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A Comparative Study of Intravenous Dexmedetomidine with Local Infiltration of Ropivacaine in Attenuation of Stress Response to Skull Pin Insertion in Craniotomies

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Abstract

Objective Skull pin insertion in patients undergoing craniotomies elicits hemodynamic and neuroendocrine stress response that may be deleterious to the patient. Various drugs and techniques have been documented in literature to abate this stress response. Against this background, we aimed to compare the efficacy of intravenous dexmedetomidine and local infiltration of ropivacaine for attenuation of stress response to pin insertion in craniotomies.

Methods Eighty-eight adult patients undergoing craniotomy under general anesthesia from March 2019 to April 2020 requiring application of head holder were randomized into two equal groups. After intubation, 0.75 μg kg^{-1} of dexmedetomidine over 10 minutes through infusion was given in group D, while local infiltration at pin sites was done with 0.5% ropivacaine, 2 mL at each site in group R. Hemodynamic parameters and levels of serum cortisol, prolactin, and blood glucose were measured before and after pin insertion. Unpaired *t*-test for continuous variables and Mann–Whitney U test was used for nonnormally distributed variables.

Results Heart rate was statistically similar between the two groups at all the observed time points. The difference in mean arterial pressure values between the two groups was found to be statistically significant only from 10 to 20 minutes after pin insertion being statistically similar at rest of the time points. Levels of serum glucose, cortisol, and prolactin values 30 minutes after pin insertion were statistically similar between both groups.

Conclusion We concluded that both interventions are equally efficacious in attenuation of hemodynamic and stress response to head holder application in patients undergoing craniotomies.

Keywords
- craniotomy
- dexmedetomidine
- ropivacaine
- hemodynamics

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Introduction

Neurosurgical head holder (skull clamp) is an essential maneuver to eliminate slight movements that can be potentially dangerous while performing microneurosurgery. Skull pin insertion elicits pain due to stimulation of scalp and periosteal nerve endings that induces not only hemodynamic response but also an increase in stress hormones.[1–3]

Various methods have been employed to abate these responses such as deepening the plane of anesthesia, opioids like fentanyl, alfentanil, and remifentanil, β-blockers, gabapentin, α-agonists (clonidine and dexmedetomidine), scalp blockade, and local anesthetic infiltration at pin insertion sites.[4] Local infiltration with ropivacaine provides sufficient analgesia and hemodynamic stability at the time of pin insertion. Dexmedetomidine is a selective α-2 adrenoreceptor agonist. It has central sympatholytic activity that leads to attenuation of hemodynamic and stress response to various noxious stimuli during anesthesia.[5,6]

We hypothesized that both intravenous (IV) dexmedetomidine and local infiltration of ropivacaine at pin insertion sites are equally efficacious in attenuation of stress response to pin insertion in craniotomies. The aim of this study was to compare the efficacy of two methods, namely IV dexmedetomidine and local infiltration of ropivacaine at pin insertion sites in attenuation of stress response to pin insertion for craniotomies. The primary objective was to assess alterations in heart rate (HR) and mean arterial pressure (MAP), while secondary objectives were to monitor the changes in serum cortisol, prolactin, and blood glucose levels following pin insertion and record any adverse event.

Material and Methods

This prospective, randomized, comparative, double-blind study was conducted after approval by the Institutional Ethics Committee from March 2019 to April 2020. Written informed and witnessed consent for participation in the study was taken from the patients. Eighty-eight adult patients of age group 18 to 65 years of either sex belonging to American Society of Anaesthesiologists physical status I to II scheduled to undergo elective craniotomy under general anesthesia requiring application of head holder were enrolled for the study (►**Fig. 1**). Surgical indications included supratentorial tumors and cysts to be operated in supine position. Exclusion criteria were patients with bradycardia (HR < 50 beats per minute), second- or third-degree heart block, uncontrolled hypertension, cardiac, renal or hepatic disease, history of β-blocker intake, Glasgow Coma Scale is 13 or less, and known allergy to local anesthetic and dexmedetomidine.

