Dexmedetomidine as an Anesthetic Adjuvant in Intracranial Surgery

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Abstract

Background: The basic principle of neuroanesthesia is to provide hemodynamic stability, provision of optimal operative conditions, maintenance of cerebral perfusion pressure, and cerebral oxygenation. Aim: This study was undertaken to see the effect of dexmedetomidine infusion on hemodynamics and its ability to act as an anesthetic adjuvant in patients undergoing supratentorial tumor surgery. Setting and Design: Prospective randomized control double blind study. Subjects and Methods: In this study, we compared two groups with 25 patients in each group. Group C patients received saline infusion during surgery and 4 μg/kg of fentanyl intravenously (i.v.) at the induction and at pin head application. Group D patients received dexmedetomidine infusion during surgery at the rate of 0.4 μg/kg/h and 2 μg/kg of fentanyl i.v. at the induction and at pin head application. Statistical Analyses Used: Parametric data were analyzed using Student’s t-test. The categorical data were studied using Chi-squared test or Fisher’s test as appropriate. Results: The vitals remained within 20% of baseline in both groups during the study period except at the time of extubation where the rise in heart rate was more than 20% in control group. The requirement of thiopentone for induction was significantly less in dexmedetomidine group. In dexmedetomidine group, less number of patients required intraoperative fentanyl (P < 0.05), and the time to rescue analgesic was also more in Group D (P < 0.05). Conclusion: Dexmedetomidine infusion started before surgery maintains hemodynamic stability intraoperatively and is effective in attenuating the cardiovascular responses to intubation, skull pin application, and extubation. It decreases the requirement of other anesthetic agents as well.

Keywords: Dexmedetomidine, hemodynamics, intracranial surgery

Introduction

The basic principle of neuroanesthesia is to provide smooth induction, hemodynamic stability, and provision of optimal operative conditions such as relaxed brain, maintenance of cerebral perfusion pressure, and cerebral oxygenation. One of the peculiarities of neuroanesthesia is smooth emergence which is much as important as smooth induction to allow early neurological assessment.

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays selective dose-dependent α₂-adrenoceptor agonist. Dexmedetomidine is a highly selective α₂-agonist that has been shown to have sedative, analgesic, and anesthetic-sparing effects without significant respiratory depression.[³] It acts at both spinal and supraspinal sites, modulates the transmission of nociceptive signals in the central nervous system. Even peripheral α₂-adrenoceptors may mediate nociception.[²]

Numerous studies have shown that dexmedetomidine blunts the stress response, but these studies are mostly done in patients undergoing general or gynecological procedures,[³⁵] studies pertaining to neurosurgical procedures are less. In addition, almost all studies have noted the effect of bolus dose of dexmedetomidine along with the infusion of the drug continuing after the bolus dose.[⁶][⁷] Hence, this study was undertaken to see the effect of dexmedetomidine infusion without giving its bolus dose on hemodynamics and its ability to act as anesthetic adjuvant in patients undergoing supratentorial tumor surgery.

The primary aim of this study was to compare the hemodynamics during laryngoscopy, intubation, skull pin application, and extubation. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

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How to cite this article: Batra A, Verma R, Bhatia VK, Chandra G, Bhushan S. Dexmedetomidine as an anesthetic adjuvant in intracranial surgery. Anesth Essays Res 2017;11:309-13.
perioperative period, and extubation in patients who received dexametomidine infusion with control group, and secondary aims were to compare the dose of thiopentone required for induction, intraoperative analgesic requirement and time to rescue analgesia, and postoperative sedation score.

**Subjects and Methods**

This prospective, randomized double-blind study was undertaken in fifty patients undergoing supratentorial tumor surgery in a tertiary care center from July 2013 to June 2014 after obtaining approval from the Institutional Review Board as well as written and informed consent from all the patients fulfilling the inclusion criteria of age between 20 and 65 years with a Glasgow Coma Scale score 14 or 15 and the American Society of Anesthesiologists (ASA) I and II, scheduled for elective intracranial surgery under general anesthesia. The exclusion criteria were pregnant or nursing mothers, patients who were on antihypertensive medications, patients with preoperative heart rate (HR) <60 beats/min, morbidly obese patients, any cardiovascular disease, renal, or hepatic diseases.

