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Effect of Different Doses of Dexmedetomidine in Supratentorial Tumor Surgery: A Randomized Control Study

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Abstract

Background: The dexmedetomidine is a highly selective α-2 adrenoreceptor agonist and frequently used as an adjuvant to anesthesia for intraoperative hemodynamic stability with infusion doses ranging from 0.2 to 0.7 µg/kg/hr. We have contemplated to study different infusion doses in patients undergoing supratentorial tumor surgery to establish the optimum dose. *Methods:* Sixty ASA grades I/II patients, aged 20-65 years scheduled for elective surgery were divided randomly into four equal groups (n=15). In groups (2, 3 & 4), dexmedetomidine was infused as a bolus dose of 1 µg/kg over15min after the induction of anesthesia; and was maintained with dexmedetomidine 0.3 µg/kg/ hr (group 2), dexmedetomidine 0.4 µg/kg/hr (group 3) and dexmedetomidine 0.5 µg/kg/ hr (group 4) as a continuous intravenous infusion at the rate of 14ml/hr during perioperative period. Group 1 received normal saline during intraoperative period. Hemodynamic changes, intraoperative brain condition, emergence characteristics and complications during the study period were assessed. *Results:* Heart rate, systolic, diastolic and mean arterial pressures were significantly lower in dexmedetomidine (group 2, 3 and 4) as compared to control (group 1) ($p<0.05$). These parameters were comparable in dexmedetomidine groups. Blunting of tachycardia response to intubation and the hypertensive response to extubation were observed in these patients. Intra-operative brain relaxation scores as assessed by surgeons were comparable in all four groups ($p>0.05$). Opioid sparing effect was seen with dexmedetomidine groups in terms of better hemodynamic stability even at lower doses. Incidence of bradycardia was 13% and hypotension was 20% which were higher in Group 4 but incidence was statistically comparable with other groups. Similarly, 3(20%) patients could not be extubated due to poor cough reflex and sedation. They were shifted to ICU for elective ventilation. *Conclusions:* Dexmedetomidine attenuates stress responses to various noxious stimuli during surgery, maintains hemodynamic stability, blunts tachycardia and hypertensive response, reduces requirements of opioids and provide good intraoperative brain conditions and early recovery. The benefit risk assessment favors an initial bolus of 1µg/ kg over 15 min followed by an infusion of 0.4 µg/kg/hr over other doses (0.3 µg/ kg/hr and 0.5 µg/kg/hr) in patients undergoing supratentorial tumor surgery.

Keywords: Dexmedetomidine; Supratentorial Tumour; Haemodynamics.

Introduction

Neurosurgical patients usually have impaired autoregulation of the cerebral circulation with cerebral blood flow (CBF) relying mainly on mean arterial pressure [1,2]. Surgical stress associated with craniotomy frequently produces sympathetic activation which is a major cause of hemodynamic changes from the start of surgery. This perioperative hypertension can lead to intracranial bleeding and prolongation of hospitalization [3]. Attenuation of hemodynamic response to nociceptive stimuli is therefore desired during neurosurgical procedures for better cerebral protection.

Dexmedetomidine, a highly selective central α2-adrenoreceptor agonist, is increasingly being used for its sedative, analgesic, anxiolytic, sympatholytic and haemodynamic stabilizing properties. It also

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provides a "conscious sedation", and analgesia without respiratory depression [4-6]. Dexmedetomidine enhances anesthesia produced by other anesthetic drugs thus consistently reduces anesthetic requirements. Dexmedetomidine has been shown to provide good intraoperative hemodynamic stability with decreased intraoperative opioid requirements. Dexmedetomidine can inhibit the stress responses thereby improving the outcomes of tracheal intubation [7]. It may also have neural protective effects [8]. A few studies have shown that dexmedetomidine has reduced shivering and requirement of anti-emetics in the postoperative period. Thus it can be a suitable anesthetic adjuvant to neurosurgical anesthesia [9].

