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A randomized controlled study to compare the effectiveness of intravenous dexmedetomidine with placebo to attenuate the haemodynamic and neuroendocrine responses to fixation of skull pin head holder for craniotomy

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ABSTRACT

The stress response to an intense painful surgical stimulus is characterized by activation of the sympathetic nervous system and an increased secretion of the pituitary hormones. The ability of the alpha agonist dexmedetomidine was tested to decrease heart rate, arterial blood pressure, and neuroendocrinal responses to skull-pin head-holder. 60 patients undergoing craniotomy were randomly distributed to receive either saline (P group) or Dexmedetomidine (D group). The placebo group received saline, whereas the treatment group (D group) received a single bolus dose of dexmedetomidine (1 microgram/kg) intravenously over 10 minutes before induction of anaesthesia. Haemodynamic parameters as heart rate, arterial blood pressure, and serial levels of cortisol, prolactin, insulin, and blood glucose were measured. Both the groups were comparable with respect to age, weight, sex and duration of surgery. The arterial blood pressure and heart rate was found to be lower in the dexmedetomidine group when compared with the placebo group ($P<0.05$). In both groups there was an increase in the plasma cortisol, prolactin, and blood glucose levels. However, the values were significantly higher in the placebo group compared with the dexmedetomidine group ($P<0.05$). The insulin levels were not significantly changed because of the administration of the dexmedetomidine. Our study demonstrates that, a single bolus dose of dexmedetomidine before induction of anesthesia attenuated the hemodynamic and neuroendocrinal responses to skull-pin insertion in patients undergoing craniotomy.

Key words: Craniotomy, hemodynamic effects, neuroendocrine response, stress response

INTRODUCTION

The stress response to an intense painful surgical stimulus is characterized by activation of the sympathetic nervous system and an increased secretion of the pituitary hormones[1]. Application of the Mayfield skull pin holder during various neurosurgical procedures results in a brief but intense, noxious stimulus. This may cause a precipitous increase in heart rate, blood pressure and intracranial

How to cite this article: Mushtaq K, Ali Z, Shah NF, Syed S, Naqash I, Ramzan AU. A randomized controlled study to compare the effectiveness of intravenous dexmedetomidine with placebo to attenuate the hemodynamic and neuroendocrine responses to fixation of skull pin head holder for craniotomy. Northern Journal of ISA 2016;1:16–23

pressure[2]. Patients with intracranial pathology have abnormal autoregulation of cerebral blood flow and are prone to increased intracranial pressure when systemic arterial pressure rises[3]. In patients with intracranial vascular lesions (cerebral aneurysms or arterio-venous malformations), an acute increase of blood pressure may cause rupture or rerupture and present with subarachnoid or intracerebral haemorrhage. Not only can an acute increase in blood pressure disrupt the intracranial milieu, but also cause extracranial complications as pulmonary oedema[4]. All these observations lead to the necessity of attenuating the responses to clamp placement during craniotomy. Because of its sympatholytic properties, dexmedetomidine was used initially to attenuate the sympathetic response to perioperative stresses such as laryngoscopy and intubation[5]. In addition to sedative effects, dexmedetomidine has significant analgesic qualities, mediated primarily through interaction at alpha-2a receptors within the spinal cord[6]. The present study was conducted to evaluate the effectiveness of intravenous dexmedetomidine to attenuate the haemodynamic and neuroendocrine responses to fixation of skull pin head holder for craniotomy in our patient population.