Balanced randomization was done using random computer-generated table. Patients were divided into two groups: Group C patients received saline infusion during surgery and 4 μg/kg of fentanyl intravenously (i.v.) at induction and at the time of pin head application. Group D patients received continuous infusion of dexametomidine at rate of 0.4 μg/kg/h during surgery and 2 μg/kg of fentanyl i.v. at induction and at the time of pin head application. Both the teams were blinded to the drugs by supplying prefilled syringes with same volume of normal saline and dexametomidine in saline. In addition, two syringes (one to be given 3 min before induction and other to be given 3 min before the application of Mayfield three-pin head holder) each containing 2 μg/kg fentanyl diluted into a volume of 10 ml were prepared for those patients who received dexametomidine. Similarly, two syringes each containing 4 μg/kg fentanyl diluted into a volume of 10 ml were prepared for those patients who received the normal saline infusion.

When the patient arrived in the operating room, a large bore i.v. catheter was inserted for drug and fluid administration. Baseline recordings of systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), HR, and oxygen saturation (SpO2) were taken. The study drug infusion was commenced approximately 20 min before the induction of anesthesia. During the infusion, SBP, DBP, MAP, HR, and SpO2 were recorded at every 5 min interval.

The patients received injection glycopyrrolate as premedication 0.2 mg i.v. The patients randomized to Group C received injection fentanyl 4 μg/kg i.v. and those randomized to the Group D received injection fentanyl 2 μg/kg i.v. in a double-blind manner 3 min before induction. Then, the patients were induced using thiopentone. Thiopentone 25 mg/ml was injected at the rate of 10 ml/min until the loss of eye lash reflex. The dose of thiopentone was recorded. Vecuronium in the dose of 0.1 mg/kg i.v. was used to provide neuromuscular blockade, and the patients were ventilated by mask for 4 min using 100% oxygen. Thirty seconds before laryngoscopy, the patients were given additional 50 μg of thiopentone. During the induction period SBP, DBP, MAP, HR, and SpO2 were recorded at 3 min intervals until 9 min after intubation. Again 3 min before pin head application, Group C received injection fentanyl 4 μg/kg i.v. and Group D received injection fentanyl 2 μg/kg i.v. in a double-blind manner. At the time of pin head application SBP, DBP, MAP, HR, SpO2 and end-tidal CO2 (EtCO2) were noted and then after every 3 min till 9 min and then at time of craniotomy and at every 30 min thereafter. EtCO2 was recorded immediately after intubation and at regular interval thereafter.

After intubation, controlled mechanical ventilation was done to maintain EtCO2 between 30 and 35 mmHg. A urinary catheter was inserted for monitoring of urinary output. Thereafter, 1 g/kg of mannitol was administered i.v. Anesthesia was maintained with nitrous oxide and oxygen (60%:40%), isoflurane (gradually increased to 1% concentration). Neuromuscular block was maintained with 0.02 mg/kg i.v. boluses of vecuronium. Bolus doses of injection fentanyl 1 μg/kg were given if HR and MAP >20% of baseline. If still, the hypertension was persisting injection labetalol was given in 10 mg increments titrating to HR >60/min. Atropine (0.6 mg i.v.) was given in case HR decreased below 50/min. Mephenetermine (6 mg i.v.) was given in case when SBP <90 mmHg or DBP <50 mmHg.

The numbers of interventions occurring when hemodynamic variables were outside the predetermined window were recorded. Isoflurane administration and the study drug infusion were discontinued at the time of skin closure.

