# Effects of scalp block with bupivacaine versus levobupivacaine on haemodynamic response to head pinning and comparative efficacies in postoperative analgesia: A randomized controlled trial

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## Abstract

**Objective:** This study was performed to determine the effects of scalp blocks with bupivacaine versus levobupivacaine on the haemodynamic response during craniotomy and the efficacies and analgesic requirements of these drugs postoperatively.

**Methods:** This randomized, prospective, placebo-controlled, double-blind study included 90 patients (age, 18–85 years; American Society of Anesthesiologists physical status, I or II). The patients were randomly divided into three groups: those who received 20 mL of 0.5% bupivacaine (Group B, n = 30), 20 mL of 0.5% levobupivacaine (Group L, n = 30), or saline as a placebo (Group C, n = 30). Scalp blocks were performed 5 min before head pinning. The primary outcome was the mean arterial pressure (MAP), and the secondary outcomes were the heart rate (HR), visual analogue scale (VAS) scores, and additional intraoperative and postoperative drug use. Postoperative pain was evaluated using a 10-cm VAS.

**Results:** During head pinning and incision, the MAP and HR were significantly higher in Group C. The additional drug requirement for intraoperative hypertension and tachycardia was significantly

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higher in Group C. There were no significant differences in MAP, HR, or VAS scores between Groups B and L.
**Conclusion:** Both bupivacaine and levobupivacaine can be effectively and safely used for scalp blocks to control haemodynamic responses and postoperative pain.

## Introduction

Various factors should be considered during anaesthesia for craniotomy, including haemodynamic stability, sufficient cerebral perfusion pressure, and avoidance of agents or procedures that increase intracranial pressure.[1]

Skull pin insertion is a fundamental and frequently used manoeuvre for stabilization of the head during surgery. However, skull pins may cause sudden haemodynamic changes despite an adequate depth of anaesthesia. In patients with impaired cerebral autoregulation, a sudden increase in the systemic blood pressure can cause an abrupt increase in the intracranial pressure, which precipitates intracranial hypertension.[1,2]

Skull pin insertion produces strong noxious stimuli even under deep anaesthesia. Blunting these noxious stimuli by blocking the nerves that supply the relevant region of the scalp is useful in terms of controlling high blood pressure and tachycardia.[3] Furthermore, scalp blocks may decrease the severity of postoperative pain due to craniotomy.[4]

The onset and duration of action, sensory block level to motor block level, and cardiotoxicity should be taken into account when selecting the most appropriate local anaesthetic agent. Bupivacaine 0.5% is widely used to provide scalp blocks. Levobupivacaine is a pure S-enantiomer of bupivacaine and is increasing in popularity because it has fewer cardiovascular side effects and is less toxic to the central nervous system.[5–8] In addition to its better systemic

toxicity profile, it provides motor block in a shorter duration of time than does the racemic bupivacaine.[5,6] Levobupivacaine may be particularly advantageous in the setting of scalp blocks, in which high volumes of local anaesthetic are administered at multiple injection sites, because the high vascularity of the scalp tissue may result in high amounts of systemic absorption and/or unintentional intravascular administration.

The present study was performed to determine the effects of scalp blocks with bupivacaine versus levobupivacaine on the haemodynamic response to head pinning and incision during craniotomy and to evaluate the efficacies and analgesic requirements of these two drugs postoperatively.

## Methods

This phase IV, randomized, prospective, placebo-controlled, double-blind study included 90 patients (American Society of Anesthesiologists physical status, I or II; age, 18–85 years) who underwent elective scheduled operations including craniotomy from March 2008 through April 2009 at the Medical Faculty of Uludağ University. Patients with uncontrolled hypertension, arrhythmia, diabetes mellitus, coagulopathy, or coronary artery disease and those with a known or suspected allergy to bupivacaine or levobupivacaine were excluded. The patients were randomly divided into three groups using a sealed-enveloped technique to receive 20 mL of 0.5% bupivacaine (Group B, n = 30), 20 mL

of 0.5% levobupivacaine (Group L, n = 30), or 20 mL of 0.9% saline as a placebo (control group, Group C, n = 30). This study was approved by the Research Ethics Committee of Uludağ University Medical Faculty (4 March 2008; Protocol number: 5/30). Written informed consent was obtained from each patient during his or her anaesthesia consultation. The clinical trial registry number of the present study is NCT02497040.

