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Original Research Article

Low Dose Dexmeditomidine for Maintaining Hemodynamic Stability in Patients Undergoing Craniotomy for Supratentorial Tumors

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Conflict of interest: Nil

Abstract:

Background and Aims: Maintaining hemodynamic stability during craniotomy and intracranial surgery is of utmost importance for the post-operative evaluation of neurological integrity and stability. Many anaesthetic techniques are in practice to ensure hemodynamic stability, among which the preoperative use of low dose dexmeditomidine during intracranial surgeries is a newer and recent method. We wanted to find out whether a low dose of dexmeditomidine followed by infusion would provide stable hemodynamics and hence this study

Methods: This was a prospective cohort study in which 60 patients of either gender or sex, ASA I or II posted for supratentorial tumor surgery were randomly divided into 2 groups. 1st group (Group D) received Inj dexmeditomidine 0.5mcg /kg over 20 minutes and the second group received saline in equal volumes (Group ND), twenty minutes before induction, followed by standard general anaesthesia as per hospital protocol for neuroanaesthesia. A maintenance dose of 0.4 mcg/ kg/hr of dexmed infusion was started after the bolus dose for group D. Hemodynamic parameters were measured during skull pin insertion, after induction, during surgery and at extubation.

Results: Qualitative data analysis was done using student t test. Quantitative data were compared between 2 groups using Chi square test. Significant increase in heart rate were noted in group ND than the dexmed group $p<0.001$. Also, systolic Bp increase was also noted in the ND group than the dexmed group $p<0.001$.But there was no statistically significant difference in diastolic Bp.

Conclusion: Dexmeditomidine bolus followed by low dose infusion provides hemodynamic stability in patients undergoing craniotomy for supratentorial surgeries.

Keywords: Hemodynamic Stability, dexmeditomidine, Craniotomy, Supratentorial Tumors.

Introduction

Anaesthetic management of craniotomy for supratentorial tumors is an area where we need some expertise. Intraoperative concerns during craniotomy generally revolve around intracranial pressure (ICP) reduction and protection against inadvertent cerebral ischemia. Maintenance of optimal systemic physiology still remains the mainstay to achieve both the goals It involves maintenance of adequate hemodynamic stability by avoiding sudden increases in Bp and heart rate which may then lead to an increase in intracranial tension which may be hazardous for the patient. So stability of cardiovascular hemodynamics should be maintained not only during the intraoperative period but also during the preop preparatory phase and by adequate planning of premedication for the patient[1]. If not done so it may lead to devastating consequences due to increased sympathetic stimulation that leads to increase in heart rate Bp, and ICP during intubation, skull pin application, craniotomy incision. This may seriously compromise the cerebral circulation leading to intracerebral haemorrhage or cerebral hypoperfusion especially in patients with compromised autoregulation and compliance. Therefore, maintaining the proper cerebral perfusion pressure and proper surgical conditions are the most important key points for managing supra and infratentorial craniotomies.[2] So proper preparation of the patient and proper preoperative management helps to prevent sudden fluctuations during intubation, Mayfield skull pinning and craniotomy incision. Adequate preop preparation with proper control of BP, control of diabetes, reduction in elevated ICP and with proper and timely premedication can help in ensuring a smooth induction without much fluctuations during key moments in induction, intubation, skull pinning and craniotomy incisions and during intraoperative periods also. Induction with intravenous agents still

remains the first choice due to its favorable effects on cerebral hemodynamics and intraoperative cerebral protection.[3] Controversy continues regarding the superiority of one agent over the other. Other modalities like skull pinning site local infiltration,[4] scalp block using local anaesthetic,[5] low dose ketamine prior to pinning,[6] IV magnesium infusion,[7] IV clonidine infusion[8] and dexmeditomidine infusion,[9] bolus doses of remifentanyl[10] have been tried to prevent drastic fluctuations in hemodynamics.

Dexmedetomidine is a potent, highly selective α2-adrenoceptor agonist (alpha 2 specificity of 1620:1) with sedative, analgesic and anxiolytic effect.[11] There are several studies where dexmeditomidine has been used in varying doses to provide hemodynamic stability during intraoperative period. An important feature of dexmeditomidine sedation is that patients remain easily rousable. In contrast to other sedative agents, dexmeditomidine is not associated with respiratory depression.[12] Dexmeditomidine has significant analgesic qualities and has been labeled as "analgesia sparing" by FDA. Fundamental research suggests that dexmeditomidine converges on a natural sleep pathway to exert its sedative effect.[13] The mechanism of action is unique and differs from those of currently used sedative agents, including clonidine. Combined, these effects can produce analgesia, sedation, and anxiolysis. Because of all these properties, we decided to do this study to assess the efficacy of dexmeditomidine to provide hemodynamic stability in patients undergoing craniotomy for supratentorial tumors with analgesia and lesser sedation.

Methodology

Type of Study

Prospective cohort study

Study Setting

Patients undergoing craniotomy for supratentorial tumors in Neurosurgery OT in Government Medical College Kozhikode were assessed for inclusionand exclusion criteria and were included in the study after obtaining written informed consent.

