Effect of Intravenous Dexmedetomidine Before Extubation on Emergence Delirium after Nasal Surgeries

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ABSTRACT

Objective: To investigate the role of single dose of dexmedetomidine (0.5 mcg/kg) in reducing the incidence and severity of postoperative emergence delirium (EmD).

Study Design: A randomised controlled trial.

Place and Duration of the Study: Department of Anaesthesia, Security Forces Hospital, Riyadh, Saudi Arabia, from 1st December 2022 to 30th March 2023.

Methodology: Patients, aged between 18-65 years, with ASA 1-3 scheduled to undergo nasal surgeries under general anaesthesia, were inducted in the study. Exclusion criteria were patient refusal, later request for removal from the study, inability to give consent, known allergy to dexmedetomidine, body mass index (BMI) more than 35, history of obstructive sleep apnoea, history of psychiatric illness, pregnancy, and presence of liver and renal diseases. The primary outcome measure of the study was the incidence of emergence delirium in the postoperative period.

Results: The frequency of EmD after nasal surgery was 52.38% in the control group compared to 14.28% in the dexmedetomidine group ($p = 0.01$). Pain scores were not statistically different between the two groups. The duration of post anaesthesia care unit (PACU) stay was significantly lesser in dexmedetomidine group ($p < 0.001$). The satisfaction score on the visual analogue scale (VAS) was also found to be higher in patients who received intravenous dexmedetomidine ($p < 0.001$).

Conclusion: The use of single dose dexmedetomidine before extubation in nasal surgeries reduces the EmD and improves patient satisfaction.

Key Words: *Dexmedetomidine, Emergence delirium, Nasal surgery, Opioid consumption, Pain control.*

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INTRODUCTION

Emergence agitation or delirium (EmD) is a postanaesthesia complication which is manifested as confusion, agitation, disorientation, and aggressive behaviour.[1] It can lead to serious consequences including haemorrhage, removal of lines, drains and catheters, self-extubation, and even falling out of the bed resulting in severe injuries. It also warrants the need for continuous monitoring, treatment and physical restraints.[2] EmD is associated with cognitive deficit, physical dependence, increased hospital stays, and higher mortality.[3]

There are no clear diagnostic criteria for EmD because of its varied clinical manifestations and hence there is wide variation in the incidence of EmD in scientific literature ranging from 5 to 27.3%.[2,4]

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The exact cause of EmD is also unknown and many risk factors have been identified including pain, presence of stress at the time of induction, induction with etomidate, use of premedication with benzodiazepines, hypoxaemia, type of surgery, awakening in hostile and noisy environment, and presence of urinary catheter.[4,5] Nasal surgeries are considered as risk factors for higher incidence of EmD. Nasal surgeries mostly necessitate awake extubation and additionally, these patients complain of difficulty in breathing due to intranasal packing. Both these factors along with intense pain postoperatively increase their risk of postoperative EmD.[4,6] Kim *et al.* in their study reported an incidence of EmD as high as 50% after nasal surgery.[1]

Various pharmacological interventions have been attempted previously to prevent postoperative EmD with conflicting results.[7,8] Dexmedetomidine has been used in different dosages and at different timings usually as intraoperative infusion with variable results. Although, it can result in postoperative hypotension, bradycardia and delayed post anaesthesia care unit (PACU) discharge.[9,10] This study was conducted to investigate the role of single dose of dexmedetomidine (0.5 mcg/kg) in reducing the frequency and severity of postoperative EmD after nasal surgeries.

METHODOLOGY

This randomised controlled trial was done at Security Forces Hospital in Riyadh, Saudi Arabia. Institutional ethical committee approval was taken with the registration number 22-619-55. The study was registered in ClinicalTrials.gov as NCT05634148. Written informed consent was taken from each patient. This study included patients aged between 18 and 65 years and ASA scores 1-3 who were scheduled to undergo nasal surgery under general anaesthesia. Exclusion criteria included patient refusal, later request for removal from the study, inability to give consent, known allergy to dexmedetomidine, body mass index (BMI) more than 35, history of obstructive sleep apnoea, history of psychiatric illness, pregnancy, and presence of liver and renal diseases. Participants were recruited and followed up between 1st December 2022 and 30th March 2023.

Upon admission to the ward, a random ID was assigned to each patient after meeting the inclusion criteria. Computer-generated random number table was used. Sealed opaque envelopes were used to determine the study groups once patient arrived in the operation theatre. The envelope was then handed over to the anaesthetist who was only responsible for preparing study medication. Primary anaesthetist was unaware of group allocation. Patients were assigned to either of two groups, Group A - Saline group (placebo) and Group B- Dexmedetomidine group. Perioperative anaesthesia and surgical techniques were standardised in both groups.