A standard anaesthesia protocol was used and routine monitoring was performed for all patients. Monitoring was carried out via electrocardiography, non-invasive blood pressure measurement, and pulse oximetry in the operating room prior to anaesthetic induction (Datex-Ohmeda Cardiocap™/5 GE, Datex Medical Instrumentation Corp., Helsinki, Finland). After premedication with 0.05 mg/kg of intravenous midazolam, neuromuscular monitoring was performed using a TOF-Watch SX (Organon Ireland Ltd., Schering-Plough Corp., Dublin, Ireland). Anaesthesia was induced with 2–3 mg/kg of intravenous propofol, 2 µg/kg of intravenous fentanyl, and 0.6 mg/kg of intravenous rocuronium. Total intravenous anaesthesia (propofol infusion at 6 mg/kg per hour) was used for anaesthetic maintenance. In addition, 0.15 mg/kg of intravenous rocuronium and 1 µg/kg of intravenous fentanyl were administered every 40 minutes for maintenance. Ventilation was mechanically controlled with a 50:50 oxygen:air mixture to achieve an end-tidal carbon dioxide level of 30–35 mmHg. A 20-gauge arterial catheter was placed in the radial artery prior to anaesthetic induction for invasive monitoring of the arterial blood pressure.

The scalp blocks were performed bilaterally after anaesthetic induction and 5 min prior to head pinning by an anaesthesiologist according to the technique described by Pinosky et al.[3] Syringes (20-mL) for the scalp blocks were prepared and numbered by a blinded assistant. The responsible anaesthesiologist performed the scalp blocks using a 23-gauge needle, which was introduced into the skin at an angle of 45° and deeply penetrated the outer margin of the scalp. As the needle was gradually withdrawn, the solutions were simultaneously injected throughout the full thickness of the scalp. The amounts of the solutions and the points at which the solutions were injected for the nerve blocks were as follows: 1) 2 mL of solution above the eyebrow to block the supraorbital and supratrochlear nerves, 2) 2 mL of solution 1.5 cm anterior to the ear at the level of the tragus to block the auriculotemporal nerves, 3) 3 mL of solution 1.5 cm posterior to the ear at the level of the tragus to block the post-auricular nerves, and 4) 3 mL of solution along the superior nuchal line, which is approximately midway between the occipital protuberance and the mastoid process, to block the greater, lesser, and third occipital nerves. Head pinning was performed by a neurosurgeon 5 min after the scalp block.

Data regarding the patients' demographic characteristics, duration of anaesthesia and surgery, additional analgesic requirements, additional drug requirements due to hypertension and tachycardia (excluding doses given during induction and maintenance as mentioned above), extubation status, and transfer to the intensive care unit or clinical ward were recorded. Systolic arterial pressure, diastolic arterial pressure, mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation, and end-tidal carbon dioxide were recorded at baseline (t1), 1 min (t2) and 5 min (t3) after the induction of anaesthesia, during (t4) and 1 min after (t5) the scalp block, during (t6) and 1 min after (t7) the head pinning, during (t8) and 1 min after (t9) the incision, and during (t10) and 1 min after (t11) skin closure.

When the systolic arterial pressure and HR values exceeded the baseline values by 20%, an additional dose of fentanyl (2 µg/kg intravenously) was administered and the

propofol infusion (9 mg/kg per hour) was increased. A >25% decrease in the MAP from baseline was defined as hypotension and treated with an ephedrine bolus (5 mg). Additionally, a >25% decrease in the HR from baseline was defined as bradycardia and treated with intravenous atropine (0.5 mg). Patients who developed intraoperative surgical complications were moved to the neurosurgical intensive care unit while under deep sedation.

