EFFECT OF INTRAOPERATIVE INFUSION OF DEXMEDETOMIDINE ON EMERGENCE AGITATION AMONG ADULTS UNDERGOING NASAL SURGERIES-A PROSPECTIVE RANDOMISED DOUBLE BLIND STUDY

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Abstract

Context: Emergence agitation (EA) is significant in patients recovering from general anaesthesia for nasal surgery.

Aim: To assess the efficacy of dexmedetomidine infusion in reducing the incidence of EA in adults undergoing nasal surgery.

Settings and Design: In this prospective randomised double blind study we recruited 56 adult patients belonging to ASA 1& 2 and aged 18-60 years.

Methods and Material: Group D [n=28] received a continuous infusion of dexmedetomidine at 0.4 μg/kg/hr from induction of anaesthesia until nasal packing. Group C [n=28] received a volume matched infusion of 0.9% saline. Incidence of EA was diagnosed on a score of 5 or more on the Ricker sedation agitation scale. Haemodynamic parameters, time of awakening and post-operative recovery characteristics in the perioperative period were also observed. Statistical analysis was performed using independent samples T-test, Chi-Square test or Fisher's Exact test.

Results: The incidence of EA was significantly lesser with 11(39.3%) subjects in Group D compared to 24(85.7%) subjects in Group C ($p < 0.01$). The mean duration of time of awakening was prolonged in group D compared to group C (11.14 min vs 5.43 min). The heart rate and mean arterial pressure were significantly lower in the study group compared to the control group (p value<0.01). The number of patients requiring rescue fentanyl in study group compared to control in Post Anaesthesia Care Unit (1 Vs 18) was significantly less.

Conclusion: Dexmedetomidine infusion during nasal surgery satisfactorily reduces the incidence of EA without increasing the adverse effects.

Keywords: Emergence agitation, Dexmedetomidine, nasal surgery.

Introduction

Emergence agitation (EA) is a transient state of marked irritation characterised by restlessness, disorientation, wild thrashing in association with shouting and screaming after the discontinuation of anaesthesia in some patients. This postanesthetic excitement may impair the quality of recovery

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from general anaesthesia[1]. It can suddenly become dangerous and have serious consequences for the patient such as self-injury, increased post-operative pain, hemorrhage, self-extubation and removal of catheters requiring physical or pharmacological restraint. Furthermore EA is also worrisome to anesthesiologists and recovery room staff raising the hospital costs[2]. The incidence of EA after general anaesthesia is 21.3% is more common after oral cavity and otolaryngological surgery than other types of surgery[3]. Despite its common occurrence and serious sequelae, EA has been studied occasionally in adults.

Various pharmacological measures have been used to reduce the incidence of EA in children anesthetized with sevoflurane, desflurane or both. In a meta-analysis, it was found that ketamine, fentanyl, propofol, α_2 agonist and providing peroperative analgesia were effective in preventing EA[4].

Dexmedetomidine (Dex) is a highly selective α2 agonist which produces sedation and anxiolysis through reduction in sympathetic central nervous system activity. It has a major advantage over other sedatives that it is associated with minimal respiratory depression. Moreover its activation of α2 receptors accentuates the action of opioids and decreases opioid consumption[5].

This study was planned to evaluate the efficacy of intraoperative infusion of Dex in reducing EA in adults undergoing nasal surgery. The hemodynamic stability and recovery characteristics in PACU were also evaluated.

Subjects and Methods

This prospective, randomized double blind placebo controlled study was initiated after obtaining approval of departmental research committee and Institutional ethics committee.

The patients were contacted one day prior to the surgery to discuss the methodology. All the subjects who provided written informed consent were assessed for inclusion and exclusion criteria and enrolled into the study. Anticipating a difference of 30% in the proportion of patients with EA after extubation, to be clinically significant for a power of 80% at 95% confidence limits, 28 patients were required in each group.

Fifty six patients aged between 18 to 60 years, belonging to ASA physical status 1 & 2 and undergoing elective nasal surgeries under general anaesthesia in which nasal packing on each side was used for 24 hours after surgery were included in the study. Subjects with known or suspected allergy to α2-receptor agonist or NSAIDS, with history of uncontrolled hypertension, heart block greater than first degree, using MAO inhibitors or adrenergic blocking drugs, with cognitive impairment, chronic use of antipsychotic medications, alcohol abuse, with clinically significant neurologic, cardiovascular, renal, hepatic or gastrointestinal tract diseases, requiring surgeries longer than 2 hrs duration were excluded from the study.