MATERIAL AND METHODS

After taking the institutional review board approval, 60 patients of either sex, undergoing elective craniotomy for resection of supratentorial tumors or clipping of cerebral aneurysms were selected for the study. Patients belonging to ASA physical status I or II and aged between 18 to 70 years were eligible. Patients with history of ischemic heart disease, second or third degree heart block, head injury, uncontrolled hypertension, uncontrolled diabetes, pregnancy and previous craniotomy incision were excluded. During the preoperative visit, all patients were clinically evaluated and investigated, and a written informed consent was taken. In all these patients a Mayfield skull-pin head-holder was used to stabilize the head position to facilitate the surgery. No patient was given any premedication. In the operation room, after establishing an intravenous line, patients were connected to the monitor for continuous monitoring of electrocardiogram, heart rate, noninvasive blood pressure and oxygen saturation. By using sealed envelope technique, patients were randomly allocated to one of the two groups to receive either intravenous dexmedetomidine hydrochloride 1 microgram/kilogram (group-D) or 0.9% normal saline as placebo (group-P), over a period of 10 minutes before induction of anaesthesia. In order to attain double blinding, the person who was not involved in recording the data, prepared the dexmedetomidine or placebo solutions to a total of 10ml volume. Anaesthesia was induced with fentanyl 2ug/kg, propofol 2mg/kg till loss of verbal reponse, followed by vecuronium bromide 0.1mg/kg body weight to facilitate tracheal intubation. Arterial and central venous catheterization was done for continuous measurement of arterial and central venous pressure after induction of anaesthesia. Anaesthesia was maintained with 1% isoflurane and 60% nitrous oxide in oxygen, with incremental doses of muscle relaxant as and when needed as determined by nerve stimulator using train of four ratio. Intra-operatively analgesia was maintained with fentanyl 1ug/kg every hour until the last 30 minutes of surgery. Patients were mechanically ventilated to maintain partial pressure of carbon dioxide between 30 and 35 mmHg. CVP was maintained between 8 to 10 mmHg. Intraoperatively, tachycardia was defined as $\geq$ 20% increase in heart rate from baseline, hypertension as 30% increase in mean arterial pressure from baseline and hypotension as $\geq$ 30% decrease in mean arterial pressure from baseline.

Haemodynamic parameters Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) were recorded at the following time intervals:

- Before administration of dexmedetomidine or placebo, baseline value (B).
- Before Induction of anesthesia (BI).
- After Induction of anesthesia (AI).
- 1 minute before pin insertion (T0).
- T1, T5, T10, T20, T30, T40 and T60, reflecting HR and MAP at 1, 5,10, 20, 30, 40 and 60 minutes respectively, after pin insertion.

Blood samples for the determination of blood glucose (G), serum insulin (I), serum cortisol (C) and serum prolactin (Pr) levels were obtained at following time intervals:

- Serum cortisol levels at baseline (BC), 30 minutes (30MC) and 60 minutes (60MC) after pin insertion.
- Serum prolactin levels at baseline (BPr), 30 minutes (30MPr) and 60 minutes (60MPr) after pin insertion.
- Serum insulin levels at baseline (BI), 30 minutes (30MI) and 60 minutes (60MI) after pin insertion.
- Serum glucose levels at baseline (BG), 30 minutes

(30MG) and 60 minutes (60MG) after pin insertion. Serum cortisol, insulin and prolactin levels were measured by Immune Radiometric Assay (IRMA), using commercially available radiolabelled kits from immunotech France supplied by Beckman Coulter in India. The assays were performed by following the manufacturer's protocols in each of the above and counts in each tube were measured using a gamma counted from Stratech Germany (PC RIAS MAS). The calculations for the standards and the samples were done using automated software and values for each patient sample were determined and analyzed. Blood levels of glucose were measured by using enzyme kits (Accurex) in an autoanalyser.

All the patients were extubated at the end of surgical procedure when fully awake and transferred to surgical intensive care unit for overnight observation.

STATISTICAL ANALYSIS

The data obtained was analyzed statistically using Mann-Whitney U test for differences between the groups and the repeated measure analysis of variance test for differences within the groups. A p-value <0.05 was considered as statistically significant.

RESULTS

A total of 60 patients were selected for the study and were randomly divided into two groups of 30 patients each. Both the groups were comparable with respect to age, weight, sex and duration of surgery. Mean age of patients was 44.40±13.12 years in group D, and 48.87±11.64 years in group P. Mean weight of patients in group D was 63.73±5.982 kgs compared to 63.87±7.001 kgs in group P. In group P, there were 17 males and 13 females, whereas in group P there were 18 males and 12 females, respectively. The difference in male/female ratio in the two groups was statistically insignificant (p value>0.05). The mean duration of surgery in group D and group P was 292.33±39.88 minutes and 294.83±52.33 minutes respectively. The two groups did not differ significantly with respect to the duration of surgery (p value>0.05). The mean time to pin insertion from the time of drug and saline administration respectively was 28.07±4.65 minutes in group D compared to 28.23±4.48 minutes in group P. The difference was again statistically insignificant (p value >0.05). The demographic data is presented in Table 1.