On arrival, patients were connected to standard ASA monitoring including pulse oximetry, ECG, and non-invasive blood pressure. Baseline measurements of heart rate, blood pressure, and oxygen saturation were recorded. After pre-oxygenation for 3 minutes, induction of anaesthesia was performed using 1.5-2 mcg/kg IV fentanyl, 2-2.5 mg/kg IV propofol followed by 0.6 mg/kg IV rocuronium. Following tracheal intubation, maintenance of anaesthesia was done using 0.8-1.2 MAC sevoflurane. Intravenous remifentanil was used in the range of 0.02-0.15 mcg/kg/minute depending on patient's haemodynamic parameters. Muscle relaxation was managed using additional boluses of IV rocuronium 0.2 mg/kg as needed. Mechanical ventilation was adjusted accordingly to maintain ETCO2 between 30-40 mmHg. IV morphine at 0.02-0.04 mg/kg was used intraoperatively depending on the assessment by the primary anaesthetist. IV dexamethasone 8 mg, IV granisetron 1 mg, IV lornoxicam 8-16 mg, and IV paracetamol 1 g were used. About 40 minutes before the expected end of the operation, study medication was administered. In the saline group, 100 ml of 0.9% saline was administered, while in the dexmedetomidine group, 0.5 mcg/kg of dexmedetomidine diluted in total of 100 ml 0.9% saline was administered. In both groups, study medication was administered using an infusion pump over a period of 30 minutes. At the end of operation, residual neuromuscular blockage was reversed using IV sugamaddex at doses of 2-4 mg/kg depending on the train of four readings. The tracheal tube was extubated after achieving adequate spontaneous regular breathing, gag reflex, facial grimaces, or eye opening and purposeful movements. All patients were then transferred to PACU for routine monitoring. Emergence agitation was scored by using a standardised scoring system named Riker sedation-agitation scale (SAS) at the time of extubation and at every 15 minutes until discharge from PACU to ward. SAS scale is a diagnostic tool to assess behaviour of patient (Table I). It comprises 3 levels of severity of sedation, 3 levels of agitation, and 1 level of calmness. It has shown an excellent level of inter-rater reliability and has been validated against other scales as well.[11]

Pain scores were measured in PACU using the numerical rating scale (NRS). Patients having NRS score ≥5 were managed using IV morphine 1-2 mg boluses. Total opioid consumption in mg was recorded in PACU. Patients were observed for any other adverse events like bradycardia (heart rate <60/minutes), hypotension (SBP <90 mmHg), tachycardia (heart rate >100/minutes, hypertension (SBP >160 mmHg), nausea and vomiting and shivering. Post operative nausea and vomiting (PONV) was graded (0-3) depending on severity. IV metoclopramide 10 mg was administered for intolerable PONV. Patients were discharged from PACU after meeting criteria in Modified Aldrete score.

The primary outcome measure of the study was the incidence of EmD. The secondary outcome measures included pain control and opioid consumption during PACU stay, and duration of stay in PACU. Additionally, the occurrence of any adverse events in the postoperative period were also recorded. Patient satisfaction was assessed using visual analogue scale (VAS).

The sample size was calculated based on the study by Kim *et al.* that showed the incidence of emergence agitation after nasal surgery as 50%.[1] ClinCalc.com sample size calculator was used. Sample size came out as 38 with 40% expected reduction in incidence of emergence agitation with IV dexmedetomidine using 80% power and 0.05 level of significance. Keeping 10% dropout, it was decided to set the sample size as 42 with 21 in each group.

All study data were entered in the statistical package for social sciences (SPSS) version 23 (SPSS Inc, Chicago, IL, USA). Continuous variables were presented as median and interquartile range, and categorical variables were presented as numbers or frequencies. Chi-square and Fisher's exact tests were performed for categorical variables and Mann-Whitney U test was performed to compare medians of continuous outcome variables. A p-value less than 0.05 was considered as statistically significant.

RESULTS

Fifty-five patients were considered for eligibility; however, 13 were excluded. Eight patients did not meet the inclusion criteria and 5 refused to participate in the study. A total of 42 patients were included in the study and randomised into two groups with 21 in each: Group A - Saline group (placebo) and Group B - Dexmedetomidine group. The CONSORT diagram is shown in Figure 1.

Table I: Standards of sedation-agitation scale scoring.

Score	Category	Description
7	Dangerous agitation	Pulling the endotracheal tube, attempting to remove catheters, climbing over the bedrail, striking at staff, and thrashing side to side
6	Very agitated	Cannot remain calm, despite frequent verbal reminders of limits; requiring physical restraint, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up; becomes calm when verbal instructions are provided
4	Calm, cooperative	Calm, easily aroused; follows commands
3	Sedated	Difficult to arouse; awakens to verbal stimuli or gentle shaking, but becomes drowsy again; follows simple instructions
2	Very sedated	Arouses upon physical stimuli, but is unable to communicate or follows commands; may move spontaneously
1	Unresponsive	Minimal or no response to noxious stimuli; unable to communicate or follow commands

Table II: Comparison of outcome variables postoperatively.