Sample Size

Calculation done using the formulan

$$= \frac{(z\alpha+z\beta)^2 \times SD^2 \times 2}{d^2}$$

zα= 1.96 , zβ=0.84
SD = Standard deviation,
d = effect size

As per R.P Kaushal[14] et al the average standard deviation was found to be 9.64 Applying that in the formula and taking d as 5 the sample size is calculated to be 59 in each group with a total of 118 patients in the study.

Inclusion Criteria

- Craniotomy for supratentorial tumours ASA I, II.
- Age 18 – 55 years.
- Preoperative Glasgow coma scale 15/15Weight 31 – 80 kg.

Exclusion Criteria

- Patient refusalHeart block.
- Known allergy to Dexmedetomidine or Propofol.
- Preoperative heart rate less than 50 beats per minute Patients on beta blockers, Coronary artery disease Left ventricular dysfunction.
- Patients with intracranial aneurysmsPregnancy.
- Morbidly obese patients.
- Patients with renal or hepatic disease.

Materials and Methods

After obtaining approval from the institutional research committee andethical committee, patients were selected as per inclusion & exclusion criteria and included in the study. A prospective cohort study was conducted in which ASA grade I or II patients between 18- 55years of age and with CT-scan proof of intracranial tumour was selected. All patients included in study underwent a pre-anesthetic examination. Informed written consent was taken from all patients in their local language. Patients were kept nilper oral for 8 hours prior to surgery. Patients were given Alprazolam 0.25mg 8 hoursprior to surgery.

Patients were classified into 2 groups Group D and Group ND. Group D constituted patients who received dexmeditomidine as a bolus dose of 0.5µg/kg over 20 minutes before induction of anesthesia, followed by a maintenance infusion of 0.4µg/kg/hr. The infusion was discontinued after closure of skin incision. Group ND constituted patients who did not receive dexmeditomidine

Upon arrival in the operating room, following monitors were attached

- Electrocardiogram
- Noninvasive blood pressure
- Pulse oximeter

Baseline parameters like heart rate (HR), NIBP, SPO_2, $EtCO_2$ were monitored. The gender, age, body weight, and operation time of each case was recorded. The blood pressures (Systolic blood pressure, diastolic blood pressure, mean blood pressure) and heart rate values recorded before the induction was considered as baseline values.

In patients who received dexmedetomidine the blood pressure and heart rate recorded before administration of dexmedetomedine was taken as

baseline values. Intravenous access with 18G cannula in the forearm and Intravenous fluid, 0.9% normal saline was started.

Anaesthesia was standard for all the patients. The patients were premedicatedwith intravenous doses of Inj. Midazolam 0.02mg/kg, Inj. Morphine 0.1mg/kg, Inj.Glycopyrolate 0.2 mg and Inj. Ondansetron 4 mg.

- Induction was achieved with Inj Propofol 2 mg/kg. Intubation was facilitated with Inj Vecuronium 0.1mg/kg.
- Anaesthesia was maintained with nitrous oxide, oxygen and Isoflurane and muscle relaxation was maintained with Inj.Vecuronium.
- Patients in both groups were mechanically ventilated with tidal volume at 8- 10 ml/kg, for an EtCO2 of 28-32 mm Hg
- Post induction, arterial line was inserted to monitor the arterial blood pressure, peripherally inserted central line was inserted and central venous pressure monitored.
- Before the skull clamp was put in place, skin region to be pinned was infiltrated with 2% Lidocaine.

The systolic arterial pressure, diastolic arterial pressure, mean arterial pressure and heart rate was recorded at induction, at intubation, at skull clamp insertion, every 10 minutes after induction for 1 hour and at extubation.

We aimed to maintain HR and mean arterial pressure (MAP) within 20 % of baseline values. Patients were monitored for hemodynamic changes and adverse events during the intraoperative period.

Bradycardia was defined as HR<50 bpm, tachycardia as a >20% increases from baseline is in HR. Hypertension as a >20% increase from baseline in MAP, andhypotension as <20% decrease from baseline in MAP. Bradycardia was treated by administration of Inj. Atropine 0.6 mg. Hypotension was treated by administration of 6 mg of Inj. Ephedrine. Refractory or persistent hypotension was defined as hypotension requiring more than 3 boluses of Ephedrine and more than 500 ml of crystalloid.

In both the groups, any rise in the heart rate or mean blood pressure (MAP),more than 20% of baseline was treated immediately in 2 successive steps. The second step followed in succession only if 1st step failed to control the rise in MAP and HR respectively.

- Step 1: Bolus injections of propofol, 1mg/kg
- Step 2: Increasing concentration of the volatile agent to 1 MAC

The study was proposed to be abandoned if any untoward event, such as persistent hypotension not responding to vasopressors but requiring inotropic support, bradycardia, anaphylaxis developed.On completion of surgery, the neuromuscular blockade was reversed with I/V Neostigmine 0.05mg/kg and Inj. Glycopyrolate 0.01 mg/kg.

The patients were extubated after giving reversal agent, adequate suction, when patient had regular respiration and was able to respond to commands. The time of extubation was recorded. The discontinuation time of dexmedetomidine infusion recorded. Postoperative analgesia was facilitated by NSAIDS (diclofenac sodium injection IV) if the patients complained of pain.

