



Comparative study of hemodynamics in Intracranial tumor surgeries with clonidine and dexmedetomidine under general anesthesia

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Abstract

Background and Aim: Perioperative hemodynamic stability is of extreme importance while administering general anesthesia to avoid intracranial hemorrhage to profound surgical stimuli associated with craniotomy. Recently alpha 2 agonists clonidine and dexmedetomidine are being used for attenuating these hemodynamic responses. As no studies compared them using intraoperative infusions throughout surgery present study is designed so.

Materials and methods: 60 patients diagnosed with intracranial tumors are randomized into two Groups of C and D of each 30. Group C received clonidine as a bolus of 0.5mic/kg intravenously (IV) 20minutes before induction and intra-operatively iv infusion at 0.5mic/kg/hr after intubation and stopped before starting of skin closure. Similarly, Group D receives Dexmedetomidine at the same doses and same time. Hemodynamics like heart rate and mean arterial blood pressure at intubation, craniotomy, and extubation and side effects of study drugs like bradycardia and hypotension compared.

Results: At intubation, the mean heart rate in Group C is 79.36 ± 7.328 beats/ min, and in Group D is 74.33 ± 6.07 , p value for mean heart rate is 0.0053(S). Mean MAP at intubation in Group C is 80.5 ± 7.645 mm Hg, and in Group D is 72.47 ± 5.869 is 0.0001(S). The mean heart rate at extubation in Group C is 71.16 ± 3.355 , and in group D 68.57 ± 4.56 , and the p-value is 0.0149(S). Mean MAP at extubation in Group C is 71.1 ± 4.278 , and in Group D is 69.03 ± 2.456 , and p-value is 0.02733 (S). 2 persons from Group C and 5 from Group D had bradycardia and 3 in Group C, and 4 in Group D had hypotension episodes, and p valve is 0.13 and 0.68(NS). P valve <0.05 statistically significant (S) and > 0.05satiistiocally nonsignificant (NS).

Conclusion: Both drugs caused attenuation of sympathetic responses like heart rate and mean arterial pressure in Intracranial tumor surgeries with an excellent operating field; however, dexmedetomidine is a preferable agent when compared to clonidine, with better hemodynamic stability and a bright surgical condition.

Introduction

Hemodynamic stability in the perioperative period is of prime importance while providing general anesthesia in cranial tumor surgeries. Profound surgical stimuli associated with craniotomy often result in **sympathetic activation**¹ and marked changes in arterial blood pressure, cerebral blood flow, and thereby changes in intracranial pressure

and cerebral perfusion pressure. Goals during neurosurgical anesthesia are intraoperative hemodynamic stability with **attenuation of sympathetic responses** to avoid intracranial hemorrhage and to allow **immediate neurological evaluation** upon emergence².

Excessive blood in the field of operation hinders visibility, which may lead to increased blood loss.

Various agents used to achieve **controlled hypotension** to limit intraoperative blood loss were associated with disadvantages, that include rebound hypertension from beta-blockers³, delayed recovery from inhaled anesthetics, resistance to vasodilators, and cyanide toxicity for nitroprusside⁴. Selective **α_2 adrenergic receptor agonists** clonidine and dexmedetomidine are being used as hypotensive agents in the last two decades.

In the recent decade, several studies have focused on clonidine and recently on dexmedetomidine as premedication to attenuate the hemodynamic responses following intubation. However, there was no comparative study between clonidine and dexmedetomidine in craniotomy cases and administering them as intraoperative infusion throughout surgery for hemodynamic stability.

This study primarily aims to assess and compare the hemodynamic effects of intravenous clonidine and intravenous dexmedetomidine in intracranial tumor surgeries under general anesthesia.