After they had emerged from anaesthesia, the patients' severity of pain was assessed at 2, 4, 8, 16, and 24 hours postoperatively using a 10-cm visual analogue scale (VAS) (0, no pain at all; 10, the worst possible pain). During the postoperative period, patients with a VAS pain score of >2 were administered diclofenac (75 mg intramuscularly), and those with a VAS pain score of >5 were administered meperidine (100 mg intramuscularly). Administration of diclofenac and meperidine was repeated as needed to a maximum frequency of three times a day. Postoperative analgesic consumption was recorded. Complications (such as bradycardia, hypotension, drug allergy, nausea, and vomiting) that developed in the postoperative care unit were also recorded. Intravenous metoclopramide (10 mg) was administered for patients with nausea and vomiting, and patients with tinnitus and blurry vision were carefully observed.

## Statistical analysis

The primary outcome measure of the study was the MAP, and the secondary outcomes were the HR, VAS scores, and additional intraoperative and postoperative drug use. A priori sample size estimation revealed that at least 84 subjects were required to achieve a power of 90% ($\alpha = 0.05$) to detect a difference in the MAP between the groups with a large effect size (0.40). Thus, 90 patients were included (30 in each group). Data analyses were performed using the Statistical Package for the Social Sciences version 13.0 (SPSS Inc., Chicago, IL, USA). Data are expressed as mean, SD, number, and percentage as appropriate. Intragroup comparisons of continuous variables were performed by a paired t-test for normally distributed variables and by the Wilcoxon test for non-normally distributed variables. For non-normally distributed variables, two-group comparisons were performed using the Mann–Whitney U test, and multiple-group comparisons were performed using the Kruskal–Wallis test. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. A p value of <0.05 was considered statistically significant.

## Results

The present study included 90 patients divided into 3 groups of 30 patients each. All patients underwent craniotomy for treatment of an intracranial mass, arteriovenous malformation, or cerebral aneurysm. The patient flow diagram is presented in Figure 1. The general characteristics and intraoperative variables of the patients in the three study groups are presented in Table 1. No significant differences were found among Groups B, L, and C with respect to age, sex, height, weight, American Society of Anesthesiologists physical status, reason for the operation, duration of anaesthesia, duration of the operation, the unit to where the patient was transferred, the postoperative extubation/intubation status, or the intraoperative fentanyl consumption (including induction, maintenance, and additional doses).

The MAPs among the three study groups at different time points are illustrated in Figure 2. In Group C, the MAP at t6, t7, t8, and t10 was significantly higher than that at baseline (t1) (p < 0.01, p < 0.05, p < 0.01, and p < 0.01, respectively). In Group B, the MAP at t6 was not significantly different from that at t1, whereas the MAP at t2, t3,
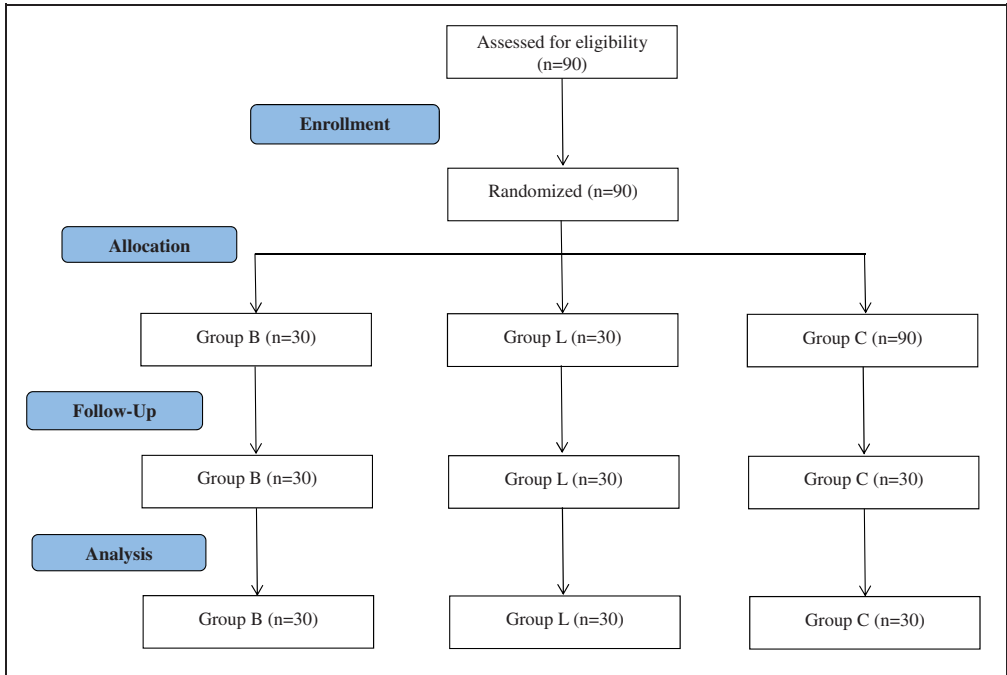
**Figure 1.** Patient flow diagram. B, bupivacaine; L, levobupivacaine; C, control.

