

STUDY TO ASSESS THE ROLE OF DEXMEDETOMIDINE IN PATIENTS WITH INTRACRANIAL TUMORS UNDERGOING CRANIOTOMY UNDER GENERAL ANESTHESIA

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ABSTRACT: BACKGROUND: Dexmedetomidine (DEX), a highly selective α -2 agonist has been shown to provide good perioperative haemodynamic stability, analgesia leading to decreased intraoperative requirements of opioids, antihypertensives and vaporising agents. It may provide neuroprotection, and hence may be considered to be a suitable adjuvant during neurosurgical anaesthesia. Recent studies have shown that Dexmedetomidine decreases brain flow and CSF pressure without ischemic insult and effectively decreases cerebral and intracranial pressure also. **AIMS:** This prospective, randomized, double-blind study was designed to assess the perioperative effect of intraoperative infusion of dexmedetomidine in patients with intracranial tumors undergoing craniotomy under general anesthesia. **METHODS AND MATERIALS:** Forty ASA-I and ASA-II patients between 18-50 yrs of age to undergo craniotomy for intracranial tumors were divided randomly into 2 groups (twenty patients in each group). Group A:--Dexmedetomidine was given as a bolus dose of 1 mcg/kg in 20 minutes before induction of anesthesia, followed by a maintenance infusion of 0.4 mcg/kg/hr. The infusion was discontinued when surgery ended. Group B:--The patients received similar volumes of normal saline. Anaesthesia was standard for all the patients in both groups. **STATISTICAL ANALYSIS USED:** Statistical tests were performed using SPSS® version 11.05. Demographic data and operation characteristics were evaluated using descriptive statistics.

- Data were expressed as mean values \pm standard deviation (SD). Changes in haemodynamic variables from baseline and a comparison of means were analysed by paired t-test for each time interval.
- Further analysis was carried out for intervals during which differences from the baseline were statistically significant.

A value of p-value < 0.05 was considered to be statistically significant.

RESULTS: The heart rate and mean arterial blood pressure decreased in patients of group A (dexmedetomidine group) more than group B (placebo group) with significant statistical difference between the two groups (P-value < 0.05). The total fentanyl requirements from induction to extubation of patients increased in patients of group B more than in patients of group A (P-value < 0.05). **CONCLUSION:** Continuous intraoperative infusion of dexmedetomidine during craniotomy for intracranial tumours under general anaesthesia maintained the haemodynamic stability, fentanyl requirements and improved significantly the outcomes.

KEYWORDS: Dexmedetomidine, Intracranial Tumour, α -2 adrenergic agonist.

INTRODUCTION: The perioperative course of patients undergoing craniotomy is frequently complicated by tachycardia and hypertensive episodes. Dexmedetomidine (DEX), a potent α -2

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adrenoreceptor agonist¹ has been shown to provide good perioperative haemodynamic stability^{2,3,4,5} due to its sympatholytic and antinociceptive properties with decreased intraoperative opioid requirements.⁶ In addition, it has been shown to have neural protective effects, and thus may be a suitable anaesthetic adjuvant to neurosurgical anaesthesia.^{7,8,9,10} We designed this study to assess the efficacy of DEX in controlling tachycardia and hypertensive responses in patients undergoing craniotomy for intracranial tumours.

METHODS: A randomized, double blind study was conducted in Gandhi Medical College , Bhopal, M.P. in which Sixty ASA grade I or II patients between 18-50 yrs of age and with CT- scan proof of Intracranial tumors were selected . After taking informed consent, patients were classified randomly into 2 groups (thirty patients in each group).

Group A:--Patients in group A received Inj. Dexmedetomidine as a bolus dose of 1 µg/kg over 20 minutes before induction of anesthesia, followed by a maintenance infusion of 0.4 µg /kg/hr. The infusion was discontinued when surgery was completed.

Group B:--Patients in group B received similar volumes of isotonic saline in the same manner.