Statistical Method

Qualitative data was analyzed using Proportional Chi-square and quantitative data analyzed using Mean Standard deviation. Categorical outcomes were compared between the study groups using Chi square test. P value <0.05 was considered statistically significant. IBM SPSS version 22 was used for statistical analysis.

Results

Table 1: Comparison of gender between study groups (n =118)

Sex	Group Dex		Group ND		Chi-square test P value
	No	%	No	%	
Male	31	52.5%	33	55.9%	0.712
Female	28	47.5%	26	44.1%	
Total	59	100.0%	59	100.0%	

A total of 118 subjects were included in the study.

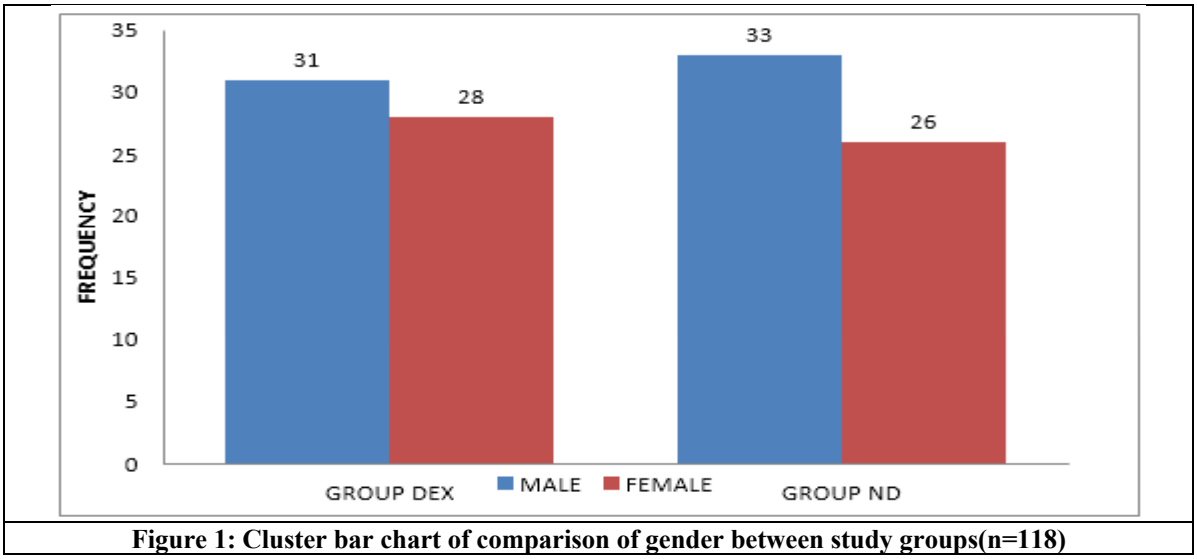

Figure 1: Cluster bar chart of comparison of gender between study groups(n=118)

Both groups were comparable in relation to gender (P value 0.712).

Table 2: Comparison of ASA status between the study groups (n=118)

ASA	Group Dex		Group ND		Chi-square testP Value
	No	%	No	%	
ASA I	33	55.9%	35	59.3%	0.709
ASA II	26	44.1%	24	40.7%	
Total	59	100.0%	59	100.0%	

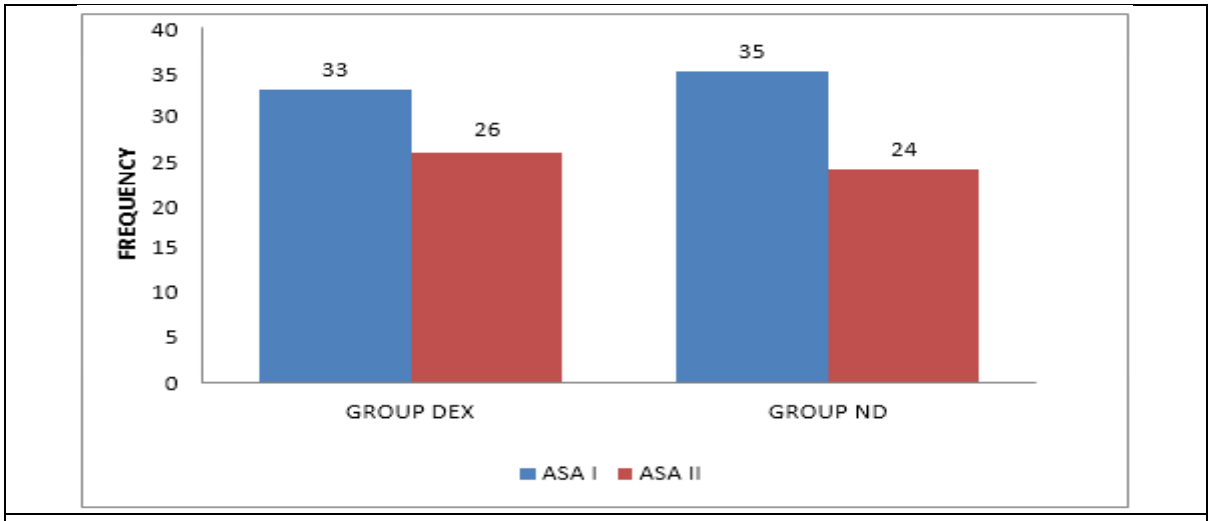

Figure 2: Cluster bar chart comparing ASA status of study groups

Both groups were comparable with respect to ASA status (p value 0.709)