t4, t5, t7, t8, t9, t10, and t11 was lower than that at t1 ($p < 0.001$, $p < 0.001$, $p < 0.01$, $p < 0.001$, $p < 0.01$, $p < 0.001$, $p < 0.001$, $p < 0.001$, and $p < 0.01$, respectively). Similarly, in Group L, the MAP at t6 was not significantly different from that at t1, whereas the MAP at t2, t3, t4, t5, t7, t8, t9, t10, and t11 was lower than that at t1 ($p < 0.001$, $p < 0.01$, $p < 0.01$, $p < 0.001$, $p < 0.01$, $p < 0.001$, $p < 0.01$, $p < 0.001$, and $p < 0.001$, respectively). Comparison of the MAP among the study groups revealed that the MAP in Groups B and L was significantly lower than that in Group C at t6 ($p < 0.01$ and $p < 0.05$, respectively) and t7 ($p < 0.01$ and $p < 0.05$, respectively). Additionally, the MAP in Groups B and L was significantly lower than that in Group C at t9 ($p < 0.001$ and $p < 0.05$, respectively).

The HRs among the three study groups at different time points are illustrated in Figure 3. In Group C, the HR at t6 and t7 was significantly higher than that at baseline

(t1) ($p < 0.001$ and $p < 0.01$, respectively). In Group B, the HR at t6 was not significantly different from that at t1, whereas the HR at t8, t9, t10, and t11 was significantly lower than that at t1 ($p < 0.001$ for each). Similarly, in Group L, the HR at t6 was not significantly different from that at t1, whereas the HR at t7, t8, t9, and t10 was significantly lower than that at t1 ($p < 0.01$ for each). Comparison of the HR among the study groups revealed that the HR in Group B was significantly different from that in Group C at t6, t7, t8, t9, t10, and t11 ($p < 0.05$, $p < 0.01$, $p < 0.01$, $p < 0.001$, $p < 0.01$, and $p < 0.01$, respectively). Additionally, the HR in Group L was significantly lower than that in Group C at t7, t8, and t9 ($p < 0.05$ for each). No significant differences were found between Groups B and L.

The additional drug requirements due to intraoperative hypertension and tachycardia are presented in Table 2. The rate of patients who required additional drugs in Group C

**Table 1.** General characteristics and intraoperative variables of the patients in the three study groups.

| | Group C (n = 30) | Group B (n = 30) | Group L (n = 30) |
|---|---|---|---|
| Age, years | 49.20 ± 9.95 | 49.03 ± 15.81 | 47.60 ± 17.31 |
| Sex | | | |
|   Female | 15 (50.0) | 19 (63.3) | 19 (63.3) |
|   Male | 15 (50.0) | 11 (36.7) | 11 (36.7) |
| Weight, kg | 80.17 ± 21.81 | 76.33 ± 13.53 | 70.53 ± 12.00 |
| Height, cm | 163.80 ± 27.96 | 167.10 ± 7.39 | 168.50 ± 8.66 |
| ASA physical status | | | |
|   I | 22 (73.3) | 15 (50.0) | 19 (63.3) |
|   II | 8 (26.7) | 15 (50.0) | 11 (36.7) |
| Reasons for operation | | | |
|   Cerebral tumour | 24 (80.0) | 18 (60.1) | 18 (60.0) |
|   Arteriovenous malformation | 0 (0.0) | 4 (13.3) | 2 (6.7) |
|   Cerebral aneurysm | 6 (20.0) | 8 (26.6) | 10 (33.3) |
| Duration of anaesthesia, min | 223.70 ± 70.97 | 228.00 ± 61.55 | 254.17 ± 70.76 |
| Duration of surgery, min | 179.17 ± 69.91 | 184.50 ± 56.62 | 207.50 ± 70.52 |
| Postoperatively | | | |
|   Extubated in the ward | 12 (40) | 7 (23.3) | 5 (16.7) |
|   Extubated in the ICU | 11 (36.7) | 14 (46.7) | 13 (43.3) |
|   Intubated in the ICU | 7 (23.3) | 9 (30) | 12 (40) |
| Intraoperative fentanyl consumption,* µg | 311.67 ± 82.72 | 277.5 ± 100.93 | 330.0 ± 110.33 |