- Anaesthesia was standard for all the patients. The patients were premedicated with intravenous doses of Inj. Midazolam-0.02 mg/kg , Inj. Fentanyl- 2 µg/kg, Inj. Glycopyrolate-0.2 mg and Inj. Ondansetron-4 mg and Inj. Pantoprazole- 40 mg.
- After the loading dose of Dexmedetomidine, Induction was achieved with i/v Thiopentone 5 mg/kg. Intubation was facilitated by intravenous Atracurium 0.5 mg/kg.
- Anaesthesia was maintained with nitrous oxide in oxygen and isoflurane and muscle relaxation was maintained with Inj. Atracurium .
- Routine monitoring consisted of NIBP, ECG, SpO₂ and EtCO₂, recorded every five minutes. The aim was to maintain HR and mean arterial pressure (MAP) within 20% of baseline values.
- On completion of surgery, the neuromuscular blockade was reversed with i/v Neostigmine-0.05mg/kg and Inj. Glycopyrolate -0.01 mg/kg.
- The standard procedure of extubation was followed and the time of extubation recorded. The discontinuation time of dexmedetomidine infusion was recorded.
- Expected side effects with the use of Dexmedetomidine are limited respiratory depression, bradycardia and reduction of blood pressure, and convulsions. The measure to control these side were ready with us except alpha -2 adrenergic antagonist e.g., Atipamezole which was not available in our Institute.

ETHICS: The study was conducted after due approval from the Institutional Ethics Committee.

STATISTICS: A total of 40 patients who underwent elective Craniotomy for intracranial tumours under general anesthesia were enrolled in this study. The patient demographics and the type and duration of surgery are shown in Table I. The mean duration of the surgical procedure was 132.56 ± 84.73 minutes. The minimum duration was 55 minutes and the maximum duration was 535 minutes.

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Description	Group A	Group B	P- value
Age (years)	35.33 ± 14.79	37.13 ± 11.22	0.761
Gender (female/male)	18/12	17/13	0.432
Weight (kg)	58.23 ± 11.47	52.23 ± 10.07	0.342
ASA physical status(I/II)	12/18	15/15	0.4534
Duration of surgery (minutes)	132.56 ± 84.73	126.56 ± 12.83	0.756

Table-1: Demographics and duration of surgery for excision of intracranial tumours

RESULTS:

	Group A [Mean ± SD]	Group B [Mean ± SD]	P -value
Baseline	82±9.08	84.4±6.09	0.827
20 min after Loading dose	65.4±5.04	84.4±6.09	0.0323
Intubation	73.4±11.93	112±12.04	0.0277
Intraoperative 30 min after induction	70.4±8.38	98.4±9.08	0.0292
60 min after induction	67.1±9.64	88.2±8.4	0.0476
At the end of sx	72±8.43	112.4±11.2	0.0364
Extubation	78.2±8.14	98.4±5.52	0.0469

TABLE-2: PULSE RATE/MINUTE

	GROUP A [MEAN ± SD]	GROUP B [MEAN ± SD]	P -VALUE
BASILINE	134.3±12.46	132.5±8.24	0.9047
20 MIN AFTER LOADING DOSE	108±8.24	132.5±8.24	0.049
INTUBATION	112.2±10.2	146.4±9.08	0.0167
INTRAOPERATIVE 30 MIN AFTER INDUCTION	110.2±12.46	141.1±9.04	0.0497
60 MIN AFTER INDUCTION	108.6±8.3	134.02±10.04	0.0461
AT THE END OF SURGERY	116.04±9.08	146.12±12.23	0.0323
EXTUBATION	122.03±8.32	148.32±9.24	0.0411

TABLE-3: SYSTOLIC BLOOD PRESSURE

In Group A 20.24% reduction in HR, and a 19.58% reduction in SBP from baseline values, was noted. There was a 10.48% reduction in HR and a 16.45% reduction in SBP during intubation. where as in non Dexmedetomidine group B, 32% increase in HR, and a 10.49% increase in SBP from baseline values during intubation.

Expected side effects with the use of Dexmedetomidine are limited respiratory depression, bradycardia and reduction of blood pressure, and convulsions. The measure to control these side were ready with us except alpha -2 adrenergic antagonist e.g., Atipamezole which was not available in our Institute. In our study none of the side effects was observed.

