Comparison of Dexmedetomidine Infusion versus Scalp Block with 0.5% Ropivacaine to Attenuate Hemodynamic Response to Skull Pin Insertion in Craniotomy: A Prospective, Randomized Controlled Trial

Georgene Singh¹ Ganesamoorthi Arimanikam^{2,✉} Karen R. Lionel¹ Smita V.³ Bijesh Yadav⁴
Appavoo Arulvelan^{5,✉} Manikandan Sethuraman³

¹Department of Neuroanaesthesiology, Christian Medical College, Vellore, Tamil Nadu, India

²Department of Anaesthesiology, Meenakshi Hospital, Thanjavur, Tamil Nadu, India

³Department of Neuroanaesthesiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India

⁴Department of Biostatistics, Christian Medical College and Hospital, Vellore, Tamil Nadu, India

⁵Department of Anaesthesiology, Apollo Hospital, Chennai, Tamil Nadu, India

Address for correspondence Georgene Singh, DM, Department of Neuroanaesthesiology, Christian Medical College, Ida Scudder Road, Vellore 632004, Tamil Nadu, India
(e-mail: georgenesingh@gmail.com).

J Neuroanaesthesiol Crit Care 2021;8:180–186.

Abstract

Background The insertion of the skull pin head holder to stabilize the head during neurosurgery causes significant periosteal stimulation, resulting in hemodynamic responses, which may lead to brain edema, intracranial hypertension, and hemorrhage in patients with intracranial space-occupying lesions and intracranial aneurysms. We compared the efficacy of dexmedetomidine infusion and 0.5% ropivacaine scalp block in attenuating the hemodynamic response to the skull pin application.

Methods A total of 65 American Society of Anesthesiologists (ASA) class I and II patients aged between 18 and 65 years with a preoperative Glasgow Coma Scale score of 15 undergoing elective craniotomy were randomized to receive either a bolus of 1 mcg/kg of dexmedetomidine followed by an infusion of 1 mcg/kg/hour (group D) or a scalp block with 0.5% ropivacaine (group S) in a single-blinded comparator study. Patients were monitored for the following hemodynamic changes following skull pin insertion: heart rate (HR), mean arterial pressure (MAP), the requirement of additional analgesia/anesthesia, and adverse events.

Results HR and MAP were comparable between the groups at baseline, before induction, and before pin insertion. HR and MAP at 1, 2, and 3 minutes after skull pin insertion were significantly higher in group D as compared with group S ($p < 0.05$) and were comparable between the groups at 5 minutes. The groups were comparable with respect to the requirement of additional analgesia, anesthesia, and incidence of adverse events.

Conclusion Scalp block with 0.5% ropivacaine is effective and superior to dexmedetomidine in attenuating the hemodynamic response to skull pin insertion in ASA I and II neurosurgical patients undergoing craniotomy. However, the hemodynamic effects achieved with dexmedetomidine were within the permissible limits.

Keywords

- ropivacaine
- scalp block
- dexmedetomidine
- hemodynamic response

published online
September 17, 2020

DOI <https://doi.org/10.1055/s-0040-1715710>
ISSN 2348-0548.

© 2020. Indian Society of Neuroanaesthesiology and Critical Care.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).
Thieme Medical and Scientific Publishers Pvt. Ltd. A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

The application of the skull pins to stabilize the head during neurosurgical procedures produces an intense nociceptive stimulus, resulting in abrupt increases in blood pressure and cerebral blood flow. These hemodynamic responses may lead to brain edema and an increase in intracranial pressure (ICP) especially in patients with impaired autoregulation.^{1,2}

Various techniques and drugs have been employed to attenuate the hemodynamic response with variable success. They include premedication with clonidine,³ gabapentin,⁴ pin-site infiltration with a local anesthetic,^{5,6} intravenous (IV) drugs such as barbiturates, opioids, lidocaine, β -blockers, subanesthetic doses of ketamine, IV α -2 agonists, scalp block, and various combinations of these in addition to providing a good plane of anesthesia with inhalation anesthetics.⁶⁻¹¹

A scalp block with local anesthetic is an effective and established method in reducing the sympathetic response to the insertion of the skull pins.¹¹ However, the disadvantages of the scalp block include multiple scalp injections, an increase in anesthesia time, and the possibility of nerve-sparing.

