Original Article

Comparison of Analgesic Effect of Levobupivacaine with Dexmedetomidine and Levobupivacaine for Scalp Block before Supratentorial Craniotomy: A Randomized Controlled Trial

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Background: Craniotomy causes acute and chronic pain. Uncontrolled postoperative pain may lead to adverse events. Perioperative scalp nerves block is not only effective in reducing intraoperative hemodynamic response, but it also reduces postoperative pain and postoperative analgesia requirement.

Objective: To compare the benefits of adding dexmedetomidine to levobupivacaine in scalp nerves block before craniotomy for the duration of analgesia in supratentorial craniotomy.

Materials and Methods: After approval by the Committee for Research, 50 supratentorial craniotomy patients were randomized into two groups. The control group received 30 mL scalp nerves block with 0.25% levobupivacaine with adrenaline 1:200,000, whereas the study group received 30 mL scalp nerves block with 0.25% levobupivacaine with adrenaline 1:200,000 plus dexmedetomidine 1 mcg/kg. The primary outcome was the time to first analgesic requirement postoperatively. The secondary outcomes included intraoperative fentanyl consumption, verbal numerical rating scale, tramadol consumption, and complications during the first 24 hours postoperatively.

Results: Patients in the study group had significantly increase time to the first analgesic requirement in postoperative period and reduced intraoperative fentanyl consumption. The median time to first analgesic requirement was 555 (360 to 1,035) minutes in the study group versus 405 (300 to 520) minutes in the control group (p=0.023). Intraoperative fentanyl consumption 125 (75 to 175) mcg in the study group was significantly lower than 200 (150 to 250) mcg in the control group (p=0.02). The verbal numerical rating scale at 1, 4, 8, 12 and 24 hours postoperatively, tramadol consumption, and complications during the first 24 hours postoperatively were not statistically significant different.

Conclusion: Preoperative scalp nerves block with 0.25% levobupivacaine with adrenaline (1:200,000) with dexmedetomidine 1 mcg/kg significantly increased the time to first analgesic requirement and reduced intraoperative fentanyl consumption compared to 0.25% levobupivacaine with adrenaline (1:200,000) without perioperative complications.

Keywords: Scalp block, Dexmedetomidine, Post-craniotomy analgesia, Supratentorial tumor, Levobupivacaine

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Brain tumors had a prevalence of 25.04 per 100,000 population in 2014 in Thailand[1]. The current treatment of brain tumor is craniotomy. Studies have shown that brain surgery causes acute (moderate to severe) and chronic pain[2]. Uncontrolled postoperative pain may lead to arterial hypertension, nausea and vomiting, restlessness, increased intracranial hypertension, postoperative intracranial hemorrhage, prolonged hospital stay, and increased healthcare expenditures[3-5]. For these reasons, postoperative pain control is essential in neurosurgery.

There are many techniques to reduce postoperative pain, such as local anesthetics infiltration, scalp

nerves block, opioids and non-opioid analgesics that include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentin, and dexmedetomidine[6]. Opioids that are commonly used to reduce postoperative pain, should be used with caution because of their side effects, which include nausea, vomiting, itching, urinary retention, respiratory depression, and brain edema[7].

Scalp nerves block is effective in reducing hemodynamic response during skull pinning and surgery[8], reducing postoperative pain and decreasing postoperative analgesia requirement[9] for approximately 12 hours[10]. There are many techniques to increase the duration of analgesia of scalp nerves block such as using longer-lasting local anesthetics and adding adjuvant to the local anesthetic[11].

Dexmedetomidine, a potent alpha-2 adrenergic receptor agonist, provides anxiolysis, analgesia, sedation without respiratory depression and hemodynamic stability[12,13]. Esmaoglu et al reported that adding dexmedetomidine to local anesthetic drugs would increase the duration of analgesia[14], Memis et al found that adding dexmedetomidine to local anesthetic drugs for intravenous regional anesthesia would reduce the visual analog scale (VAS) pain scores, decrease intraoperative analgesia requirement, and prolong time to first analgesic requirements and duration of postoperative pain[15].