A preoperative anxiety scoring using visual analogue scale ranging from 1 to 10 was obtained on the day prior to surgery. All patients were premedicated with oral alprazolam 0.25 mg, pantoprazole 40 mg and metoclopramide 10 mg on the night prior to surgery and at 5 am on the day of surgery.

On the day of surgery patients were randomly assigned to either of the following two groups: Group C (control group) and Group D (Dexmedetomidine group) using computer generated random sequence allocation. Concealment was ensured using sequentially numbered, opaque sealed envelope.

Study drugs were prepared by observer 1, not involved in the data collection, in unlabelled 50 ml syringes. Dex (1ml = 100µg) was diluted with normal saline (49 ml) to a concentration of 2µg/ml in 50 ml syringe and control group drug was loaded with 50 ml normal saline as placebo

Patient was then shifted to the operation theatre where intravenous access was secured by a second observer. Monitoring with 5 electrode ECG, non-invasive blood pressure (BP), pulse oximetry, and end tidal carbon dioxide was established. The study drug (Dex/ normal saline) infusion was started at 0.4 µcg/kg/hr just before anaesthetic induction. Baseline readings were noted and monitored at every 5 minute intervals for first 30 minutes of surgery and then every 15 minutes till the end of surgery and extubation. Intravenous (IV) access was secured and infusion of the study drug was started as per the group and

recommended infusion rate.

General anesthesia was induced by a combined use of fentanyl 2µg/kg and Propofol 2-2.5mg/kg. After confirming the ability to ventilate the lungs, IV vecuronium 0.1 mg/kg was used for neuromuscular blockade. Ventilation was assisted with 2% isoflurane in 100% oxygen for 3 minutes, followed by laryngoscopy and orotracheal intubation was performed using either 7 or 7.5 mm internal diameter polyvinyl chloride cuffed orotracheal tube in women and either 8 or 8.5 mm internal diameter polyvinyl chloride cuffed orotracheal tube in men. Maintenance of anesthesia was achieved with Isoflurane 1-1.2 MAC, 66% N_2O, 33% O_2.

Once the surgery was completed, oral suction was performed, and reversal of neuromuscular blockade was done with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg after confirming the return of neuromuscular function using train-of-four peripheral nerve stimulation. Subsequently, isoflurane was turned off (defined as 'time zero' in the emergence process) in both groups, and mechanical ventilation was then converted to manual ventilation with 100% oxygen at 5 litre/ min. The patients were not disturbed, except by continual verbal requests to open their eyes. All other stimuli were prevented.

Extubation was performed once subject was breathing spontaneously, following verbal commands, having intact gag reflex and able to generate tidal volume of 6ml/kg body weight and no fade detected with a DBS stimulus at 40 mA using PNS.

The following observations were noted at the end of surgery by a third observer blinded to the study:

1) Time zero (TZ): Time of expired Isoflurane concentration of 0.6 following completion of the procedure

2) Time of awakening or just before extubation (TJE): Time from TZ till the patient is awake

3) Time to 5 minutes after extubation (T5E): Time from TZ to 5 min after tracheal extubation

4) RSA grade (RSA = Ricker sedation-agitation scale) was recorded for TJE and T5E

The level of EA was assessed using Ricker sedation-agitation scale and complications at emergence were recorded. RSA Grade ≥ 7 was considered as dangerous EA. Assessment of postoperative pain was done on an 11-point numerical rating scale (NRS) for pain. Postoperative nausea and vomiting was done on a 4 point nausea and vomiting scale. BP and heart rate were monitored periodically. Readiness to discharge from post anesthetic care unit was assessed by Aldrete score. Subjects were discharged from post anesthetic care unit on an Aldrete score of ≥ 12. Medications were administered, if required as per standard protocol and were well managed.

Statistical analysis was done using SPSS version 20 for Windows. Parametric data were analysed using Independent Samples T-test and nonparametric data were analysed using Chi-Square test or Fisher's Exact test. A P-value less than 0.05 was considered statistically significant.

Results

A total of 56 patients undergoing Functional Endoscopic Sinus Surgery (FESS) and Septoplasty under general anesthesia aged 18 to 60 years were included in the study.

The number of subjects exhibiting EA with a Ricker sedation agitation score of 5 to 7 was lesser in Group D n=11 (39.3%) compared to Group C n=24 (85.7%), $p<0.05$ (Figure 1). None of the subjects in Group D had EA at 5 min after extubation and only one subject in Group C had an EA which was statistically insignificant.