At the end of surgery, the neuromuscular block was antagonized with i.v. neostigmine (0.05 mg/kg) and glycopyrrolate (0.2 mg/mg of neostigmine). Nitrous oxide was discontinued after skin closure. The patient was extubated when patient’s respiration was adequate and neuromuscular block was reversed, and the patient was able to follow simple commands. Again SBP, DBP, MAP, HR, and SpO2 were recorded from the time of suctioning until 9 min after extubation at interval of 3 min.

The pain was assessed on a 10 point visual analog score immediately after surgery then at 15, 30, 60, and 90 min. At any time when the score was 5, the patient was given rescue analgesic in the form of diclofenac (2 mg/kg i.v.) and if still not relieved tramadol (2 mg/kg i.v.) was given. Time of giving rescue analgesic was noted.

Patient’s sedation was assessed by the Ramsay Sedation Score [Table 1] after extubation and at 30 min, 1 h, and 2 h later. Scoring was stopped when the patient had a sedation score of 1 or 2.

**Statistical analysis**

The statistical analysis was done using Statistical Package for Social Sciences, version 15.0 (IBM, Lucknow, Uttar Pradesh, India) statistical analysis software. Sample size was
calculated using the previous study\[8\] taking HR as the main parameter (mean ± standard deviation [SD] 10–15 beats/min) considering 5% margin of error and 80% power and considering a difference of 15 beats/min as clinically significant. The sample size was calculated as 25 using the formula \( \frac{(Z_\alpha + Z_\beta)^2 \times (\sigma_1^2 + \sigma_2^2)}{d^2} \). The values were represented in number (%) and mean ± SD. Parametric data were reported as arithmetic mean ± SD and analyzed using Student’s t-test. The categorical data were studied using Chi-squared test or the Fisher’s exact test as appropriate. A \( P < 0.05 \) was considered statistically significant.

**Results**

The two groups were comparable to each other with respect to age, sex, weight, ASA grading, and duration of surgery [Table 2].

In our study, it was observed that amount of thiopentone required for induction was significantly higher in Group C (337.00 ± 36.17 mg) as compared to Group D (280.00 ± 42.08 mg) (\( P < 0.001 \)).

We observed that there was a progressive decrease in HR in Group D after giving the infusion, but intraoperative HR remained within 20% of baseline. In control group, not such a pattern was observed, and there was an increase in HR, but it remained within 20% of baseline during the whole observed period except at the time of extubation when rise in HR was more than 20% in control group. Similar observation was made for the MAP except during the time intervals from at 60 min after craniotomy to 240 min after craniotomy when decrease in, it was more than 20% in Group D [Figures 1 and 2].

Table 3 shows the perioperative complications. In Group D, 2 (8%) patients developed bradycardia requiring atropine administration while none of the patients in Group C developed bradycardia. On the other hand, 5 (20%) patients in Group C developed tachycardia requiring supplementation with fentanyl. In addition, there were few episodes of hypotension in Group C compared to Group B. In the present study, none of the patients in Group D required antihypertensive medication, but in Group C 4 (16%) patients needed intraoperative labetalol.

Time to extubation was found to be significantly higher in Group C (8.60 ± 1.61 min) as compared to Group D (5.32 ± 1.46 min) (\( P < 0.001 \)). Although this difference of few minutes may not be clinically relevant; however, this signifies that dexmedetomidine does not cause respiratory depression and patient remains readily arousable.

**Time for rescue analgesia was higher in Group D (63.60 ± 19.98 min) as compared to Group C (45.00 ± 18.37 min), and this difference was found to be statistically significant (\( P < 0.001 \)).**

Sedation score of Group C was found to be higher than that of Group D at the time of extubation and at 30 min after

| Table 1: Ramsay sedation score |
|-----------------------------|
| Score | Response |
| 1 | Anxious or restless or both |
| 2 | Cooperative oriented and tranquil |
| 3 | Responding to commands |
| 4 | Brisk response to stimulus |
| 5 | Sluggish response to stimulus |
| 6 | No response to stimulus |