Objective

The aim of the present study was to compare the effect of levobupivacaine with dexmedetomidine and levobupivacaine for scalp block before craniotomy to reduce postoperative pain in supratentorial craniotomy.

Materials and Methods

The present study approved by The Committee for Research, Faculty of Medicine Ramathibodi Hospital Mahidol University (COA No. MURA2019/399), was a prospective, single center, randomized controlled trial between June 2019 and December 2019 for supratentorial craniotomy. The clinical trial number was TCTR20200317002. Inclusion criteria were patients 1) 18 to 65 years old, 2) the American Society of Anesthesiologist (ASA) classification I-III, 3) elective supratentorial craniotomy, and 4) first time of supratentorial craniotomy. Exclusion criteria were patients 1) that refuse to participate, 2) chronic pain, 3) allergy to local anesthetic drugs and dexmedetomidine, 4) allergy to tramadol, 5) taking B-blockers, 6) systolic blood pressure of less than 90 mmHg and heart rate of less than 50 bpm before surgery, 7) coagulopathy, and 8) scalp infection.

To calculate the sample size, the Esmaoglu et al[14] study was used and their time to first dose of analgesia of the levobupivacaine group of patients was 108.7±164.04 minute. In the authors' review of Vallapu et al[16] study, dexmedetomidine 1 mg/kg added to levobupivacaine would increase the time to first analgesia by 150 minutes. Considering a two-tailed alpha of 5% and a statistical power of 80% for the study, nineteen patients should be included in both groups. Assuming a dropout rate of approximately 20%, 25 patients were required in each group.

During the preoperative visit, the anesthesiologist discussed the benefits and side effects with the patients and the verbal numerical rating scale was explained to the patients. They were taught on how to verbalize the pain on a scale of 10 points scale (0 point=no pain and 10 point=the worst pain imaginable). On the morning of the surgery, sedative premedication was not given to all the patients.

Fifty adult signed the written informed consents for the study. Patients were randomly allocated into two groups by using computer generated randomization, the dexmedetomidine group (DG) and the levobupivacaine group (PG).

The patient was inducted after standard monitoring and A-line was done after intubation. All patients received fentanyl 1 to 2 mcg/kg, propofol 1 to 2 mg/kg and atracurium 0.5 mg/kg or cisatracurium 0.2 mg/kg for intubation. The urinary catheter was inserted after tracheal intubation.

After tracheal intubation, scalp nerves block technique described by Pinosky et al[17] was performed 10 minutes before skull pinning by an anesthesiologist.

Group DG received 30 mL scalp nerves block bilaterally with 0.25% levobupivacaine with adrenaline 1:200,000 plus dexmedetomidine 1 mcg/kg.

Group PG received 30 mL scalp nerves block bilaterally with 0.25% levobupivacaine with adrenaline 1:200,000.

The supraorbital nerve was blocked with 1.5 mL of local anesthetic solution above the supraorbital notch, with the needle perpendicular to the skin and the supratrocheal nerve was blocked with 1.5 mL of local anesthetic solution. The auriculotemporal nerve was blocked with 2 mL of local anesthetic solution, 1.5 cm anterior to the tragus of the ear with the needle perpendicular to the skin. The zygomaticotemporal nerve was blocked between auriculotemporal and

supraorbital nerve with 2 mL of local anesthetic solution[18]. The postauricular branches of the greater auricular nerve was blocked 1.5 cm posterior to the tragus of the ear with 2 mL of local anesthetic solution. The greater and lesser, occipital nerves were blocked with infiltration along the superior nuchal line between the occipital protuberance and the mastoid process with 6 mL of local anesthetic solution. Scalp block was done bilaterally with total volume of 30 mL.