Table 3: Comparison of weight, age and duration of surgery between studygroups (n=118)

Variables	Group Dex		Group ND		Unpaired 't' testP value
	Mean	SD	Mean	SD	
Weight	54.85	5.82	53.68	6.03	0.286
Age	50.37	4.99	51.24	2.46	0.235
Duration of surgery	1.97	0.22	2.04	0.31	0.201

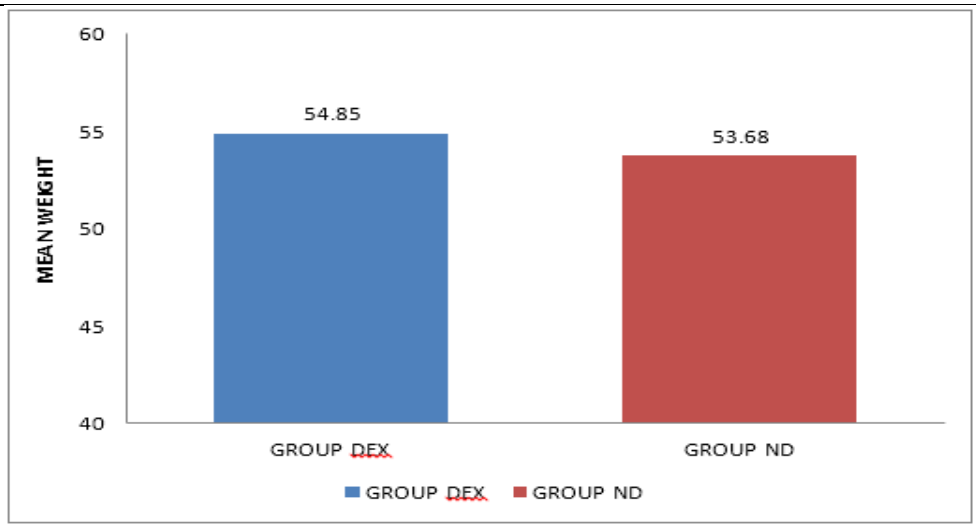

Figure 3: Bar chart of comparison of weight between study groups (n=118)

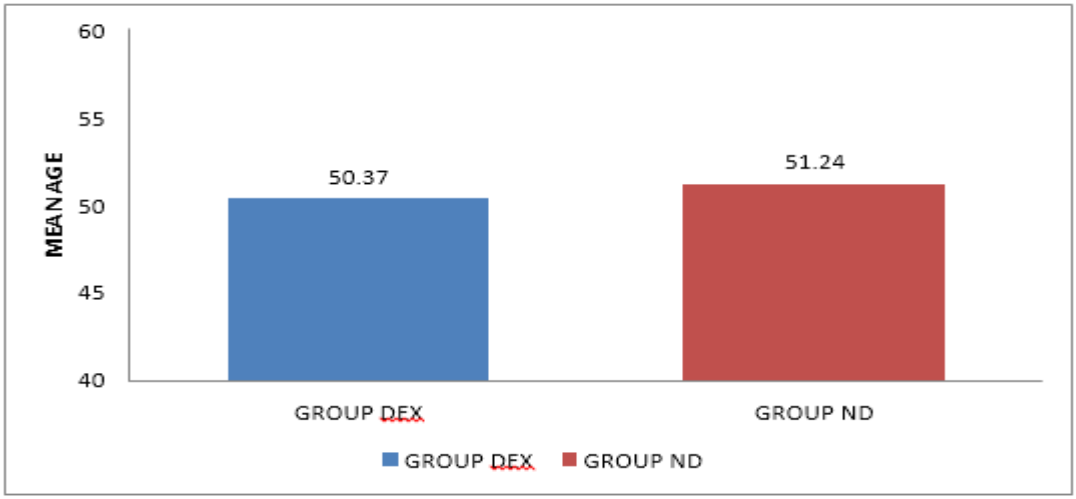

Figure 4: Bar chart showing comparison of age between study groups (n=118)