No significant difference for all overall intergroup comparisons.
*Total intraoperative fentanyl dose including induction, maintenance, and additional dose
Data are presented as mean ± SD and number (%), where appropriate.
C, control; B, bupivacaine; L, levobupivacaine; ASA, American Society of Anesthesiologists; ICU, intensive care unit.
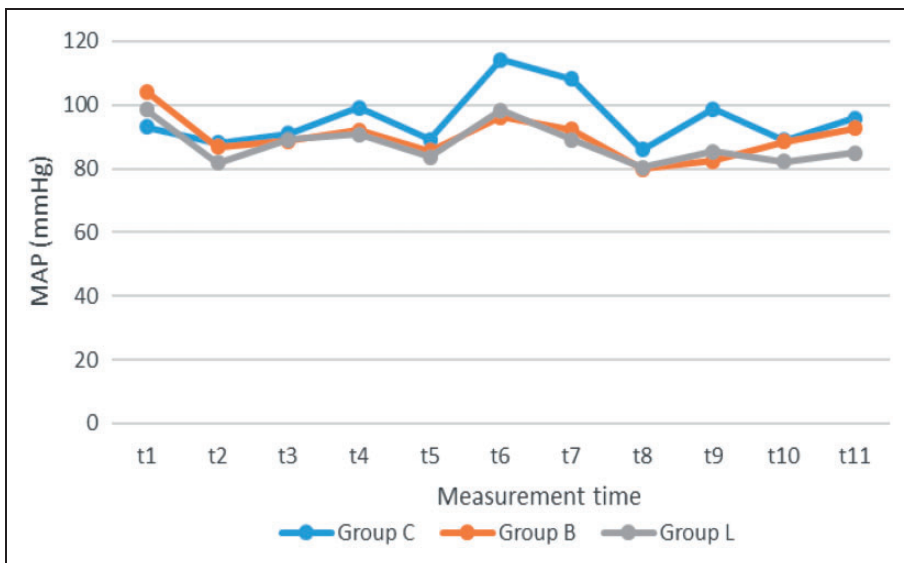


**Figure 2.** Mean arterial pressure in the three study groups at different time points. B, bupivacaine; L, levobupivacaine; C, control; MAP, mean arterial pressure.
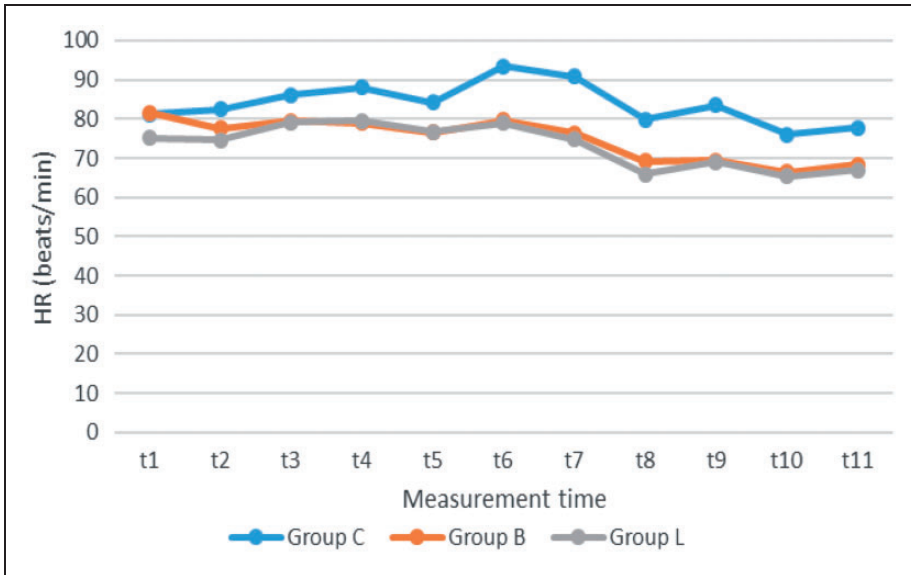
**Figure 3.** Heart rate in the three study groups at different time points. B, bupivacaine; L, levobupivacaine; C, control; HR, heart rate.