Several studies have shown that dexmedetomidine when used in titrated doses intaoperatively shows better maintenance of hemodynamic stability and fast postoperative recovery, with the loading dose of 1 μg/kg over 10 minutes, followed by a maintenance infusion of 0.2 to 0.7 μg/kg/hr [9-11]. However, hypotension remains concern with increasing doses of dexmedetomidine.

Though, the dexmedetomidine is used widely as an adjuvant, the data on appropriate doses to be used in neuroanesthesia is scanty. Therefore, this dose ranging study was designed with an aim to find a clinically appropriate dose that would ensure intaoperative hemodynamic stability and fast recovery in patients undergoing supratentorial tumour surgery.

Material and Methods

The study was a prospective, randomized, double blind comparative study. The study was conducted at Nizam's institute of Medical Sciences, Hyderabad in compliance with all applicable regulations and good clinical practice guidelines. The study was approved by Institutional Ethics Committee. Written inform consents were obtained from patients before the enrollment.

Study Population

Patients scheduled for elective supratentorial tumor surgery, with age between 20-65 years, of either gender, with American Society of Anesthesiologists (ASA) class I or II, Glasgow coma scale score of 14 to15 and with Mallampati classification of I or II were included in the study.

Morbid obese patients, pregnant or lactating women, preoperative heart rate of <45 beats/ min, having second or third degree AV block, history of lung, liver or kidney diseases, having hypersensitivity to dexmedetomidine, history of drug or alcohol abuse, taking anti-hypertensive medication like α-methyldopa, clonidine or other α2- adrenergic agonist, participated in other drug study during the preceding one month were excluded from the study.

Randomization Procedure

Using computer-based simple randomization method patients were allocated equally to four different groups. Group 1 patients received continuous intravenous infusion of normal saline at the rate of 14ml/hr while in Groups 2, 3 and 4 dexmedetomidine was infused as a bolus dose of 1 μg/kg in 15mins after the induction of anesthesia; and was maintained with dexmedetomidine 0.3 μg/kg/ hr (Group 2), dexmedetomidine 0.4 μg/kg/hr (Group 3) and dexmedetomidine 0.5μg/kg/hr (Group 4) as a continuous intravenous infusion at the rate of 14ml/hr during perioperative period. The case conducting anesthesiologist and recording anesthesiologist were unaware of the concentration of the drug being infused as the drug dose syringe for perioperative infusion was filled by another anesthesiologist after randomization.

Outcome Measures

Primary outcome was to assess intra-operative hemodymanic responses to dexmedetomidine; this includes change in blood pressure: systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) and heart rate (HR). Secondary outcomes include assessment of intraoperative fentanyl requirement, intraoperative brain conditions, assessment of emergence characteristics and assessment of complications if occurred.

Study Procedure

All the patients were kept fasting overnight and were premedicated with tablet ranitidine 150mg orally 12 hours prior to surgery and on the day of the surgery. In the operation theatre after connecting the patients to standard monitoring, intravenous access was secured with minimum of two large bore cannula for drug and continuous fluid administration. Arterial switch cannula was used for invasive blood pressure monitoring and central venous pressure was also monitored. Baseline values for heart rate, systolic blood pressure,

diastolic blood pressure and mean arterial pressure were recorded before induction.

All patients were premedicated with intravenous fentanyl 2 μg/kg and intravenous glycoprrolate 0.1 mg prior to induction. Induction of anesthesia was done with intravenous thiopentone sodium 5-6 mg/kg titrated to the loss of eye lash reflex. Following induction, patients were ventilated with (50:50) oxygen in air mixture. Endotracheal intubation was done after administering intravenous atracurium 0.6 mg/kg. Anesthesia was maintained with air in oxygen (60:40%) along with isoflurane 0.4 MAC (Monitored on Datex Ohmeda workstation) and neuromuscular blockade was maintained by intravenous atracurium infusion 5μg/kg/min. Scalp block was administered to all patients with mixture of lignocaine (1%) & bupivacaine (0.25%), total volume of 20cc.