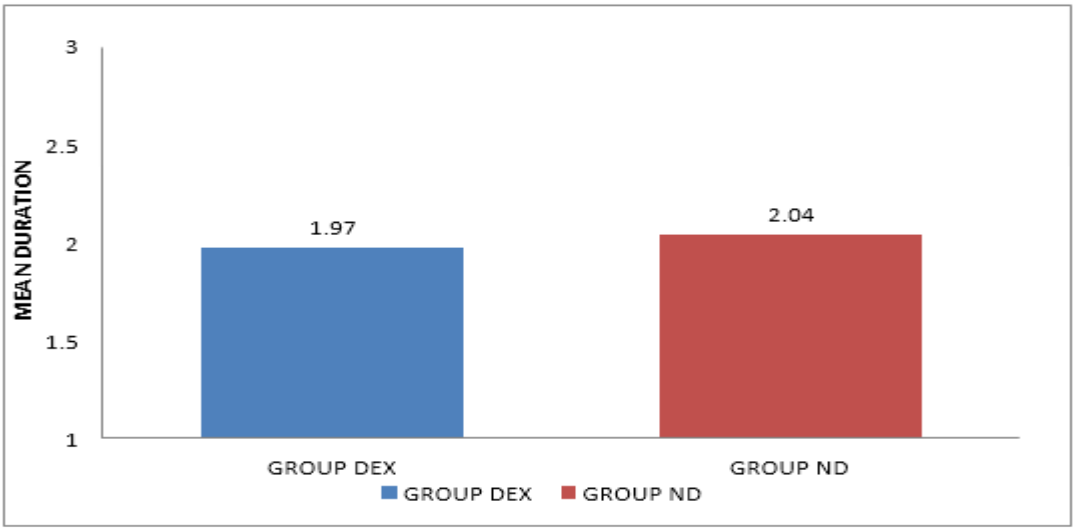

Figure 5: Bar chart showing comparison of duration of surgery between two groups (n=118)

Both groups were comparable with respect to weight, age and duration ofsurgery with p values 0.286, 0.235, 0.201 respectively.

Table 4: Comparison of heart rate between two groups (n=118)

Heart rate	Group Dex		Group ND		Unpaired 't'test P value
	Mean	SD	Mean	SD	
Baseline	85.51	11.99	81.00	11.11	0.036
Induction	88.10	13.14	87.75	9.36	0.866
At intubation	87.12	11.81	86.76	6.33	0.839
At skull clampinsertion	84.42	11.13	106.47	6.31	<0.001
10 minutes afterinduction	81.64	9.97	94.98	7.42	<0.001
20 minutes afterinduction	81.36	11.21	94.56	6.54	<0.001
30 minutes afterinduction	79.61	11.21	94.61	6.96	<0.001
40 minutes afterinduction	80.08	10.14	92.56	6.73	<0.001
50 minutes afterinduction	80.47	9.57	92.66	5.88	<0.001
60 minutes afterinduction	80.88	9.71	91.42	5.72	<0.001
Extubation	85.92	12.53	100.12	7.93	<0.001

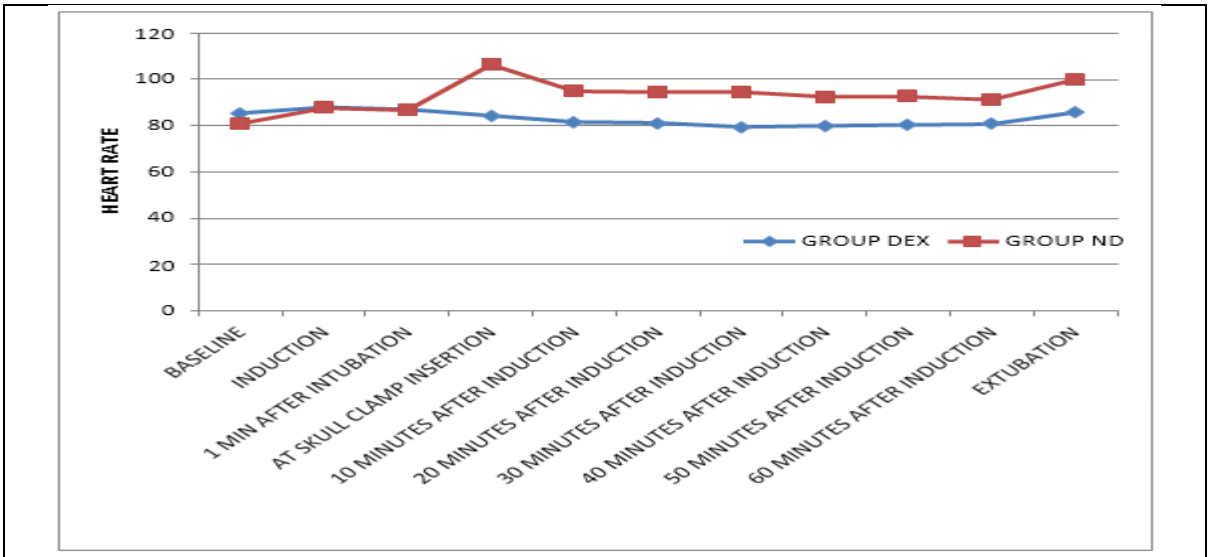

Figure 6: Line diagram of comparison of heart rate between study groups(n=118)

There is statistically significant decrease in heart rate seen in the Dex groupsince the P value is <0.05 from the time of skull clamp insertion.

