

# Comparison of effects of dexmedetomidine added to ropivacaine versus ropivacaine alone infiltration scalp block for attenuation of the haemodynamic response to skull pin placement in neurosurgical procedures: A double-blind, randomised clinical trial

**Address for correspondence:**  
Dr. Aloka Samantaray,  
Department of Anaesthesiology  
and Critical care, Sri  
Venkateswara Institute  
of Medical Sciences,  
Tirupati – 517507,  
Andhra Pradesh, India.  
E-mail: aloksvims@gmail.com

**Submitted:** 25-May-2021

**Revised:** 06-Sep-2021

**Accepted:** 20-Oct-2021

**Published:** 23-Nov-2021

**Sahana B. N, Sri Devi Radhapuram, Aloka Samantaray, Natham Hemanth, Hemalatha Pasupuleti, Hanumantha Rao Mangu**

Department of Anaesthesiology and Critical care, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh, India

## ABSTRACT

**Background and Aims:** Skull pin head holder application is intensely painful and is accompanied with abrupt increase in heart rate and arterial blood pressure. We aimed to determine the effects of adding dexmedetomidine to ropivacaine scalp block in attenuating the haemodynamic response to skull pin insertion in neurosurgical procedures. **Methods:** Sixty patients were randomly allocated to receive scalp block with 25 ml of 0.5% ropivacaine added with either normal saline (control group) or dexmedetomidine (1 µg/kg) after anesthesia induction. A standard uniform general endotracheal anaesthesia protocol was followed in all study subjects. Heart rate and blood pressure measurements were made at baseline, 1, 3, 5, 10, and 15 min following skull pin placement. Student's independent *t*-test, Chi-square test and repeated measure analysis of variance were used to analyse the obtained data. **Results:** There was no significant attenuation of heart rate ( $P = 0.418$ ), systolic ( $P = 0.542$ ), diastolic ( $P = 0.793$ ) and mean blood pressure ( $P = 0.478$ ) with addition of dexmedetomidine to ropivacaine. **Conclusions:** The addition of dexmedetomidine (1 µg/kg) to 25 ml of 0.5% ropivacaine offers no additional benefit over 25 ml of 0.5% ropivacaine alone scalp block in attenuating the haemodynamic response to skull pin placement in neurosurgical procedures.

**Key words:** Blood pressure, dexmedetomidine, heart rate, nerve block, ropivacaine

### Access this article online

Website: [www.ijaweb.org](http://www.ijaweb.org)

DOI: 10.4103/ija.ija\_450\_21

Quick response code



## INTRODUCTION

The use of skull pin head holder to stabilise the head during craniotomy produces a strong noxious stimulus and sympathetic activation, resulting in abrupt increase in heart rate and arterial blood pressure<sup>[1,2]</sup> and may increase the cerebral blood flow and intracranial pressure.<sup>[3]</sup> Different anaesthetic and pharmacological techniques have been used to attenuate haemodynamic response to skull pin placement.<sup>[4,5]</sup>

Of the various methods mentioned, scalp block with local anaesthetic (LA) drug is commonly used. To prolong or for added effect, we add adjuvants to LAs. Alpha 2 agonists are one among the various adjuvants

used along with LAs in scalp block. Previous studies have shown beneficial effect of adding clonidine to LAs like bupivacaine in attenuating haemodynamic response to skull pin insertion.<sup>[2]</sup> Proposed mechanisms

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**How to cite this article:** Sahana BN, Sri Devi R, Samantaray A, Hemanth N, Pasupuleti H, Mangu HR. Comparison of effects of dexmedetomidine added to ropivacaine versus ropivacaine alone infiltration scalp block for attenuation of the haemodynamic response to skull pin placement in neurosurgical procedures: A double-blind, randomised clinical trial. *Indian J Anaesth* 2021;65:782-8.

include central analgesia, vasoconstriction and anti-inflammatory effects. Ropivacaine is a longer acting LA which exhibits differential blockade predominantly on sensory nerve fibres and has less cardio and neurotoxicity.<sup>[6]</sup> We hypothesised that the addition of dexmedetomidine, an alpha 2 agonist to ropivacaine will have a better haemodynamic profile compared to ropivacaine alone during skull pin application. A prospective study was conducted to compare the effects of ropivacaine with and without dexmedetomidine in infiltration scalp block for attenuating adverse haemodynamic response to skull pin insertion.