After intubation the study drug loading was done and intraoperative infusion for maintenance was started as per the group allotted. The study drug was discontinued at start of dural closure. At the end of surgery, after eye opening or response to verbal command, the residual neuromuscular blockade was antagonized with intravenous neostigmine 0.05 mg/kg and glycopyrolate 0.01 mg/kg. The tracheal extubation was performed in all patients after meeting the regular extubation criteria except in those with poor cough reflex or preoperative lower cranial nerve lesions. However their emergence characteristics like time for extubation and incidence of bucking and coughing were noted. Standard monitoring was done with ECG and pulse oximeter throughout the study period. Entropy leads were applied to forehead for monitoring of depth of anesthesia intra-operatively and was kept at 40-60. HR and invasive blood pressures (SBP, DBP and MAP) were monitored before induction (baseline) and thereafter at induction, intubation, pin application, 5 min after pin application, incision, every 30 min up to 120 min, then at starting of skin closure, pin removal and at extubation.

The intraoperative brain condition was assessed by the surgeon at the time of raising of bone flap, dural reflection and dural closure and graded as: satisfied (grade1), not satisfied but can manage (grade 2) and not satisfied and intervention required (grade 3).

Rescue Measures

Intraoperative bradycardia was defined as HR < 50 /min and was treated with atropine 0.6 mg IV. Hypotension was defined as mean arterial pressure of < 90 mmHg and was treated with IV fluids and mephentermine 6 mg IV.

Statistical Analysis

A priori sample size was calculated using G power software [12] with α=0.05, (1- β) = 0.90, effect size of 0.12, number of measurement 14, number groups 4, correlation among repeated measures 0.7 total the sample size estimated was 56 but considering the drop outs of cases during the study which can be due to hemodynamic incidents and other incidents, 60 patients 15 in each group were studied.

Normal distribution of the data was ascertained using Anderson-Darling test and homogeneity of variance is tested by modified Levene equal variance test. Continuous data like hemodynamic variables was expressed as Mean (standard deviation), categorical data as frequency & percentages and ordinal data as median. Haemodynamic variables were analyzed repeated measures of ANOVA followed by post hoc analysis with Tukey-kramer multiple comparison test. Other continuous variables were analyzed by ANOVA followed by Tukey-kramer test. Chi-Square test was used for categorical data whereas Kruskal- Wallis rank test was used to analyze ordinal data. P value of < 0.05 was considered as statistically significant. Statistical analysis was carried out using NCSS Version 10. [13].

Results

All patients were comparable with respect to age, weight and gender ratio (p> 0.05). (Table 1) Distributions of patients with supratentorial tumor were similar in all the groups. Most common tumor in all the patients was glioma 28 (47%) followed by meningioma 22 (37%), neurocytoma 4 (6%), pituitary adenoma 3 (5%) and craniopharyngioma 3 (5%).Intraoperative brain relaxation assessed and graded by the surgeons was also comparable between all four groups (p>0.05) (Table 2).

Hemodynamic Parameters

Baseline HR, SBP, DBP and MAP measurements were comparable between the groups. HR, SBP, DBP and MAP measurements were significantly different between the groups at almost all of the time intervals throughout surgery (Figs.1- 4).

Significant increase in HR was noted in group 1 patients at pin application and at pin removal and extubation. On contrary, HR was relatively stable in dexmedetomidine patients with gradual fall noted till 120 minutes, higher in group 4 compared to other dexmedetomidine groups. However multiple comparison tests confirms that fall in HR was comparable in all three dexmedetomidine groups (p>0.05). Intra-operatively, 2 (13.3%) group 4 patients had bradycardia and were treated with atropine.