DISCUSSION: Dexmedetomidine is a highly selective α_2 agonist. It has potent sympatholytic, anxiolytic, sedative and analgesic properties mediated through α_2 -adrenoreceptors in the central and peripheral nervous system.¹¹ It causes a dose-dependent decrease in arterial blood pressure and HR associated with a decrease in serum norepinephrine concentrations.⁴ The effect of α_2 -agonists on haemodynamics is biphasic: an immediate increase in systemic arterial pressure (mediated by stimulation of peripheral α_{2B} -adrenoceptors) followed by a longer lasting reduction in pressure caused by stimulation of α_2 -adrenoceptors in the central nervous system.⁵ These actions may have contributed to the findings in the haemodynamic profile in patients who received Dexmedetomidine in our study.

Dexmedetomidine is a highly selective α_2 -agonist that has been shown to have sedative, analgesic and anaesthetic sparing effects.^{12, 13} Dexmedetomidine-induced sedation qualitatively resembles normal sleep from which patients can easily be aroused. This type of sedation is termed as co-operative or arousable, to distinguish it from sedation that is caused by drugs acting on gamma-amino butyric acid receptors, such as benzodiazepines or Propofol, which reduce consciousness.^{14,15}

In some earlier reports, oral clonidine, another α_2 agonist, premedication provided attenuation of the hypertensive response to laryngoscopy and intubation.^{16,17} In patients undergoing general or gynaecological surgery, numerous studies have shown that Dexmedetomidine blunts the cardiovascular responses to intubation,^{13,18,19} and our findings in craniotomy patients were in accordance with them. In addition to this beneficial property of α_2 -agonists, they have also been reported to increase the risk of hypotension and bradycardia. These effects have most often been seen in young healthy volunteers or after rapid bolus administration.^{5,19,20} In our study there was no difference between the groups in the occurrence of bradycardia or hypotension.

Numerous studies have shown that Dexmedetomidine reduces the analgesic and anesthetic requirements in the perioperative period.^{18,21} In our study, Dexmedetomidine was used as an adjuvant to anesthetic agent in the intraoperative period as a continuous infusion, supplemented by Sevoflurane only during significant hemodynamic fluctuations which may have caused concern about hypertension and tachycardia as well as awareness in the intraoperative period. Fentanyl was given as a rescue analgesic.²²

In numerous studies, it has been shown to reduce the isoflurane requirements dose-dependently up to 90%.^{18,21,23} It has also been shown that Dexmedetomidine potentiates analgesia caused by fentanyl in animals^{24,25} and reduces its dose requirements in humans during surgery.¹³ The fentanyl dose in the placebo group was twice that given in the Dexmedetomidine groups, as it was considered unethical not to provide adequate analgesia to the placebo group. Although it was

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not our main objective to study the anesthetic sparing effect, it was clear also in our results, as the haemodynamic stability was better maintained in the Dexmedetomidine group receiving less fentanyl, compared with the placebo group.

The haemodynamic responses to intracranial surgery are most often seen at the start or the end of the surgery. Similarly, the manipulation of certain structures within the brain may produce cardiovascular changes. During supratentorial tumour surgery, such responses are infrequent, however. In the present study, the need to treat hypertension or tachycardia was similar in both groups.

After surgery, hypertension may lead to postoperative intracranial haematomas.²⁶ The hemodynamic responses to emergence from anesthesia and extubation are blunted with Dexmedetomidine,^{19,27} and the centrally mediated sympatholytic effect has continued well into the postoperative period.¹⁹ Also, in our study, Dexmedetomidine attenuated cardiovascular responses to the emergence from anesthesia, but the advantageous effect did not extend to the recovery period as the infusion was discontinued at the time of extubation.

Expected side effects with the use of Dexmedetomidine are limited respiratory depression, bradycardia and reduction of blood pressure, and convulsions. The measure to control these side were ready with us except alpha -2 adrenergic antagonist e.g., Atipamezole which was not available in our Institute. In our study none of the side effects was observed.

