8 ± 12.3
Total no. of morphine requests (median/range)	68 ± 56 (55/5-185)	29 ± 41 (9/0-170)	46 ± 46 (28/0-183)

Values are mean ± SD.

* $P < 0.05$ (levobupivacaine vs clonidine).† $P < 0.01$ (levobupivacaine vs levobupivacaine/clonidine).‡ $P < 0.01$ (vs other two groups).**Table 3.** Mean Postoperative Visual Analog Pain Scores (mm) on Passive Movement

Time (h)	Levobupivacaine	Levobupivacaine/ clonidine	Clonidine
0 h	4.1 ± 16.4 (0-80)	3.6 ± 11.0 (0-50)	1.0 ± 5.5 (0-30)
4 h	22.3 ± 24.9 (0-72)	2.5 ± 6.0 (0-20)	7.4 ± 16.6 (0-65)
8 h	8.5 ± 13.9 (0-48)	1.3 ± 5.4 (0-26)	12.4 ± 19.9 (0-70)
12 h	13.8 ± 23.2 (0-78)	1.3 ± 5.0 (0-20)	12.5 ± 18.2 (0-50)
16 h	8.0 ± 11.3 (0-30)	5.4 ± 10.9 (0-40)	25.2 ± 25.7 (0-80)
20 h	12.8 ± 19.7 (0-70)	12.6 ± 21.4 (0-84)	19.4 ± 20.6 (0-55)
24 h	7.7 ± 12.3 (0-45)	9.4 ± 13.8 (0-41)	16.2 ± 26.4 (0-100)

Values are mean ± SD (range).

Group LC, which contained proportionately more women than the other two groups (Table 1).

The onset of sensory blockade was rapid, with most patients achieving a sensory block above the level of T10 by the time the final 5 mL of epidural levobupivacaine had been administered. In six patients, the T10 level was not reached until the second assessment, 5 min after the completion of the epidural injection. In four cases (two from Group L and two from C), the patients received an additional 5 mL of epidural levobupivacaine as the block had not reached T10 after 30 min. This level was achieved within 5 min of the final 5 mL in all four patients.

The onset of motor block was rapid, and assessment immediately after the final 5-mL epidural injection showed that one patient (Group C) already had full (grade 3) motor block, while the remainder had grade 0 ($n = 39$), grade 1 ($n = 36$), or grade 2 ($n = 14$) blocks.

There were no differences among the groups in terms of their intraoperative course: the duration of surgery was 68 ± 11 , 70 ± 12 , and 68 ± 13 (mean ± SD) min, and the intraoperative blood losses were 502 ± 327 , 532 ± 249 , and 539 ± 400 (mean ± SD) mL for Groups L, C, and LC, respectively.

The time until the first request for analgesia and the total postoperative morphine requirements were significantly different among the three groups (Table 2), Group LC having the lowest requirements and the longest interval before analgesia was requested. Morphine consumption by the patients in Group C was significantly higher than in Group LC patients but significantly lower than that of patients in Group L,

who also had the shortest period until analgesia was requested.

The VAS scores recorded on passive movement of the operated limb are summarized in Table 3. These were generally satisfactory for all groups, the mean score being below 30 mm and the median score 0 mm at almost every assessment. Group LC had the lowest scores at most of the assessments, but this difference did not achieve statistical significance. In all groups, the patients appeared to have had effective pain relief.

The pattern of postoperative sensory and motor blockade was different among the three groups (Figs. 1 and 2).

The motor and sensory block in Group C regressed rapidly. The motor block in Group LC was much more intense than that of the other two groups. However, the motor block was not profound in the majority of patients in the LC group and was comparable to that of the other two groups by the conclusion of the epidural infusion (Fig. 2).

Blood pressures were similar in the clonidine groups (C and LC) and were lower than in Group L. The difference between the mean systolic pressures amounted to approximately 10 mm Hg, and although statistically significant ($P < 0.05$), this was not thought to be of major clinical importance (Fig. 3).