Dexmedetomidine, a selective α -2-adrenoceptor agonist, has sedative, analgesic, and anesthetic-sparing effects, and it decreases heart rate (HR), mean arterial pressure (MAP), and sympathetic nervous system activity in a dose-dependent fashion.¹² It is being used commonly in neurosurgical patients as an adjuvant drug for the maintenance of anesthesia and analgesia.^{13,14} It has also been shown to attenuate the hemodynamic response to the insertion of pins during neurosurgery.¹⁰

In our study, we compared the effectiveness of dexmedetomidine infusion and scalp block with ropivacaine in attenuating the hemodynamic response to skull pin application in neurosurgical patients. We hypothesized that the infusion of dexmedetomidine would provide comparable hemodynamic stability as the scalp block in obtunding the hemodynamic response.

Methods

Participants

A total of 65 American Society of Anesthesiologists (ASA) class I and II patients aged between 18 and 65 years of both genders with a preoperative Glasgow Coma Scale score of 15 were recruited. Patients with preoperative HR < 45 beats per minute (bpm), first- or second-degree heart blocks, known allergy to local anesthetics or dexmedetomidine, on treatment with β -blockers, left ventricular dysfunction, pregnancy, intracranial aneurysms, patient refusal, and redo craniotomies were excluded. The principal investigator discussed the details of the study with the patient on the night before the surgery, and written informed consent was obtained from the patient in their regional language.

Study Design

No sedative premedication was administered to either group. Standard monitoring with a pulse oximeter and three-lead electrocardiogram (ECG) was established at baseline (BL).

Invasive blood pressure monitoring was established by cannulating the radial artery under local anesthesia.

Patients were randomized into two groups to receive either dexmedetomidine (Dexem, Themis Medicare) infusion (group D) or scalp block with 0.5% ropivacaine (group S). Stratified block randomization was allocated by a biostatistician, not directly involved in the study, using the SAS software (SAS Institute Inc.). The randomization sequence was handed over to the attending anesthesiologist. The patients and the investigators were blinded to the drug/technique administered. The randomization code was confidentially preserved and unblinded at the end of the study.

Patients in group D were given a bolus dose of dexmedetomidine (1 μ g/kg) as an infusion over 10 minutes at baseline (BL). A maintenance dose of 1 μ g/kg/hour was continued from the time of induction until 5 minutes after pinning, which was the duration of the study.

Induction of anesthesia was achieved with a standard induction protocol for all patients with propofol (2 mg/kg), fentanyl (2 mcg/kg), and vecuronium (0.15 mg/kg). After endotracheal intubation, end-tidal carbon dioxide (etCO₂) and end-tidal isoflurane monitoring was established. Anesthesia was maintained with 0.8 MAC (minimum alveolar concentration) of sevoflurane with an FiO₂ (fraction of inspired oxygen) of 50%. The patient's ventilation was controlled to maintain etCO₂ between 33 and 38 mm of Hg.

In the patients assigned to group S, a bilateral scalp block was performed with 30 mL of 0.5% ropivacaine, 15 mL on each side, by the principal investigator soon after endotracheal intubation. The technique described by Pinosky et al was followed.¹¹ Skull pins were applied 5 minutes after completion of the block and the head was fixed on a Mayfield clamp (Integra LifeSciences) by the neurosurgeon.

Outcome Measures

All observations were recorded by a physician using the multiparameter monitor, who was blinded to the group adopted by the attending anesthesiologist. The hemodynamic responses such as HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial blood pressure (MAP) were recorded at BL (soon after establishing monitoring), BL before induction of anaesthesia (BL) (that is after obtaining IV access in group S and after the bolus dose of dexmedetomidine infusion in group D) at 1 minute before application of skull pins (BP) and at 0, 1, 2, 3, 4, and 5 minutes after pinning (T0, T1, T2, T3, T4, T5).