## METHODS

This prospective, randomised, double-blind, controlled study was conducted after obtaining approval from Institutional Ethics Committee and written informed consent from each study participant. Recruitment of study participants was done after registering the trial with Clinical Trials Registry-India [CTRI/2019/08/020826] and carried out in accordance with the Declaration of Helsinki (2013) to protect the safety and wellbeing of all individuals. The study was conducted in the neurosurgical operation theatre of a tertiary care university teaching hospital from August 2019 to April 2020.

All adult patients of either sex aged 18--65 years of age, belonging to American Society of Anesthesiologists physical status (ASA PS) grading I and II scheduled for elective craniotomies requiring placement of Mayfield skull pins under general anaesthesia were included in the study.

The exclusion criteria were patients with uncontrolled hypertension, preoperative bradycardia (heart rate <60/min), ischaemic heart disease, cardiac arrhythmias, severe hepatic and renal disease, past history of craniotomy, allergy to study drugs, preoperatively on alpha and beta blocker, inability to give consent, pregnancy and lactation.

Sixty patients were randomly allocated to one of the two groups using computer generated random blocks of 6 with allocation ratio of 1:1. Allocation sequence was kept in sequential sealed coded envelope. A block (sealed envelope) was chosen at random and the treatments were allocated according to the permutations in that block. The random blocks were maintained by a statistician not involved in the study. Concealment

was achieved by preparing two sets of ready-to-inject syringes with equal volumes (30 ml) by a resident trainee not participating in the study on the day of surgery, before the performance of the block for each patient. The patient and the anaesthesiologist performing the block were blinded to the patients' allocation. Apart from the statistician responsible for random code generation and the research assistant involved in preparing the medication syringe, all other investigators were blinded for assessment and data analysis.

The control group received 25 ml 0.5% ropivacaine and normal saline for the scalp block and dexmedetomidine group received 25 ml of 0.5% ropivacaine and dexmedetomidine (1 µg/kg) for the scalp block.

The sample size was calculated based on a previous study<sup>[7]</sup> where the maximum mean increase in heart rate and arterial pressure was by 11.4 beats per minute [standard deviation (SD), 10.9] and 13.4 mmHg (SD, 16.9), respectively, at 1 min following scalp block.

We assumed that a 10% difference in heart rate (HR) and mean arterial pressure (MAP) would give a clinically meaningful effect size with similar SD. This yielded a sample size of 25 patients per group with an alpha error of 0.05 and 80% power to the study. Considering a drop out of five patients per group, we recruited a total of 60 patients for our study. The data was entered into Microsoft excel spread sheet and analysed by appropriate statistical software Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, IL USA). Results having *P* value of <0.05 were considered significant.

All patients received alprazolam 0.25 mg and ranitidine 150 mg orally on the night before surgery and also in the morning on the day of the surgery.

In the operation theatre, an intravenous (IV) line was secured. Patients were monitored with electrocardiography, invasive blood pressure (BP), pulse oximetry and end tidal carbon dioxide. Anaesthesia induction and intubation included use of IV midazolam 0.03 mg/kg, fentanyl 2 µg/kg, propofol 1 mg/kg, lignocaine 1 mg/kg and vecuronium 0.1 mg/kg. Anaesthesia was maintained with 50% oxygen in air using a constant gas flow within a narrow end-tidal concentration range of isoflurane. Bilateral scalp block was given after anaesthesia induction using the study drug (An investigator not involved in data collection

and analysis would be performing scalp block) with a 25 gauge needle to block the supraorbital nerve and supra-trochlear nerve near the supraorbital groove, zygomatic-temporal nerve 1 cm away from outer canthus of the eye, auriculo-temporal nerve near the tragus, and the lesser occipital nerve and greater occipital nerve on the line joining mastoid process and occipital protuberance. Time interval of 15 min was given between intubation and skull pin fixation to reduce the bias of intubation causing an increase in the haemodynamic response.