**Table 2: Demographic profile of study population**

| Variables | Group C (\( n=25 \)) | Group D (\( n=25 \)) | \( P \) |
|----------|----------------------|----------------------|--------|
| Mean age (years) | 39.24±12.82 | 37.24±12.48 | 0.7^1 |
| Female:male | 10:15 | 12:13 | 0.6 |
| Mean body weight (kg) | 60.52±7.36 | 60.24±7.86 | 0.9 |
| Duration of surgery (min) | 249.76±23.35 | 253.36±21.74 | 0.6 |

^1Not significant

**Table 3: Complications in study population**

| Complications | Group C (\( n=25 \)) (%) | Group D (\( n=25 \)) (%) | \( P \) |
|---------------|---------------------------|---------------------------|--------|
| Number of patients required atropine for bradycardia | 0 (0) | 2 (8) | 0.49^1 |
| Number of patients required fentanyl for tachycardia | 5 (20) | 0 | 0.05^* |
| Number of patients required labetalol | 4 (16) | 0 | 0.1^1 |
| Number of patients required mephentermine for hypotension | 4 (16) | 5 (20) | 1^1 |

^1Not significant, ^*Significant

![Figure 1: Heart rate in study population](image1)

![Figure 2: Mean arterial pressure in study population](image2)
extubation, and this difference was found to be statistically significant. At 1 h sedation score of 2.00 ± 0.00 was found of Group C only, i.e., 11 patients recorded sedation score of 2 while sedation score was not recorded by any of the Group D patients, no statistical comparisons could be made.

**DISCUSSION**

Maintaining hemodynamic stability during intracranial surgery is one of the most important tasks because hypertension may lead to hemorrhage and vasogenic edema and a low blood pressure may result in cerebral ischemia in areas of impaired autoregulation.[9] Moreover, systemic hypertension associated with emergence from anesthesia has long been believed to contribute to intracranial hemorrhage and cerebral edema following craniotomy.[10] Hence, one should not only focus on maintaining the stability of vitals intraoperatively but also at the time of emergence.

In our study, we have studied the role of dexmedetomidine as an anesthetic adjuvant in neurosurgery and observed that dexmedetomidine infusion started before surgery maintains hemodynamic stability throughout the study period, reduces the amount of anesthetic drug required for induction, decreases the requirement of analgesic drug intraoperatively, and increases the time to rescue analgesia postoperatively without any residual sedation.

Many studies have shown that dexmedetomidine provides blunting of pressor response during laryngoscopy and intubation, skull pin application as well as to extubation, and emergence from anesthesia.[8,11,12] In our study, we too observed that dexmedetomidine infusion started 20 min before the start of surgery was effective in providing hemodynamic stability during critical points such as at intubation, pin head application, extubation, and also throughout the surgery as vitals remained within 20% of baseline. In control group, it was observed that at the time of intubation and pin head application rise in HR and MAP from baseline were not significant, but these values were found to be significant at the time of extubation. Gurulingappa et al. also observed that fentanyl in a dose of 4 μg/kg before intubation provides the similar results.[13] Although studying the effect of fentanyl was not the aim of the study but it became apparent in the results. The dose of fentanyl in control group was twice that in dexmedetomidine group as giving ineffective analgesia to the patients would be unethical.

In our study, it was also observed that infusion of dexmedetomidine reduces the amount of thiopentone required for induction. Yildiz et al., Basar et al., and Keniya et al. also observed the same.[14-16] Dexmedetomidine is the drug with opioid-sparing effect, and it has been observed in various studies in humans.[11,14,17] It was also evident in our study as only a few patients required intraoperatively supplementation with fentanyl and time to rescue analgesia was also delayed in Group D.