In both the groups, any rise in the HR or MAP, more than 20% of BL, was treated immediately with one of the following three options as per the discretion of the attending anesthesiologist: bolus of fentanyl 1 μ g/kg or bolus injections of propofol 1 mg/kg or by increasing concentration of the volatile agent to 1 MAC.

Bradycardia was defined as HR < 50 bpm, tachycardia as a > 20% increase from BL in HR, hypertension as a > 20% increase from BL in MAP, and hypotension as < 20% decrease from BL in MAP.

Bradycardia was treated by the administration of atropine 0.6 mg. Hypotension was treated by the administration

of 5-mg boluses of ephedrine. Refractory hypotension was defined as hypotension requiring more than three boluses of ephedrine and more than 500 mL of crystalloid.

Patients were also monitored for adverse events such as intravascular injection of ropivacaine, anaphylaxis, refractory hypotension, refractory bradycardia, refractory tachycardia, hypotension, or hypertension with the use of dexmedetomidine.

Any adverse event was immediately reported to the primary investigator, and the patient was withdrawn from the study.

Statistical Analysis

Assuming that an increase in the HR of up to 5 bpm from the BL in patients receiving dexmedetomidine infusion will be comparable with that of the ropivacaine group and a standard deviation (SD) of 8 in both arms, 32 patients requiring skull pin application for the fixation of head-on Mayfield clamp were recruited in each arm to provide 80% power and a 5% α error. The data were entered in Microsoft Excel and analyzed using SPSS Version 25.0 (IBM Corp.). Summary statistics were used for reporting demographic and clinical characteristics. All categorical variables were reported using frequencies and percentages, and continuous variables were expressed in terms of mean $\pm$ SD or median (interquartile range). The categorical variables between the groups D and S were compared using the Fisher exact test. The follow-up variables HR, SBP, MAP, and DBP were analyzed using the GEE (generalized estimating equation). The GEE has been used to assess for any statistical significance from BL to T0–T5 (7 time points BL, T0–T5). Differences were considered significant at $p < 0.05$.

Results

Between May 2011 and September 2012, 65 patients were enrolled, of which 31 patients were randomized to group D and 34 patients to group S. ►Fig. 1 depicts the CONSORT (Consolidated Standards of Reporting Trials) flowchart for the study participants. The patients in both groups were comparable with respect to the age, weight, gender, and ASA class (►Table 1).

Heart Rate

The changes in the mean HR over time in the two groups are depicted in ►Table 2 and ►Fig. 2. In group D, the BL mean HR was 78.35 bpm. The mean HR at BP was 76.94 bpm. After the insertion of pins, there was a statistically significant increase in HR from the first to the third minute (T1–T3) and returned to the BL thereafter (T4, T5).

In group S, the BL mean HR was 76.6 bpm and the mean HR at BP was 71.59 bpm. After the application of pins, there was no change in the HR from the start to the fifth minute (T0–T5) after pinning.

Blood Pressure

The variations in the blood pressure, MAP, SBP, and DBP, in the two groups are depicted in ►Table 2. The MAP, SBP, and

DBP recordings in the groups D and S at BL were comparable. In group D, the BL MAP was 97.8 mm Hg, and after the bolus administration of dexmedetomidine it was 92.35 mm Hg. There was no significant change in the MAP with the infusion of a bolus dose of dexmedetomidine, and the MAP values at BL and BP were comparable. Soon after the application of the skull pins, there was a statistically significant increase in the MAP in group D as compared with group S at T1, T2, and T3 (►Fig. 3) with a return to the BL at T4&T5. A similar trend was observed with the DBP as well with comparable values at BL and BP and significant increases at T1 to T3. There was no significant change in the SBP between the groups except at T2. GEE comparing group D and group S from the BL to T0–T5 was used, which shows a significant increase in HR, MAP, and DBP in group D (►Table 3).