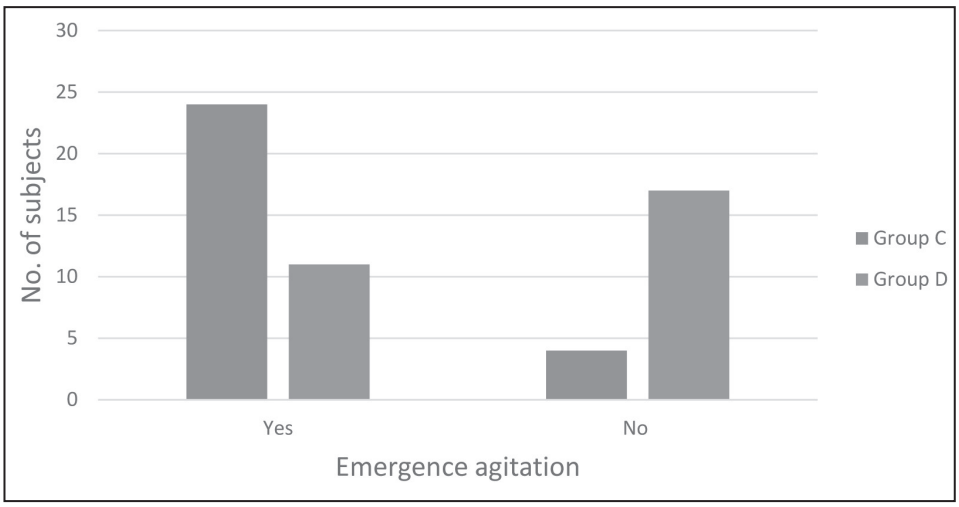
There were no statistically significant differences between the intervention and control group with respect to age, gender, weight and ASA grades (Table 1). In the

Table 1

Patient characteristics (Mean ± SD) or numbers.

Characteristics	Group C3 (n=28)	Group D (n=28)	*P*-value
Age (years)	38.3 ± **11.7**	35.5 ± **11.8**	0.74
Weight (kg)	60.7 ± **8.0**	67.2 ± **10.6**	0.06
Gender (Male/ Female)	25/3	21/7	0.163
ASAPS (1/2)	24/4	20/8	0.193

Fig. 1
Emergence agitation among study participants



intra-operative period, HR and mean arterial pressure (MAP) were significantly lower in the intervention group compared to the control group (Table 2). Time taken for awakening (TA) was 11.14 ± 2.718 minutes in Group D and 5.43 ± 1.168 minutes in Group C and this difference was statistically significant ($p < 0.01$).

In the PACU, the HR and MAP were statistically lower in Group D compared to group C (Table 3).

The pre-operative anxiety score P (Mean ± SD) were 5.54 ± 0.793 and 5.46 ± 0.881 in Group C and Group D respectively; however no significant difference was noted ($p = 0.751$). Rescue analgesic was needed in 18 (64.3%) subjects in Group C and only in 1 (3.6%) patient in Group D and this difference was statistically significant ($P < 0.05$).

Length of stay in PACU in Group D and Group C were 121.07 ± 9.9 and 120.0 ± 0.0 minutes respectively no statistically significant difference.

Discussion

The intraoperative continuous infusion of Dex at 0.4 μg/kg/hr reduced the incidence of EA in patients undergoing nasal surgeries. EA was lesser in patients

Table 2
Data is presented as (Mean ± SD).

Time Intervals (minutes)	Heart rate (beats/min)		P-value	Mean Arterial Pressure (mmHg)		P-value
	Group C (n=28)	Group D (n=28)		Group C	Group D	
0	82.7 ± **11.8**	80.3 ± **10.6**	0.436	88.3 ± **12.9**	82.6 ± **10.9**	0.077
15	81.2 ± **9.9**	67.6 ± **8.9**	<0.01	83.8 ± 13.6	69.2 ± **10.5**	<0.01
30	80.9 ± **9.0**	60.6 ± **5.9**		80.1 ± **6.9**	62.4 ± **6.2**	
45	81.4 ± **8.4**	60.1 ± **5.7**		82.2 ± **7.2**	62.1 ± **3.9**	
60	81.5 ± **9.2**	59.8 ± **5.3**		82.5 ± **8.0**	61.8 ± **3.5**	
75	82.5 ± **6.8**	60 ± **6.4**		83.8 ± **10.5**	62.5 ± **6.2**	
90	82.5 ± **7.3**	59.8 ± **5.2**		84.0 ± **7.3**	61.3 ± **3.5**	
105	81 ± **8.2**	61.2 ± **5.5**		85.7 ± **6.2**	63.5 ± **3.9**	

Table 3

Comparison of haemodynamic parameters between the study and control groups Data is presented as (Mean ± SD).