The SBP as compared to group 1, statistically significant difference was seen in dexmedetomidine groups from the time of intubation till extubation (p< 0.05). Multiple comparison tests confirms that fall in SBP was comparable in all dexmedetomidine groups (p>0.05). Intra-operatively, 3(20%) group 4; 2 (13.3%) group 3; and 1 (6.66%) group 1 patient had hypotension and were treated with injection Mephentermine. A Gradual fall in DBP were seen in dexmedetomidine groups with greater fall noted with group 4. As compared to control group, statistically significant difference was noted in all dexmedetomidine groups from post incision (60 mins) till extubation (p< 0.05). Multiple comparison tests confirms that variation in DBP was comparable in all dexmedetomidine groups (p>0.05).

The intra-operative MAP is summarized in Table 6. Significant variations were noted in control group patients at pin application and thereafter at pin removal and extubation. Gradual fall in MAP were seen in all dexmedetomidine groups with greater fall noted with group 4. As compared to control group, statistically significant difference was noted in dexmedetomidine groups from the time of pin application till extubation (p< 0.05). Multiple comparison tests confirms that variation in MAP was comparable in dexmedetomidine groups (p>0.05).

Fentanyl Requirement

Group1 patients had maximum requirement of fentanyl, followed by group 2 and group 3. Group 4 patients didn't require IV fentanyl at all (p<0.05). Other parameters like intravenous fluids requirements, urine output, blood loss and blood transfusion were comparable in all the 4 groups (p>0.05) (Table 3).

Table 1: Demographic profile of patients in all groups

Parameter	Group1 (Normal saline)	Group2 (DMD 0.3µg)	Group3 (DMD 0.4µg)	Group4 (DMD 0.5µg)	p Value
Age (Yrs)	43.26	34.66	38.4	40.33	
Mean±SD	±15.37	±9.27	±13.23	±13.86	0.34
Weight (Kgs)	54.93	53.13	56.4	60.26	0.47
Mean±SD	±13.26	±6.80	±12.29	±16.39	
Sex (M/F)	7/8	8/7	7/8	8/7	.096

Table 2: Brain relaxation assessment as done by surgeon

Parameter	Group1 (Yes/No)	Group2 (Yes/No)	Group3 (Yes/No)	Group4 (Yes/No)	P value
Grade I	1	1	1	1	0.57
Grade II	1	1	1	1	0.36
Grade III	1	1	1	1	1

Table 3: Changes in intraoperative parameters and requirement of fentanyl in all groups

Parameter	Group 1 (Normal saline)	Group 2 (DMD 0.3µg)	Group 3 (DMD 0.4µg)	Group 4 (DMD 0.5µg)	p Value
Fentanyl(µg)	145.66±53.28	85.33±49.26	40.66±78.14	0	0.0001*
IVF(ml)	2546.66±434.02	2946.67±838.21	2786.67±692.68	2646.67±161.79	0.51
Urine output (ml)	1343.33±680	1533.33±980.28	1100±648.90	973.33±254.86	0.52
Blood Loss(ml)	543.33±141.25	590±202.84	503.33±81.21	500±123.92	0.29
Blood transfusion units	3	4	0	1	0.13

Table 4: Comparison of emergence characteristics in all groups

Variable	Group1	Group2	Group3	Group4	P Value
Bucking	5 (33.33%)	2 (13.33%)	1(6.67 %)	0	0.045*
Coughing (Yes/No)	3 (20%)	2 (13.33%)	0	0 (Nil)	0.117
Extubated (Yes/No)	14 (93.3%)	15 (100%)	14 (93.35 %)	12 (80%)	0.25
Time to extubation (min) Mean SD	15.40 ±1.12	15.47± 1.35	16.06 ±1.27	16.53± 1.06	0.035*