Materials and Methodology

The present study was done in 60 patients diagnosed with an intracranial tumor in Tertiary care hospital, North Coastal Andhra Pradesh, from January 2018 to August 2019. Before the study, permission from the Institutional Scientific and Ethics Committee and written consent from patients participating in the study after explaining them about the study in their language were taken. Inclusion criteria in the study were patients aged between 18 and 65 yrs, diagnosed with an intracranial tumor, physical status system classification by American Society Of Anaesthesiologists 1 and 2, Mallampati score of Airway 1 and 2 and posted for elective surgery. Patients who are associated with morbid obesity cerebrovascular disease, renal disease, hepatic disease, with heart rate less than 60, ejection fraction less than 45% were excluded. Pregnant and lactating mothers, coagulopathic, psychiatry patients, and who participated in any other study in the last month were excluded.

All 60 patients in the study were evaluated with detail history, general, and systemic examination and were divided randomly into two groups; Group C and Group D of 30 each. Randomization was done before starting the study with the pre-allocation of a patient into a group using computer-generated randomization. On arrival in the operating room, the patient data confirmed, and baseline parameters were noted after 5 min of settling. A large-bore intravenous (IV) 18 G cannula was inserted. Under LA and aseptic precautions, a central venous line was secured in the right subclavian vein using a modified Seldinger technique and for invasive arterial blood pressure (Mindray) monitoring, left radial artery cannulated.

All the patients in Group C received Inj. Clonidine of 0.5 mic/kg and similarly, Group D patients received Inj. Dexmedetomidine of 0.5 mic/kg IV 20 minutes before the induction of anesthesia. All patients were premedicated with Inj. Glycopyrrolate 0.2 mg IV, Inj. Fentanyl two $\mu\text{g}/\text{kg}$ and Inj. Midazolam 1 mg IV 5 minutes before induction and induced with Inj. Thiopentone sufficient to abolish eyelash reflex, followed by Inj. Vecuronium 0.1 mg/kg to facilitate tracheal intubation, which was done with an appropriate size endotracheal tube.

Anesthesia was maintained with controlled mechanical ventilation, N₂O in O₂ (60:40), Isoflurane 1%, Inj. Fentanyl 1 $\mu\text{g}/\text{kg}$, and Inj. Vecuronium in 0.02 mg /kg boluses every 30 minutes.. All the patients in Group C received Inj Clonidine maintenance infusion in a dose of 0.5 $\mu\text{g}/\text{kg}/\text{hr}$, and all patients in Group D received Inj Dexmedetomidine infusion at a dose of 0.5 $\mu\text{g}/\text{kg}/\text{hr}$. The amount of drug needed according to weight and time was calculated and diluted in 100 ml normal saline and given intravenously through a syringe pump. Maintenance study drug infusion was soon started after intubation and discontinued at the start of skin closure. Similarly, isoflurane was terminated at the start of skin closure, and N₂O after skin closure. At the end of anesthesia, the neuromuscular blockade was antagonized with

Inj. Neostigmine 0.04 mg/kg and inj. Glycopyrrolate 0.02 mg/kg intravenously. Patients were extubated when respiration was sufficient, adequate muscle power, and patients were able to obey simple commands. At the end of the surgery, all the patients were transferred to the neurosurgical intensive care unit and monitored. All episodes of hemodynamic derangements lasting longer than 2 minutes were identified, treated, and recorded.

Data Collection

Patient details, ASA status, MPG, hemodynamic parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP),

mean arterial pressure (MAP), oxygen saturation (SPO₂), respiratory rate (RR) at different events of surgery were entered in the proforma datasheet.

Side effects of study drug

The common side effects of the study drugs are bradycardia and hypotension. Patients requiring atropine for bradycardia (HR < 55 beats/min) and mephenteramine for hypotension (MAP < 60 mm hg) were noted.

Statistical Data Analysis

Data entered in Microsoft MS Excel and analysis done in MS Excel and SPSS. Tests of significance applied where ever applicable. A p-value of 0.05 is taken as the level of significance.