**Table 2.** Additional drug requirements due to intraoperative hypertension and tachycardia.

|  | Group C n = 30 | Group B n = 30 | Group L n = 30 | p |
|---|---|---|---|---|
| Additional drug requirement, *n (%) |  |  |  |  |
| Present | 16 (53.3) | 1 (3.3) | 2 (6.6) | <0.001 |
| Absent | 14 (46.7) | 29 (96.7) | 28 (93.4) |  |

*Other than induction and maintenance doses of fentanyl
C, control; B, bupivacaine; L, levobupivacaine.
Intergroup comparisons: C vs. B, p < 0.001; C vs. L, p < 0.001; B vs. L, p = 1.000

was significantly higher than that in Groups B and L (p = 0.001). There was no difference in the additional drug requirement between Groups B and L.

The VAS scores of the conscious patients in the three study groups are shown in Figure 4. The VAS scores at 2 hours postoperatively were significantly different among Groups C, B, and L (p = 0.044). In addition, the VAS scores of the conscious patients in Group C were significantly higher than those of the conscious patients in Groups B and L at 2 hours postoperatively (p < 0.05 for each). There was no difference in the VAS scores at 2 hours postoperatively between Groups B and L. Additionally, there was no significant difference in postoperative analgesic requirements in the postoperative care unit among the three groups (Table 3).
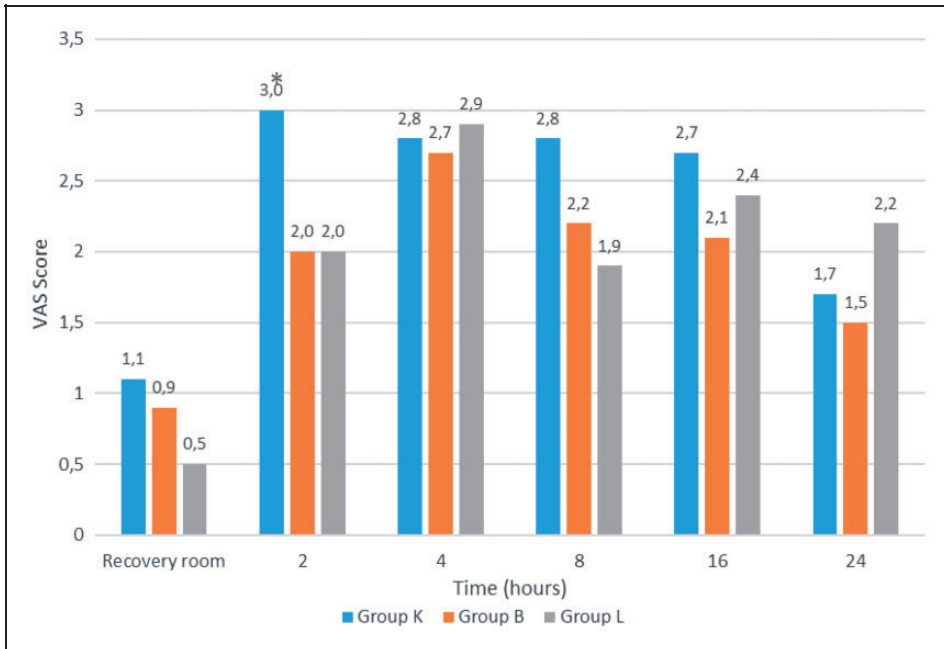
**Figure 4.** Visual analogue scale scores of the conscious patients in the three study groups.
*Significantly different at p < 0.05 compared with Groups B and L. B, bupivacaine; L, levobupivacaine; C, control. Figures over the bars denote the mean visual analogue scale scores. VAS visual analogue scale

