Randomized comparison between dexmedetomidine and midazolam for prevention of emergence agitation after nasal surgeries

ABSTRACT
Background: Emergence agitation (EA) in nasal surgeries is seen in around 22% of patients, which can go to dangerous levels. Dexmedetomidine is effective in prevention of EA in such patients. Midazolam given as premedication fails to prevent EA due to its short half-life. In this study, we compared efficacy of dexmedetomidine and midazolam by intravenous infusion for prevention of EA in adult nasal surgeries.

Materials and Methods: Seventy patients belonging to American society of anesthesiologist Status I and II, between 18 and 60 years of age posted for elective nasal surgeries were randomly divided into two groups. Group D received intravenous dexmedetomidine 0.5 mcg/kg over 15 min followed by 0.1 mcg/kg/h. Group M received intravenous midazolam 0.02 mg/kg over 15 min followed by 0.02 mg/kg/h. EA scores, emergence times, and hemodynamic parameters were monitored and compared between the groups. Statistical analysis was done by independent t-test, Mann–Whitney U-test, and Chi-square test as applicable.

Results: Incidence of EA was comparable between the groups (P = 0.23). Two patients in midazolam group developed dangerous agitation while none in dexmedetomidine group. Patients in midazolam group (12.4%) were agitated even in postoperative period, which was not seen with dexmedetomidine group. Hypotension and bradycardia were seen more in dexmedetomidine group.

Conclusion: Efficacy of midazolam when given as an intravenous infusion is comparable to dexmedetomidine in prevention of EA in nasal surgeries.

Key words: Dexmedetomidine; emergence agitation; intravenous infusion; midazolam; nasal surgical procedures

Introduction
Emergence agitation (EA) is defined as state of mental confusion, agitation, and disinhibition manifesting as hyperexcitability, restlessness, and hallucinations during emergence from general anesthesia. It usually occurs between initial 30 and 60 min following emergence from anesthesia which may last up to 45 min and up to 48 h in extreme cases. During this phase, efforts to reorient patients by verbal or
other means are ineffective.\textsuperscript{[1]} Different studies have reported different incidence in adult population due to variability of the scale used for assessment of EA.\textsuperscript{[2,3]} The incidence of EA in nasal surgeries is 22%.\textsuperscript{[4]} The possibility of developing agitation is high during nasal surgeries due to sense of suffocation. The agitation usually resolves spontaneously but can be dangerous sometimes, leading to self-extubation, pulling of urinary catheters, or thrashing side to side. It causes demand on human resources and imposes risk of injury to patient and staff. This level of dangerous agitation is seen in 26% of the agitations. Although the exact pathogenesis is not clearly understood, the precipitating factors are supposed to be preoperative anxiety, postoperative pain, use of sevoflurane anesthesia, and posttraumatic stress disorder.\textsuperscript{[5]} The condition is eight times more common in pediatric population and hence studied extensively in that age group. There are very few studies about incidence, prophylaxis, and treatment of EA in adults.

Benzodiazepines, opioids, and alpha 2 adrenoceptor (AR) agonist-like dexmedetomidine have been tried for prevention of EA. Opioids and alpha 2 AR agonist have been found to be effective in prevention of EA.\textsuperscript{[6]} Benzodiazepines, like midazolam, when given single bolus dose as premedication is not effective in preventing EA occurring during recovery from anesthesia due to its short half-life.\textsuperscript{[3]} Midazolam given as bolus dose at the end of surgery is helpful in preventing agitation.\textsuperscript{[6]} There are no studies on effect of midazolam infusion in prevention of EA. Dexmedetomidine, a highly selective alpha 2 AR agonist, given as infusion has been proven to be effective in prevention of EA in nasal surgeries.\textsuperscript{[7]} Midazolam and dexmedetomidine have been compared for various clinical parameters but not for their efficacy in prevention of EA in adults. A previous study in pediatric population has evaluated incidence of EA as a secondary outcome while comparing midazolam versus dexmedetomidine as premedication.\textsuperscript{[8]} To our knowledge, no study has compared efficacy of midazolam and dexmedetomidine by intravenous infusion in preventing EA.