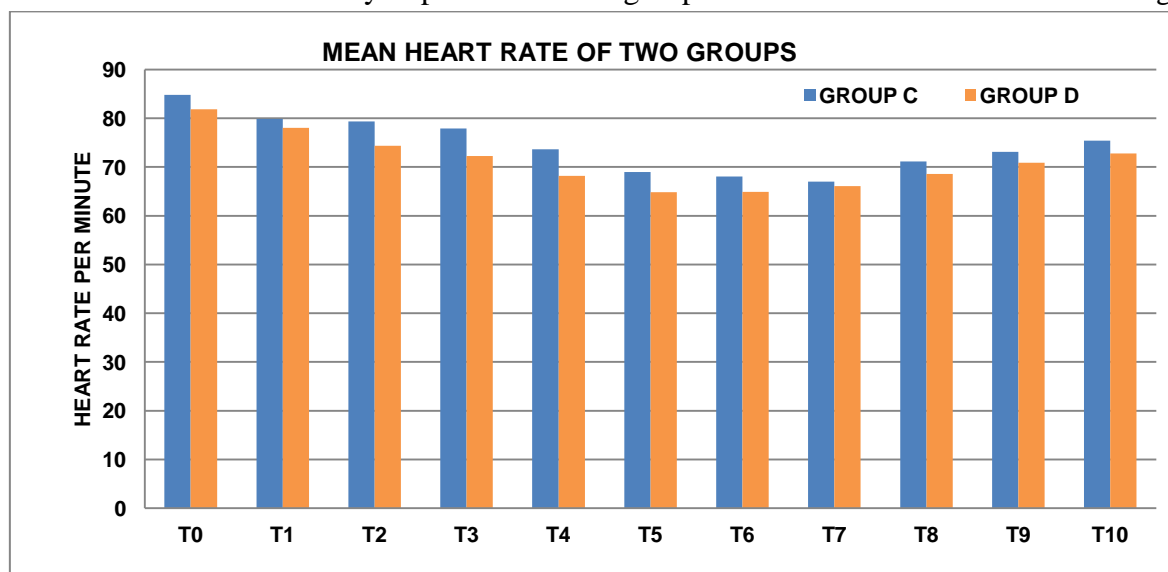
Results

Table 1: Comparison of mean heart rates of Study Population in Two Groups C & D at Different Periods During Surgery

	GROUP C (n=30) Mean +/- SD	GROUP D (n=30) Mean +/- SD	P VALUE	SIGNIFICANCE
T0	84.8 ± 10.39	81.86 ± 10.51	0.2804	NS
T1	79.9 ± 8.506	78.06 ± 8.286	0.3992	NS
T2	79.36 ± 7.328	74.33 ± 6.07	0.0053*	S
T3	77.93 ± 7.042	72.33 ± 5.136	0.0008*	S
T4	73.63 ± 6.348	68.2 ± 4.578	0.003*	S
T5	68.97 ± 7.007	64.8 ± 5.741	0.0145*	S
T6	68.1 ± 5.44	64.93 ± 5.046	0.0240*	S
T7	67.03 ± 4.557	66.07 ± 4.242	0.4017	NS
T8	71.16 ± 3.355	68.57 ± 4.56	0.0149*	S
T9	73.1 ± 4.73	70.9 ± 5.24	0.0932*	S
T10	75.4 ± 4.97	72.8 ± 5.61	0.0626	NS