Dexmedetomidine has been shown to have minimal effects on respiration,^{12,20} and ventilatory weaning and tracheal extubation has been successfully carried out in critically ill patients under continuing Dexmedetomidine sedation.²⁸ In our study, the patients in the Dexmedetomidine group were extubated earlier than patients in the placebo group. The difference of a few minutes, although statistically significant, is probably not clinically important. It may, however, reflect the lack of respiratory depression of Dexmedetomidine.²⁹

In recent studies administration of Dexmedetomidine to achieve serum levels of 0.6mg/ml and 1.2 mg/ml produced the reduction of CSF pressure and concomitant reduction of CMRO₂.⁴ Dexmedetomidine has been used in neurosurgical procedures involving neurophysiologic monitoring. Cortical evoked potential, amplitude and latencies are minimally affected when using dexmedetomidine intraoperatively when patients underwent craniotomies.³⁰

'The golden standard' of neuroanaesthesia includes maintenance of anaesthesia with isoflurane or propofol with fentanyl.³¹ Recently, new agents, such as sevoflurane, desflurane and remifentanyl, have been added to this. High concentrations of volatile anesthetics can blunt the carbon dioxide response and render CBF pressure passively.³² Even with low concentrations, hyperventilation is needed to counteract the vasodilatation caused by the volatile anesthetics, to avoid increases in the intracranial pressure in patients with mass occupying lesions. In dogs, administration of Dexmedetomidine significantly attenuated isoflurane- and sevoflurane-induced dilation of cerebral arterioles.³³ In the present study, we administered sevoflurane, and moderate hyperventilation was used.

Limitations: Estimating the anesthetic depth by changes mediated by autonomic nervous system (e.g. increases in arterial pressure and HR) is difficult during Dexmedetomidine anesthesia as it increases hemodynamic stability. In our series there were no cases of awareness, suggesting adequate anesthetic depth. BIS monitoring was not used, as it was not available in our Institute. The

Sevoflurane concentrations were almost similar in both the groups in our study. Unfortunately, the postoperative pain-scores were not recorded. Despite greater hemodynamic stability in the Dexmedetomidine group, there were still occasions of intraoperative hypertension and tachycardia requiring treatment in both groups. Perhaps these responses could have been prevented by a higher dose of Dexmedetomidine, as it has been reported to potentiate the depressive effect of halothane on the hypertensive response to stimulation of pressor sites in the central nervous system in experimental animals.² Our study compared two groups, one receiving Dexmedetomidine and other receiving saline in the same manner and volume. Fentanyl was given in both the groups as premedication.

Controversy exists about the neuroprotective effects of Dexmedetomidine. In animal studies, Dexmedetomidine has improved neurological outcome from transient incomplete and focal ischaemia.^{7,8} This effect has been related to reduced sympathetic outflow, and it has been shown that a reduction in circulating catecholamines rather than cerebral catecholamine concentrations mediate neuroprotection after cerebral ischaemia.³⁴ On the other hand, Dexmedetomidine is a direct cerebral vasoconstrictor that may override the cerebral pressure autoregulation.³⁵ In a recent study using positron emission tomography Dexmedetomidine decreased global CBF in human volunteers while at the same time decreasing systemic arterial pressure and cardiac output.³⁶ This may predispose to cerebral ischemia, although in animal studies the vasodilatory response to hypoxia has been preserved.³⁷ Dexmedetomidine has been successfully used for sedation during awake craniotomy,³⁸ but in patients undergoing awake carotid endarterectomy, the need for shunting was 3-fold in the Dexmedetomidine -sedated patients (Non-Significant because of the small number of patients).³⁰

This study protocol does not allow us to make any conclusions about possible neuroprotective or cerebral vasoconstrictive effects of DEX in elective intracranial tumour patients. We have, however, demonstrated the safety and feasibility of Dexmedetomidine in these patients in terms of cardiorespiratory stability. More such studies on neuroprotection are warranted in clinical settings.

Conclusion: In our study, a loading dose of 1 µg/kg Dexmedetomidine was given over 20 minutes, followed by a continuous infusion of 0.4 µg/kg/hour. The following results were found:

Blunted pressor response to intubation

Hemodynamic stability in the perioperative period.

An acceptable recovery profile of the patients who were enrolled in the study.

In conclusion, DEX significantly attenuated the haemodynamic responses to intubation and the emergence from anaesthesia. In addition, it increased intraoperative cardiovascular stability. Most of the effects were concentration-dependent, and the higher dose was more effective than the lower dose. Patients receiving DEX had their tracheal tubes removed faster than those in the placebo group, indicating preserved respiratory function.

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