The primary outcome of the study was to analyse and compare the change in HR, using lead II of electrocardiogram, systolic BP, diastolic BP and mean BP at different time points after skull pin placement from baseline in both the groups using invasive blood pressure monitoring. The secondary outcome was to analyse and compare predefined adverse haemodynamics during the study period. Recording of the HR, systolic BP, diastolic BP and mean BP were done at following times: baseline (before scalp block), 1, 3, 5, 10 and 15 min after scalp block. Bradycardia (HR <50 beats/min), tachycardia (>30% increase from baseline HR), hypertension (>30% from baseline mean BP) and hypotension (<30% from baseline mean BP) was recorded and treated. Intravenous propofol in increments of 10 mg up to 1 mg/kg was administered to treat hypertension. Bradycardia was treated by administration of IV atropine 0.5 mg. Hypotension was initially treated by decreasing the inspired isoflurane concentration to 0.5% and if persistent, by administration of IV ephedrine in 3 mg boluses. Short acting esmolol (100 µg/kg) bolus was administered for persistent tachycardia (>30 s).

Independent Student “*t*-test “was used to compare the continuous variables between the two groups. Chi-square test and Fisher’s exact test were used to analyse the categorical data and for testing the association between the variables. Wilcoxon signed rank test (2 tailed) was used for non-normal distributed data. Intragroup comparisons of haemodynamic variables were made with base line as control value using repeated measure analysis of variance (ANOVA) followed by *post-hoc* Bonferroni correction. The results were considered significant when  $P < 0.05$ .

## RESULTS

We enrolled 60 patients into the study and completed the study protocol with no post-randomisation drop

out and no test subjects were lost to follow-up during the study period [Figure 1].

Both the groups were comparable demographically [Table 1]. There was no significant difference in HR, SBP, DBP and MAP between the two groups at predefined time intervals following skull pin insertion [Tables 2 and 3]. However, there was a statistically significant effect of time within the group when compared to base line [Table 4]. The pair wise comparison revealed a significant increase in HR, SBP and MAP at 1 and 3 min after skull pin insertion in both the groups. The DBP values rose significantly at 1 min in ropivacaine group as opposed to both at 1 and 3 min following skull pin insertion in the control group [Table 4].

In the dexmedetomidine group, out of 30 patients, three patients had bradycardia, none had hypotension, one patient had tachycardia and none had hypertension. In the control group, out of 30 patients, one patient had bradycardia, one had hypotension, none had tachycardia and one patient had hypertension [Figure 2].

## DISCUSSION

The major finding of our study is that the addition of dexmedetomidine offers no additional advantage over ropivacaine alone when used for scalp block to attenuate haemodynamic response to skull pin placement. The acute sympathetic activity in response to skull pin insertion has been first observed way back in the seventies.<sup>[8]</sup> Local anaesthesia infiltration is the cornerstone to blunt the noxious stimuli of skull pin insertion, and is typically provided by means of a scalp block, which when performed well with agents such as bupivacaine, levobupivacaine or ropivacaine can provide good and safe analgesia for 8 h or longer.<sup>[9,10]</sup>

In the late 1980s, the first randomised controlled trial concluded that bupivacaine scalp infiltration has a favourable haemodynamic response to craniotomy in comparison to placebo group.<sup>[11]</sup> Different researchers have tried several pharmacological methods to attenuate the haemodynamic response to skull pin fixation with varying success rates. The pharmacological method mainly uses different LAs as infiltration targeting major sensory innervations to scalp<sup>[12]</sup> or administration of vaso-regulatory drugs.<sup>[13]</sup>

Additional doses of potent narcotics<sup>[14]</sup> and deepening of anaesthesia has also been suggested by the

