

Effect of adjunctive dexmedetomidine on anesthesia and analgesia requirement and recovery characteristics during Bispectral Index-guided anesthesia for cerebello-pontine angle surgeries: A randomized clinical trial

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Abstract

Background and Aims: The study was conceived to elucidate the effects of dexmedetomidine as an anesthetic adjunct to propofol (total intravenous anesthesia) on anesthetic dose reduction and anesthesia recovery parameters in cerebello-pontine angle (CPA) surgeries.

Material and Methods: This prospective randomized study was conducted on 49 patients (25 with dexmedetomidine, 24 without). After standardized anesthetic induction, anesthesia was maintained using propofol (via target controlled infusion, titrated to maintain BIS between 40 and 60), fentanyl (0.5 µg/kg/hour) and either dexmedetomidine (0.5 µg/kg/hour) or a sham infusion. Neuromuscular blocking agents were excluded to allow cranial nerve EMG monitoring. Adverse hemodynamic events, recovery parameters (time to opening eyes, obeying commands, and extubation) and postoperative sedation score, shivering score, nausea, and vomiting score were recorded.

Results: Propofol and fentanyl utilization (as total dose, adjusted for duration of surgery and body weight, and number of extra boluses) was significantly lower in the dexmedetomidine group. There was no difference in any of the recovery parameters between the two groups. Incidence of bradycardia was significantly higher with dexmedetomidine, while no difference was found for hypotension, hypertension, and tachycardia.

Conclusion: Dexmedetomidine–fentanyl–propofol anesthesia compares favorably with fentanyl–propofol anesthesia during CPA neurosurgical procedures with regard to anesthesia recovery times, but with lower intraoperative opioid and hypnotic utilization rates.

Keywords: Bispectral index, cerebello-pontine angle, dexmedetomidine

Introduction

Cerebello-pontine angle (CPA) surgeries tend to carry the surgeon's knife uncomfortably close to the brainstem, putting

various cranial nerves at risk for damage. Cranial nerve monitoring usually employed to circumvent such an adverse event, requires changes in anesthetic management by exclusion of neuromuscular blocking agents and avoidance or dose reduction of inhalational agents.^[1,2] At our institute, a total intravenous anesthesia (TIVA) protocol devoid of neuromuscular blocking

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agents is practised. However, prolonged infusion of propofol TIVA is fraught with risks, such as hypotension, delayed awakening, and metabolic acidosis, popularly described as “propofol infusion syndrome.”^[3] High doses of opioids are associated with adverse effects, such as postoperative nausea and vomiting, and postoperative respiratory depression that are undesirable in neurosurgical patients. Dexmedetomidine is increasingly used as an anesthetic adjuvant and has been demonstrated to reduce anesthetic requirement and provide hemodynamic stability during neurosurgery.^[4] The only systematic review evaluating dexmedetomidine as an adjuvant during neurosurgery confirmed significant beneficial outcomes such as reduction in intraoperative opioid and anesthetic consumption, lower heart rate and blood pressure, reduced shivering and PONV, lower postoperative pain and analgesic requirement, and early extubation.^[5] However, the beneficial effect of dexmedetomidine has not been tested during TIVA and when neuromuscular blockade is excluded. We hypothesised that high dose of propofol and fentanyl with its consequent adverse effects can be minimized with adjunctive use of dexmedetomidine during electromyogram monitoring for CPA surgeries. This study aimed to evaluate the effect of dexmedetomidine on intraoperative propofol and fentanyl consumption and postoperative recovery characteristics during CPA surgeries.

Material and Methods

This was a prospective randomized parallel-group, nonfunded, single-center study conducted at after institutional ethics committee approval. The trial was registered retrospectively at clinical trial registry of India vide registration number CTRI/2017/01/007667.

The primary objective of this study was to confirm the anesthetic sparing effect of dexmedetomidine during TIVA without neuromuscular blocking agents. Secondary objectives were determining the analgesic sparing effect, comparing anesthesia recovery parameters, incidence of adverse intraoperative hemodynamic events, and utilization of other analgesic and hemodynamic drugs.

All consecutive consenting patients of either sex undergoing surgery for CPA tumor and aged between 18 and 60 years were included in this study. Our exclusions were patients with significant cardiovascular involvement as evidenced by arrhythmia on electrocardiogram, baseline heart rate <50 and >100/min, hypertension on antihypertensive drugs or cardiac failure, impaired hepatic or renal function, and allergy to egg.