The objective of the study was to compare efficacy of dexmedetomidine and midazolam for prevention of EA after nasal surgeries. Primary outcome of the study was to compare incidence of EA between midazolam and dexmedetomidine group. The secondary outcome was to compare perioperative hemodynamic parameters, sedation scores, and emergence time.

**Materials and Methods**

This was a prospective randomized double-blinded study conducted over a period of 9 months from September 2016 to May 2017 after approval from the Institutional Ethics Committee (IEC No. 2016/234). The trial is registered with Clinical Trial Registry of India (CTRI/2017/03/008044). Patients between 18 and 60 years of age of American society of anesthesiologist (ASA) physical Status I and II, of either sex, posted for elective nasal surgeries with nasal packing on each side were included in the study. Patients with ASA physical Status III and above, with cardiac rhythm disturbances, psychiatric illness, and anxiety disorder, with a history suggestive of posttraumatic stress disorder and obstructive sleep apnea were excluded from the study. Pregnant patients and emergency surgeries were also excluded from the study. Protocol was explained to all the patients and informed valid consent was obtained. All the patients were informed about the fact that postsurgery after regaining consciousness, they would have nasal blockage due to packing of nose which would necessitate to breathe through mouth. All the patients were fasted 8 h before start of anesthesia. Patients were randomly divided into two groups by block randomization method with block size of four depending on the drug they would receive. Group D received injection dexmedetomidine and Group M received injection midazolam. After shifting the patients to operating table, standard monitors such as pulse oximeter ($SpO_2$), electrocardiogram, and noninvasive blood pressure were connected. Baseline parameters were noted. Intravenous line was started with 18-gauge cannula. Both the groups received infusion through syringes preloaded by pharmacy personnel through syringe pump. For Group D, 100 mcg of dexmedetomidine (Dexmed, manufactured in India by Neon Private Limited) was mixed with normal saline to total volume of 50 ml. For Group M, 5 mg of midazolam (Mizolam, manufactured in India by VHE medical sciences limited and marketed by Neon Private Limited) was mixed with normal saline to total volume of 50 ml. All the patients received glycopyrrolate 5 mcg/kg and fentanyl 2 mcg/kg intravenous as bolus. Then, infusion was started by an independent investigator who was not a part of anesthetic management. For Group D, dexmedetomidine was given as 0.5 mcg/kg as loading dose over 15 min and then 0.1 mcg/kg/h as infusion. For Group M, midazolam was given as 0.02 mg/kg as loading dose over 15 min and then 0.02 mg/kg/h as infusion. Time of start of infusion was noted. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were noted at 5 and 15 min from starting of infusion. Once loading dose was given, patients were preoxygenated for 5 min and then were induced with injection propofol 2 mg/kg and injection vecuronium 0.1 mg/kg. Patients were intubated with appropriate size endotracheal tube and connected to circle system. Anesthesia was maintained on oxygen, nitrous oxide, and sevoflurane 1%–2% to maintain bispectral index of 40–60. HR, SBP, DBP, MAP, and end-tidal $CO_2$ (EtCO$_2$) were
monitored every 15 min till end of surgery. All patients received injection ondansetron 4 mg intravenously as prophylaxis for nausea-vomiting at the end of the surgery. Fall in MAP of more than 20% of baseline value was taken as hypotension, which was treated with boluses of ephedrine and intravenous fluids. HR <50/min was taken as bradycardia and was treated with 0.6 mg of injection atropine. A total number of episodes of bradycardia were noted. Increase in HR and MAP more than 20% of baselines was treated with top-up doses of fentanyl. Total requirement of top-up doses of fentanyl was noted. Infusion and inhalational agent both were stopped at end of surgery, when the nasal cavity packing started and that time was noted. Neuromuscular blockade was reversed and time taken for eye opening after discontinuation of infusion was noted. Time of eye opening on verbal commands was taken as time of consciousness. Duration of 5 min from the time of regaining of consciousness was taken as emergence. Patients were monitored as per Riker Sedation-Agitation Scale (RSAS),\(^{[9]}\) for agitation score of 1–7. Score 1 - unarousable to noxious stimuli, score 2 - very sedated, responds to painful stimuli but not to verbal commands, score 3 - sedated, awakens with commands or gentle touch but drifts off again, score 4 - calm and quiet, easily arouses with verbal commands and communicates, score 5 - anxious with mild agitation but calms down on verbal commands, score 6 - very agitated and requires physical restraint, and score 7 - dangerous agitation, pulling of intravenous cannula, thrashing side to side. Score at emergence was noted and then was monitored every 5 min for initial 30 min and then every 15 min for next 90 min. Score of 5 and above was taken as agitation. Score of 3 and below was taken as drowsiness. Score of 4 was taken as ideal with no agitation and drowsiness. Score during defined emergence time was taken as incidence of agitation. Injection diclofenac 1 mg/kg intramuscular was given on demand for pain, but the analgesic requirement was not counted and analyzed as it was not a study parameter.