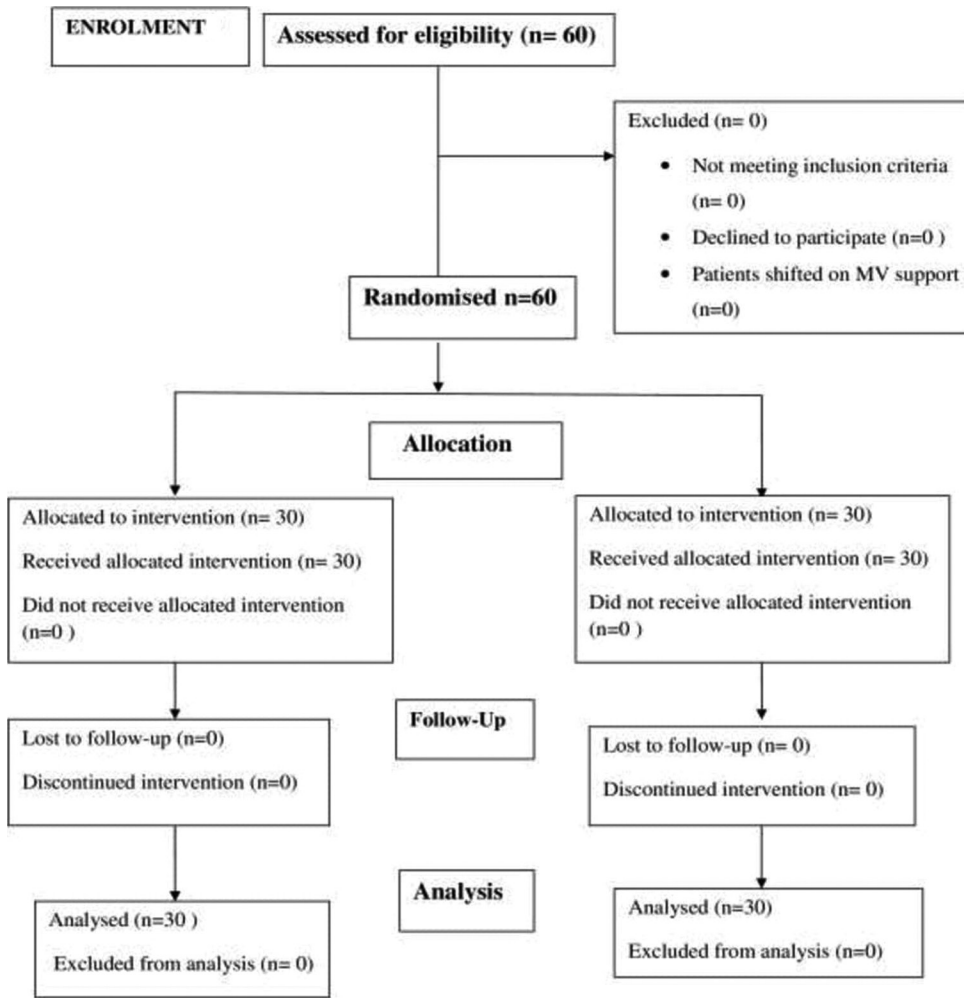


Figure 1: CONSORT diagram; MV: Mechanical ventilation

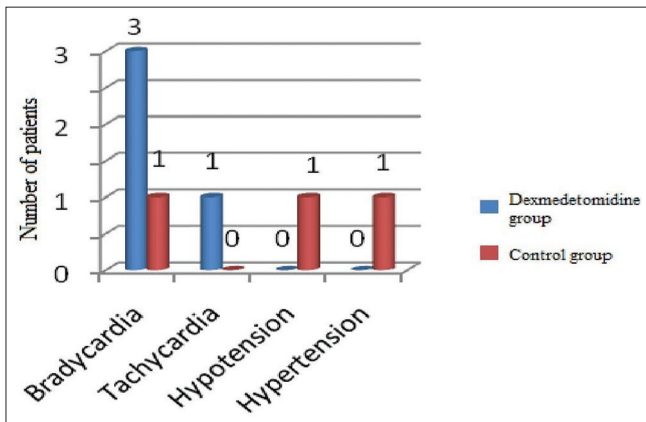


Figure 2: Episodes of bradycardia, tachycardia, hypotension, hypertension

investigators as a measure to reduce the deleterious effects of heightened haemodynamic response to skull pin fixation.

There are two studies from Turkey which not only effectively demonstrated the superiority of scalp block

over simple LA infiltration (0.5% plain bupivacaine) for blunting the haemodynamic response to the pin head holder application and the skin incision in infratentorial craniotomies but also opined that a simple 0.5% bupivacaine infiltration of skull pin insertion site 5 min before pinning does not attenuate the acute sympathetic response to head pinning.<sup>[15,16]</sup> A systematic review and meta-analysis favoured use of regional scalp block to provide postoperative pain relief after craniotomy.<sup>[17]</sup>

Yaoxin Yang<sup>[18]</sup> observed that use of ropivacaine alone in different concentrations (0.2, 0.3 and 0.5%) resulted not only in a dose-dependent prolonged analgesia, but both 0.2 and 0.5% ropivacaine resulted in blunted haemodynamic response to noxious stimuli during incision, drilling, and sawing skull bone. Similar to our study, they also observed that both HR and mean arterial pressure showed statistically significant changes over time with no difference between the groups and almost similar trend changes in MBP and HR.