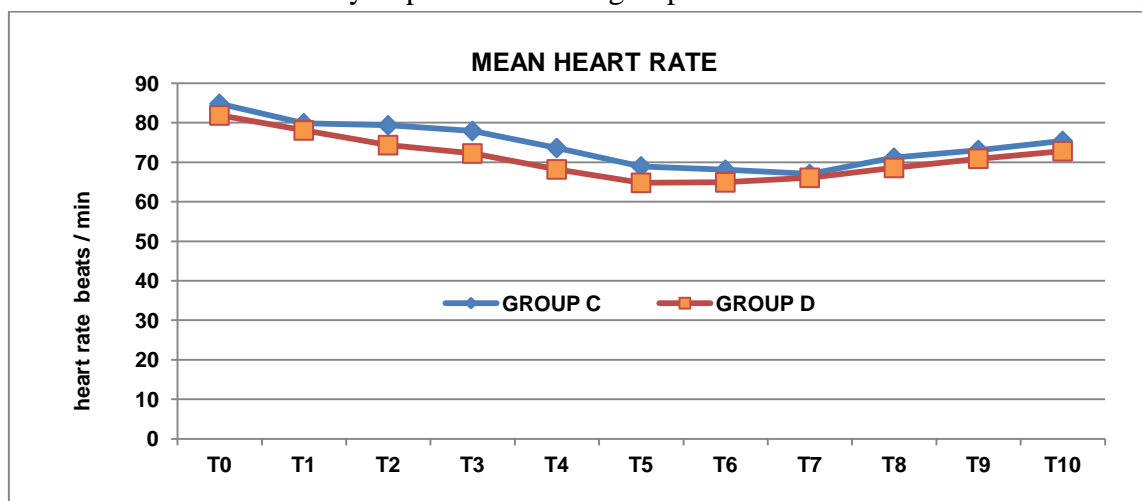
T0-baseline, T1-15mins after bolus, T2-At intubation, T3-5mins after intubation, T4-at Craniotomy, T5,6,7-30 mins, 90 mins, and 150 mins aft Craniotomy, T8-At extubation, T9-5mins after extubation, T10-1hr after extubation

Figure 1: Mean Heart Rates of Study Population in two groups C & D At Different Periods During Surgery



NS : Non Significant (p value > 0.05) ; S, * : Significant (p valve < 0.05)

Figure 2: Mean Heart Rates of Study Population in two groups C & D At Different Periods During Surgery



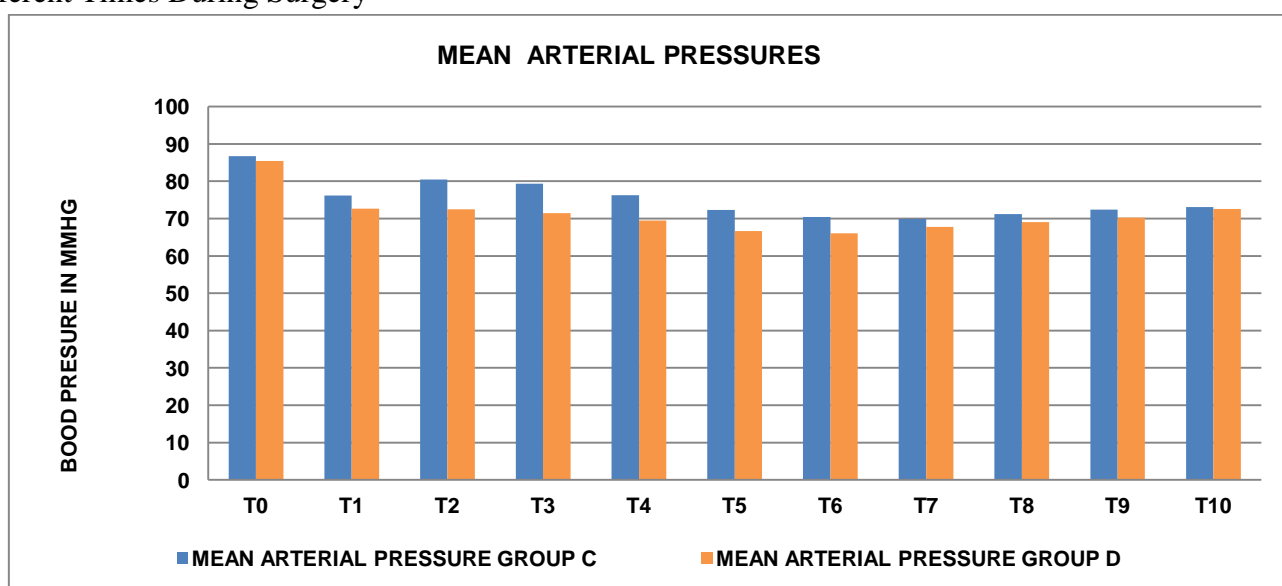
NS : Non Significant (p value > 0.05) ; S, * : Significant (p value < 0.05)