Blood pressure and heart rate ware reported at 5-minute and 10-minute after scalp block, before skull pinning, after skull pinning, and at post-anesthetic care unit (PACU).

Anesthesia was maintained by oxygen, air, sevoflurane, fentanyl, atracurium or cisatracurium. Ondansetron 8 mg intravenous was administered 30 minutes before the end of the surgery. Muscle relaxant was reversed with atropine 0.02 mg/kg and neostigmine 0.05 mg/kg intravenous, and the patients were extubated as standard extubation criteria.

All the patients were monitored at PACU for at least one hour and were monitored in the neurosurgical intensive care unit for at least 24 hours postoperatively. The intubated patients after surgery were excluded from the study. Postoperative analgesia was maintained with 50 mg tramadol intravenously when the patient requested or verbal numerical rating scale greater than 4.

The verbal numerical rating scale was recorded if the Glasgow Coma Score (GCS) was greater than 14 by the research team at the 1, 4, 8, 12, and 24 hours postoperatively. Patients were given the first dose of postoperative analgesia when verbal numerical rating scale was greater than 4 or when the patients requested. The patient, surgeon, and evaluation nurses were blind to the group. Tramadol consumption during the first 24 hours postoperatively was recorded. Postoperative complications due to scalp nerves block and tramadol medication, including hypotension, bradycardia, respiratory depression, nerve injury, nausea, vomiting, itching, and sedation were recorded for 24 hours postoperatively. Nausea is a condition in which the patients feel uncomfortable and need to vomit, defined by a scale with 0=absent, 1=nausea and 2=nausea and vomiting. Sedation was assessed, defined by absent=awake until a little sleepy but easy to wake up, present=response to light tactile stimuli until no response.

The surgeons, patients and assessors were blinded to the study but the anesthesiologist who did the scalp block did not blind to the patient groups.

The primary outcome was the time to first analgesic requirement postoperatively, Secondary outcomes were intraoperative fentanyl consumption, verbal numerical rating scale at 1, 4, 8, 12 and 24 hours postoperatively, tramadol requirement during the first 24 hours postoperatively and complications during the first 24 hour postoperatively included hypotension (systolic blood pressure of less than 90 mmHg), bradycardia (heart rate of less than 50 bpm), nerves injury, nausea and vomiting, itching, and sedation.

Statistical analysis

Continuous data were analyzed as mean ± standard deviation (SD), median and tested with student t-tests or Mann-Whitney U test. Categorical data were compared using chi-square test or Fisher's exact test. Interval data were compared using repeated measures analysis of covariance (ANCOVA). Data were expressed as the median (interquartile range). Values of p-value of less than 0.05 was considered significant.

Results

Fifty patients were enrolled and followed-up in the present randomized control study and included 25 patients in each group (presented in Figure 1). Seven patients were not analyzed because two had intraventricular hemorrhage and one was unconscious at the end of anesthesia in group DG, and one had intraoperative massive bleeding and three were unconscious at the end of anesthesia in group PG. The remaining 43 patients were analyzed. The patients' demographics, ASA physical status, underlying diseases, duration of anesthesia, anticonvulsant, and corticosteroid administration were similar in both groups (Table 1). Female gender, body mass index (BMI) were significantly higher in the group PG than in DG.

The median time to the first analgesic requirement (555 versus 405 minutes) was significantly longer in the group DG compared to the group PG (p=0.023). Intraoperative fentanyl consumption was significantly lower in the group DG (75 to 175 mcg) compared to the group PG (150 to 250 mcg) (p=0.020) (Table 2).