Requirements of Additional Analgesia/Anesthesia

Additional boluses of fentanyl were required by four patients in group D and two patients in the group S, propofol was required for two patients in the group D and one patient in group S. One patient in group D required an increase in the concentration of inhalational anesthetic. Though the numbers of patients requiring additional analgesia/anesthesia were more in group D, it did not have statistical significance because of the small numbers in the study (►Table 4).

Adverse Hemodynamic Events

In group D, four patients had hypotension, four had hypertension, and two had tachycardia, whereas in group S, two patients had hypertension and one patient had tachycardia (►Table 4). This difference was not statistically significant. None of the patients developed refractory hypotension or other adverse events that required discontinuation of the study.

Discussion

In our study, we compared the effect of IV dexmedetomidine and a scalp block with 0.5% ropivacaine in attenuating the response to skull pin insertion. We observed that there was a statistically significant increase in the HR and MAP pressure in the first-, second-, and third-minute post skull pin insertion in group D as compared with group S. At the end of the fourth and fifth minutes, the HR and MAP returned to BL values and were comparable in both groups. Although there were four patients in the dexmedetomidine group and one patient in group S who had hypotension, the difference was not statistically significant. The hypotension may be due to the increased requirement of additional anesthetic and analgesic drugs to obtund the hypertensive response to pinning in group D. We did not observe any bradycardia in our study. The incidences of adverse hemodynamic events and requirements of additional analgesia were comparable between the groups.

The scalp is densely innervated with C-fibers.¹⁵ The hemodynamic response to skull pin insertion causes significant tachycardia and hypertension. Abnormal autoregulation exists in the peritumoral region, where a sudden increase

Fig. 1 CONSORT (Consolidated Standards of Reporting Trials) diagram depicting the flow of study patients.

Table 1 Demographic details

Variables	Group D, n = 31 (%)	Group S, n = 34 (%)
Gender	Male	18 (58.11)
	Female	13 (41.9)
Age (years)	Mean $\pm$ SD	40.03 $\pm$ 12.01
Weight (kg)	Mean $\pm$ SD	59.32 $\pm$ 10.99
ASA	Class I	23 (74.21)
	Class II	8 (25.81)

Abbreviations: ASA, American Society of Anesthesiologists; group D, dexmedetomidine; group S, scalp block; SD, standard deviation.

in blood pressure results in an increase in blood volume and blood flow, leading to increases in the ICP.^{2,16} In the past, administration of opioids to blunt the hemodynamic response to pin insertion in patients with brain tumors

was feared to cause an increase in ICP. However, Jamali et al demonstrated that the administration of narcotics does not alter ICP despite the increase in blood pressure caused by the skull pin insertion.¹⁷ These hemodynamic fluctuations are equally undesirable in those with coronary heart disease in whom the myocardium is vulnerable to hemodynamic stress response and may precipitate myocardial ischemia and pulmonary edema.¹⁸

Scalp block is quite effective in attenuating the hemodynamic^{10,19} and sympathoadrenal response²⁰ to skull pin insertion and in providing postoperative analgesia.²¹ Ropivacaine is a long-acting amide local anesthetic agent with a low potential for cardiotoxicity and central nervous system toxicity due to its reduced lipophilicity as compared with bupivacaine,²² making it an ideal drug for nerve blocks requiring large volumes and in areas such as the scalp, which are highly vascularized. Although both pin-site infiltration and scalp block are effective in attenuating the hemodynamic response