After selection of the eligible patients, randomization to the study group was performed at 1:1 ratio by a computer-generated random number table. Group F received only fentanyl and group D received dexmedetomidine and fentanyl.

On arrival in the operation theatre, intraoperative monitoring (electrocardiograph, pulse oximetry, noninvasive blood pressure, and bispectral index (BIS)) was applied. Anesthesia was induced with propofol 2 mg/kg, fentanyl 2 µg/kg, and lignocaine 1.5 mg/kg. Vecuronium 0.12 mg/kg was administered to facilitate tracheal intubation. Anesthesia was maintained with propofol TIVA via a target controlled infusion (TCI) device [Fresenius Kabi India Pvt Ltd] using Schnider pharmacokinetic model, titrated to a BIS target of 40–60. Either fentanyl infusion (0.5 µg/kg/hour) or fentanyl + dexmedetomidine infusion (both at 0.5 µg/kg/hr) was administered based on the randomization from beginning to end of surgery. Neuromuscular blocking agents were excluded (due to institution of cranial nerve EMG monitoring) and additional boluses of 1 µg/kg fentanyl administered at the discretion of attending anesthesiologist based on hemodynamic exacerbations. If an increase in BIS was observed for >5 minutes with associated hemodynamic activation, a bolus of 1 mg/kg propofol was administered along with an increase in the TCI effect site concentration target of 0.5 µg/mL. The attending anesthesiologist was blinded by providing fentanyl (4 µg/mL) or premixed fentanyl and dexmedetomidine (both 4 µg/mL) as colorless solutions in an unlabelled 50 mL syringe for constant infusion at 0.125 mL/kg/hour.

Hemodynamic measurements were recorded at 5-minute intervals with the aim of detecting adverse hemodynamic events. Hypertension was defined as increase in the mean arterial pressure (MAP) by >30% of the baseline for >5 minutes. Hypotension was defined as a decrease in MAP by >30% of the baseline. Bradycardia was defined as a decrease in heart rate to <45/minute for >5 minutes. Tachycardia was defined as an increase in heart rate by >30% of the baseline for >5 minutes. When hypotension was observed, fluid bolus and/or transfusion was administered if hypovolemia/blood loss was presumed to be the cause. If hypotension persisted for >5 min despite the above measures, inj. mephentermine 6 mg boluses were administered and recorded. If bradycardia was associated with hypotension, other than during cranial nerve/brainstem stimulation, atropine 0.01 mg/kg was administered as treatment.

The study drug infusions were stopped at the beginning of skin closure and the patients were administered 1 g paracetamol IV. Time to opening eyes, obeying commands, and extubation were assessed after discontinuation of anesthetics. Extubation

was left at the discretion of the attending anesthesiologist; however, any extra drugs administered before extubation were recorded (including antiemetics, antiepileptics, analgesics, hemodynamic agents). All monitoring parameters were also recorded just after extubation.

Sample size calculation

Since there was no precedent of a similar study protocol and population in relevant literature, we did a pilot study of four cases in each group to find a difference in propofol consumption. Effect size d was found to be 1.2, with total propofol dose of 1804 ± 295 mg in dexmedetomidine group vs. 2327 ± 548 mg in fentanyl group. With a two-tailed hypothesis, and keeping α -error of 0.05 and aiming for a power of 0.95, sample size was found to be 20 in each group. Figuring in an attrition rate of 20%, 25 subjects per group was decided for recruitment.

Statistical analysis

All statistical tests were performed using SPSS® ver. 16 software (Statistical Package for the Social Sciences, Chicago). Quantitative variables were described as means and standard deviations, qualitative variables as percentages, and variables on ordinal scale as medians and interquartile range. Error bars for graphical depiction of quantitative data indicate standard deviations. Qualitative variables were analyzed between the groups with Chi-square test or Fisher's exact test as appropriate. Normally distributed quantitative variables were analyzed using independent samples student t -test between the groups and paired samples t -test for within-group analysis across time points. Non-normally distributed quantitative data and ordinal data were analyzed using Mann-Whitney U -test for between-group comparison and Wilcoxon signed ranks test for within-group comparison across time points. Correlation analysis was conducted using Spearman's test. P value of <0.05 was taken as level of statistical significance.