Time Intervals (minutes)	Heart rate		P-value	Mean Arterial Pressure		P-value
	Group C (n=28)	Group D (n=28)		Group C (n=28)	Group D (n=28)	
5	81.9 ± **9.9**	65.2 ± **6.2**	<0.01	84.7 ± **7.6**	65.3 ± **6.1**	<0.01
10	80.1 ± **9**	64.1 ± **5.7**		82.3 ± **7.2**	63 ± **5**	
15	79.2 ± **7.8**	64.1 ± **5.8**		82.1 ± **8**	62.9 ± **4.5**	
30	79.1 ± **7.4**	63.4 ± **4.7**		81.9 ± **7.2**	63.4 ± **4.8**	
60	79.9 ± **7.2**	62.9 ± **5**		79.3 ± **5.6**	63.2 ± **4.2**	
90	78.7 ± **7.8**	64 ± **5.7**		80.4 ± **5.4**	63 ± **4.1**	
120	80.6 ± **7.3**	62.7 ± **3.9**		80.8 ± **5.4**	63.2 ± **4.2**	

who received intraoperative Dex. In a study conducted by Kim et al, with dex infusion at 0.4µg/kg/hr on adult patients undergoing nasal surgery, the time from desflurane discontinuation to extubation (8.7 min in Group D vs 7.8 min in Group C, P=0.092) was not different, however the time to verbal response was longer in Group D compared with Group C (8.1 min vs 7.0 min, P<0.044). The incidence of emergence agitation was lower in Group D than in Group C (28% vs 52%, P<0.041), Agitation subsided within 5 min after extubation in all patients[6]. Similar results were reported by Patel et al and Erdil et al[6,7,8]. Its noteworthy that in a study by Chen JY et al intraoperative Dex bolus, followed by infusion decreased EA in children undergoing strabismus surgery by 57-70%[9]. Thus role of Dex in minimizing EA among paediatric and adult patients undergoing select surgery has been strongly supported by these studies.

Dex is a sedative as well as hypnotic anesthetic agent and at low dose, it produces a sedative effect that mimics natural stage 2 NREM sleep, patients remains drowsy but are cooperative and arousable[8]. This mechanism of action probably explains the reduction in the proportion of patients experiencing EA in the study group compared to control group.

In the current study, we observed that HR and MAP was lesser in the study group compared to the control group. Although this difference was statistically significant, it wasn't clinically significant and did not require therapeutic intervention. The lower HR and MAP observed in Group D could be explained by the decreased sympathetic outflow and circulating levels of catecholamines that are caused by Dex. The goal of providing stable hemodynamics was fulfilled with Dex. The incidence of hypotension that required treatment with mephenteramine was not different between the two groups and no patient in Group D had bradycardia. In a study conducted by Kim et al with an infusion of 0.4 µg/kg/hr of Dex, there was no significant difference in intraoperative MAP and HR values in either of the two groups[6]. Similar observations were reported in studies conducted by Patel et al[7] and Tufanogullari et al[10] among children and adults respectively.

The EA was mainly seen just before extubation, which can be attributed to various factors like presence of endotracheal tube, patient not completely out of anesthesia, and blood in nasal and oral cavity. This would further ascertain the fact that these factors could be precipitating EA prior to extubation. However it was found that patient calmed down five minutes after extubation since the above mentioned factors no more existed and in addition, intraoperative Dex infusion

could have facilitated the reduction of EA.

Preoperative anxiety can itself be an independent cause of EA. The effect of preoperative anxiety using a subjective visual analogue scale on EA was unique in this study compared to other studies. It was found that preoperative anxiety had no bearing on EA as it was equal in the patients who had EA and in whom agitation was absent. Kain ZN et al studied the correlation between preoperative anxiety and EA. Regression analysis showed that the odds of having marked symptoms of emergence delirium increased by 10% for each increment of 10 points in the child's state preoperative anxiety score (mYPAS)[11].

In the PACU, MAP and HR were more stable in Group D compared to Group C. None of the patients in either group was agitated in the postoperative care unit. Our results were consistent with the study conducted by Gurbet et al who showed no significant differences in MAP and HR in PACU between the control and Dex group[5].

In summary, although intraoperative infusion of low dose of Dex successfully reduced the incidence of EA facilitating smooth recovery in adults undergoing nasal surgery and preserved the hemodynamic stability it requires close cardiovascular monitoring. The analgesic sparing effect of Dex makes it an ideal component of multi-modal analgesia.

Limitations of the study: The subjects could not be followed post-operatively beyond two hours. Hence the post-operative opioid sparing effect of dex and antiemetic requirements could not be assessed beyond 2 hours.

Acknowledgement

The authors acknowledge the Head of the Department of Anaesthesia for the support and thank all the participants for cooperating to carry out the study.

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