Table 2 Comparison of the hemodynamic variables between the two groups

Time	Group	HR (mean $\pm$ SD)	p-Value	SBP (mean $\pm$ SD)	p-Value	MAP (mean $\pm$ SD)	p-Value	DBP (mean $\pm$ SD)	p-Value
BL	D	78.35 $\pm$ 10.81	0.561	129.94 $\pm$ 13.97	0.59	97.83 $\pm$ 16.36	0.763	74.29 $\pm$ 12.11	0.65
	S	76.62 $\pm$ 12.96		127.65 $\pm$ 19.26		96.62 $\pm$ 15.79		75.97 $\pm$ 16.91	
BI	D	72.23 $\pm$ 10.71	0.926	127.39 $\pm$ 16.22	0.31	92.35 $\pm$ 12.65	0.655	74.29 $\pm$ 12.11	0.65
	S	71.94 $\pm$ 13.63		121.18 $\pm$ 29.62		90.62 $\pm$ 17.82		75.97 $\pm$ 16.91	
BP	D	76.94 $\pm$ 13.95	0.112	114.94 $\pm$ 21.93	0.94	86.81 $\pm$ 18.32	0.976	71.16 $\pm$ 16.03	0.80
	S	71.59 $\pm$ 12.82		114.53 $\pm$ 19.5		86.68 $\pm$ 16.24		70.24 $\pm$ 13.92	
T0	D	78.48 $\pm$ 14.98	0.087	119.29 $\pm$ 20.24	0.55	92.58 $\pm$ 16.42	0.403	76.39 $\pm$ 14.25	0.28
	S	72.50 $\pm$ 12.73		116.68 $\pm$ 14.54		89.50 $\pm$ 12.99		72.88 $\pm$ 11.78	
T1	D	81.94 $\pm$ 15.17	0.007 ^a	125.00 $\pm$ 18.69	0.09	97.61 $\pm$ 15.88	0.028 ^a	80.87 $\pm$ 13.86	0.03 ^a
	S	72.26 $\pm$ 12.58		117.71 $\pm$ 14.85		87.79 $\pm$ 18.93		73.71 $\pm$ 11.69	
T2	D	80.23 $\pm$ 15.17	0.015 ^a	125.23 $\pm$ 14.15	0.008 ^a	97.77 $\pm$ 11.09	0.003 ^a	81.13 $\pm$ 10.21	0.001 ^a
	S	71.70 $\pm$ 11.99		115.03 $\pm$ 15.51		88.29 $\pm$ 13.67		71.65 $\pm$ 12.23	
T3	D	77.00 $\pm$ 14.12	0.049 ^a	121.13 $\pm$ 16.65	0.07	94.26 $\pm$ 13.69	0.044 ^a	78.29 $\pm$ 12.83	0.01 ^a
	S	70.62 $\pm$ 11.49		113.41 $\pm$ 17.54		86.82 $\pm$ 15.27		69.88 $\pm$ 13.45	
T4	D	75.65 $\pm$ 13.4	0.077	118.45 $\pm$ 19.64	0.20	91.48 $\pm$ 15.21	0.097	75.68 $\pm$ 14.76	0.05
	S	70.12 $\pm$ 10.78		112.44 $\pm$ 17.59		85.18 $\pm$ 14.92		68.68 $\pm$ 13.31	
T5	D	75.00 $\pm$ 13.31	0.092	114.48 $\pm$ 17.54	0.39	87.39 $\pm$ 14.56	0.427	72.19 $\pm$ 12.60	0.19
	S	70.00 $\pm$ 10.16		110.82 $\pm$ 16.39		84.53 $\pm$ 14.26		68.00 $\pm$ 12.72	

Abbreviations: BI, before induction; BL, baseline; BP, before pinning; D, dexmedetomidine; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; S, scalp block; SBP, systolic blood pressure.

^aSignificant at $p < 0.05$.