After shifting the patient to operating room, all routine monitors such as HR, electrocardiograph, noninvasive blood pressure, and pulse oximetry (GE Datex-Ohmeda, TruStat Oximeter, GE healthcare, Heksinki, Finland) were attached. Baseline parameters like HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP, and saturation of oxygen were recorded.

IV access was obtained; blood sample (preop) for serum cortisol, prolactin, and blood glucose was drawn, and 10 mL kg^{-1} of normal saline was infused.

Induction of anesthesia was done with IV fentanyl (2 μg/kg) and sleep dose of thiopentone (3–5 mg/kg). Mask ventilation was checked and vecuronium bromide (0.1 mg/kg) was administered. After 3 minutes (mins) of mask ventilation, airway was secured with cuffed endotracheal tube of appropriate size. Intraarterial cannula, central venous catheter, and Foley's catheter were secured. Maintenance of anesthesia was done with isoflurane (0.9–1.0 minimal anaesthetic concentration [MAC]), oxygen (35%), and nitrous oxide (65%).

The patients were randomized into two groups on the basis of computer-generated randomization number: group D ($n = 44$) received 0.75 μg/kg of dexmedetomidine (Dextomid, Neon Laboratories Ltd, Mumbai, Maharashtra, India) over 10 minutes through infusion and local infiltration at pin sites was done with normal saline. Group R ($n = 44$) received equal volume of normal saline at the same rate and infiltration at pin sites was done with 0.5% ropivacaine (ROPIN, Neon Laboratories Ltd, Mumbai, Maharashtra, India) 2 mL at each site.

All the drugs were prepared by anesthesiologist who had not participated further in collection of data or management of patient. Local infiltration and collection of data were done by the anesthesiologist blinded to the drugs and group allocation. Results were interpreted by the statistician blinded to the group allocation.

After 10 minutes of injection of 2 mL of ropivacaine/placebo (depending upon the group) at each insertion site, application of Sugita head clamp was done. Total time taken for insertion of pins was recorded. Monitoring of vitals (HR, SBP, DBP, MAP) was done continuously and recorded at following intervals: baseline (awake), after administration of IV study drug/placebo (Tad), before skull pin insertion (Tap), and 1 (T1), 3 (T3), 5 (T5), 10 (T10), 15 (T15), and 20 (T20) minutes after skull pin insertion.

If there was tachycardia (increase in HR > 20% of baseline) and/or hypertension (increase in MAP > 20% of baseline), the management was done in the following stepwise manner: first, injection fentanyl 1 μg kg^{-1} was administered and second, injection propofol in increments of 20 mg (maximum of 1 mg kg^{-1}) was administered. Bradycardia was defined as HR less than 60 beats per minute but was treated with injection atropine (0.6 mg IV) only when HR less than 50 beats per minute or associated with hypotension. Hypotension (decrease in MAP < 20% of baseline) was managed with IV fluids and injection ephedrine 6 mg IV.

At 30 minutes following application of head clamp, blood was drawn from central venous catheter for serum cortisol, serum prolactin, and blood glucose levels. Former two investigations were done using enzyme-linked immunosorbent assay test and the samples were stored at −20°C, while blood glucose levels were estimated using Randox Autoanalyzer (RX DaytoNa^{+}, Randox, Crumlin, County Antrim, United Kingdom). Surgical incision was given after the recording of variables and blood sample collection. Rest of the anesthesia was managed as per standard protocol.