**Table 3.** Additional postoperative analgesic requirements in the study groups.

| | Number of conscious patients requiring additional analgesia | | | |
|---|---|---|---|---|
| | Group C (n = 23) | Group B (n = 21) | Group L (n = 17) | p |
| Postoperative care unit | 2 (8.7) | 2 (9.5) | 0 (0.0) | 0.435 |
| 2 h postoperatively | 10 (43.5) | 4 (19.0) | 3 (17.6) | 0.106 |
| 4 h postoperatively | 8 (34.8) | 8 (38.1) | 8 (47.1) | 0.727 |
| 8 h postoperatively | 8 (34.8) | 6 (28.6) | 4 (23.5) | 0.738 |
| 16 h postoperatively | 8 (34.8) | 2 (9.5) | 2 (11.8) | 0.068 |
| 24 h postoperatively | 0 (0.0) | 2 (9.5) | 2 (11.8) | 0.263 |

Data are presented as number (%).
C, control; B, bupivacaine; L, levobupivacaine.

No intraoperative arrhythmia or asystole was observed. No central nervous symptoms (such as tinnitus, paraesthesia, or deafness) related to local anaesthetic toxicity occurred during the postoperative period.

## Discussion

Prevention of acute hypertension secondary to noxious stimulation, such as head pinning, is highly desirable in patients

undergoing neurosurgery.[3] In contrast, sudden or prolonged reductions in blood pressure following the use of antihypertensive agents, opioids, and intravenous anaesthetics that blunt the haemodynamic response to head pinning are undesirable.[9,10] The scalp block is an easy and effective method of blunting the blood pressure response and decreasing morbidity after craniotomy.[11]

Several studies to date have tested the efficacy of a number of local anaesthetic agents, including bupivacaine and levobupivacaine, in blunting the haemodynamic response and enhancing postoperative pain control.[3,12–16] To the best of our knowledge, however, no previous study has compared bupivacaine and levobupivacaine directly. The present study has demonstrated that scalp nerve blocks with bupivacaine and levobupivacaine allow for the maintenance of better haemodynamic stability than did blocks with the control agent, with no significant differences between bupivacaine and levobupivacaine.

Although bupivacaine with or without epinephrine has been most frequently used and recommended for scalp blocks in previous studies, its use is associated with an increased risk of depressed cardiac contractility and conductivity.[6] Conversely, levobupivacaine is a pure S-enantiomer of bupivacaine and is gaining popularity because it leads to fewer cardiovascular side effects and is less toxic to the central nervous system.[5–7] However, research on the effects of levobupivacaine scalp blocks on haemodynamics and postoperative recovery[15–17] as well as studies on the levobupivacaine plasma concentration after this procedure are relatively scarce.[18]

The scalp block method used in the present study was first described by Pinosky et al.[3] in 1996. In their study, Pinosky et al.[3] compared the efficacy of saline (as a control) and 0.5% bupivacaine to induce a block in the supraorbital, supratrochlear, great auricular, auriculotemporal, and greater and lesser occipital nerves and reported that bupivacaine successfully blunted the haemodynamic response to head pinning. In another study, Geze et al.[14] evaluated the effects of scalp blocks using 20 mL of 0.5% bupivacaine versus local infiltration on the haemodynamic and stress responses to skull pin insertion during craniotomy and found that the scalp block provided better haemodynamics and reduced the stress response during and after skull pin placement. In the study by Pinosky et al.,[3] 9 of 10 patients in the control group and none of the patients in the block group required rescue drugs. Lee et al.[19] also showed the efficacy of bupivacaine in blunting the haemodynamic response and reducing the need for rescue drugs due to hypertension and tachycardia. However, in a series of 120 patients, Yıldız et al.[9] reported that local scalp infiltration with 0.25% bupivacaine had no advantage over a large intravenous bolus of fentanyl just before skull pin insertion, and they advocated the use of the latter because of its simplicity.