Fig. 2 Graph comparing variation in heart rate (mean $\pm$ SD, in beats per minute) between the two groups with respect to various time points.

to skull pin insertion, scalp block is superior in controlling the hemodynamic response to skull pin insertion and has the added advantage that the neurosurgeon has the opportunity to reposition the pins without the need for further maneuvers to blunt the sympathetic response.²¹ In a recent study, Theerth et al have compared the analgesic nociceptive index in patients receiving scalp block and pin-site infiltration. They have shown that the scalp block reduced the autonomic response to the noxious stimulus of skull pin application better than the pin-site infiltration.²³

Fig. 3 Graph comparing variation in MAP (mean $\pm$ SD, in mm Hg) between the two groups with respect to various time points. Time points in the X-axis: BL, before induction of anesthesia (after obtaining intravenous access in the S group and after bolus administration of dexmedetomidine in the D group); BL, baseline (soon after establishing monitors) BP, 1 minute before application of skull pins; MAP, mean arterial pressure; T0, at application of skull pins; T1, 1 minute after application of skull pins; T2, 2 minute after application of skull pins; T3, 3 minute after application of skull pins; T4, 4 minutes after application of skull pins; T5, 5 minutes after application of skull pins.

The α -2 agonists are a new class of drugs, which produce effects both within the peripheral and central nervous

Table 3 Comparison of two interventions using the generalized estimating equation

Parameters	β	95% CI	p-Value
HR			
Group D	6.12	(0.37–11.87)	0.037 ^a
Group S	Reference		
SBP			
Group D	5.68	(-1.02 to 12.38)	0.096
Group S	Reference		
MAP			
Group D	5.74	(0.39–11.44)	0.048 ^a
Group S	Reference		
DBP			
Group D	5.44	(0.26–4.23)	0.039 ^a
Group S	Reference		

^aSignificant at $p < 0.05$.

Abbreviations: CI, confidence interval; DBP, diastolic blood pressure; Group D, dexmedetomidine; Group S, scalp block; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

Table 4 Comparison of the requirement of additional analgesia and adverse hemodynamic events between the two groups during skull pin insertion

Requirement of additional analgesia	Group D, n (%)	Group S, n (%)	p-Value
Fentanyl	4 (12.5)	2 (6.06)	0.329
Propofol	2 (6.25)	1 (3.03)	0.500
Increase in inhalational agent	1 (3.13)	0 (0)	0.477
Adverse hemodynamic events			
Hypotension	4 (12.5)	1 (3.03)	0.132
Hypertension	4 (12.5)	2 (6.06)	0.329
Tachycardia	2 (6.25)	1 (3.03)	0.500
Bradycardia	0	0	

Abbreviations: Group D, dexmedetomidine; Group S, scalp block.

systems and are responsible for sedation, analgesia, and sympatholytic effects.²⁴ Dexmedetomidine is a highly selective α -2 agonist with a specificity of 1,620:1 for α -2: α -1 and is known to provide hemodynamic stability during periods of stress by inhibition of noradrenaline release from the presynaptic neuron.¹³ IV infusion of low doses of dexmedetomidine decreases the HR and the systemic vascular resistance, indirectly decreasing the cardiac output and the SBP. Dexmedetomidine does not alter ICP, maintains the oxygen supply–demand relationship, and decreases the cerebrovascular dilatation produced by volatile anesthetics, thus making it an ideal drug for intracranial surgery.^{25–27}

Many studies have shown that the use of IV dexmedetomidine helps obtund the hemodynamic response to skull pin insertion,^{10,28} but some have shown a higher incidence of hypotension and bradycardia with its use.²⁹

Although both the techniques, scalp block and dexmedetomidine infusion, prove themselves to be superior to other treatment modalities/placebo, data on the comparison between these two techniques are as yet unavailable, although dexmedetomidine is being widely used in neurosurgical practice. Hence, we undertook this study to compare the two techniques. Ours is the first study to compare these two established techniques, which has shown that the use of scalp block is superior to dexmedetomidine infusion in attenuating the hemodynamic response to skull pin insertion and is an alternative option especially in patients where the addition of other systemic drugs may contribute to undesirable hemodynamic alterations.