The VAS scores at 1, 4, 8, 12 and 24 hours postoperatively were not statistically significant different between the groups (p=0.367) (Figure 2). The SBP, DBP and heart rates at 5 and 10 minutes after scalp nerves block, before skull pinning, after skull pinning, and at PACU were not statistically significant in both groups (p=0.474, p=0.221 and p=0.668, respectively) (Figure 3, 4). Postoperative

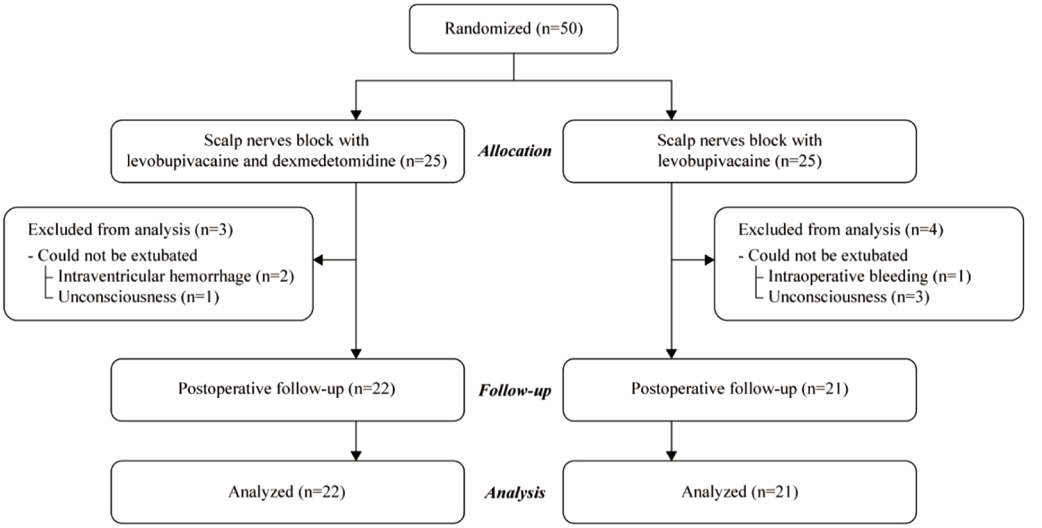

Figure 1. Flowchart of the patients in the present study.

Table 1. Patients' demographics and anesthetic data

	DG (n=22) n (%)	PG (n=21) n (%)	p-value
Sex (female/male)	11/11	17/4	0.033*
Age (years); mean±SD	48.23±14.31	50.62±8.66	0.514
Body weight (kg); mean±SD	60.9±118.86	64.2±14.43	0.525
Height (cm); mean±SD	162.95±10.62	157.48±7.53	0.058
Body mass index (kg/m^2); mean±SD	22.55±4.5	25.74±4.64	0.028*
ASA physical status (2/3)	10/12	10/11	0.887
Diabetes mellitus	3 (13.64)	6 (28.57)	0.281
Hypertension	6 (27.27)	7 (33.33)	0.665
Corticosteroid used	10 (45.45)	12 (57.14)	0.443
Anticonvulsant drug	11 (50.00)	10 (47.62)	0.876
Duration of anesthesia (minute); median (IQR)	255 (210 to 330)	300 (240 to 375)	0.122

DG=dexmedetomidine group; PG=levobupivacaine group; ASA=American Society of Anesthesiologists; SD=standard deviation; IQR=interquartile range

* p<0.05, statistically significant

Table 2. Intraoperative fentanyl and time to 1st rescue analgesia post operatively

	DG (n=22) Median (IQR)	PG (n=21) Median (IQR)	p-value
Intraoperative fentanyl (mcg)	125 (75 to 175)	200 (150 to 250)	0.020*
Time to 1st rescue analgesia post operatively (minute)	555 (360 to 1,035)	405 (300 to 520)	0.023*

DG=dexmedetomidine group; PG=levobupivacaine group; IQR=interquartile range

All outcome analyses in this table were adjusted for sex and BMI using linear regression