Table 1 : Demographic data

Parameter	Group	N	Mean ± SD	Range	P-value	Remarks
Age (in years)	Group D	30	44.40±13.124	25-68	0.196	NS
	Group P	30	48.87±11.649	23-70		
Weight (in kilograms)	Group D	30	63.73±5.982	54-76	0.271	NS.
	Group P	30	63.87±7.001	52-76		
Duration of surgery (in minutes)	Group D	30	292.33±39.886	220-360	0.214	NS
	Group P	30	294.83±52.333	180-360		

Table 1 Demographic data of the study population

HEMODYNAMIC VARIABLES

In group P, baseline HR and MAP were 79.53±10.08 bpm and 92.47±6.93 mmHg respectively. After 1 minute of pin attachment HR and MAP increased to 106.83±10.07 bpm and 110.27±6.63 mmHg respectively. This was statistically significant when compared to baseline values (p<0.001). At 5 minutes, 10 minutes, 20 minutes both HR and MAP showed a significant difference compared to the baseline (p<0.05). At 30 minutes only HR was raised significantly compared to the baseline. At 40 minutes and 60 minutes heart rate and mean arterial pressure were still higher when compared to baseline but the difference was statistically insignificant (p>0.05).

In group D the baseline HR and MAP were 79.87±10.24 bpm and 92.53±5.26 mmHg respectively. After administration of dexmedetomidine HR declined significantly to 71.97±7.5 bpm and MAP dropped to (84.77±5.13 mmHg) over a period of 5-7 minutes (p<0.05). However, 1 minute after pin insertion (T1) there was a significant increase in the HR and MAP compared to the baseline (B). HR increased to a maximum of 93.53±8.89 bpm and MAP to 102.50±6.65 mmHg respectively. HR increase was sustained for 5 minutes after pin insertion and then decreased to below baseline values at 10 min and remained so for the first 60 min after pin insertion. MAP on the other hand was noticed to be higher than the baseline at 5min, 10min, and 20min after pin insertion. At 30min, 40min, and 60 MAP was insignificantly lower than the baseline (p>0.05). The hemodynamic parameters are presented in Table 2.

Baseline HR between the two groups was not statistically different. After induction of anaesthesia and before skull pin insertion, dexmedetomidine significantly decreased HR and MAP when compared with the placebo group

(*P*<0.05). Pin attachment significantly increased HR and MAP in group P compared to group D at 1 and 5 minutes after pin insertion (*P*<0.05). Figure 1 shows a comparison of heart rate and Figure 2 represents the blood pressure changes between the dexmedetomidine and placebo groups.

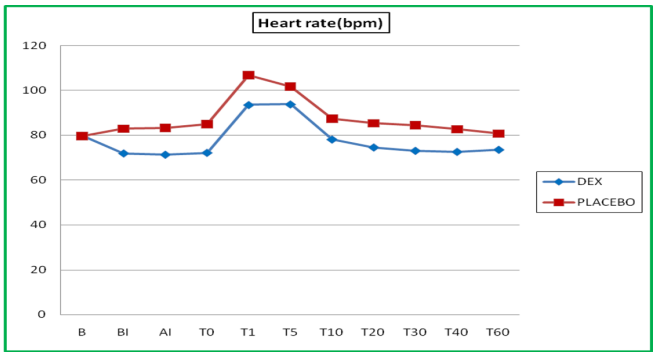

Figure 1: Line diagram comparing the heart rate between the dexmedetomidine group (group D) and placebo group (group P) at Baseline (B), Before Induction (BI), After Induction (AI), before pin insertion (TO), 1 minute (TI), 5 minute(T5), 10 minute (T10), 2 minutes (T20), 30 minutes (T30), 40 minutes (T40) and 60 minutes (T60) after pin insertion

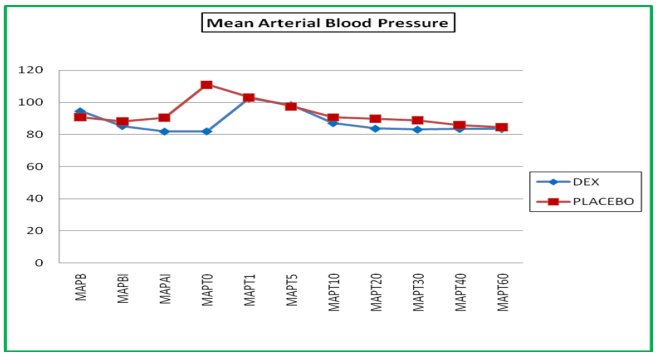

Figure 2: Line diagram comparing the mean arterial pressure between the dexmedetomidine group (group D) and placebo group (group P) at Baseline (B), Before Induction (BI), After Induction (AI), before pininsertion (TO), 1 minute (TI), 5 minute (T5), 10 minute (T10), 20 minutes (T20), 30 minutes (T30), 40 minutes (T40) and 60 minutes (T60) after pin insertion