Table 1: Patient characteristics

Variables	Control group (n=30)	Dexmedetomidine group (n=30)	P
Age (years)	43.8±11.4	41.2±13.0	0.410
Gender (Males/Females) (n)	10/20	11/19	0.780
Weight (kg)	60.9±8.0	58.9±9.6	0.390
Body mass index (kg/m <sup>2</sup> )	23.9±2.9	23.3±3.1	0.380
ASA PS (grade I/II) (n)	21/9	21/9	1.000

n=number of patients; ASA PS, American Society of Anesthesiologists Physical Status

Table 2: Comparison of heart rate in beats per minute between the study groups

Parameter	Control group (n=30)	Dexmedetomidine group (n=30)	P
HRBL	77.9±12.7	81.1±13.4	0.357
HR1	84.9±14.8	87.2±17.0	0.574
HR3	83.7±13.0	85.6±15.6	0.612
HR5	79.9±13.0	83.3±14.4	0.347
HR10	78.0±13.4	81.6±13.1	0.293
HR15	76.6±12.6	81.3±13.6	0.177
F <sup>#</sup>	32.649 (P<0.001)	20.614 (P<0.001)	

n=number of patients; HR, heart rate. BL=baseline and 1, 3, 5, 10, 15 represent the predefined time points after scalp block. <sup>#</sup>Repeated measure ANOVA test

Table 3: Comparison of systolic (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) in mm of Hg between the study groups

Parameter	Control group (n=30)	Dexmedetomidine group (n=30)	P
SBPBL	123.2±19.9	121.0±15.9	0.634
SBP1	132.1±20.9	131.1±20.0	0.851
SBP3	128.2±18.6	129.1±19.5	0.861
SBP5	126.0±19.2	124.7±16.9	0.787
SBP10	123.9±18.0	121.4±15.7	0.565
SBP15	120.5±18.0	118.0±15.7	0.580
F <sup>#</sup>	30.073 (P<0.001)	17.364 (P<0.001)	
DBPBL	76.6±11.9	76.9±9.5	0.896
DBP1	81.4±13.5	83.8±11.0	0.444
DBP3	79.1±12.1	81.2±11.9	0.490
DBP5	76.4±10.6	78.3±9.3	0.474
DBP10	74.2±15.8	76.6±8.8	0.478
DBP15	73.9±9.0	74.3±8.9	0.876
F <sup>#</sup>	15.004 (P<0.001)	23.325 (P<0.001)	
MBPBL	92.4±15.0	91.6±11.0	0.830
MBP1	98.6±15.8	99.7±13.6	0.768
MBP3	95.7±14.4	97.2±14.3	0.675
MBP5	92.7±13.5	93.9±11.8	0.724
MBP10	92.1±12.2	91.5±10.6	0.858
MBP15	89.4±12.0	88.7±10.5	0.811
F <sup>#</sup>	20.660 (P<0.001)	21.111 (P<0.001)	

Data are presented as Mean±SD. n=number of patients. BL=baseline and 1, 3, 5, 10, 15 represent the predefined time points after scalp block. <sup>#</sup>Repeated measure ANOVA test

Several investigators have used an alpha-2 agonist along with LAs like bupivacaine and ropivacaine through intrathecal and epidural route and demonstrated improved efficacy of LA in terms of sensory block

characteristics.<sup>[19,20]</sup> Few investigators have used an alpha-2 agonist along with LA in peripheral nerve blocks.<sup>[21]</sup> Few other investigators have proposed anaesthetic enhancing effect of alpha-2 agonists when given perineurally along with bupivacaine. The extent of analgesia when a drug is injected near the nerve root depends on the extent to which the injected anaesthetic solution penetrates into nerve layers.<sup>[22]</sup>

Andersen JH *et al.*<sup>[23]</sup> established the peripheral mechanism of dexmedetomidine as a LA in their study on healthy volunteers. In their study, they observed bradycardia among three patients who were athletes and received 100 µg of dexmedetomidine added to 0.5% ropivacaine for peripheral nerve block. In contrast, we administered a lower dose of dexmedetomidine (1 µg/kg) but still, three patients had HR below 60/min during the study period.

In a study, Kakkar *et al.*<sup>[24]</sup> demonstrated that both clonidine and dexmedetomidine were effective for preventing haemodynamic response to tracheal intubation, but dexmedetomidine was associated with more side effects such as hypotension and bradycardia. The Wajekar *et al.*<sup>[2]</sup> study observed hypotension and bradycardia in two patients each after adding 2 µg/kg dexmedetomidine to 0.25% bupivacaine for scalp block. In contrast, our study results showed bradycardia requiring treatment in two patients but none of our patients had hypotension.