Table 5: Comparison of systolic blood pressure between two study groups(n=118)

SBP	Group Dex		Group ND		Unpaired't' test P value
	Mean	SD	Mean	SD	
Baseline	133.47	10.48	119.32	11.41	<0.001
Induction	125.76	9.59	136.02	8.74	<0.001
At intubation	123.19	9.28	124.56	5.82	0.338
At skull clamp insertion	119.31	9.36	148.80	4.97	<0.001
10 minutes after induction	117.66	8.54	122.05	12.01	0.024
20 minutes after induction	114.31	8.10	117.41	8.54	0.045
30 minutes after induction	113.41	7.32	113.32	6.65	0.948
40 minutes after induction	111.80	6.55	112.39	6.44	0.621
50 minutes after induction	110.88	6.55	115.83	6.92	<0.001
60 minutes after induction	109.51	6.78	114.22	6.27	<0.001
Extubation	109.75	6.30	131.63	6.96	<0.001

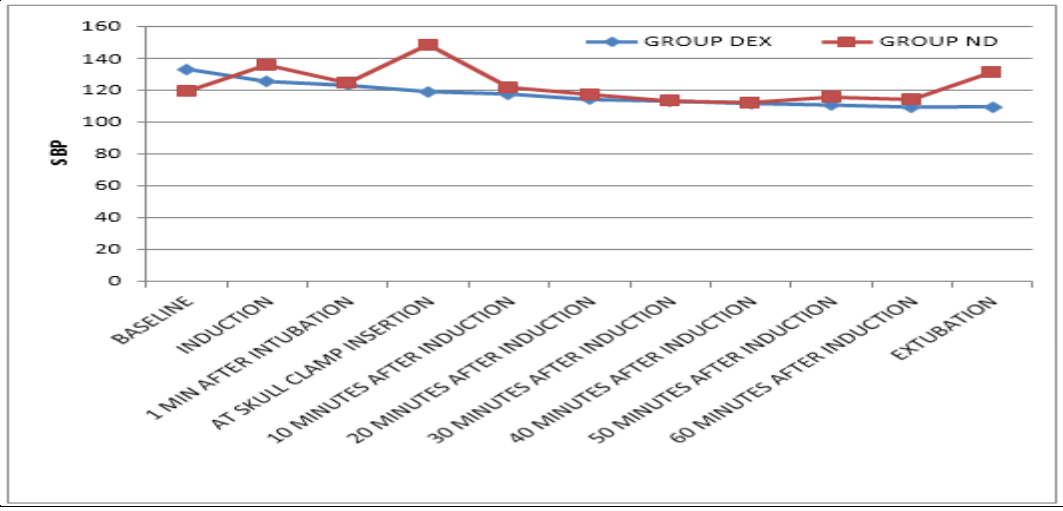

Figure 7: Line diagram showing comparison of systolic BP between twogroups (n=118)

There is statistically significant decrease in systolic BP in the DEX group asseen from the results at induction (P value <0.001), during skull clamp insertion (P value<0.001), during the intraoperative period except at 30 and 40 minutes after induction and at extubation (P value <0.001).

Table 6: Comparison of diastolic BP between two study groups (n=118)

DBP	Group DEX		Group ND		Unpaired 't'test P Value
	Mean	SD	Mean	SD	
Baseline	69.75	9.95	55.27	4.03	<0.001
Induction	67.37	10.19	61.83	8.78	0.002
At intubation	66.20	9.38	62.22	8.80	0.019
At skull clamp insertion	64.20	9.20	61.92	8.85	0.171
10 minutes after induction	62.88	8.87	60.47	9.29	0.153
20 minutes after induction	62.12	8.75	60.07	10.62	0.255
30 minutes after induction	60.95	8.38	60.47	10.12	0.782
40 minutes after induction	59.92	7.71	60.10	10.58	0.913
50 minutes after induction	59.07	8.40	60.63	10.73	0.381
60 minutes after induction	58.58	7.60	60.88	10.43	0.173
Extubation	56.95	7.71	63.81	10.97	<0.001

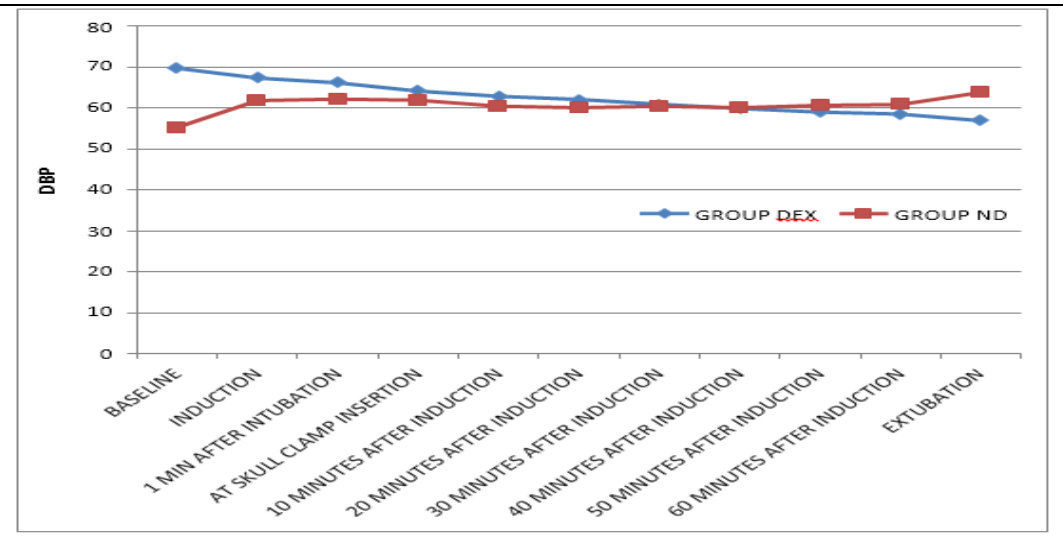

Figure 8: Line diagram depicting comparison of diastolic BP between twostudy groups (n=118)

There is no statistically significant difference in diastolic BP between two study groups except at the time of extubation where the DEX group had a decrease in BP which was statistically significant (P value <0.001).