The most frequently observed adverse events in patients receiving dexmedetomidine for the Intensive Care Unit sedation include hypotension, hypertension, bradycardia, atrial fibrillation, and hypoxia.[18] Usually, the bolus dose is associated with such complications,[19] so in our study, we used continuous infusion only, and we have observed that continuous infusion without giving bolus dose is also effective in attenuating the stress responses during surgery. In the previous studies in which both bolus with continuous infusion was used the incidence of bradycardia was 5–10% and of hypotension was 20–40%,[7,11] and in our study, the incidence of bradycardia was 8%, and hypotension was 20% which is comparable. Hence, further studies can be done to compare dexmedetomidine infusion with dexmedetomidine bolus plus infusion.

One of the main goals after craniotomy is rapid awakening from anesthesia to allow neurosurgical assessment of the patient and early detection of cerebral complication. Dexmedetomidine is the drug which has been studied for awake craniotomy, and it has been found that use of dexmedetomidine infusion is associated with shorter arousal time as compared to propofol without causing any respiratory depression.[20] Ilhan et al. and Tanskanen et al. also observed that the dexmedetomidine infusion results in faster recovery after general anesthesia without causing any respiratory depression.[7,8] Similar to these studies, we also reported that mean time to extubation was less in Group D as compared to Group C. This indicates that dexmedetomidine does not cause significant respiratory depression and also patient remain alert and conscious after stopping infusion and so, neurologic assessment can be done early.

However, there are certain limitations of our study, the depth of anesthesia could not be measured. Bispectral index (BIS) technique itself has some technical problems in intracranial surgery such as after scalp elevation; the montage system loses brain contact resulting in poor signal transference.[21] In addition, the sympathetic response to lighter plane of anesthesia (increased HR and blood pressure) are masked by continuous dexmedetomidine infusion. Another major drawback was that the effect of dexmedetomidine on cerebral perfusion and intracranial pressure was not studied. Neuroprotective effect of dexmedetomidine is controversial. Some studies have favored the neuroprotective effect after cerebral ischemia by reducing the sympathetic outflow, thus decreasing the systemic catecholamine levels.[22] On the other hand, few have observed its direct vasoconstrictor action which overcomes the cerebral autoregulation.[23] In our study, we cannot comment on neuroprotective or detrimental effect of dexmedetomidine. Further studies need to be done to observe if any neuroprotection is provided by dexmedetomidine.

**CONCLUSION**

Thus, it can be concluded that during neurosurgery dexmedetomidine infusion started before surgery maintains hemodynamic stability intraoperatively, reduces the amount of anesthetic drug required for induction, decreases the
requirement of analgesic drug, and increases the time to rescue analgesia postoperatively without any residual sedation.