Results

50 patients were recruited. One patient in the fentanyl group was excluded due to intraoperative BIS sensor failure. 49 patients (Group D, $n = 25$ and Group F, $n = 24$) were included in final analysis [Figure 1].

The demographic parameters and perioperative characteristics were comparable between the two groups [Table 1].

Anesthetic and analgesic consumption during surgery

The anesthetic and analgesic doses were compared as such, and after adjustment for total body weight and duration of anesthesia. The extra boluses of propofol and fentanyl

required were also compared between the groups. There was a significant reduction in total fentanyl and propofol consumption with use of dexmedetomidine, and the difference persisted after adjustment for body weight and duration of anesthesia. Propofol boluses were infrequently used by the attending anesthesiologists intraoperatively and did not differ significantly between the two groups. The number of fentanyl boluses administered was significantly less in the dexmedetomidine group [Figures 2 and 3].

Hemodynamic adverse events

The dexmedetomidine group recorded a significantly higher incidence of bradycardia (36% vs. 0%) than the fentanyl group ($P = 0.002$). The incidence of hypertension, hypotension, and tachycardia were not significantly different between the two groups [Figure 4]

Anesthesia recovery parameters

Most patients (85%) had onset of spontaneous respiration during the intraoperative period as neuromuscular blocking drugs were excluded after the intubating dose was administered. Fentanyl administration and ventilatory adjustment overcame attempts at spontaneous respiration. The mean time to eye opening, time to obeying commands, and time to extubation were higher in dexmedetomidine group, although the difference was not statistically significant [Table 2].

Rescue drug utilization

Utilization of labetalol, mephentermine, atropine, and morphine were compared between the two groups as dichotomous

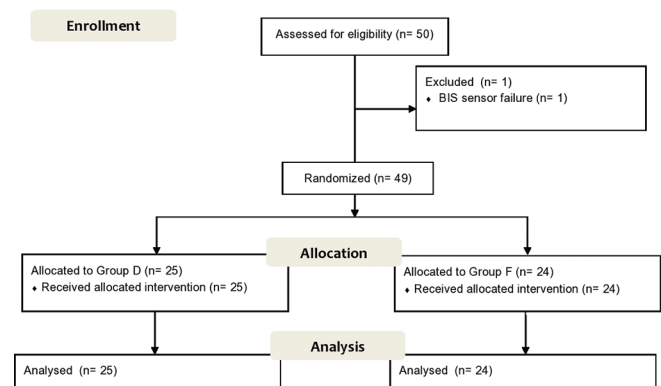


Figure 1: CONSORT flow diagram

Table 1: Demographic variables

Parameters	Dexmedetomidine	Fentanyl	P
Age (years)	41.5 (10.5)	41.2 (12.1)	0.924
Sex (M/F) (%)	56/44	33/67	0.111
BMI (kg/m ²)	23.81 (4.41)	23.0 (4.1)	0.525
Duration of Surgery (min)	336.0 (102.6)	339.0 (95.0)	0.919
Duration of Anaesthesia (min)	394.5 (105.3)	401.3 (94.8)	0.815

variables. Morphine was used as intraoperative analgesic agent at the discretion of the attending anesthesiologist, when fentanyl boluses were deemed to be subefficacious in a given

patient, based on hemodynamic variables. There was no significant difference between utilization rates of any of the drugs [Table 3].

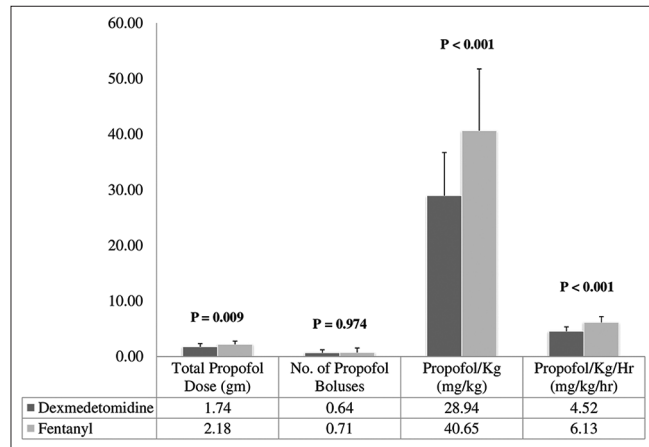


Figure 2: Propofol requirement during surgery in fentanyl only and dexmedetomidine (with fentanyl) groups

