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Midazolam Effect on Agitation Postnasal Surgery: A Double Blinded Randomized Controlled Trial

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Abstract

Objective: *Postoperative agitation is a common complication, it's incidence post head and neck surgery is around 11-26%. Avoiding such complication is mandatory to facilitate patient's recovery and reduce risk of postoperative agitation related complications. Our study aims to detect the incidence of agitation following nasal surgery, and to determine the midazolam effect on agitation, when administered just before emergence from anaesthesia.*

Methods*: This is a prospective, single centre, double blinded randomized controlled trial. An ethical approval was obtained from research ethical board in the hospital. Subjects were randomly assigned into two groups. In the midazolam group, patients received 0.03 mg.kg-1 midazolam intravenously just before emergence from anaesthesia. On the other hand, placebo group's patients received normal saline of similar volume to midazolam. Midazolam and normal saline syringes were prepared and coded by a research assistant who was not involved in clinical work or patients' data collection. Patients otherwise received the same anaesthetic technique. The maximum Richmond Agitation Sedation Scale score from the time of extubation to patient's handover to recovery unit was documented.*

Results: *The study included 100 subjects, 50 in each group. 15% of agitated patients were in the midazolam group as compared to 22% in the placebo group, p value: 0.147. Longer surgical duration is associated with 1.6 folds increase in the incidence of agitation postnasal surgery.*

Conclusions: *Although midazolam was associated with a lower incidence of agitation following nasal surgery, it wasn't statistically significant. Longer surgical duration was the most important risk factor for agitation.*

Key-words: *Agitation, Emergence, General Anaesthesia, Midazolam, Nasal Surgery, Rhinoplasty.*

Introduction

Postoperative agitation is a common complication, it's incidence post head and neck surgery is ranging between 11 and 26% according to some cohorts [1]. Avoiding such complication is mandatory to facilitate patient's recovery and reduce the risk of postoperative agitation related complications such as; self extubation, hypoxia, bleeding, pulling catheters out, falling down and harm to attending healthcare workers [2,3].

There are several well-known risk factors for agitation following nasal surgery, including: younger age, male sex, smoking, presence of endotracheal tube, presence of urinary catheter, pain, longer surgical duration, alcohol use disorders and sevoflurane anaesthesia [1,4].

Midazolam is a short acting benzodiazepine with an antegrade amnestic effect. It is commonly used as an anxiolytic premedication before anaesthetics, sedative, anticonvulsant and as an adjunct to intravenous hypnotics for induction of general anaesthesia [5,6].

We think that intravenous administration of a small dose of midazolam just before emergence from general anaesthesia could reduce the incidence and severity of agitation following nasal surgery. A subject that is not extensively investigated in the literature to date, to the best of our knowledge. The aim of our study is to detect the incidence of agitation following nasal surgery in our institution, and to determine wither intravenous midazolam, when administered just before emergence from general anaesthesia, is effective to prevent agitation following nasal surgery or not.

Materials and Methods

This is a prospective, single centre, with equal randomization (1:1), double-blind, placebo-controlled, parallel-group study conducted in the Royal Medical Services in Amman, Jordan from December 2021 to March 2022. An ethical approval was obtained from the local research ethical board in the Jordanian Royal Medical Services on December 15, 2021. Subjects with American Society of Anesthesiologists (ASA) of either grade 1 or 2, aged from 16 to 59 years, undergoing nasal surgery such as; septoplasty (SP), open septorhinoplasty (OSRP) and functional endoscopic sinus surgery (FESS) were included in the study.

A sample size of 100, 50 in each group (midazolam group and placebo group) was found to be enough to achieve the study purposes using G*Power computer program, considering alpha set at 0.05; medium effect size and study power 80%. A computerized random number generator was utilized to provide the random codes for midazolam and normal saline syringes, simple randomization sequence was created using Stata 9.0 (StataCorp, College Station, TX) statistical software with a 1:1 allocation by a research assistant who was not involved in clinical work or patients' data collection, then he prepared midazolam

and placebo syringes, sealed them in sequentially numbered identical opaque containers according to the allocation sequence.

Eligibility for patient's inclusion into the study was determined by the main investigator, then the attending anaesthetic nurse provided the sequentially numbered opaque containers to be opened just before emergence from general anaesthesia and the syringe code was documented clearly at anaesthetic chart by the main investigator. Patients, invistigators; including outcome assessor and data analyst, in addition to anaesthetic nurses were kept blinded for allocation.

In the midazolam group, patients received 0.03 mg.kg-1 midazolam intravenously just before emergence from general anaesthesia. On the other hand, placebo group's patients received normal saline of similar volume to midazolam just before emergence from general anaesthesia. Midazolam and placebo syringes looked identical, colourless and of similar volume (3 ml). Patients otherwise received the same general anaesthetic technique, including medications and equipments by the same anaesthetist. The maximum Richmond Agitation Sedation Scale (RASS) score, table 1, from the time of extubation till patient's handover to post anaesthesia care unit (PACU) was observed and documented by the same anaesthetist and it was the basis for agitation diagnosis, therefor, the primary outcome was RASS score of +2 or more. No changes to outcomes after commencement of the trial to be reported.