Two studies have tested the intraoperative haemodynamic effects of levobupivacaine scalp blocks during craniotomy. In a retrospective study by Pardey Bracho et al.,[16] patients who received a scalp nerve block with levobupivacaine prior to skull pin placement and incision were compared with controls in terms of haemodynamic stability and anaesthesia/analgesia requirements. The scalp nerve block resulted in good intraoperative haemodynamic stability and reductions in the required doses of anaesthetics and opioids. Additionally, the outcomes of levobupivacaine scalp blocks in paediatric patients were evaluated in a case series of three patients who received the blocks before craniotomy.[17] Levobupivacaine resulted in good haemodynamic stability and reduced the need for opioids during the first 24 hours. In line with these previous findings, the present study revealed better intraoperative haemodynamics in the levobupivacaine than control group as evidenced by the significantly lower MAP and HR during head pinning and incision.

Moreover, similar to previous studies, the additional intraoperative drug requirement in the control group was significantly higher than that in both the bupivacaine and levobupivacaine groups.

There is concern about the incidence and severity of pain after craniotomy,[4] but the ideal analgesic for postoperative pain after craniotomy is not yet available.[20] Nguyen et al.[4] evaluated 30 patients who were randomised to receive a scalp block with either ropivacaine or normal saline. Over a 48-h postoperative period, the pain scores were lower after ropivacaine infiltration; however, the time to first rescue analgesic administration and the need for rescue drugs differed between the two groups. More recently, Ayoub et al.[21] evaluated the efficacy of transitional analgesia with either a scalp nerve block or morphine after remifentanil-based anaesthesia in 50 patients undergoing craniotomy. They reported that the quality of transitional analgesia and postoperative haemodynamics obtained by the scalp block were similar to those obtained by morphine; however, morphine administration was associated with a higher incidence of nausea and vomiting. In a study by Bala et al.,[22] patients who underwent supratentorial craniotomy (n = 40) were randomised to receive a scalp block with either bupivacaine or placebo after skin closure; as a rescue analgesic, either intramuscular diclofenac or intravenous tramadol was given. The authors reported that the patients who did not receive a scalp block experienced moderate to severe pain more frequently and thereby required rescue medication at a higher rate; after 6 h postoperatively, however, their pain scores were similar to those of the patients who received a scalp block. In a recent study, Hwang et al.[15] tested the efficacy of levobupivacaine scalp blocks on patient recovery in a prospective, randomised, double-blind study. The levobupivacaine block or saline injection was performed after surgery when the patient was still under general anaesthesia, and patients were compared with controls in terms of postoperative pain control. The postoperative pain scores and pain-controlled analgesia consumption were lower, and the time from recovery to the first use of patient-controlled analgesia and rescue analgesics were longer in the levobupivacaine group than control group. In addition, antihypertensive agent use was lower and postoperative nausea and vomiting was less frequent in the scalp block group. Thus, the scalp block with levobupivacaine immediately after the operation resulted in a better postoperative recovery profile. In the present study, the VAS scores were not significantly different among the groups after the second postoperative hour. We believe that performance of the scalp block 5 min before head pinning shortened the postoperative analgesic efficacy and the patients' postoperative unconsciousness limited the evaluation of postoperative pain.

The scalp is a highly vascularized tissue, and this characteristic can increase the risk of local anaesthetic toxicity. In the present study, no intraoperative or postoperative local anaesthetic-related toxicity was observed. However, the QTc interval was not monitored and the blood levels of the drugs were not measured, both of which may represent important limitations of this study. Further studies are needed to examine and compare the toxicity profiles of the two agents.

In conclusion, scalp blocks may preserve the haemodynamic profile by blunting the sympathetic responses to intraoperative stimulation and decreasing the severity of pain in the early postoperative period. The clinical effects of bupivacaine and levobupivacaine were similar, and no significant difference was observed between their postoperative analgesic effects. Therefore, levobupivacaine, which is known to be less toxic than bupivacaine, could be safely and effectively used for scalp blocks.

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## Declaration of conflicting interest

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