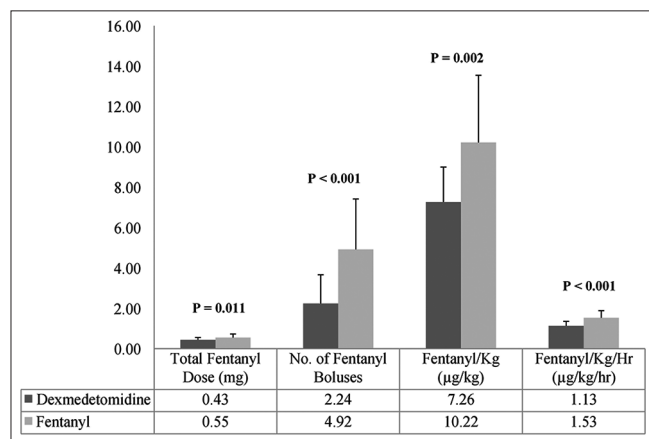


Figure 3: Fentanyl requirement during surgery in fentanyl only and dexmedetomidine (with fentanyl) groups

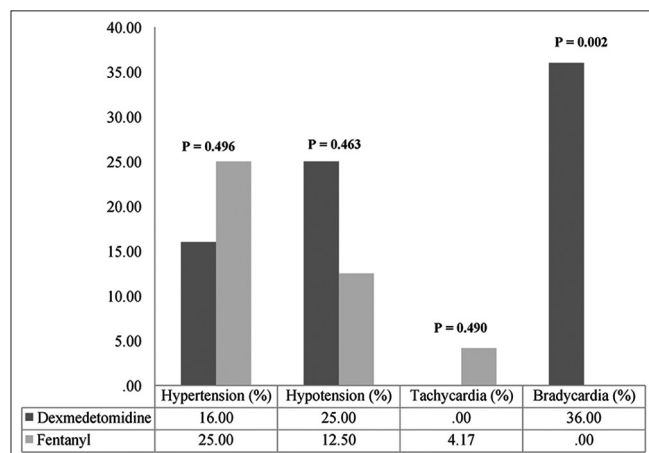


Figure 4: Hemodynamic events during surgery in fentanyl only and dexmedetomidine (with fentanyl) groups

Discussion

This study reconfirmed the findings of earlier studies regarding anesthetic and analgesic sparing effects of dexmedetomidine during CPA surgeries. Interestingly, despite the reduced propofol and fentanyl consumption, a similar recovery profile was observed in both fentanyl-based and dexmedetomidine-based anesthetic techniques.

We performed a systematic search of the literature for dexmedetomidine as an anesthetic adjunct using Google Scholar and PubMed databases with keywords “dexmedetomidine anesthetic sparing.” The search revealed 50 results, which were collated and separated according to the relevance to our keywords. Data regarding significant intraoperative anesthetic/analgesic sparing (yes/no) and recovery parameters (significantly faster times to extubation with dexmedetomidine – yes/no) was collected. Animal studies, case reports, retrospective studies, review articles, and irrelevant studies were excluded, which resulted in 17 relevant results [Table 4].

Anesthetic and analgesic sparing effect

Anesthetic sparing effect of dexmedetomidine was demonstrated in all the articles studying this effect.^[6-22] Our study echoes this finding with a significant reduction in propofol utilization. The difference in patient population (infratentorial intracranial procedures), anesthetic technique (neuromuscular blockade-free anesthesia), and the longer duration of surgery (397.8 ± 99.2 min) in our study did not alter this outcome.

Table 2: Recovery characteristics after surgery in fentanyl only and dexmedetomidine (with fentanyl) groups

	Dexmedetomidine	Fentanyl	P
Time to opening eyes	21.1±14.8	13.9±4.7	0.166
Time to obeying commands	21.8±14.6	15.1±4.7	0.280
Extubation Time	19.9±13.8	13.5±4.2	0.359

Table 3: Rescue drug utilization during surgery in fentanyl only and dexmedetomidine (with fentanyl) groups

	Dexmedetomidine	Fentanyl	P
Labetalol (%)	12.0	12.5	1.000
Mephentermine (%)	24.0	8.3	0.247
Atropine (%)	12.0	0	0.235
Morphine (%)	8.0	12.5	0.667