Table 7: Comparison of mean BP between two study groups (n=118)

MAP	Group Dex		Group ND		Unpaired 't'test P Value
	Mean	SD	Mean	SD	
Baseline	91.08	7.58	77.27	5.39	<0.001
Induction	86.68	7.10	86.61	7.78	0.961
At intubation	85.22	6.44	83.15	6.31	0.081
At skull clamp insertion	82.63	6.19	90.92	6.11	<0.001
10 minutes after induction	80.92	5.92	80.80	3.67	0.896
20 minutes after induction	79.46	5.55	79.19	6.29	0.804
30 minutes after induction	78.25	5.21	78.08	6.17	0.872
40 minutes after induction	77.00	5.45	77.47	6.95	0.681
50 minutes after induction	76.27	6.10	79.05	6.27	0.016
60 minutes after induction	75.36	5.49	78.81	7.80	0.006
Extubation	74.31	5.86	86.68	8.47	<0.001

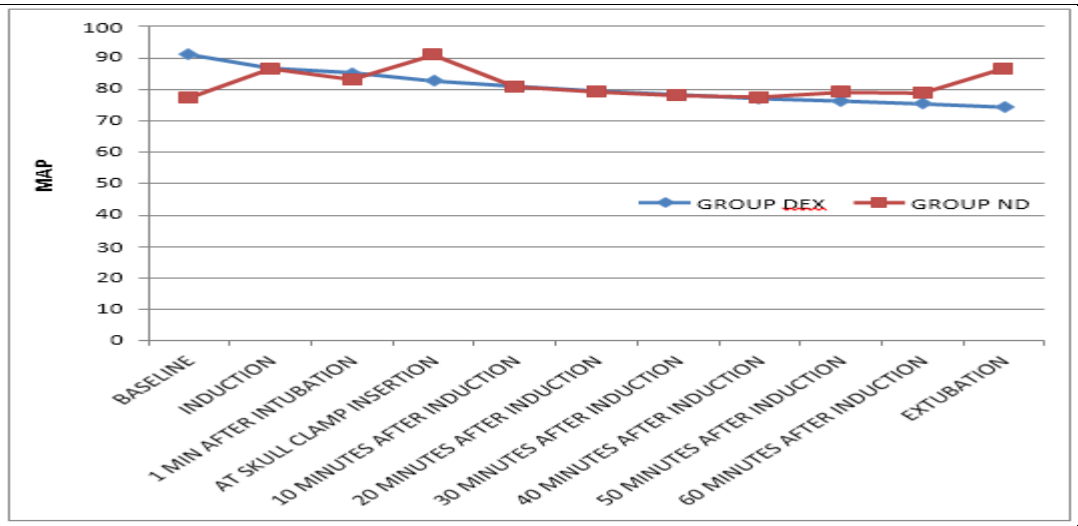

Figure 9: Line diagram depicting comparison of mean BP between two studypopulation (n=118)

There is a statistically significant decrease in mean BP occurring after intubation, at skull clamp insertion, 50 minutes, 1 hour after surgery and at extubation (P value <0.001).

Discussion

Data on the perioperative use of dexmedetomidine in patients undergoing craniotomy indicates that it offers greater hemodynamic stability at incision and emergence. Dexmedetomidine, alpha 2 adrenoceptor agonist used as adjuvant to anaesthetic agents. Relatively recent studies have shown that dexmedetomidine is able to decrease circulating plasma norepinephrine and epinephrine concentration in approximately 50%,[15] decreases brain blood flow by directly acting on post-synaptic alpha 2 receptors, decreases CSF pressure without ischemic suffering and effectively decrease brain metabolism and intracranial pressure and also, able to decrease injury caused by focal ischemia.[16] These properties provide stable perioperative cerebral haemodynamics, avoids sudden rise in intracranial pressure and prevents acute brain swelling. The clinical characteristics of dexmeditomidine make this intravenous agent a potentially attractive adjunct for neuroanaesthesia and in the neurological intensive care unit. Perioperative haemodynamics stability is one of the most important concepts of neuroanaesthesia. During surgery, low arterial pressure predisposes patient to cerebral ischemia, as auto regulation of the cerebral blood flow is often impaired near tumors and traumatized areas. Hemodynamic stability is also important for rapid and smooth recovery which is preferred for immediate neurological evaluation. Studies have proven hemodynamic stability of dexmeditomidine and are preferred as an anaesthetic adjuvant for various neurosurgical procedures.[17]