There was one postoperative death, in a patient from Group LC. This patient, who had no significant cardiac risk factors, had had an uneventful hospital stay but collapsed and died at home 9 days after discharge. The cause of death was not established but was thought to be cardiac in origin and unrelated to

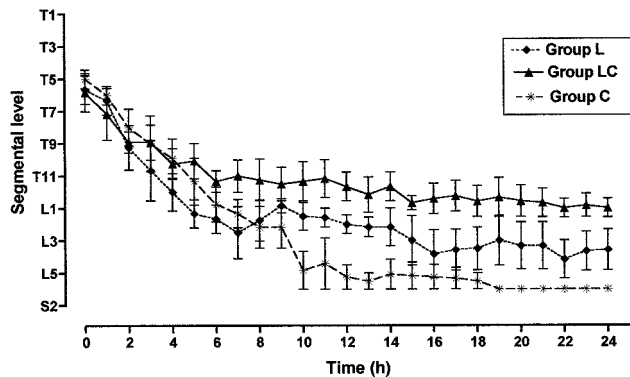


Figure 1. Postoperative sensory block (median, interquartile range). L = levobupivacaine, C = clonidine.

his anesthesia. There were no differences between the groups in terms of other adverse events, such as hypotension and cardiac arrhythmias, but there was a higher incidence of nausea in Group L (14 patients) compared with 6 patients in Group LC and 4 patients in Group C.

Discussion

Bupivacaine possesses an asymmetric carbon atom and can therefore take the form of two enantiomers, levo- and dex-bupivacaine. These have identical physical properties, but their chemical groups occupy different positions and therefore form different three-dimensional relationships in the asymmetric environment of receptors and enzymes. This can result in differences in both receptor affinity and intrinsic activity of the enantiomers (6), leading to differences in their toxicities, distribution, protein binding, metabolism, and elimination (7,8).

Clonidine, a partial α_2 -adrenergic agonist, has a variety of different actions, including antihypertensive properties and the ability to potentiate the effects of local anesthetics. This has been demonstrated in a variety of clinical settings (4,9) and has been shown to result in the prolongation of the sensory blockade and a reduction in the amount or the concentration of local anesthetic required to produce postoperative analgesia. Previous work with epidural infusions has shown that 150 μ g of clonidine, when added to bupivacaine 0.25% approximately doubled the duration of the analgesia produced (4).

In a study of epidural infusions of levobupivacaine in patients undergoing hip or knee surgery, significantly longer analgesia was achieved with levobupivacaine 0.25% than 0.125% or 0.0625% (10). The incidence of motor block was similar in the 0.125% and the 0.25% groups, and the latter provided the most effective pain relief as assessed by using VAS.

The results of the present study demonstrate that epidural infusions of levobupivacaine are potentiated

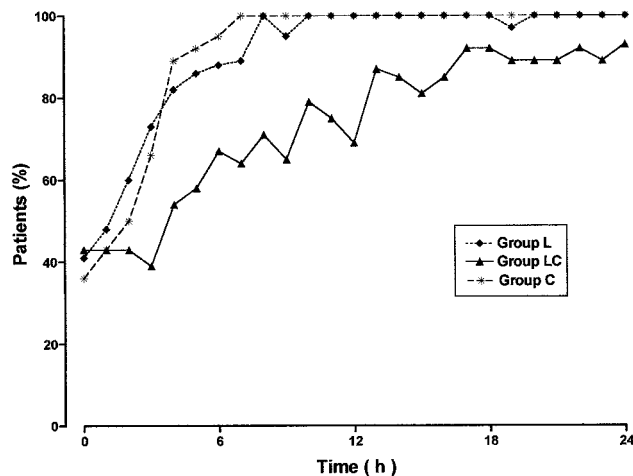


Figure 2. Patients with minimal postoperative motor block (Bromage score 0 or 1). L = levobupivacaine, C = clonidine.