* p<0.05, statistically significant

Table 3. Post-operative analgesic consumption and side effects

	DG (n=22)	PG (n=21)	p-value
Tramadol dosage in 24 hours (mg); median (IQR)	75 (50 to 100)	100 (50 to 100)	0.462
Side effects in 24 hours; n (%)			
Hypotension	-	-	-
Bradycardia	-	-	-
Nerve injury	-	-	-
Nausea/vomiting			0.646
• 0=absent	20 (90.91)	18 (85.71)	
• 1=nausea	1 (4.55)	3 (14.29)	
• 2=nausea and vomiting	1 (4.55)	0 (0.00)	

DG=dexmedetomidine group; PG=levobupivacaine group; IQR=interquartile range

Analysis of tramadol consumption difference were adjusted for sex and BMI using linear regression

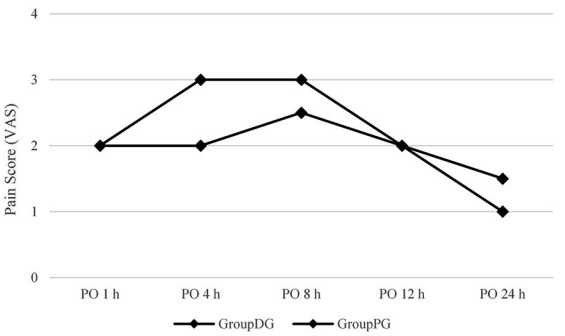

Figure 2. Postoperative pain scores between two groups. Pain was assessed using repeated-measures ANCOVA* models incorporating sex, and BMI as covariates.

* ANCOVA (analysis of covariance) was used to control two variables (gender and sex) which were significantly different in the two study groups and may affect the authors' repeated measurement such as pain scores

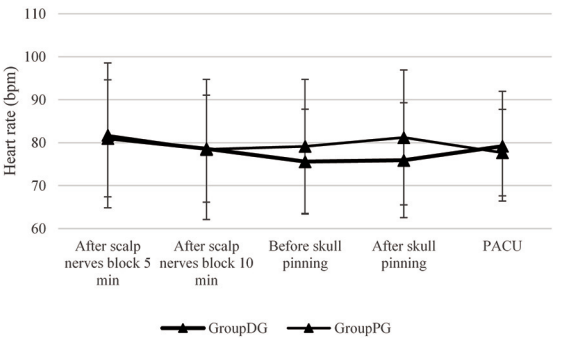

Figure 3. Perioperative heart rate between two groups. Heart rate was assessed using repeated-measures ANCOVA models incorporating sex, and BMI as covariates.

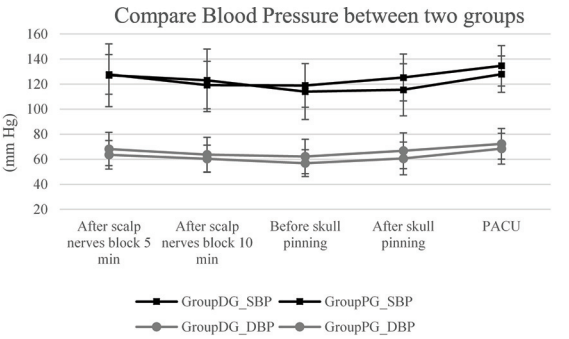

Figure 4. Perioperative blood pressure between two groups. Blood pressures were assessed using repeated-measures ANCOVA models incorporating sex, and BMI as covariates.

tramadol consumption was not statistically significant in both groups (p=0.462) (Table 3).

Complications during the first 24 hours postoperatively are presented in Table 3. None of the patients were presented with hypotension, bradycardia, nerve injury, itching, and sedation postoperatively. Nausea or vomiting occurred in two patients in group DG and three patients in group PG, which was not statistically significant (p=0.646).