**Financial support and sponsorship**
Nil.

**Conflicts of interest**
There are no conflicts of interest.

**References**

1. Ebert TJ, Hall JE, Barney JA, Ulrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. Anesthesiology 2000;93:382-94.
2. Nakamura M, Ferreira SH. Peripheral analgesic action of clonidine: Mediation by release of endogenous enkephalin-like substances. Eur J Pharmacol 1988;146:223-8.
3. Aho M, Erkola O, Kallio A, Scheinin H, Korttila K. Dexmedetomidine infusion for maintenance of anesthesia in patients undergoing abdominal hysterectomy. Anesth Analg 1992;75:940-6.
4. Scheinin B, Lindgren L, Randell T, Scheinin H, Scheinin M. Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thionepentone and preoperative fentanyl. Br J Anaesth 1992;68:126-31.
5. Lawrence CJ, De Lange S. Effects of a single pre-operative dexmedetomidine dose on isoflurane requirements and peri-operative haemodynamic stability. Anaesthesia 1997;52:736-44.
6. Soliman RN, Hassan AR, Rashwan AM, Omar AM. Prospective, randomized study to assess the role of dexmedetomidine in patients with supratentorial tumors undergoing craniotomy under general anaesthesia. Middle East J Anaesthesiol 2011;21:325-34.
7. Ilhan O, Koruk S, Serin G, Erkutlu I, Oner U. Dexmedetomidine in the supratentorial craniotomy. Eurasian J Med 2010;42:61-5.
8. Tanskanen PE, Kytjö JV, Randell TT, Aantaa RE. Dexmedetomidine as an anesthetic adjuvant in patients undergoing intracranial tumour surgery: A double-blind, randomized and placebo-controlled study. Br J Anaesth 2006;97:658-65.
9. Bruder N, Ravussin P. Supratentorial masses. In: Cottrell JE, Young WL, editor. Cottrell’s and Young’s Neuroanaesthesia. 5th ed. U.S.A: Elsevier; 2010. p. 186-200.
10. Basali A, Mascha EJ, Kalfas I, Schubert A. Relation between perioperative hypertension and intracranial hemorrhage after craniotomy. Anesthesiology 2000;93:48-54.
11. Bekker A, Sturaitis M, Bloom M, Moric M, Golfinos J, Parker E, et al. The effect of dexmedetomidine on perioperative hemodynamics in patients undergoing craniotomy. Anesth Analg 2008;107:1340-7.
12. Uyar AS, Yagmururdur H, Fidan Y, Topkaya C, Basar H. Dexmedetomidine attenuates the hemodynamic and neuroendocirinal responses to skull-pin head-holder application during craniotomy. J Neurosurg Anesthesiol 2008;20:174-9.
13. Gurulingappa, Aleem MA, Awati MN, Adarsh S. Attenuation of cardiovascular responses to direct laryngoscopy and intubation-a comparative study between iv bolus fentanyl, lignocaine and placebo (NS). J Clin Diagn Res 2012;6:1749-52.
14. Yıldız M, Tavan A, Tuncer S, Reiski R, Yosunkaya A, Otelecioglu S. Effect of dexmedetomidine on haemodynamic responses to laryngoscopy and intubation: Perioperative haemodynamics and anaesthetic requirements. Drugs R D 2006;7:43-52.
15. Basar H, Akpinar S, Doganci I, Buyukcocak U, Kaymak C, Sert O, et al. The effects of preanaesthetic, single-dose dexmedetomidine on induction, hemodynamic, and cardiovascular parameters. J Clin Anesth 2008;20:431-6.
16. Keniya VM, Ladi S, Nahjadi R. Dexmedetomidine attenuates sympathoadrenal response to tracheal intubation and reduces perioperative anaesthetic requirement. Indian J Anaesth 2011;55:352-7.
17. Gopalakrishna KN, Dash PK, Chatterjee N, Easwer HV, Ganesamoorthi A. Dexmedetomidine as an anesthetic adjuvant in patients undergoing transphenoidal resection of pituitary tumor. J Neurosurg Anesthesiol 2015;27:209-15.
18. Venn RM, Ground RM. Comparison between dexmedetomidine and propofol for sedation in the intensive care unit. Patient and clinician perceptions. Br J Anaesth 2001;87:684-90.
19. Vuyk J, Sitsen E, Reekers M. Intravenous anaesthetics. In: Miller RD, editor. Miller’s Anaesthesia. 8th ed. Philadelphia: Elsevier; 2015. p. 858.
20. Shen SL, Zheng JY, Zhang J, Wang WY, Jin T, Zhu J, et al. Comparison of dexmedetomidine and propofol for conscious sedation in awake craniotomy: A prospective, double-blind, randomized, and controlled clinical trial. Ann Pharmacother 2013;47:1391-9.
21. Akavipat P, Hungsawanich N, Jansin R. Alternative placement of bispectral index electrode for monitoring depth of anesthesia during neurosurgery. Acta Med Okayama 2014;68:151-5.
22. Engelhard K, Werner C, Kaspar S, Möllenberg O, Blobner M, Bachl M, et al. Effect of the alpha2-agonist dexmedetomidine on cerebral neurotransmitter concentrations during cerebral ischemia in rats. Anesthesiology 2002;96:450-7.
23. Arulvelan A, Manikandan S, Easwer HV, Krishnakumar K. Cerebral vascular effects of loading dose of dexmedetomidine: A Transcranial Color Doppler study. Indian J Crit Care Med 2016;20:9-13.