Table 8: Mean of Mean Arterial Pressures of Study Population in two Groups C & D At Different Periods During Surgery

	GROUP C (n=30) Mean +/- SD	GROUP D (n=30) Mean +/- SD	P VALUE	SIGNIFICANCE
T0	86.733± 9.25	85.433 ± 9.290	0.5891	NS
T1	76.17 ± 7.029	72.7 ± 6.64	0.0541	NS
T2	80.5 ± 7.645	72.47 ± 5.869	0.0001*	S
T3	79.37 ± 9.279	71.43 ± 5.207	0.0001*	S
T4	76.27 ± 8.45	69.53 ± 4.072	0.0002*	S
T5	72.367 ± 7.167	66.667 ± 3.33	0.0002*	S
T6	70.4 ± 6.317	66.1 ± 3.33	0.0017*	S
T7	69.93 ± 5.164	67.77 ± 2.186	0.0392*	S
T8	71.1± 4.278	69.03 ± 2.456	0.02733	S
T9	72.27 ± 5.033	70.27 ± 2.462	0.0543	NS
T10	73.07 ± 4.45	72.6 ± 4.484	0.6854	NS

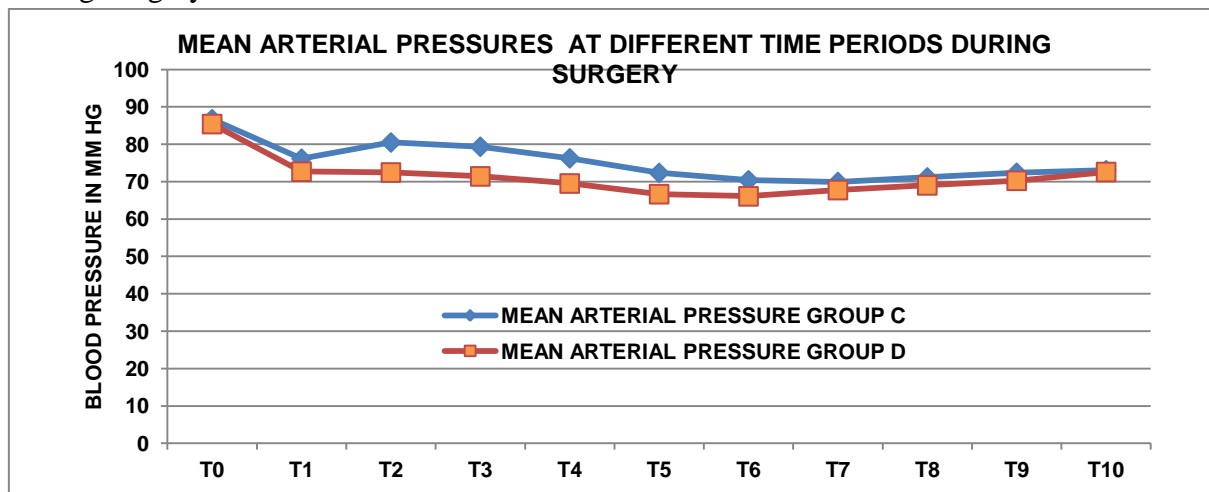
NS : Non Significant (p-value > 0.05) ; S, * :Significant (p value < 0.05)

Figure 3: Comparison of mean of mean Arterial Pressures of Study Population in two Groups C & D At Different Times During Surgery



NS : Non Significant (p value > 0.05) ; S, * : Significant (p value < 0.05)

Figure 4: Comparison of mean Arterial Pressures of Study Population in two Groups C & D At Different Times During Surgery