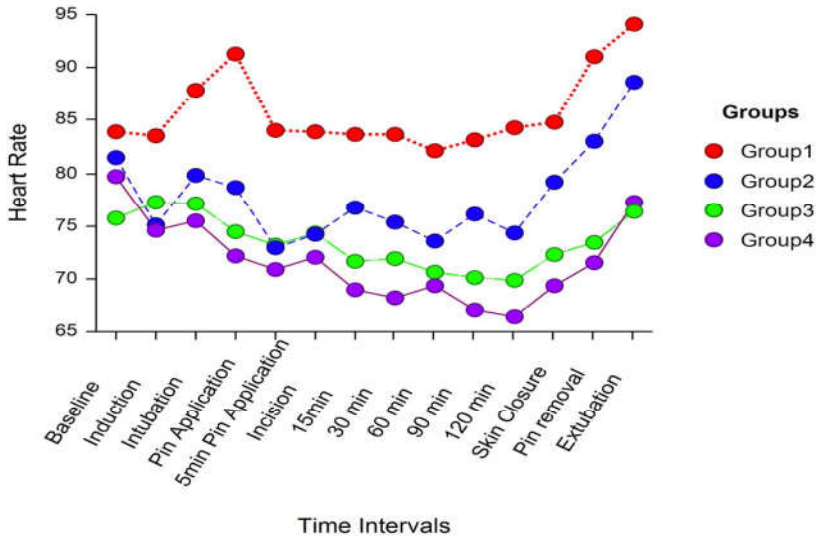

Fig. 1: Heart Rate (HR) changes in all the groups at different time intervals

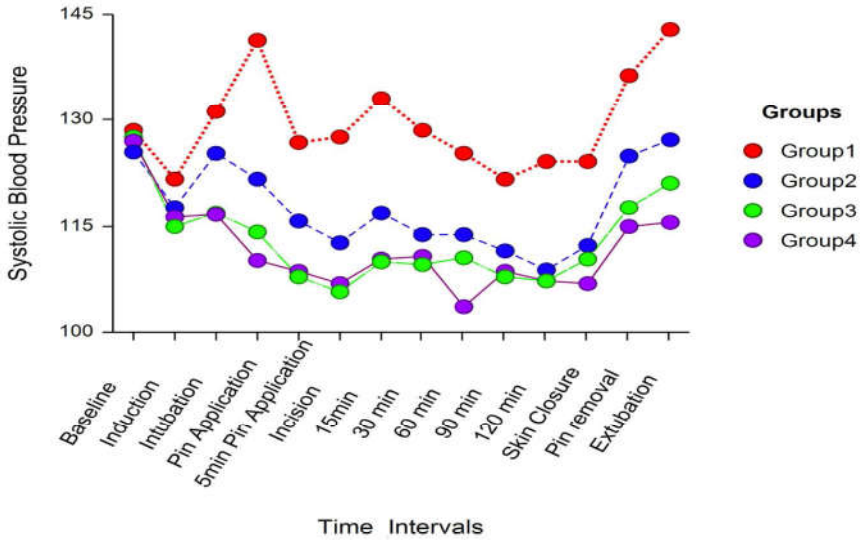

Fig. 2: Systolic Blood Pressure (SBP) changes in all the groups at different time intervals

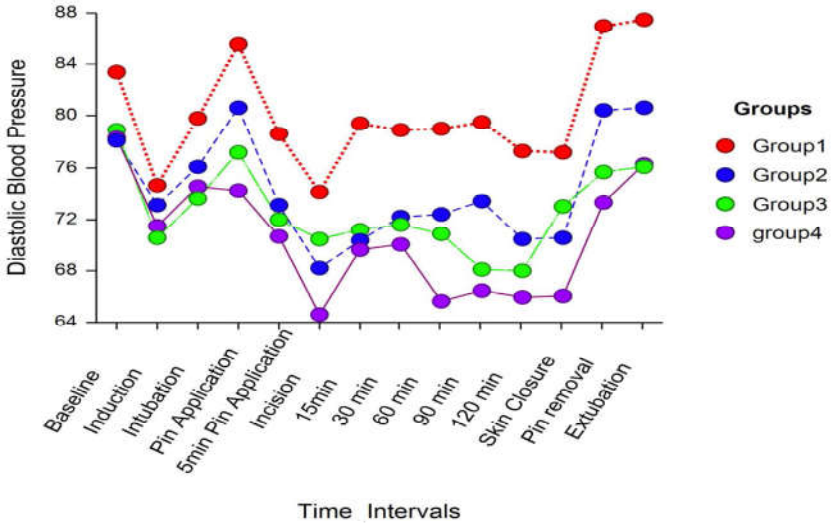

Fig. 3: Daistolic Blood Pressure (DBP) changes in all the groups at different time intervals