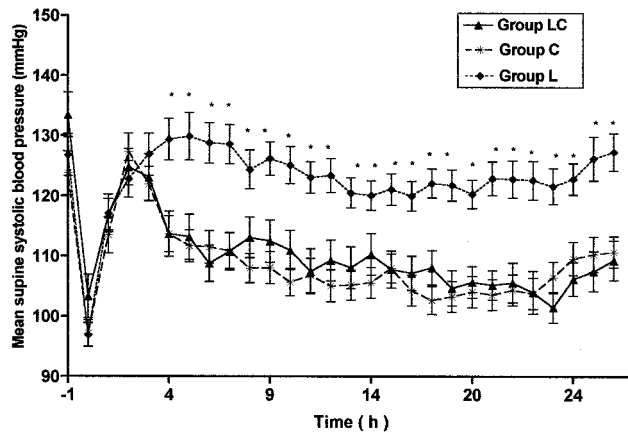


Figure 3. Mean \pm SD postoperative systolic blood pressure (mm Hg). L = levobupivacaine, C = clonidine. *Difference between groups: $P < 0.05$.

by the addition of clonidine. The increase in efficacy of the combination of clonidine and levobupivacaine compared with levobupivacaine alone was demonstrated by the increase in the time to first request for analgesia (from 5 to 13 h) and an accompanying decrease in the total morphine consumption. VAS scores were also lower in the combination group, but all three groups appear to have had reasonable pain relief, as might be expected given that they all had free access to a PCA system. The clinical relevance of the small differences in pain scores is therefore open to question, but the improved analgesia may have contributed to the reduction in blood pressure in the clonidine groups.

Another effect of the clonidine was that the motor blockade produced by the levobupivacaine was also increased, particularly in the early part of the study. This is a well recognized property of the drug (5) and was not a particular problem, as the patients were not

required to mobilize. It might, however, be a drawback in other settings. The sensory blockade was also slower to regress in the combination group, but this was again not considered to be a major problem.

Postoperative nausea was less common in the clonidine groups postoperatively, and this probably reflects the lower consumption of morphine by these patients.

In conclusion, although clonidine lowered blood pressure and increased the degree of motor and sensory block, the combination of clonidine and levobupivacaine, administered by the epidural route, was well tolerated and produced significantly improved postoperative pain management compared with either drug used alone.

References

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine and bupivacaine. *Anesthesiology* 1979;51:285-7.
2. Huang YF, Pryor ME, Mather LE, Veering BT. Cardiovascular and central nervous system effects of intravenous levobupivacaine and bupivacaine in sheep. *Anesth Analg* 1998;86:797-804.
3. Bardsley H, Gristwood R, Watson N, Nimmo W. The local anaesthetic activity of levobupivacaine does not differ from racemic bupivacaine ("Marcain"): first clinical evidence. *Exp Opin Invest Drugs* 1997;6:1883-5.
4. Carabine UA, Milligan KR, Moore J. Extradural clonidine and bupivacaine for postoperative analgesia. *Br J Anaesth* 1992;68:132-5.
5. Carabine UA, Milligan KR, Mulholland D, Moore J. Extradural clonidine infusions for analgesia after total hip replacement. *Br J Anaesth* 1992;68:338-43.
6. Burm AGL, Van Der Meer AD, Van Kleef JW, et al. Pharmacokinetics of the enantiomers of bupivacaine following intravenous administration of the racemate. *Br J Clin Pharmacol* 1994;38:125-9.
7. Tucker GT, Lennard MS. Enantiomer specific pharmacokinetics. *Pharmacol Therap* 1990;45:309-29.
8. Vanhoutte F, Vereecke J, Verbeke N, Carmeliet E. Stereoselective effects of the enantiomers of bupivacaine on the electrophysiological properties of the guinea-pig papillary muscle. *Br J Pharmacol* 1991;103:1275-81.
9. Racle JP, Benkhadra A, Poy JY, Gleizal B. Prolongation of isobaric bupivacaine spinal anesthesia with epinephrine and clonidine for hip surgery in the elderly. *Anesth Analg* 1987;66:442-6.
10. Murdoch J, Dickson U, Wilson P, et al. Levobupivacaine administered as a continuous epidural infusion for postoperative pain in patients undergoing elective surgery. *Internat Mon Reg Anesth* 1998;10:9.