Limitations

Although randomized and controlled, our study could not be double-blinded since multiple placebo injections for a scalp block would not be ethical. Our study included only ASA I and ASA II patients. Patients with cardiac diseases may be at a high risk of developing significant bradycardia and hypotension, which have been the undesirable side effects with dexmedetomidine.^{27,28} Whether either of these techniques could have had a distinct advantage over the other in those with severely raised ICP could not be addressed in our study since only elective patients well optimized for surgery were included. Although hemodynamics was measured, direct estimation of ICP would have been an ideal measure to show elevation of ICP, if any. Plasma catecholamine levels for assessing sympathoadrenal response were not measured. The study focused only on the effects of both the techniques on the hemodynamic effects of skull pin insertion, and a difference in the HR of 5 bpm may not be clinically significant regardless of ASA status. Measurement of hemodynamic data throughout the surgery and extubation would have thrown more light on the benefit of both the techniques in craniotomy.

Conclusion

Scalp blockade with 0.5% ropivacaine is effective and superior to dexmedetomidine. However, considering the clinical insignificance of the hemodynamic variation, we would conclude that both techniques are acceptable options in attenuating the hemodynamic response to skull pin insertion in ASA I and II patients after craniotomy.

Conflict of Interest

None declared.

References

- Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev* 1990;2(2):161–192
- Schutta HS, Kassell NF, Langfitt TW. Brain swelling produced by injury and aggravated by arterial hypertension. A light and electron microscopic study. *Brain* 1968;91(2):281–294
- Jellish WS, Theard MA, Cheng MA, Leonetti JP, Crowder CM, Tempelhoff R. The effects of clonidine premedication and scalp