Table 4: Results of literature review for anesthetic sparing efficacy of dexmedetomidine

Author/ Year of Publication	Patient population	Number of Patients	Dexmed dose	Anaesthetic/ analgesic	Anaesthetic titration criteria	Anaesthetic Sparing	Analgesic Sparing	Recovery Parameter
Soliman <i>et al</i> /2011 ⁶	Supratentorial Craniotomy	40; 20 per group	1 µg/kg → 0.4 µg/kg/hr IV	Sevoflurane/ Fentanyl	Hemodynamic	Yes	Yes	Yes
Kanda H <i>et al</i> /2009 ⁷	Cardiovascular Surgery	24; 12 per group	6 µg/kg → 0.7 µg/kg/hr IV	Propofol/ Fentanyl	NA	Yes	Yes	NA
Keniya VM <i>et al</i> /2011 ⁸	Surgery >3 h duration	60; 30 per group	1 µg/kg → 0.2-0.7 µg/ kg/hr IV	Isoflurane/ Fentanyl	Hemodynamic	Yes	Yes	No
Bajwa SJ/2012 ⁹	Elective Surgery	100; 50 per group	1 µg/kg IV	Isoflurane/ N2O/Fentanyl	Hemodynamic	Yes	Yes	Yes
Ravipati P <i>et al</i> /2014 ¹⁰	Burn Dressing	60; 30 per group	1 µg/kg IM	Propofol/ Ketamine	Hemodynamic	Yes	Yes	Yes
Khalil <i>et al</i> /2013 ¹¹	Off-pump coronary artery bypass grafting	50; 25 per group	0.5 µg/kg/ hr IV	NA/Morphine + Fentanyl	Hemodynamic	NA	Yes	Yes
Patel CR <i>et al</i> /2013 ¹²	Elective Surgery	60; 30 per group	1 µg/kg → 0.2-0.8 µg/ kg/hr IV	Sevoflurane/ Fentanyl	Entropy	Yes	NA	NA
Tufanogullari B <i>et al</i> /2008 ¹³	Laparoscopic bariatric surgery	80; 20 per group	0.2/0.4/0.8 µg/kg/hr IV	Desflurane/ Fentanyl	Hemodynamic	Yes	NA	No
Vora KS <i>et al</i> /2015 ¹⁴	Laparoscopic surgery	70; 35 per group	1 µg/kg → 0.5 µg/kg/hr IV	Isoflurane/ N2O/Fentanyl	Hemodynamic	Yes	Yes	NA
Ngwenyama NE <i>et al</i> /2008 ¹⁵	Posterior spinal fusion	36; 12 in Dexmedetomidine/ 24 in Remifentanyl	0.5 µg/kg/ hr IV	Propofol/ Remifentanyl	Bispectral Index	Yes	No	NA
Kang WS <i>et al</i> /2012 ¹⁶	Breast Surgery	20; 10 per group	1 µg/kg → 0.6 µg/kg/hr IV	Propofol/ Remifentanyl	Bispectral Index	Yes	NA	No
Gupta N <i>et al</i> /2013 ¹⁷	Paediatric Spinal dysraphism (8-12 yrs)	36; 18 per group	1 µg/kg → 0.5 µg/kg/hr IV	Sevoflurane/ Fentanyl	Bispectral Index	Yes	Yes	No
Kunisawa T <i>et al</i> /2011 ¹⁸	Cardiopulmonary bypass	22; 11 per group	1 µg/kg → 0.7 µg/kg/hr IV	Propofol/ Fentanyl	Bispectral Index	Yes	NA	NA
Wu X <i>et al</i> /2015 ¹⁹	Elective Surgery	90; 30 per group	0.5/1 µg/kg → 0.17/0.33 µg/kg/hr IV	Propofol/ Remifentanyl	Bispectral Index	Yes	No	NA
Patel A <i>et al</i> /2010 ²⁰	Paediatric tonsillectomy and adenoidectomy (2-10 years)	122; 61 per group	2 µg/kg → 0.7 µg/kg/hr IV	Sevoflurane/ N2O/Fentanyl	Hemodynamic	Yes	No	Yes
Sen S <i>et al</i> /2013 ²¹	Spine surgery	70; 35 per group	1 µg/kg → 0.2 µg/kg/hr IV	Propofol/ N2O/Fentanyl	Bispectral Index	Yes	NA	NA
Turgut N <i>et al</i> /2009 ²²	Supratentorial Craniotomies	50; 25 per group	1 µg/kg → 0.2-1 µg/kg/ hr IV	Propofol/ Remifentanyl	Bispectral Index	Yes	NA	No