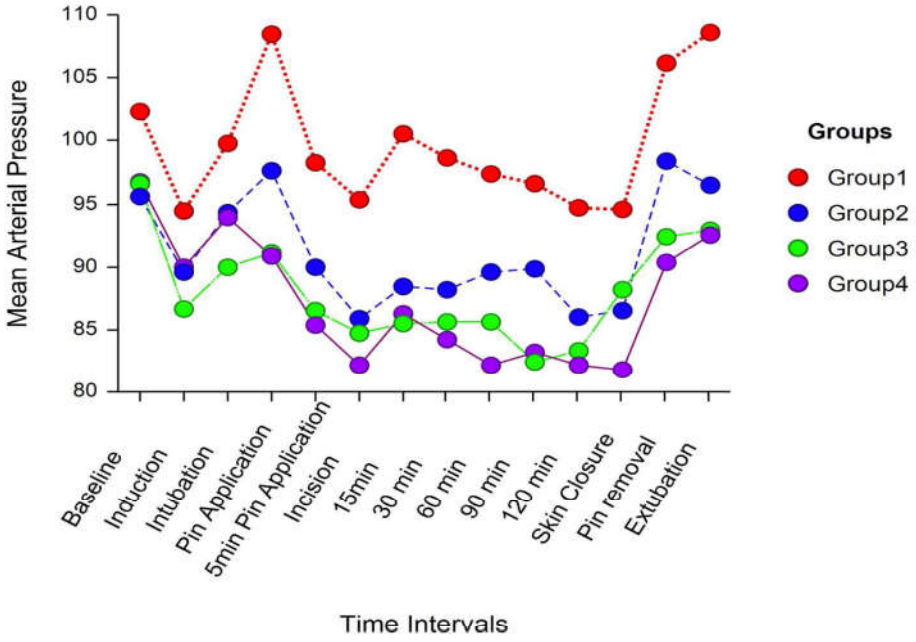

Fig. 4: Mean Arterial Blood Pressure (MAP) changes in all the groups at different time intervals

Emergence Characteristics

In postoperative period, bucking was reported in 14 patients (93%) of group 1; 3(20%) patients of group 2 and 3 and it was absent in all patients of group 4. Cough reflex was present in 14 patients (93%) of group 1; all patients of group 2 and 4 and in only 11 patients (73%) of group 3.

Extubation was successful in 14 patients (93%) of group 1 and 3, all patients in group 2 and 12 patients (80%) of group 4. Three patients in group 4 and one patient in group 1 and 3 were not extubated due to poor cough reflex and sedation and were shifted to intensive care unit for elective ventilation (Table 4).

Discussion

This dose ranging study was planned to find a clinically appropriate dose of dexmedetomidine that can be combined with anesthetics to ensure perioperative hemodynamic stability and fast recovery without respiratory depression. Such combination would reduce the requirement of anesthetic agents and thus decrease the risk of affecting cerebral autoregulation. Three different infusion doses (0.3, 0.4 and 0.5 µg/kg/hr) were studied in neurosurgical patients. The dose of continuous intravenous infusion of dexmedetomidine in each group was based on a previous studies in which the intended level of sedation, attenuated intubation response and haemdynamic stability were achieved at a dose ranging from 0.2-0.8 µg/kg/hr [14-18]. Further, studies were also considered that used doses in the range of 0.5 µg/kg/hr for successful extubation [19,20].