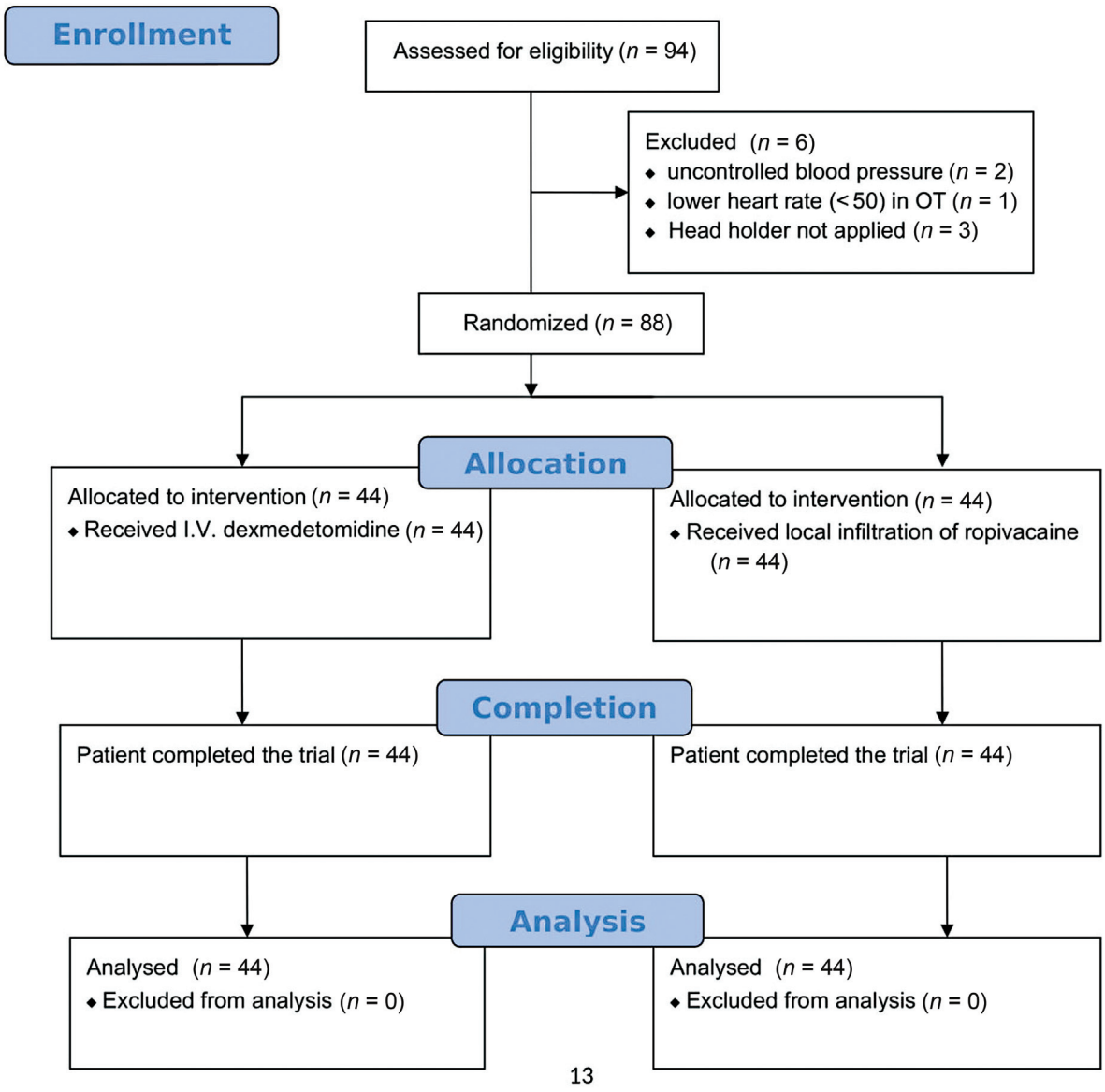

Fig. 1 Consort flow diagram.

A sample size of 38 per group was required to detect mean difference of at least 10 in MAP and HR with a power of 90% at 5% significance level. The difference of 10 was taken from both previous studies and clinical experience.[7] To compensate for a few dropouts, 44 patients per group were enrolled. SPSS software was used for statistical analysis. Continuous variables were compared using the unpaired *t*-test, whereas the Mann–Whitney U test was used for those variables that were not normally distributed. Categorical variables were analyzed using either the chi-squared test or Fisher's exact test. For all statistical tests, a *p*-value less than 0.05 was considered as significant.