With regards to the analgesic consumption, our findings are in agreement with most other studies included in the literature review.^[6-11,14,17] Of the three studies with contradicting claims, two studies used remifentanyl as the primary analgesic, which cannot be directly compared with fentanyl, used as analgesic in our study.^[15,19] The third study by Patel *et al.*, included pediatric population for short-duration surgeries and hence also cannot be compared directly.. In this study too, the intraoperative rescue by fentanyl was significantly less in dexmedetomidine group, although the total fentanyl dosages remained comparable.^[20] The discrepancy is probably due to

the shorter duration of surgeries in their study (~70 minutes), which obviates the use of extra fentanyl in the intraoperative period.

Effect on recovery parameters

Of the 10 studies assessing the effect of dexmedetomidine on the time to extubation, 5 documented a shorter time to extubation,^[6,9-11,20] 4 found no difference,^[8,13,16,17] and one study observed a longer extubation time.^[22] The study with longer extubation time directly compared dexmedetomidine and remifentanyl as primary analgesic agent and hence such a

result is expected due to the shorter half-life of remifentanyl.^[22] The five studies observing a significant reduction in the extubation time used hemodynamic criteria for anesthetic titration as against BIS in our study. Hemodynamic variability when used as an anesthetic titration criterion, leads to overdosing of hypnotic agent with significantly higher propofol infusion rates and total propofol dose.^[23] Considering the hemodynamic depressive effect of dexmedetomidine and a higher propofol/inhalational agent usage with hemodynamic criterion, it is not surprising that these studies found faster times to extubation in the dexmedetomidine group. One of these studies used propofol as the primary anesthetic agent, in short duration burn dressing population with ketamine and dexmedetomidine administered as intramuscular injection for analgesia. Thus, direct comparison with this study is not possible.^[10]

Of the four studies observing no difference in extubation times with dexmedetomidine, three studies had utilized isoflurane, desflurane, and sevoflurane as the anesthetic agents, therefore making direct comparison difficult.^[8,13,20] The study utilizing propofol as the primary anesthetic agent used a fixed dose remifentanyl as the primary analgesic. The other difference from our protocol was the of rocuronium for neuromuscular blockade. The extubation time in that study (9 ± 3 min with dexmedetomidine vs. 11 ± 4 min without) was shorter than our study. This may be explained by the longer operating time in our study and difference in the patient population studied (elective breast surgery vs. CPA surgery).^[16]

The similar recovery times in both the groups in our study despite the lower dose of propofol and fentanyl used in dexmedetomidine group can be explained by the sedation effect of dexmedetomidine which probably negates the effect of reduced dose of propofol and fentanyl.

Hemodynamic adverse events

Dexmedetomidine, being a central α -2 agonist, causes reduction in the tonic sympathetic output from the brain and has been shown in most previous studies to result in bradycardia and in some instances, hypotension.^[24] Our study confirms this fact, although the incidence of hypotension was not significantly different from the fentanyl group. CPA surgeries are associated with brainstem manipulation-induced transient bradycardia, which is used as a sign by the surgeon to modify his surgical approach. In our study, we defined bradycardia as heart rate <45 for >5 minutes, to rule out brainstem manipulation-induced events. Also, only clinically significant bradycardia (i.e., associated with hypotension) was treated with atropine. Considering the atropine utilization rate, the incidence of clinically relevant bradycardia was not significantly different between the two groups.

Conclusion

Dexmedetomidine–fentanyl–propofol anesthesia compares favorably with fentanyl–propofol anesthesia during CPA neurosurgical procedures with respect to recovery characteristics, though propofol and fentanyl consumption is reduced when dexmedetomidine is used as an anesthetic adjuvant. No additional clinical advantage in terms of recovery from anesthesia was obtained by incorporating dexmedetomidine in the currently used anesthetic technique for facilitating cranial nerve monitoring during CPA tumor surgeries.

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Conflicts of interest

There are no conflicts of interest.

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