The heart rate and mean arterial blood pressure, decreased in patients who were administered dexmedetomidine more than placebo group with significant statistical difference between the two groups (P-value <0.05) in a study by Soliman et al.[18] This result was similar to that observed in our study. the hemodynamic stability of dexmeditomidine

Jadhav et al conducted a study which aimed to assess the effect of dexmedetomidine on intraoperative hemodynamic stability and to assess the

intraoperative requirements of analgesic and other anaesthetic agents. 60 patients were divided into 2 groups.one group received dexmedetomidine as bolus and infusion and other received placebo. The mean HR, the mean DBP and the mean MAP were lower in the group that received dexmedetomidine as compared to group that received placebo and the difference was statistically significant. The outcome of the study was comparable to that observed with the present study.[19]

Talke P et al., studied, the hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery.[20] It was found that during emergence from anaesthesia, heart rate was slower with dexmedetomidine (73+11 bpm) than placebo (83+20 bpm) (p=0.006) and the percentage of time the heart rate was within the predetermined hemodynamic limits was more frequent with dexmedetomidine (p<0.05). So, they concluded that dexmedetomidine attenuates increases in heart rate during emergence from anaesthesia. In the present study at the time of extubation the mean HR in Group Dex and in Group non dex was 85.92+12.53 bpm and 100.12+7.93 bpm, respectively. The HR in Group Dex was significantly lower as compared to Group Non Dex (p-value <0.005). Thus, observation in present study was similar to that of above study.

Tanskanen PE et al., studied 54 patients undergoing intracranial tumour surgery randomized to receive in a double-blind manner a continuous dexmedetomidine infusion (plasma target concentration 0.2 or 0.4 ng/ml) or placebo, beginning 20 minutes before anaesthesia and continuing until the start of skin closure.[21] They found that, the median percentage of time points when systolic blood pressure was within more or less than 20% of the intraoperative mean was 72, 77 and 85 in placebo, DEX-0.2 and DEX-0.4 groups, respectively (p<0.01), DEX-0.4 groups differed significantly from the other groups. Tachycardiac response to intubation is blunted with DEX (p <0.01) as well as the hypertensive response to extubation (p <0.01). The heart rate variability in DEX-0.4 group from placebo (93 vs. 82%, p <0.01) was statistically significant. So, they concluded, dexmedetomidine increased perioperative haemodynamic stability in patients undergoing brain tumour surgery.

In the present study like above study dexmedetomidine blunted tachycardia and hypertensive response to and extubation but a statistically significant decrease in heart rate or blood pressure during intubation was not seen. But it produced a statistically significant decrease in heart rate and blood pressure during pin insertion.

Bakhamees HS et al., studied 80 morbidly obese patients undergoing laparoscopic gastric bypass who were randomly assigned to one of two study groups(); Group D (40 patients) received dexmedetomidine (0.8 µg/kg bolus, then as infusion 0.4 µg/kg/ hr) and Group P (40 patients) received normal saline (placebo) in the same volume and rate. dexmedetomidine showed significant decrease of intraoperative and postoperative mean blood pressure, heart rate. They concluded that, dexmedetomidine offers better control of intraoperative and postoperative haemodynamics.[22] As in above study, in the present study there was significant decrease in MAP and HR in Dexmedetomidine. Thus, results of present study are in concurrence with this study.

Bekker A et al., studied the effect of dexmedetomidine on perioperative haemodynamics in patients undergoing craniotomy.[23] In this study, 72 patients scheduled for elective craniotomy were randomly assigned to receive either sevoflurane-opioid or sevoflurane-opioid-dexmedetomidine anaesthesia. They concluded that intraoperative dexmedetomidine infusion was effective for blunting the increases in SBP perioperatively. In the present study dexmedetomidine obtunded the rise in SBP at the time of induction, pin insertion and extubation as compared to placebo. Thus the observations in present study were similar to that of above study.

Keniya VM et al., studied 60 patients scheduled for elective surgery of more than three hours into two groups;[24] one is the control group which received isoflurane-opioid and the other is study group which received isoflurane-opioid- dexmedetomidine anaesthesia. After tracheal intubation, maximal average increase was 8% in systolic and 11% in diastolic blood pressure in dexmedetomidine group, as compared to 40% and 25%, respectively, in the control group. Also, the average increase in heart rate was 7% and 21% in the dexmedetomidine and control groups, respectively. Hence they concluded that dexmedetomidine is effective in attenuating sympathoadrenal response to tracheal intubation. In the present study at the time of intubation the changes in heart rate, systolic BP and diastolic BP were not statistically significant but was statistically significant during induction, skull clamp insertion and intraoperative period.

Limitations of the Study

This study is an observational study; more randomized trials are required to reach a definite conclusion. The sample size is small. The study needs to be with a larger sample size for better assessment of outcomes.

Conclusion

It is concluded from this study that low dose dexmedetomidine 0.5 □g/kg 20 minutes before induction and 0.4□g/kg/hr as maintenance gives

hemodynamic stability in patients undergoing craniotomy for supratentorial tumours as evidenced by the stability in heart rate and mean arterial blood pressure during the surgery.

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