Statistical analysis

Sample size calculations were based on previous study\(^{[6]}\) with difference of incidence of EA between two groups of 30%. Thirty-two patients per group were included to avoid possible dropouts. The statistical analysis was done using statistical package for social sciences (SPSS) for Windows, version 23, Armonk, NY: IBM corporation and its licensors 2015. The distribution of data was analyzed with Shapiro–Wilk test. Normally distributed data such as patient’s characteristics and duration of infusion were analyzed with independent t-test and data were expressed as mean ± standard deviation. Abnormally distributed parameters such as recovery time, agitation scores, MAP, and HR at different times were analyzed using Mann–Whitney U-test and were expressed as median ± standard error of mean (SEM). Incidence of agitation between two groups was compared with Chi-square test and data were expressed as frequency and percentage. P value <0.05 was considered statistically significant for two-sided test. The graph of MAP values during infusion expressed as median ± SEM was obtained against time intervals. A number of patients going for hypotension at different time intervals were calculated as percent of total patients in each group at that time. The graph for the percent of patients going for hypotension was plotted against time. Changes in HR at different time points were plotted in graph for each group. HR at different time points was compared with Mann–Whitney U-test and expressed as median ± SEM. Few surgeries lasted for <1h, hence graphs are plotted only for 30 min of infusion duration.

Results

Total seventy patients were included in study with 35 in each group. Thirty-five patients in Group D and 33 patients in Group M were analyzed. Two patients in midazolam group were excluded from analysis due to protocol violation.

The patient’s characteristics [Table 1] were comparable. Total duration of surgery, duration of infusion (P = 0.19), and inhalational agent (P = 0.18) were comparable between two groups. Time taken for eye opening [Table 2] after discontinuation of infusion agent was similar in both groups (P = 0.77). Incidence of agitation was more in midazolam group. 42.4% of patients were agitated in group M as compared to 28.6% in group D. However, this difference was statistically insignificant (P = 0.23). The distribution of RSAS score is shown in Figure 1. Maximum number of

### Table 1: Patient characteristics

| Parameter | Group D | Group M | P |
|-----------|---------|---------|---|
| Age       | 34.62±11.72 | 30.12±8.78 | 0.079 |
| Weight (kg) | 63.82±11.52 | 59.51±11.64 | 0.130 |
| Height (cm) | 163.65±10.37 | 161.09±9.45 | 0.291 |
| Sex (male/female) | 22/13 | 24/9 | |