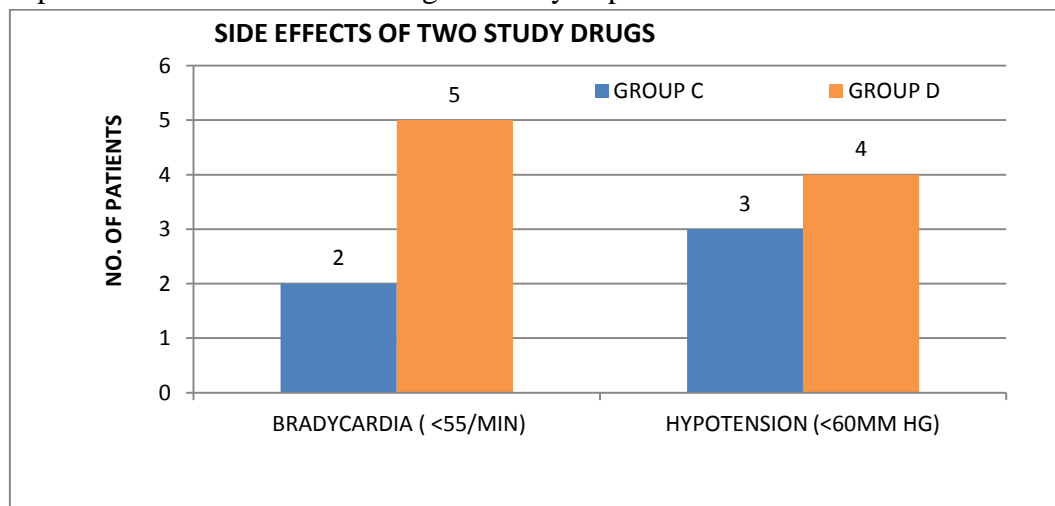
NS : Non Significant (p-value > 0.05) ; S, * : Significant (p valve < 0.05)

Table 3: Comparison of Side Effects of Study Drugs in Study Population

	GROUP C (n=30)	GROUP D (n=30)	P VALUE	SIGNIFICANCE
BRADYCARDIA (< 55 beats /MIN)	2 (6.67 %)	5(20%)	0.1371	NS
HYPOTENSION (< 60 mm Hg)	3 (10%)	4 (13.34%)	0.6895	NS

P Value > 0,05 ; NS: Not Significant

Figure 5: Comparison of Side Effects of Drugs in Study Population



Discussion

Perioperative hemodynamic stability is one of the essential concepts in providing anesthesia to intracranial tumor surgery. Surgical stimuli associated with craniotomy results in marked changes in arterial blood pressure and intracranial pressure (ICP)¹. Alpha 2 agonists act on α₂-adrenergic receptors in the locus coeruleus, provides relatively fast onset of sedative

properties. They have sympatholytic properties with anesthetic sparing effect, sedative, analgesic properties without significant respiratory depression. They provide excellent perioperative hemodynamic stability with decreased intraoperative opioid requirements.

The mean age of study population in Clonidine Group C was 41.87 +/- 12.73 years, and in Dexmedetomidine Group D was 42.93 +/- 12.37

years_The mean weight of patients in Group C was 64.6 +/- 9.62 kg. The mean weight of patients in Group D was 63.6 +/- 10.1 kg. In Group C, there were 16(53.34%)males and 14 (46.67%) females. In Group D, there were 17(56.67%) males and 13 (43.34%) females. The mean duration of surgery in Clonidine Group C was 178.26 +/- 8.85 minutes, and in Dexmedetomidine Group D was 174.96 +/- 5.25 minutes.

Thus demographic data like age, sex, and weight; patient characteristics like ASA and MPG, baseline parameters for hemodynamic variables like heart rate, systolic blood pressures, diastolic blood pressures, mean arterial pressures were statistically comparable in the two groups

At intubation, the mean heart rate in Group C is 79.36 ± 7.328 minutes, **mean arterial pressures** in Group C is 80.5 ± 7.645 mm hg which are less than the baseline mean HR 84.8 ± 10.39 and MAP 86.733 ± 9.25 respectively, implying the effectiveness of clonidine on hemodynamic responses, which is mostly due to the bolus dose given 20minutes before induction and suggesting its use as premedication. These present study results were comparable with studies of **Gupta et al.**⁵ and **Jitin Bajaj et al.**⁶, where they used clonidine as premedication orally at varying doses at different times in the preoperative period. Moreover, in present study, we used a bolus dose of IV clonidine 0.5 mic/kg 20 minutes before induction, which also exhibited similar results. Higher doses of clonidine in **Jitin Bajaj et al.**⁶ study showed adverse effects, which implies the dose-dependent decrease in heart rate and mean arterial pressures.