- infiltration of lidocaine on hemodynamic responses to laryngoscopy and skull pin head-holder insertion during skull base procedures. *Skull Base* 2001;11(3):169–176
- 4 Misra S, Koshy T, Unnikrishnan KP, Suneel PR, Chatterjee N. Gabapentin premedication decreases the hemodynamic response to skull pin insertion in patients undergoing craniotomy. *J Neurosurg Anesthesiol* 2011;23(2):110–117
 - 5 Ozköse Z, Yardim S, Yurtlu S, Doğulu F, Kaymaz M, Paşaoğlu A. The effects of intravenous fentanyl and lidocaine infiltration on the hemodynamic response to skull pin placement. *Neurosurg Rev* 2001;24(1):35–37
 - 6 Yildiz K, Madenoglu H, Dogru K, Kotanoglu MS, Akin A, Boyaci A. The effects of intravenous fentanyl and intravenous fentanyl combined with bupivacaine infiltration on the hemodynamic response to skull pin insertion. *J Neurosurg Anesthesiol* 2005;17(1):9–12
 - 7 Doblar DD, Lim YC, Baykan N, Frenette L. A comparison of alfentanil, esmolol, lidocaine, and thiopental sodium on the hemodynamic response to insertion of headrest skull pins. *J Clin Anesth* 1996;8(1):31–35
 - 8 Agarwal A, Sinha PK, Pandey CM, Gaur A, Pandey CK, Kaushik S. Effect of a subanesthetic dose of intravenous ketamine and/or local anesthetic infiltration on hemodynamic responses to skull-pin placement: a prospective, placebo-controlled, randomized, double-blind study. *J Neurosurg Anesthesiol* 2001;13(3):189–194
 - 9 Bharne S, Bidkar PU, Badhe AS, Parida S, Ramesh AS. Comparison of intravenous labetalol and bupivacaine scalp block on the hemodynamic and entropy changes following skull pin application: a randomized, open label clinical trial. *Asian J Neurosurg* 2016;11(1):60–65
 - 10 Uyar AS, Yagmurdu H, Fidan Y, Topkaya C, Basar H. Dexmedetomidine attenuates the hemodynamic and neuroendocrine responses to skull-pin head-holder application during craniotomy. *J Neurosurg Anesthesiol* 2008;20(3):174–179
 - 11 Pinovsky ML, Fishman RL, Reeves ST, et al. The effect of bupivacaine skull block on the hemodynamic response to craniotomy. *Anesth Analg* 1996;83(6):1256–1261
 - 12 Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. *Proc Bayl Univ Med Cent* 2001;14(1):13–21
 - 13 Bekker A, Sturaitis M, Bloom M, et al. The effect of dexmedetomidine on perioperative hemodynamics in patients undergoing craniotomy. *Anesth Analg* 2008;107(4):1340–1347
 - 14 Bekker A, Sturaitis MK. Dexmedetomidine for neurological surgery. *Neurosurgery* 2005;57(1(Suppl)):1–10
 - 15 Quiney N, Cooper R, Stoneham M, Walters F. Pain after craniotomy. A time for reappraisal? *Br J Neurosurg* 1996;10(3):295–299
 - 16 Alexander SC, Lassen NA. Cerebral circulatory response to acute brain disease: implications for anesthetic practice. *Anesthesiology* 1970;32(1):60–68
 - 17 Jamali S, Archer D, Ravussin P, Bonnafoos M, David P, Ecoffey C. The effect of skull-pin insertion on cerebrospinal fluid pressure and cerebral perfusion pressure: influence of sufentanil and fentanyl. *Anesth Analg* 1997;84(6):1292–1296
 - 18 Roy WL, Edelist G, Gilbert B. Myocardial ischemia during non-cardiac surgical procedures in patients with coronary-artery disease. *Anesthesiology* 1979;51(5):393–397
 - 19 Smith F, van der Merwe C, Becker P. Attenuation of the hemodynamic response to placement of the Mayfield skull pin head holder: alfentanil versus scalp block. *South Afr J Anaesth Analg* 2002;8(4):4–11
 - 20 Geze S, Yilmaz AA, Tuzuner F. The effect of scalp block and local infiltration on the haemodynamic and stress response to skull-pin placement for craniotomy. *Eur J Anaesthesiol* 2009;26(4):298–303
 - 21 Bala I, Gupta B, Bhardwaj N, Ghai B, Khosla VK. Effect of scalp block on postoperative pain relief in craniotomy patients. *Anaesth Intensive Care* 2006;34(2):224–227
 - 22 Kuthiala G, Chaudhary G. Ropivacaine: a review of its pharmacology and clinical use. *Indian J Anaesth* 2011;55(2):104–110
 - 23 Theerth KA, Sriganesh K, Chakrabarti D, Reddy KRM, Rao GSU. Analgesia nociception index and hemodynamic changes during skull pin application for supratentorial craniotomies in patients receiving scalp block versus pin-site infiltration: a randomized controlled trial. *Saudi J Anaesth* 2019;13(4):306–311
 - 24 Giovannitti JA Jr, Thoms SM, Crawford JJ. Alpha-2 adrenergic receptor agonists: a review of current clinical applications. *Anesth Prog* 2015;62(1):31–39
 - 25 Zornow MH, Scheller MS, Sheehan PB, Strnat MAP, Matsumoto M. Intracranial pressure effects of dexmedetomidine in rabbits. *Anesth Analg* 1992;75(2):232–237
 - 26 Fragen RJ, Fitzgerald PC. Effect of dexmedetomidine on the minimum alveolar concentration (MAC) of sevoflurane in adults age 55 to 70 years. *J Clin Anesth* 1999;11(6):466–470
 - 27 Drummond JC, Dao AV, Roth DM, et al. Effect of dexmedetomidine on cerebral blood flow velocity, cerebral metabolic rate, and carbon dioxide response in normal humans. *Anesthesiology* 2008;108(2):225–232
 - 28 Dawlatly AB, Abdullah K, Watidy SA, Jamjoom Z, Murshid WR, Delvi B. Effect of small dose intravenous dexmedetomidine and/or local anesthetic infiltration on hemodynamic responses to skull pin placement. *Pan Arab J Neurosurg* 2006;10(1):29–33
 - 29 Paul A, Krishna HM. Comparison between intravenous dexmedetomidine and local lignocaine infiltration to attenuate the haemodynamic response to skull pin head holder application during craniotomy. *Indian J Anaesth* 2015;59(12):785–788