NEUROENDOCRINE RESPONSES

In group P, the serum cortisol levels at baseline were 18.97±3.24 mcg/dl. At 30min and 60min, values were 57.63±6.56 mcg/dl and 124.43±9.28 mcg/dl respectively. This difference in cortisol level at 30min and 60min compared to the baseline was highly significant statistically (p<0.001). The baseline cortisol concentration in the group D was 19.87±3.51 mcg/dl. At 30 minutes and 60 minutes the peak plasma levels observed were 34.77±6.81 mcg/dl and 61.97±6.35 mcg/dl, respectively. This increase was statistically significant when compared to baseline values (p value<0.05). At baseline there was no difference between the cortisol levels of two groups. But at 30 minutes and 60 minutes the increase in cortisol levels was more in group P when compared to group D. This increase was stastistically significant (p<0.001).

Baseline serum prolactin levels in group P were 13.00±2.15ng/dl. After pin attachment there was a massive rise in serum prolactin level at 30 min of 226.70±38.69 ng/dl which was statistically highly significant (p<0.001). At 60 min, the prolactin levels dropped to 144.23±22.44 ng/dl which was still significantly higher compared to the baseline (p<0.001). Prolactin concentration at baseline in group D was 13.90±2.60 ng/dl. The levels increased after pin insertion, with peak plasma levels observed at 30 minutes of 154.93±21.68 ng/dl and then declining to 120.00±21.63 ng/dl at 60 minutes. The values for prolactin at 30 and 60 minutes were significantly higher compared to baseline in group D (p<0.001). There was no difference between baseline serum prolactin levels between two groups. Comparing the serum prolactin concentration at 30 min and 60 min between two groups yielded us highly significant differences at both the time intervals. Also our findings clearly confirmed the fact that serum prolactin levels rise in response to stress, but the change is only transitory. Table 3 shows the changes in neuroendocrine hormones at different stages of the surgery, and Table 4 shows the comparison of neuroendocrine hormones between the dexmedetomidine and placebo groups.

In group P, baseline insulin concentration was 8.21±1.08 µu/dl. Serum insulin showed a decreasing trend after pin insertion and the levels were significantly lower compared to baseline. At 30 minutes and 60 minutes values were 7.86±1.08 µu/dl and 5.77±1.17 µu/dl respectively. This difference when compared to baseline was statistically significant (p<0.05). Serum insulin concentration at baseline in group D was 8.21±1.16 µu/dl. The levels decreased after pin insertion to 7.76±1.15 µu/dl at 30min and the lowest values were observed at 60min of 7.34±1.14 µu/dl. The difference with the baseline was significant both at 30 min and 60 min (p<0.05). There was a statistically significant difference in serum concentration of insulin between the two groups at 30min and 60min (p<0.001).

The baseline plasma glucose concentration in group P was 90.00±4.29 mg/dl. There was a steady increase in plasma glucose concentration at 30 minutes (133.80±5.57 mg/dl) and at 60 minutes peak glucose concentration of 166.10±6.88 mg/dl was observed. This increase was statistically significant when compared to baseline (p<0.05). In group D baseline plasma glucose levels