Results

Both the groups were statistically similar with respect to demographic variables, volume of drug infiltrated, number of attempts, and duration of pin insertion ($p > 0.05$) (►**Table 1**). HR was statistically similar between the two groups at all the observed time points (►**Fig. 2**). The difference in MAP values between the two groups was found to be statistically significant only at T10, T15, and T20 being statistically similar at rest of the time points (►**Fig. 3**). After study drug administration and pin insertion, hypotension was observed in 14 patients (31.8%) in group D, while no patient had any such episode in group R. Of these 14 patients in group D, 13 patients were treated for hypotension with IV fluids and decreasing concentration of isoflurane, while 1 patient required 6 mg IV ephedrine in addition. While five patients in group D had bradycardia, no such episode was seen in group R ($p > 0.05$). However, it did not require treatment. Levels of serum glucose, cortisol, and prolactin values at baseline and 30 minutes after pin insertion were statistically similar between both the groups (►**Table 2**).

Table 1 Demographic variables between the two groups

Demographic parameters	Group R	Group D	*p*-Value
Age (years)	41.10 ± 12.99	37.61 ± 13.24	0.229
Sex (F/M)	22/22	21/23	0.831
ASA status (1/2)	33/11	30/14	0.478
Height (cm)	158.56 ± 5.35	157.48 ± 6.19	0.264
Weight (kg)	60.57 ± 6.73	57.41 ± 10.86	0.105
Pin-insertion duration (s)	83.0 (67.00–106.50)	80 (61.25–89.75)	0.321
Number of attempts of pin-insertion (1/2/3)	42/1/1	44/0/0	0.359
Volume infiltrated (8 mL/10 mL)	42/2	44/0	0.494

Abbreviation: ASA, American Society of Anaesthesiologists.

Discussion

Skull pin insertion is an intense nociceptive stimulus that leads to significant hemodynamic and neuroendocrine response.[8] A multitude of drugs have shown attenuation of this noxious stimulus and accompanying sympathetic stimulation without altering the dynamics of internal milieu. Regional techniques such as scalp blockade and local infiltration are well recognized in neurosurgery to prevent stress response to pin insertion.[4–10]

Various doses of dexmedetomidine have been administered in previous studies, but the optimal dose that is effective and at the same time exhibits minimum adverse effects should be adopted. Most of the studies have used 1 µg/kg over 10 minutes, but it was observed by Kondavagilu et al that low dose of 0.5 µg/kg IV infusion of dexmedetomidine is as effective as 1 µg/kg for the attenuation of stress response to pin insertion.[11] Therefore, we chose a dose of 0.75 µg/kg IV dexmedetomidine in our study.

It is well established in literature that infiltration at pin sites with various local anesthetic drugs is also effective in attenuation of such stress responses. Ropivacaine, an S-enantiomer of S-1-propyl-2,6-pipecoloxylidide, is an amino amide local anesthetic with chemical structure similar to bupivacaine but has fewer side effects and is long lasting as compared with bupivacaine. High pKa and low lipid solubility of a local anesthetic favor blockade of C type nerve fibers over A type of fibers. Thus, ropivacaine when compared with bupivacaine exhibits differential blockade predominantly on sensory nerve fibers. Its use in neurosurgery for local infiltration as well as in scalp block is well documented.[11,12] We chose 0.5% ropivacaine for infiltration as it has an additional vasoconstriction effect in addition to its local anesthetic properties. Moreover, local infiltration has advantages over