In another study, dexmedetomidine (0.25 µg/kg) along with 1% lignocaine infiltration was used before skull pinning and attenuation of haemodynamic response to skull pinning was observed in comparison to placebo or only dexmedetomidine IV infusion group. However, this study enrolled only seven patients per group and was very much underpowered to generalise the study results.<sup>[25]</sup> Similarly, a study by Kondavagilu RK *et al.*<sup>[3]</sup> used two doses of dexmedetomidine (0.5 µg/kg and 1 µg/kg) intravenous and observed a comparable attenuation in both the groups with respect to HR. There were no differences between the two doses of dexmedetomidine in terms of significant intraoperative haemodynamic variations necessitating additional measures except that one patient from each group had tachycardia which is similar to our study.

The reason for the negative result in the current study is partly explained by the fact that an active control like ropivacaine was used in both the groups as a

**Table 4: Pairwise comparison of mean heart rate (HR) (beats per minute), systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean blood pressure (MBP) in mm Hg of over the study duration using RM ANOVA**

Change from Baseline to	Control group		Dexmedetomidine group	
	Mean difference	P	Mean difference	P
HR1	6.967	0.000	6.167	0.001
HR3	5.733	0.000	4.500	0.002
HR5	1.967	0.476	2.200	0.552
HR10	0.033	1.000	0.533	1.000
HR15	1.300	1.000	0.200	1.000
SBP1	8.833	0.000	10.067	0.001
SBP3	5.000	0.022	8.100	0.024
SBP5	2.767	0.617	3.733	0.259
SBP10	0.700	1.000	0.400	1.000
SBP15	2.767	0.041	2.967	0.139
DBP1	4.800	0.003	6.900	0.001
DBP3	2.500	0.169	4.300	0.010
DBP5	0.133	1.000	1.367	1.000
DBP10	2.367	1.000	0.367	1.000
DBP15	2.633	0.229	2.633	0.061
MBP1	6.233	0.001	8.100	0.002
MBP3	3.300	0.049	5.600	0.014
MBP5	0.333	1.000	2.233	0.643
MBP10	0.300	1.000	0.100	1.000
MBP15	2.933	0.073	2.900	0.019

BL=baseline and 1, 3, 5, 10, 15 represent the predefined time points after scalp block

standard treatment and thus the addition of a weak analgesic like dexmedetomidine in low dose through perineural route could not have added any beneficial effect in attenuating the haemodynamic response to a short, sharp, acute, noxious stimulus like skull pin insertion. The prolongation of duration of analgesia with addition of dexmedetomidine to LA during peripheral nerve block has been adequately established in various systematic reviews which include only trials involving peripheral nerve blocks.<sup>[26]</sup> Unlike previous studies, the current study aimed to evaluate the efficacy of dexmedetomidine added to ropivacaine for scalp block in patients who have received general anaesthesia. The influence of general anaesthesia might have differently contributed to the negative results obtained from the current study.

The strength of the study was that it was a prospective, randomised, double-blind controlled study regarding attenuation of adverse haemodynamic response after a specific procedure, with detailed time- scaled assessment. There was no loss of study subjects after randomisation and no missing of the data. It is likely that the study cohort was representative with an adequately powered sample size, favouring external validity.

The major limitations of the study include not instituting an objective measure to monitor nociception index or catecholamine level to reflect actual sympathetic response to skull pin insertion and the effects of the study drugs. Secondly, despite the use of a narrow concentration range of isoflurane along with constant gas flow for anaesthesia maintenance, there still exists a possibility that different patients might have had different levels of anaesthesia depth. All these factors might have contributed to the negative findings in the current study.

The study reemphasises the fact that skull pin insertion is a noxious stimulus of very high magnitude and simple addition of dexmedetomidine to LA infiltration may not be able to blunt this noxious stimulus completely. Future studies should be directed to use other adjuvants to LA infiltration along with bispectral index guided anaesthesia and analgesia nociception monitoring to study the control of haemodynamic response to skull pin insertion more effectively.

## CONCLUSION

Based on our study results, we conclude that the addition of dexmedetomidine at a dose of 1 µg/kg to 25 ml of 0.5% ropivacaine offers no additional benefit over 25 ml of 0.5% ropivacaine for scalp block in attenuating the haemodynamic response to skull pin placement in neurosurgical procedures.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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