Table 2: Heart rate and mean arterial pressure at different time intervals

GROUP		HEART RATE		Mean Arterial Pressure	
	Time interval	Mean±SD	p-value (bpm)	Mean±SD	p-value (mm Hg)
D	B	79.87±10.24	<0.001	90.53±5.26	<0.001
	BI	71.97±7.5		84.77±5.13	
P	B	79.53±10.08	0.002	92.47±6.93	0.001
	BI	82.87±6.2		87.93±5.58	
D	B	79.87±10.24	<0.001	90.53±5.26	<0.001
	AI	71.4±8.87		83.87±8.41	
P	B	79.53±10.08	0.001	90.53±5.26	0.001
	AI	83.27±6.91		87.40±3.51	
D	B	79.87±10.24	<0.001	90.53±5.26	<0.001
	T0	72.23±9.64		84.10±7.79	
P	B	79.53±10.08	<0.001	90.53±5.26	0.006
	T0	84.97±6.42		88.37±4.10	
D	B	79.87±10.24	<0.001	90.53±5.26	<0.001
	T1	93.53±8.89		102.50±6.65	
P	P	79.53±10.08	<0.001	90.53±5.26	<0.001
	T1	106.83 ±10.07		110.27±6.63	
D	B	79.87±10.24	<0.001	90.53±5.26	<0.001
	T5	93.8±11.69		99.73±7.91	
P	B	79.53±10.08	<0.001	90.53±5.26	<0.001
	T5	101.67 ±8.21		108.93±6.22	
D	B	79.87±10.24	0.300	90.53±5.26	0.037
	T10	78.17±7.13		96.20±5.29	
P	B	79.53±10.08	<0.001	90.53±5.26	<0.001
	T10	87.37 ± 8.35		101.10±8.93	
D	B	79.87±10.24	0.002	90.53±5.26	0.287
	T20	74.63±5.13		94.17±4.61	
P	B	79.53±10.08	0.003	90.53±5.26	0.001
	T20	85.3 ± 7.43		97.37±4.98	
D	B	79.87±10.24	<0.001	90.53±5.26	0.136
	T30	73.13±5.06		90.63±5.43	
P	B	79.53±10.08	0.008	90.53±5.26	0.329
	T30	84.37 ± 6.09		94.03±4.69	
D	B	79.87±10.24	<0.001	90.53±5.26	0.142
	T40	72.67±5.53		89.87±7.00	
P	B	79.53±10.08	0.079	90.53±5.26	0.312
	T40	82.63 ± 6.28		93.87±4.16	
D	B	79.87±10.24	<0.001	90.53±5.26	0.055
	T60	73.6±5.11		90.23±4.89	
P	B	79.53±10.08	0.553	90.53±5.26	0.755
	T60	80.7 ± 8.64		92.93±3.71	

D = Dexmedetomidine group; P = Placebo Group, B baseline; before induction (BI), after induction (AI), before pin insertion (TO), 1 minute (TI), 5 minute (T5), 10 minute (T10), 20 minutes (T20), 30 minutes (T30), 40minutes (T40) and 60 minutes (T60) after pin insertion. p-value <0.05 statistically significant bpm=beats per minute, mm Hg = mm of mercury.

Table 3: Mean serum cortisol, serum prolactin; serum Insulin and Blood glucose levels in group D and group P at different time intervals and a comparison of neuroendocrine responses of baseline versus 30 minutes and 60 minutes

Group		Baseline	30M	60M	P-value	
		Mean±SD	Mean±SD	Mean SD	B vs 30M	B vs 60M
Cortisol Level (mcg/dl)	D	19.87±3.51	34.77±6.81	61.97±6.35	<0.001	<0.001
	P	18.97±3.24	57.63±6.56	124.43±9.28	<0.001	<0.001
Prolactin Level (ng/dl)	D	13.90±2.60	154.93±21.68	120.00±21.63	<0.001	<0.001
	P	13.00±2.15	226.70±38.69	144.23±22.44	<0.001	<0.001
Insulin Level (µu/dl)	D	8.21±1.16	7.76±1.15	7.34±1.14	<0.001	<0.001
	P	8.21±1.08	7.86±1.08	5.77±1.17	<0.001	<0.001
Glucose Level (mg/dl)	D	91.23±5.12	113.20±5.83	134.50±6.07	<0.001	<0.001
	P	90.00±4.29	133.80±5.57	166.10±6.88	<0.001	<0.001

D = dexmedetomidine, P = placebo; B = Baseline, 30 M = 30 minutes; 60 M = 60 minutes mcg/dl=micrograms per decilitre, ng/dl=nano grams per decilitre, µu/dl=micro units/decilitre, mg/dl=milligrams/decilitre

Table 4: Comparison of serum cortisol, prolactin, insulin and glucose levels in the two groups at different time intervals

Group		Baseline		30M		60M	
		Mean±SD	P-value	Mean±SD	P-value	Mean±SD	P-value
Cortisol Level (mcg/dl)	D	19.87±3.51	0.307	34.77±6.81	<0.001	61.97±6.35	<0.001
	P	18.97±3.24		57.63±6.56		124.43±9.28	
Prolactin Level (ng/dl)	D	13.90±2.60	0.150	154.93±21.68	<0.001	120.00±21.63	<0.001
	P	13.00±2.15		226.70±38.69		144.23±22.44	
Insulin Level (µu/dl)	D	8.21±1.16	1.000	7.76±1.15	0.730	7.34±1.14	<0.001
	P	8.21±1.08		7.86±1.08		5.77±1.17	
Glucose Level (mg/dl)	D	91.23±5.12	0.316	113.20±5.83	<0.001	134.50±6.07	<0.001
	P	90.00±4.29		133.80±5.57		166.10±6.88	