Discussion

The present study showed that scalp nerves block in patients who underwent supratentorial craniotomy with 0.25% levobupivacaine with adrenaline (1:200,000) and dexmedetomidine (1 mcg/kg) increased the median time to the first analgesic requirement by 555 (360 to 1,035) minutes versus 405 (300 to 520) minutes, and reduced intraoperative fentanyl consumption by 125 (75 to 175) mcg versus 200 (150 to 250) mcg when compared to 0.25% levobupivacaine with adrenaline (1:200,000) group.

Uncontrolled postoperative pain may lead to adverse effects[3-5]. Tsaousi et al[19], showed that 60% of post craniotomy patients had moderate to severe pain in the early postoperative, or chronic postoperative pain but there were no definite recommended interventions to reduce post craniotomy pain.

Scalp block is not only effective in reducing intraoperative hemodynamic response, it also reduces postoperative pain and postoperative analgesia requirement[8,9]. Many studies have shown the analgesic effect of scalp nerves block. Guilfoyle et al[10] found that preoperative scalp block had significantly decreased in pain scores up to four hours postoperatively and had a significantly decrease in pain score up to 12 hours postoperatively when scalp block was used at the end of surgery. There was a significant reduction in the narcotics requirement in the scalp block at the first 24 hours postoperatively[10]. Hwang et al[9] found that scalp block with levobupivacaine after surgery decreased postoperative pain and PCA consumption. Akcil et al[20] found a similar outcome that 20 mL scalp block with 0.5% bupivacaine decreased morphine consumption in postoperative 24 hours in infratentorial craniotomy. In the present study, the authors chose 0.25% levobupivacaine for scalp nerves block because it increases the duration and has less systemic toxicity.

Dexmedetomidine, a potent alpha-2 adrenergic receptor agonist, which is found in Locus Ceruleus, provides anxiolysis, analgesia, and sedation without respiratory depression[12,13]. This mechanism of dexmedetomidine inhibits the release of norepinephrine and terminates the propagation of pain signals leading to analgesia[13]. Dexmedetomidine prolongs the duration of analgesia by hyperpolarization-activated cation current, which produce a selective sensory effect in C-fibers than in A alpha fibers[21]. The scalp is highly innervated by C fiber, which can explain the mechanism. In many studies, the effect of adding dexmedetomidine to local anesthetic agent or peripheral nerves block have been found to prolong the duration of analgesia. Esmaoglu et al[14] found that dexmedetomidine added to levobupivacaine for axillary brachial plexus block shortened the onset and prolonged the duration of the block and postoperative analgesia as compared to levobupivacaine alone. Agarwal et al[22] have found similar effects from dexmedetomidine added to bupivacaine for supraclavicular brachial plexus block significantly shortened the onset time and prolonged the duration of analgesia.

Vallapu et al[16] found that the addition of dexmedetomidine (1 mcg/kg) to 0.25% bupivacaine with 20 mL in scalp block after the closure of scalp incision prolonged the pain-free period and the rescue analgesic requirement was significantly lower in dexmedetomidine group. The pain-free period was 12 (8 to 16) hours in group BDNB (scalp block with bupivacaine and dexmedetomidine) compared to 8 (8 to 12) hours in group BDI (incision site infiltration with bupivacaine and dexmedetomidine) and 4 (4 to 8) hours for group BI (incision site infiltration with bupivacaine). El-Aziz et al[11] studied the addition of dexmedetomidine (1.5 mcg/kg) to 0.5% levobupivacaine with a volume of 36 mL in scalp nerves block in supratentorial craniotomy. They found that in group of dexmedetomidine with levobupivacaine, the duration of analgesia was increased and gave better postoperative hemodynamic control. The VAS was significantly different at 16 hours and 24 hours postoperative (VAS at 16 hours was 3 (2 to 4) in dexmedetomidine group and 5 (3 to 5) in control group, VAS at 24 hours was 4 (3 to 5) in dexmedetomidine group and 5 (4 to 5) in control group, $p<0.001$). Heart rate and mean arterial blood pressure of two groups at 5 minutes, 4, 8, 16 and 24 hours after extubation were significantly different. In the present study, the authors used 0.25% levobupivacaine with adrenaline 1:200,000 and dexmedetomidine 1 mcg/kg with a volume 30 mL instead of 0.5% levobupivacaine with dexmedetomidine 1.5 mcg/kg with a volume 36 mL as El-Aziz et al[11] study. The mean patient weight of the present study was 60.91±18.86 kg in group DG and 64.2±14.43 kg in group PG that 0.5% levobupivacaine 36 mL could lead to local anesthetic systemic toxicity. The time to the first analgesic requirement in the study group was 9.25 hours (6 to 17.25 hours) and in the control group was 6.75 hours (5 to 8.67 hours) that was significantly different. The SBP, DBP, and heart rate were comparable and were not significantly different.