### Table 2: Emergence and agitation

| Parameter | Group D | Group M | P |
|-----------|---------|---------|---|
| Duration of surgery (min) | 78.45±34.81 | 87.33±44.43 | 0.36 |
| Duration of infusion (min) | 94.08±36.51 | 107.12±44.81 | 0.19 |
| Duration of inhalational (min) | 89.14±36.93 | 102.66±45.20 | 0.18 |
| Eye opening (min) median±SEM | 10±0.62 | 10.71±0.60 | 0.77 |
| Emergence agitation, n (%) | 10 (28.6) | 14 (42.4) | 0.23 |
| Patients requiring top-up fentanyl (n) | 10 | 12 | 0.74 |

SEM: Standard error of mean
patients had scored 4 in Group D and score of 3 in Group M at emergence. Score of seven was noted in two patients in Group M while no patient in Group D had score of seven. In postanesthesia care unit (PACU), five patients in group D were sedated with score of 3, while none in Group M. 12.4% of patients were agitated even in PACU with score of 6 and 7 in Group M, while no patient in Group D was agitated in PACU. There was no significant difference between two groups comparing MAP median values during 30 min of infusion [Table 3]. However, numbers of hypotensive episodes were more in Group D. The percent of patients going for hypotensive episodes at different time intervals [Figure 2] was significantly higher with dexmedetomidine than midazolam with $P = 0.001$ (confidence interval = 10.13–34.33). The fall in HR was more in Group D than Group M as shown in Figure 3. However, episodes of bradycardia were similar in both groups with only one patient in each group going for bradycardia.

**Discussion**

Our results suggest that the incidence of EA is comparable between midazolam and dexmedetomidine group. Time taken for eye opening was similar in both groups. The fall in HR and episodes of hypotension were more in dexmedetomidine group.

Etiology of EA is not clear, but it is proposed that it could be due to variation in neurologic recovery rate in different brain areas, thus explaining the higher incidence of EA with less soluble inhalational agents which lead to faster wake up from anesthesia.\[11\] Sevoflurane directly excites locus coeruleus neurons, thus causing excitation and EA.\[12\] Dexmedetomidine is highly selective alpha 2 AR agonist which is proven effective in prevention of EA due to its analgesic and sedative properties which result from effect of dexmedetomidine on central alpha 2 receptors in locus coeruleus.\[13,14\] Midazolam acts on gamma-aminobutyric acid receptors and this inhibition is the reason for its role in prevention and treatment of EA. Many studies have compared dexmedetomidine with midazolam given as infusion for sedation in the Intensive Care Unit (ICU).\[15\] Efficacy of dexmedetomidine in prevention of EA after nasal surgeries is proven. Studies regarding efficacy of midazolam in prevention of EA are mainly done in pediatric population and its role is controversial.\[5\] To our knowledge, this is the first study to compare midazolam with dexmedetomidine for prevention of EA in nasal surgeries and also in adults.

Previous study done by Kim et al. in adult nasal surgeries has proved that dexmedetomidine infusion reduces incidence

![Figure 1: Scores at emergence](image1)

![Figure 2: Incidence of hypotension](image2)

![Figure 3: Fall in HR](image3)

**Table 3: Hemodynamic characteristics**

| Parameter (median±SEM) | Group D | Group M | P   |
|------------------------|---------|---------|-----|
| MAP baseline           | 97±1.94 | 99±1.74 | 0.56|
| MAP 5 min              | 81±1.95 | 84±2.41 | 0.37|
| MAP 15 min             | 82±2.72 | 84±2.41 | 0.73|
| MAP 30 min             | 77±2.41 | 79±2.10 | 0.64|

MAP: Mean arterial pressure; SEM: Standard error of mean
of EA by 50% as compared to placebo.[7] The incidence of EA in dexmedetomidine group was 28%, but there was no difference in number of patients having score of 7 between groups. In our study, incidence of EA in dexmedetomidine group was similar and 42.4% in midazolam group. However, no patient in dexmedetomidine group had score of 7, but two patients in midazolam group had score of 7. Kim et al. used dexmedetomidine as 0.4 mcg/kg as infusion without any loading dose. That could have been the reason for more incidence of dangerous agitation than ours.[16,17] The recommended dose of dexmedetomidine is 0.2–0.7 mcg/kg/h. This dose is studied mainly for procedural and ICU sedation. Dexmedetomidine is known to cause hemodynamic disturbances,[18] which can add to the effects of general anesthetic agents. Also after 60 min of infusion, there is no difference in sedation scores between different doses of dexmedetomidine.[19] Hence, in our study, we selected lower dose of dexmedetomidine intending to study its effect on EA.