	Control group (Group A)		Dexmedetomidine group (Group B)		p-value
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	
NRS at extubation	2 (0-3.5)	2 (2.1)	0 (0-2)	0.86 (1.27)	0.044*
NRS at 15 minutes postoperatively	2 (0.5-2.5)	1.76 (1.578)	1 (0-2)	1.43 (1.399)	0.499
NRS at 30 minutes postoperatively	1 (0-2)	1.24 (1.091)	1 (0-1.5)	0.95 (1.024)	0.341
NRS at 60 minutes postoperatively	1 (0-1.5)	0.95 (0.865)	1 (0-1)	0.62 (0.59)	0.221
PACU opioids consumption (mg)	0 (0-2.5)	1 (1.7)	0 (0-1)	0.98 (1.188)	0.713
Duration of PACU stay (in minutes)	49 (37.5-60)	47.67 (11.12)	31 (30-35)	33.67 (6.24)	0.00*
Satisfaction score	8 (7-8)	7.71 (0.956)	9 (8-9)	8.86 (0.727)	0.00*

**Indicates p-value less than 0.05 and statistically significant. Mann-Whitney U test was used to compare outcome variables.*

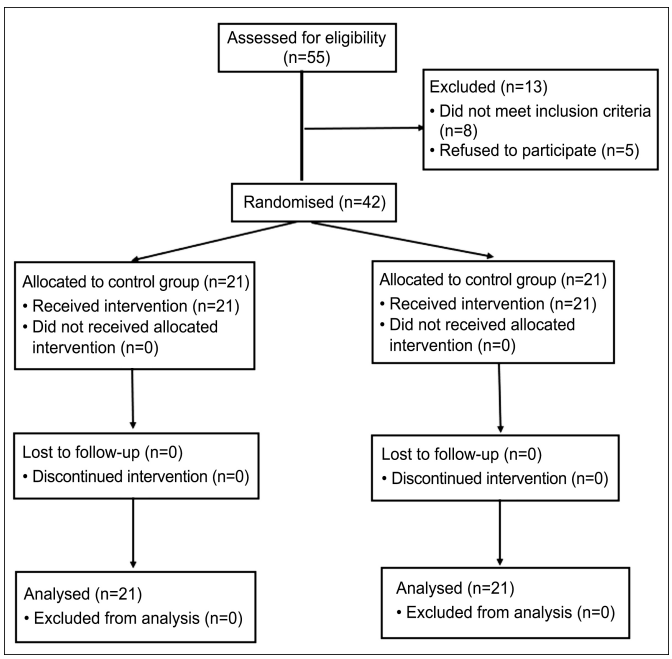

Figure 1: CONSORT flow diagram.

Mean age in Group A was 34.38 (SD-11.56) years *vs.* 30.1 (SD-8.024) years in Group B. Eight out of 21 patients were females in Group A *vs.* 5 in Group B. Majority of surgeries were septoplasty/septorhinoplasty as 76% *vs.* 69% in Group A *vs.* Group B. This was followed by functional endoscopic sinus surgery (FESS) as 24 and 31 in Group A *vs.* Group B. There was no significant difference in demographics of patients between Group A and B. All outcome data in the study was found to have non-normal distribution.

NRS at extubation was statistically different between the two groups (p = 0.044). NRS at other time points during the first 60 minutes in PACU were not statistically different as shown in Table II. The duration of PACU stay was found to be statistically lesser in Group B (p <0.001). The satisfaction level of patients as assessed by VAS in postoperative period was also better with Group B (p <0.001) as shown in Table II.

Eleven patients (52.38%) in Group A were diagnosed as having delirium on Riker agitation scale in postoperative period compared to 3 (14.28%) patients in Group B and the difference was statistically significant using Fisher's exact test (p = 0.01). Ten (47.6%) patients in Group A needed treatment of delirium in the postoperative period while 3 (14.3%) in Group B needed treatment. In Group A, 7 patients needed IV propofol to treat postoperative delirium followed by fentanyl in one patient and pethidine in one patient. While in Group B, one patient received propofol, one patient received fentanyl, and one received combination therapy. Only one patient in each group had PONV and needed antiemetics.