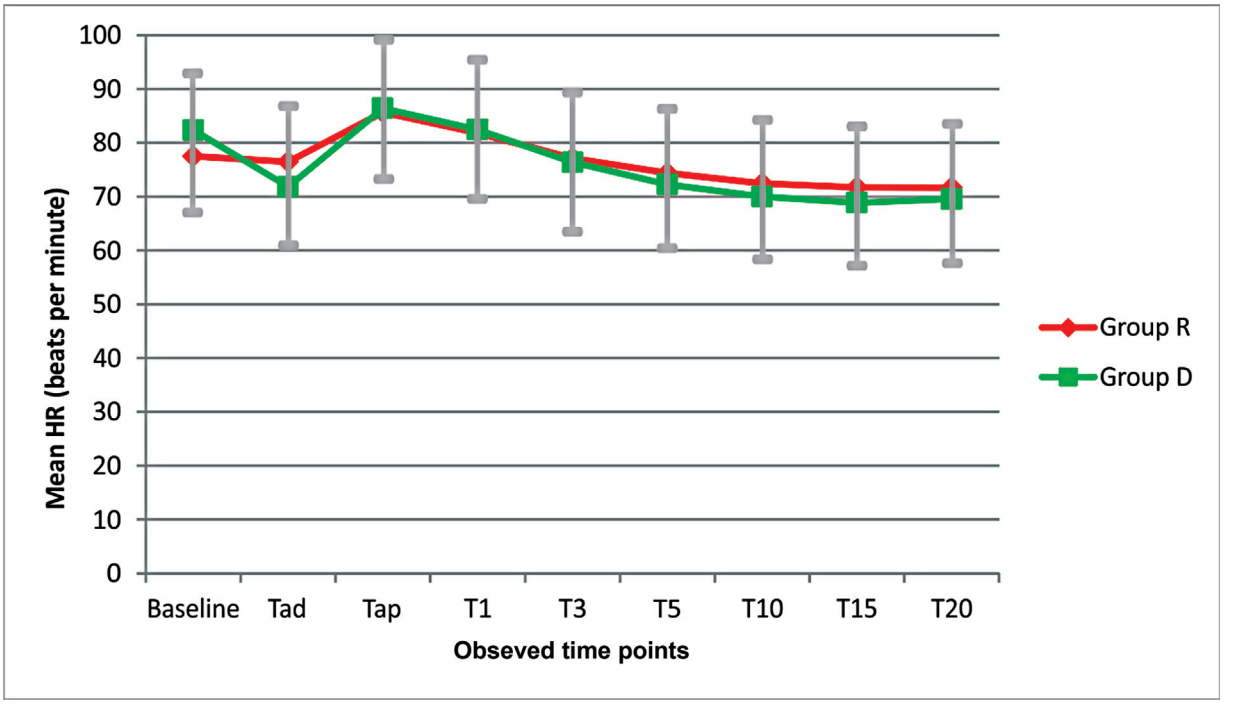

Fig. 2 Variations in heart rate (HR) between group R and group D.