Adams et al. reviewed six studies comparing midazolam and dexmedetomidine for sedation in ICU.[19] Although different sedation scales were used, the primary outcome was target sedation score which was comparable between dexmedetomidine and midazolam group. In our study, we found no significant difference in agitation scores between two groups. Senoglu et al. compared sedation between dexmedetomidine and midazolam using RSAS scale and found no difference in scores, which is similar to our results.[20] Propofol can prevent EA by same mechanism of action like midazolam, but both of them possess no analgesic properties. Dexmedetomidine is considered effective for prevention of EA due to its analgesic as well as sedative action. However, none of the three above-mentioned drugs has shown any benefit in reduction of EA when combined with analgesic agent.[5] When dexmedetomidine was compared with other analgesic agents such as fentanyl, there was no difference in emergence characteristics between them.[21] In our study also, the requirement of fentanyl and incidence of EA were comparable in both the groups. Both midazolam and propofol failed to reduce EA when given as premedication or induction agent. Propofol is effective in prevention of EA as infusion and as bolus before extubation. [5] Midazolam given as bolus before extubation reduces agitation without delaying emergence.[6] The short half-life of midazolam makes premedication dose ineffective at the end of surgery. However, when it is given in the end or combined with other long-acting benzodiazepine, it reduces incidence of EA significantly.[6,22] In our study, we gave midazolam by infusion till end of surgery and found that incidence of EA and emergence times were comparable to that of dexmedetomidine.

Dexmedetomidine can cause hemodynamic disturbances such as hypotension (30%), bradycardia (9%), and dose-dependent hypertension.[18] When dexmedetomidine was compared to midazolam, Esmaoglu et al. found that there was a significant fall in HR and MAP with dexmedetomidine at infusion rate of 0.1 mcg/kg.[23] Our results are similar to them with more number of hypotensive episodes with dexmedetomidine. Riker et al. noted that there was fall in HR with both midazolam and dexmedetomidine but more with dexmedetomidine which is similar to our findings.[24] After review of multiple studies with different doses, Adams et al. concluded that though clinical profile of dexmedetomidine is better over midazolam, its superiority could not be proven due to statistical insignificance.[15] We feel that in the present study dexmedetomidine group was clinically better in many ways in prevention of EA. First, the maximum number of patient in dexmedetomidine had ideal score of 4, which were 3 (sedated) in other group. Second, no patient in dexmedetomidine group reached level of dangerous agitation. Third, no patient had agitation in PACU after emergence time was over while midazolam group around 12% patients were agitated in PACU. Entotracheal tube is a proven risk factor for the development of agitation.[6] We feel that this could be the reason for comparable incidence of agitation between two groups during emergence times. Direct sedative effect through action on locus coeruleus and beneficial effects on various body systems makes dexmedetomidine clinically better in postoperative period.[25] Although dexmedetomidine has better clinical profile over midazolam in prevention of EA, its superiority cannot be proven statistically with the present study. Future studies on different loading and maintenance doses are needed to evaluate efficacy of dexmedetomidine over midazolam for prevention of EA.

Our study has few limitations. As a secondary outcome, we compared only emergence times and did not see the recovery profile till discharge time. Another limitation we feel is the scoring system used for agitation. Most of the studies done in adults have used sedation scale for assessment of agitation, which do not differentiate properly between different levels of agitation. Future research to design simple and efficient scales for agitation assessment is needed.

**Conclusion**

We conclude that midazolam given as intravenous infusion is comparable to dexmedetomidine for prevention of EA after nasal surgeries.

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

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