A biphasic effect of dexmedetomidine on haemodynamics causing an immediate increase in systemic arterial pressure followed by a longer lasting reduction in pressure is well known [12]. To mitigate the risk of initial transient hypertension, the loading dose of 1 µg/kg slowly over a period of 15 mins was used in all dexmedetomidine groups. Therefore, we haven't seen tachycardia and hypertensive response to dexmedetomidine administration in our study. Further, all dexmedetomidine groups showed hemodynamic stability compared to control group at various time points. Though the reduction with 0.4 µg and 0.5 µg dose was more as compared to 0.3µg dose at various time points (e.g. intubation and pin application and from skin closure to extubation) overall findings within the three groups were comparable.

Our results corroborated with the findings of other authors. Patel CR et al, concluded that dexmedetomidine given in a loading dose of 1 µg/kg over 10 minutes followed by infusion of 0.2–0.8 µg/kg attenuated the hemodynamic response in perioperative period [11]. Similarly, other studies concluded that dexmedetomidine in bolus dose (1 µg/kg) followed by continuous infusion (0.2 and 0.4 µg/kg/hr) [21], (0.4 µg/kg/hr)

[11], (0.2 and 0.4 µg/kg/hr) [8], (0.4-0.5 µg/kg/min)[9], (0.25-0.7 µg/kg/hr)[22] improves haemodynamic stability with higher doses being more effective than the lower dose.

We noticed a sudden drop in hemodynamics (HR, DBP, SBP, MAP) in few patients at 60 min with 0.5µg/kg/hr dose that was sustained for some time and was treated with atropine and mephentermine. These findings may be attributed to increased concentration of the drug and decreased central sympathetic outflow over a period of time. Apparently, this was not seen with lower doses (0.3 and 0.4 µg/kg/hr).

Bradycardia and hypotension are usual findings of dexmedetomidine infusion, occurs due to reflex response to transient hypertension due to rapid bolus infusion [12,13,23]. Subsequent hypotension and bradycardia occurs due to decrease in central sympathetic out-flow. We observed similar pattern in our study however the magnitude of effect was very less except group 4 patients who experience severe hypotension as discussed above.

In present study, all three doses attenuate haemodynamic response to the emergence from anesthesia and extubation in similar fashion, and it differs significantly from control group. This shows that the centrally mediated sympatholytic effect of dexmedetomidine has continued well into the postoperative period. Other studies have also shown similar blunting action [17,21,22] dexmedetomidine acts on spinal α-2 receptors and mediate its analgesic effect. It has been found to prolong analgesia when used as an adjuvant to anaesthetics; thus reducing the opioid requirement by 30 to 50%[23,26]. We too observed dose dependent opioid sparing effect as evident by decreased requirement of fentanyl 85.33 µg, 40.66 µg, 0.0 µg to maintain hemodynamic stability at 0.3, 0.4 and 0.5 µgkg-1 hr-1 doses respectively. Not surprisingly, the highest dose of fentanyl required the control group (145.66). These results are consistent with several other studies [9,10].

Dexmedetomidine also inhibits hypercapnic cerebral vasodilation, [27] and causes potent venous vasoconstrictive [28]. Both these actions are mediated by direct activation of cerebral α-2 receptors and decreases MAP and cerebral blood flow (CBF) and thus provides clinically superior surgical area [29,30]. In our study, cerebral swelling was determined by surgeons using brain relaxation score that was comparable among all four groups.

Dexmedetomidine patients (3 in group 4 and 1 in group 3) were ventilated due to sedation and poor cough reflex in postoperative period. The longer sedation could be explained by longer elimination half-life of this drug [31]. However, unlike opioids sedation was not associated with respiratory depression. These results are consistent with the previous studies wherein delayed recovery and longer discharge time were reported with dexmedetomidine [32-35].

Conclusion

Dexmedetomidine attenuates stress responses to various noxious stimuli during surgery, maintains haemodynamic stability, blunts tachycardia and hypertensive response, reduces requirements of opioids and provide good intra-operative brain conditions and early recovery. The benefit risk assessment favours an initial bolus of 1µg/kg over 15 min followed by an infusion of 0.4 µg/kg/hr over other doses (0.3 µg/kg/hr and 0.5 µg/kg/hr) in patients undergoing supratentorial tumor surgery.

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