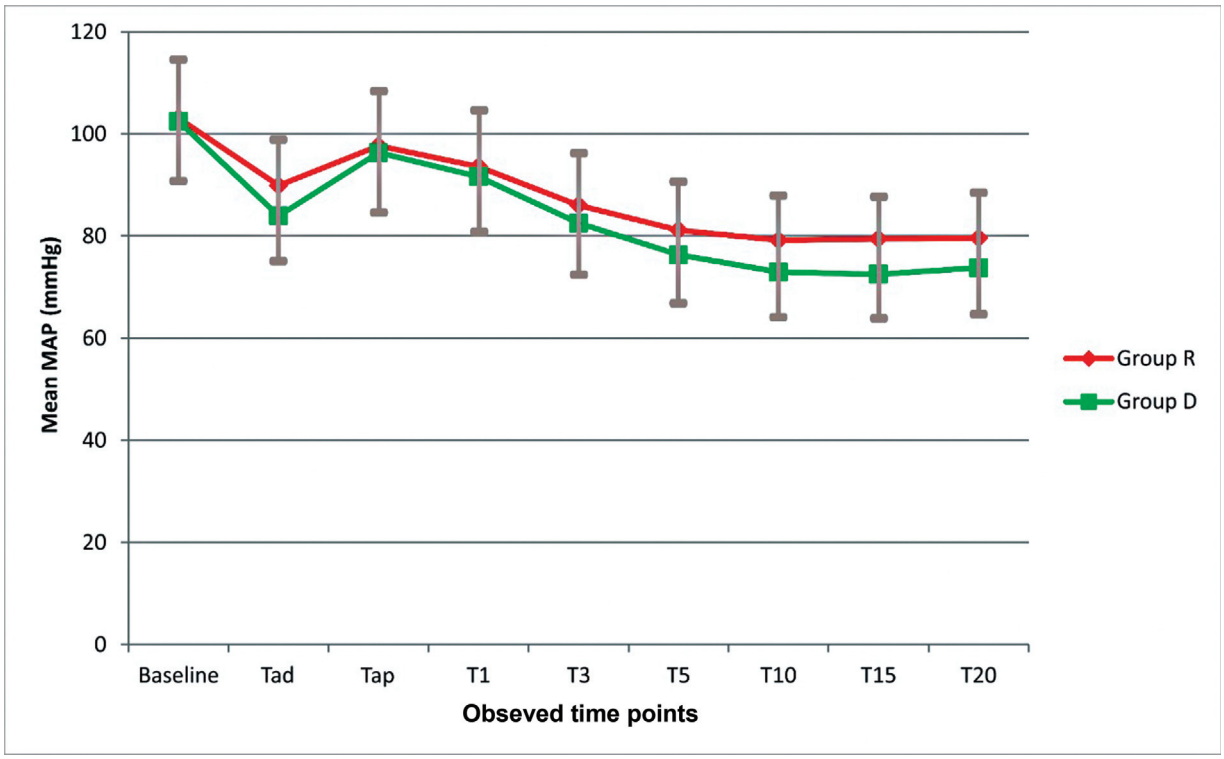

Fig. 3 Variations in mean arterial pressure (MAP) between group R and group D.

Table 2 Levels of stress hormones at baseline and 30 minutes after pin insertion

		Group R	Group D	*p*-Value (intergroup)
		Median (IQR)	Median (IQR)	
Blood glucose (mg/dL)	Preop	82.50 (65.00–98.00)	72.50 (56.00–93.00)	0.152
	30 minutes	104.00 (93.00–116.75)	98.00 (84.25–115.00)	0.354
Serum prolactin (ng/mL)	Preop	10.94 (7.67–15.50)	8.93 (6.07–12.70)	0.066
	30 minutes	18.23 (15.01–23.33)	16.85 (14.31–22.47)	0.528
Serum cortisol (μg/mL)	Preop	6.59 (4.00–10.37)	6.08 (4.85–9.82)	0.963
	30 minutes	13.42 (9.48–17.16)	11.59 (9.78–14.42)	0.245

Abbreviation: IQR, interquartile range.

scalp block as it is easier to perform, does not require expertise, and is less time consuming.

In our study, we observed that HR values were statistically similar between both the groups at all the observed time points, while MAP values were statistically similar between the two groups at all time points except T10-T20 where values were statistically significant. Though the attenuation of MAP in response to pin insertion was maintained throughout, there was more than 20% decrease in MAP values from T5-T20 as compared with baseline in both the groups. But this decrease was more in group D (26–29% from baseline) than group R (21–22%) leading to statistical significant difference at T10 to T20 between the two groups ($p < 0.020$). This can be attributed to hypotension caused by dexmedetomidine. Our findings are similar to what was observed by Paul and Krishna where authors compared IV dexmedetomidine and lignocaine infiltration.[7] However, these are in contrast to previous four studies,[4,5,11,13] where HR and MAP variation between the two groups were statistically significant. This is because these studies compared dexmedetomidine with normal saline/fentanyl and there was better attenuation of hemodynamic response in dexmedetomidine group as compared with placebo or fentanyl.