DISCUSSION

General anaesthesia for some surgeries is frequently linked with occurrence of EmD. Scientific literature quotes higher incidence of EmD in ENT, oral and ophthalmologic surgeries.[12] Yu *et al.* reported an incidence of 21.3% for EmD after all surgeries but 55.4% after ENT surgery only.[4] Kim *et al.* also reported an incidence of EmD as 55.4 after ENT surgeries. They showed that patients who underwent nasal surgeries reported a sense of suffocation due to presence of intranasal packing resulting in EmD.[1] Various pharmacological interventions have been used to reduce the incidence of EmD. These include propofol, midazolam, opioids like fentanyl and remifentanil, N-methyl-D-aspartate (NMDA) receptors antagonists like magnesium and ketamine, and alpha-2 agonists like clonidine, and dexmedetomidine. All of these medications have variable success in reducing EmD but at the expense of delayed recovery.[1,4,13]

Dexmedetomidine is widely used in ICU settings to control delirium. It is also used in anaesthesia practice because of its sparing characteristics. It has anxiolytic, analgesic, anti-sympathetic, and sedative effects with lesser risk of respiratory depression. Studies suggest that these effects are mediated by two mechanisms including inhibition of tumour necrosis factor (TNF) production and inhibition of nucleus coeruleus.[14,15]

Lee *et al.* demonstrated in a meta-analysis that intraoperative dexmedetomidine reduces postoperative pain and EmD in adults.[16] Duan *et al*. and Zeng *et al*. also showed a beneficial effect of the use of dexmedetomidine on EmD when given intraoperatively and postoperatively.[17,18] Despite its beneficial role, there is no consensus on the optimal dose and timing of its administration to reduce EmD. Zhu *et al.* reported prolonged sedation, longer extubation time, and prolonged PACU stay with the use of dexmedetomidine.[10] Kim *et al*. reported residual sedation and other haemodynamic alterations like bradycardia and hypotension etc.[19]

This study demonstrated that 14.28% of patients who received intravenous dexmedetomidine for nasal surgery developed EmD compared to 52.38% of patients in the control group. Kim *et al.* used 0.4 mcg/kg/hr intravenous dexmedetomidine in their study and showed an incidence of 28% in the dexmedetomidine group *vs.* 52% in the control group.[19] Lee *et al.* randomised patients undergoing laparoscopic surgery into three groups.[20] The first group received intravenous dexmedetomidine as 1 mcg/kg bolus followed by 0.2-0.7 mcg/kg/hr while second group received dexmedetomidine bolus only. The third group in the study received intravenous saline only. They reported an incidence of EmD as 9.5%, 18.4%, and 24.8%, respectively ($p < 0.05$) in three groups. In contrast, Yang *et al.* did not find any significant difference in the incidence of EmD by dexmedetomidine after maxillofacial surgery.[21]

These results showed that pain score and opioid consumption were not statistically different between the two groups. Although studies by Kim *et al.* and Lawrence *et al*. reported a significant decrease in postoperative pain in dexmedetomidine group.[19,22]

Another finding in this study was a significantly lower PACU duration of stay in patients who received intravenous dexmedetomidine that contrasted with the results reported by Zhu *et al.*[10] Yu *et al.* also showed significantly delayed recovery in patients who received dexmedetomidine.[4] Another study by Garg *et al*. reported that use of dexmedetomidine may prolong PACU duration.[23] Kim *et al*. also reported a significantly prolonged PACU stay in patients receiving intraoperative dexmedetomidine.[19]

In this study, there was no significant increase in the occurrence of any haemodynamic or respiratory adverse events in the dexmedetomidine group. This was in contrast to the findings in the study by Kim *et al.* that reported haemodynamic events like bradycardia and hypotension.[19] This could be due to the fact that intravenous dexmedetomidine was used as bolus. While in this study, the total dose (0.5 mcg/kg) was slowly infused over 30 minutes towards the end of the surgery.

There were a few limitations of this study's results. Firstly, this was a single-centric study. The number of participants enrolled was small, so these results could not be generalised. Also, pain scores and other side effects were not monitored after discharge from PACU.

CONCLUSION

The use of single dose of intravenous dexmedetomidine before extubation after nasal surgery reduces the incidence of emergence delirium (EmD). It reduces the duration of PACU stay and increases patient's satisfaction level after nasal surgery.

ETHICAL APPROVAL:
Ethical approval was taken from the Review Board of the Security Forces Hospital, Riyadh, Saudi Arabia (Research no. 22-619-55).

PATIENTS' CONSENT:
Informed written consent was taken from each patient for participation in the study, and publication of study results.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
AUH: Concept, literature search, ethical approval, conduct of the study, data analysis, manuscript writing, and editing.
MY: Literature search, ethical approval, conduct of the study, and manuscript editing.
MZM, AA: Literature search, conduct of study, and manuscript editing.
All authors approved the final version of the manuscript to be published.

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