At intubation, the mean heart rate in Group D is 74.33 ± 6.07 minutes, and **mean arterial pressures** in Group D is 72.47 ± 5.869 , a **significant reduction** from baseline HR(81.86 ± 10.51), and baseline MAP (85.433 ± 9.290) were observed. Thus dexmedetomidine is also useful in attenuating the hemodynamic responses to laryngoscopy and intubation. Our study results were in concurrence to the study results of **Uyar et al.**⁷, where they used @ 1mic/kg dose (higher

dose than present study) as premedication to blunt the intubation responses. The study results were also **more similar** to **Keshri et al.**⁸ low dose dexmedetomidine group.

When both groups C and D were compared for the mean heart rate and mean MAP at intubation, **both are effective in attenuating the intubation response.**but the p valve for mean heart rate is 0.0053 and p valve for MAP is 0.0001 (< 0.05) which are **statistically significant**. It indicates that Group D is superior to Group C in attenuating the hemodynamic responses to laryngoscopy and intubation. Our study results were similar to studies of **Sarkar et al.**⁹ and **Jan et al.**¹⁰. So, dexmedetomidine is superior to clonidine in attenuating the hemodynamic responses to intubation as it has high alpha 2 binding selectivity compared to clonidine.

In the present study, the mean heart rate and mean arterial pressures of **both groups C and D** decreased gradually and were maintained in the normal range throughout the **intraoperative period** soon after skin incision to closure. When they were compared in both groups, a p-value of less than 0.05 was observed at periods like skin incision T3, at craniotomy T4 and intraoperatively T5 to T8, and thus dexmedetomidine group showed better hemodynamic control than clonidine group. These results were in concurrence with the studies of **Nalini Jadhav et al.**¹¹ and **Tanskanen PE et al.**¹²

The mean heart rate at **extubation** in group c is 71.16 ± 3.355 , and in group D 68.57 ± 4.56 . The p-value is 0.0149, which is statistically significant. The mean MAP at extubation in Group C is 71.1 ± 4.278 , and in Group D is 69.03 ± 2.456 . The p-value is 0.02733 (<0.05) and was statistically significant. It implies that in Group D is better in attenuation of extubation response had occurred Our observations at extubation were in concurrence to the studies of **Dilip Kotari et al.**¹³ with similar doses of dexmedetomidine and also in concurrence with **Talke et al.**¹⁴, where dexmedetomidine had a lesser increase in mean

arterial pressure and heart rate for extubation responses.

In our study, two persons in Group C (6.67 %) and five persons from Group D (20%) had bradycardia (HR < 55 beats/min) episodes and required atropine 0.6mg IV. Furthermore, three persons in Group C (10 %) and four persons (13.33 %) in Group D had hypotension episodes (MAP < 60mmhg), and required mephenteramine for correction. Our study results are similar to **Soliman R et al.**¹⁵ study concerning the side effects of dexmedetomidine.

Limitations

A small sample size limits the study. Furthermore, the study lacks a placebo group. The depth of anesthesia could not be measured as the Bispectral Index (BIS) technique has some technical problems in intracranial surgery, such as after scalp elevation (weak signal transference). Another limitation was that the effect of clonidine and dexmedetomidine on cerebral perfusion and intracranial pressure was not studied.

Conclusion

The study concludes that both dexmedetomidine and clonidine caused attenuation of sympathetic responses like heart rate and mean arterial pressure in Intracranial tumor surgeries with a good operating field, However dexmedetomidine is a preferable agent when compared to clonidine, with better hemodynamic stability and a clear surgical condition.

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