The intragroup variations in HR observed in our study in D group were almost similar to that observed in previous studies evaluating dexmedetomidine. A significant decrease in HR was observed after IV infusion of dexmedetomidine. It increased after pin insertion for 1 to 2 minutes and then returned to baseline. Subsequently, sustained decrease in HR was seen from T3 to T20. The decrease was statistically significant at Tad as compared with baseline. The lowest values of HR were observed at Tad and T15. The previous

studies observed similar sequential changes in HR with time.[4,5,7,14]

The hypothalamic pituitary-axis is the main controller of the endocrine system that in turn controls most of the body's metabolic functioning. The endocrine hormones such as glucagon, cortisol, and catecholamines are major mediators of the metabolic response to stress.[15] Serum glucose, cortisol, and prolactin values were estimated at baseline and 30 minutes after pin insertion. The levels were statistically similar between both the groups at both the time points. Stress hormone levels increased similarly in both the groups with pin insertion compared with the baseline, but the rise in levels was clinically insignificant.[4,5,13] Hence, both interventions are equally efficacious in attenuation of stress response to pin insertion. In three previous studies, statistically significant difference was observed in plasma levels of serum cortisol, prolactin, and glucose. The authors in these studies compared dexmedetomidine with normal saline (placebo) and concluded that dexmedetomidine causes attenuation of stress response to pin insertion, while we compared dexmedetomidine with active comparator.[4,5,13] This is the most likely explanation for discordance of our findings.

After study drug administration and pin insertion, hypotension was observed in 14 patients (31.8%) in group D, while no patient had any such episode in group R. Of these 14 patients in group D, 13 patients were treated for hypotension with IV fluids and decreasing concentration of isoflurane, while 1 patient required 6mg IV ephedrine in addition. Discontinuation of drug was not required in any patient. This statistically significant difference in occurrence of hypotensive episodes may be attributed to the sympatholytic properties of dexmedetomidine. Although fluid bolus was given at the time of induction of anesthesia, neurosurgical patients are likely to be fluid depleted due to use of mannitol, vomiting or decreased oral intake thus increasing the chances of hypotension. Incidence of hypotension following dexmedetomidine may be as high as 40% depending upon several physiological variables. Paul and Krishna reported that the incidence of hypotension and bradycardia was significantly higher with dexmedetomidine than lignocaine (19 patients [73%] in dexmedetomidine group vs. 5 [19.2%] in lignocaine group).[7] Thongrong et al observed that dexmedetomidine group had more hypotensive events than the fentanyl group ($p > 0.05$) (7 patients [23.3] in group D vs. 2 [6.7%] in fentanyl group). However, the authors concluded that hypotension may not be an adverse effect from dexmedetomidine in all cases as occasionally, the hemodynamic response to skull pin insertion can manifest itself as bradycardia or hypotension.[14]

Our study had few noteworthy limitations. We did not follow up the patients postoperatively to see whether hypotension had any adverse effect on patient's outcome. Intracranial pressure monitoring was not available. Stress hormones levels were done only at 30 minutes after pin insertion considering their peak levels at this time, their repetition after regular intervals could have been done. Catecholamine levels were not assessed. There was no control group in our study, but we considered it unethical to expose the patients to extreme variations in cardiovascular changes.

Conclusion

We conclude that prior administration of both dexmedetomidine and ropivacaine ablated the potential hemodynamic activation and attenuated the stress response to skull pin insertion. However, the hypotensive events were more with IV bolus dose of 0.75 µg/kg dexmedetomidine than with pin site infiltration of 0.5% ropivacaine during the study period. Stress hormone levels increased similarly in both the groups with pin insertion compared with the baseline, but the rise in levels was clinically insignificant. However, further studies comprising of a greater number of patients, different doses of drugs, and inclusion of a control group are warranted to reinforce our results and establish superiority of one technique over other.

Main Points

- Skull pin insertion elicits pain due to stimulation of scalp and periosteal nerve endings.
- It leads to hemodynamic and neuroendocrine response that may be detrimental.
- Both dexmedetomidine infusion and lignocaine infiltration attenuate this hemodynamic and stress response.

Funding
None.

Conflict of Interest
None declared.

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