Legend: D = dexmedetomidine, P = placebo; B = Baseline, 30 M = 30 minutes; 60 M = 60 minutes mcg/dl=micrograms per decilitre, ng/dl=nano grams per decilitre, µu/dl=micro units/decilitre, mg/dl=milligrams/decilitre

were 91.23±5.12 mg/dl. At 30 and 60 minutes the plasma levels were 113.20±5.83 mg/dl and 134.50±6.07 mg/dl respectively. The difference with the baseline was significant statistically at both the time intervals. Mean serum glucose level in group D was 91.23±5.124 mg/dl compared to 90.00±4.291 mg/dl in group P at baseline, the difference being insignificant statistically ($p>0.05$). A steady rise in serum glucose concentration was observed in both the groups after pin insertion at 30 min and 60min. However, plasma glucose values were significantly higher in group P compared to group D at 30 min and 60 min after pin insertion ($p<0.001$) [Table 3, Table 4].

DISCUSSION

The goals of neuroanaesthesia are to provide good operating conditions and to ensure stable haemodynamics without sudden increase in the intracranial pressure or acute brain swelling[7]. A marked hypertensive response is often seen when the mayfield skull-pin device is applied to stabilize the head of the anaesthetized patient for neurosurgery[8]. A noxious stimulus given to the scalp, either in the form of scalp incision or skull-pins placement results in acute hypertension even in an otherwise healthy, adequately anaesthetized patients[9,10]. Sudden increases in blood pressure can increase blood flow and volume in intracranial blood vessels, and consequently increase intracranial pressure[2,4,11]. Such an abrupt increase in blood pressure may lead to myocardial ischaemia[12] cardiac failure, intracranial haemorrhage in a susceptible patient[13]. Also the stress response to surgery is invariably associated with an increase in pituitary hormones[14]. This leads to secondary effects on hormone secretion from target organs[1]. Several reports have investigated the effects of dexmedetomidine on haemodynamics in patients undergoing neurosurgery[15–18]. But there is scanty literature available till date regarding the use of dexmedetomidine to attenuate the neuroendocrine responses to skull-pin placement for craniotomies.

Uyar et al[19] author conducted a study on patients undergoing craniotomy and head fixation with Mayfield head-holder. They reported a significant increase in the HR and MAP at 1 and 5 minutes after pin attachment in the placebo group when compared with the group that received dexmedetomidine ($p<0.05$).

Similar results were seen by Tanskanen et al.,[20] who observed that intraoperative dexmedetomidine infusion in craniotomy patients decreased haemodynamic responses to various noxious stimuli.

Turan G. et al., and Soliman R. N. et al.,[21,22] found that in patients undergoing intracranial surgery, administration of dexmedetomidine decreases MAP and HR significantly when compared to other group of patients who received placebo ($p<0.01$).

Comparing the effect of dexmeditomidine on haemodynamic response, with the placebo (saline), we found that the pin attachment significantly increased HR and MAP in group P compared to group D at 1 and 5 minutes after pin insertion. The increase was statistically significant ($P<0.05$). These findings were consistent with the findings of above mentioned studies.

We compared the level of cortisol in two groups and observed that, the increase in cortisol levels at 30 and 60 minutes was more in group P when compared to group D. This increase was stastistically significant ($p<0.001$).

Comparing the serum prolactin concentration at 30 min and 60 min between two groups yielded us a highly significant difference at both the time intervals. Also our findings clearly confirmed the fact that serum prolactin levels rise in response to stress, but the change is only transitory.

A steady rise in serum glucose concentration was observed in both the groups after pin insertion at 30 min and 60 min. However, plasma glucose values were significantly higher in group P compared to group D at 30 min and 60 min after pin insertion ($p<0.001$). Also, there was a statistically significant difference in serum concentration of insulin between the two groups at 30 min and 60 min ($p<0.001$).

In agreement with our study, Uyar et al.[19] found that plasma concentration of cortisol and glucose had increased significantly in the placebo group, than in the dexmedetomidine group.

In another study conducted by Mukhtar et al.,[23] they observed that dexmedetomidine did inhibit the hyperglycaemic response to surgery significantly more than placebo. These results were similar to our study.

CONCLUSION

The present study concludes that preoperative administration of dexmedetomidine at a dose of 1µg/kg over a period of 10 minutes before induction of anaesthesia can be a useful adjuvant in neurosurgical procedures. It attenuates the haemodynamic and neuroendocrinal response to skull-pin placement for craniotomies. Further studies are required to determine the safety and efficacy of using dexmedetomidine in patients with higher ASA status and in patients with associated cardiac disease.

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