The intraoperative fentanyl consumption in the study group (125 mcg) was significantly different from the control group (200 mcg). Tramadol requirement and complications during the first 24 hours postoperatively were comparable and were not significantly different.

Dexmedetomidine may lead to adverse effects include hypotension and bradycardia[12,13]. In the present study, there was no incidence of hypotension and bradycardia in the 24 postoperative hours.

There are many options for perioperative pain management in neurosurgery. Opioids are commonly used for moderate to severe pain, but their side

effects include respiratory depression, hypercapnia, cerebral edema, and increased intracranial pressure[23]. Tramadol is an option for mild to moderate pain. Rahimi et al[24] found that the addition of tramadol with acetaminophen for pain management after craniotomy could produce better pain control and decrease the side effects of narcotics. Sudheer et al[25] found that vomiting and retching occurred in 50% of patients with tramadol compared with 20% of patients with morphine and 29% of patients with codeine. In the present study, as the authors used tramadol for postoperative pain management, nausea and vomiting occurred in five patients in both groups. Both groups were treated with metoclopramide. Other options of nonopioids include NSAIDs and paracetamol. William et al[26] found that administration of intravenous parecoxib at dural closure did not significantly reduce morphine consumption or pain intensity for the 24 hours after surgery without major morbidity. Sivakumar et al[27] found that postoperative administration of intravenous acetaminophen did not have significantly reduce the opioids consumption in supratentorial craniotomy. Multimodal analgesia is often required to manage postoperative craniotomy pain. Scalp block is a good adjunct in multimodal analgesia for supratentorial craniotomy.

Limitation

There were some limitations in the present study. The bias may come from the anesthesiologist who did the scalp block and were not blinded to the patient groups. Even though they did not evaluate the pain score, the nurses who evaluated the verbal numerical rating scale at the neurosurgical intensive care unit postoperatively were not the same person.

Conclusion

Preoperative scalp nerves block with 0.25% levobupivacaine with adrenaline (1:200,000) with dexmedetomidine 1 mcg/kg increased time to the first analgesic requirement post supratentorial craniotomy compared to 0.25% levobupivacaine with adrenaline (1:200,000) and reduced intraoperative fentanyl consumption. The authors recommend 0.25% levobupivacaine with adrenaline (1:200,000) with dexmedetomidine 1 mcg/kg after induction as a multimodal analgesia for supratentorial craniotomy.

What is already known on this topic?

Postoperative scalp block with levobupivacaine with dexmedetomidine increased duration of analgesia and gave better postoperative hemodynamic control.

What this study adds?

Preoperative scalp block with 0.25% levobupivacaine with adrenaline (1:200,000) with dexmedetomidine 1 mcg/kg increased time to the first analgesic requirement compared to 0.25% levobupivacaine with adrenaline (1:200,000) and reduced intraoperative opioids consumption, even though the pain score and tramadol consumption do not show a difference. Therefore, giving dexmedetomidine along should benefit the first 10 hours after the operation, with a dose of levobupivacaine that does not exceed the systemic toxic dose.

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Conflicts of interest

The authors declare no conflict of interest.

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