Anaesthetic technique: No premedication was given to any patient. All patients received intravenous fentanyl 1.5 mcg.kg-1, propofol 2 mg.kg-1 and cisatracurium 0.2 mg.kg-1 for induction of general anaesthesia. This was followed by manual ventilation for 4 minutes and intubation. Anaesthesia was maintained by 1 MAC of desflurane for all patients, in addition to remifentanil infusion (0.02 – 2.0 mcg.kg-1.minute-1) to aid analgesia and controlled hypotension with a mean arterial pressure not less than 60 mm Hg. An oropharngeal pack was inserted for everyone and taken out gently before emergence and extubation. All patients received dexamethasone 8 mg, ondansetron 4 mg, 1 gram of paracetamol and 0.1 mg.kg-1 morphine intravenously. Morphine was given at the end of surgery by the time of turning the remifentanil infusion off. Midazolam or normal saline was randomly and blindly administered to patients using a 3 ml syringe (1mg.ml-1) at time of turning the remifentanil infusion off. By the end of surgery, desflurane was turned off and nobody received reversal for the cisatracurium, then smooth suctioning of the oral cavity was performed followed by awake extubation. No stimulation was used to aid patient's recovery except for gentle verbal commands.

Statistical analysis: The categorical data expressed in frequencies and percentages, the scale data expressed in mean (SD). Multiple logistic binary regression was used to predict agitation from several predictors, chi square of independence was used to explore the association between categorical data. Additionally, independent sample t test was used for mean differences, alpha level set at 0.05 deemed statistically significant and SPSS IBM software ver 26 was used to analyze data.

Results

The total number of patients who were assessed for eligibility between December 2021 and March 2022 was 123. 23 had an ASA grade greater than 2, so they were excluded. 100 subjects were included, (N=50) in the midazolam group and (N=50) in the placebo group. The trial was terminated once the sample size was achieved. Demographic variables were comparable in the two groups, table 2. Risk factors of agitation following nasal surgery are shown in table 3. 15% of agitated patients were in the midazolam group as compared to 22% in the placebo group, p value: 0.147, table 4. Table 5 shows the importance of different variables as risk factors for agitation following nasal surgery. Longer surgical duration is associated with 1.6 folds increase in the incidence of agitation following nasal surgery.

Score	Term	Description
+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10 seconds)
-3	Moderate sedation	Movement or eye opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Table 1. Richmond Agitation Sedation Scale (RASS)

	Midazolam	N	Placebo	N	P value
Age (yr)	26.9 (9.3)	50	25.4 (7.7)	50	0.362
Sex (M)	27%	27	25%	25	0.689
Sex (F)	23%	23	25%	25	0.689
BMI* (Kg.m^{-2})	22.7 (3.3)	50	22.8 (3.2)	50	0.945

Table 2. Patient demographics in the studied groups.

Values are mean (SD) or percentages.

* Body Mass Index.

	Midazolam	N	Placebo	N	P value
Age (yr)	26.9 (9.3)	50	25.4 (7.6)	50	0.362
Sex (M)	27%	27	25%	25	0.689
Smoking	23%	23	21%	21%	0.687
Surgical duration (Hours)	2.1 (0.71)	50	2.2 (0.64)	50	0.326

Table 3. Risk factors of agitation following nasal surgery.

Values are mean (SD) or percentages.

	Midazolam	N	Placebo	N	P value	Total
Agitated	15%	15	22%	22	0.15	37
Non-agitated	35%	35	28%	28	0.15	63
Total		50		50		100

Table 4. Agitation following nasal surgery.

Values are numbers and percentages.

	B	Wald	df†	P value	OR‡	95% CI§ for Odds ratio	
						Lower	Upper
Age	-0.04	1.6	1	0.20	0.96	0.90	1.0
Male sex	0.18	0.14	1	0.70	1.2	0.46	3.1
Smoking	0.39	0.61	1	0.43	1.5	0.55	3.9
BMI*	0.05	0.48	1	0.48	1.1	0.91	1.2
Surgical duration	0.47	2.1	1	0.14	1.6	0.85	3.0

Table 5. Importance of risk factors for agitation following nasal surgery.

* Body Mass Index.

† Degrees of freedom.

‡ Odds Ratio.

§ Confidence Interval.

Discussion

This study demonstrates no significant difference between both groups (midazolam and placebo) in terms of demographic variables, table 2, and risk factors for agitation following nasal surgery, table 3. The incidence of postnasal surgical agitation is lower when a pre-emergence intravenous 0.03 mg.kg-1 midazolam is administered. However, this was not significantly different from placebo from the statistical point of view, p value: 0.147, table 4.

Interestingly, our study demonstrated that the longer surgical duration is being associated with 1.6 folds increase in the incidence of agitation following nasal surgery, and it was found to be the most important risk factor for agitation among the others including; younger age, male sex and smoking, table 5.

There are several studies in the literature on the effect of different medications in prevention of postoperative agitation, however most of these studies were conducted on children following sevoflurane anaesthesia [7-20]. Akhlaghi et al.[21] conducted an RCT on adults undergoing ketamine sedation to examine the effects of midazolam and haloperidol premedication on recovery agitation, they demonstrated that midazolam 0.05 mg.kg-1 or haloperidol 5 mg intravenously significantly reduces ketamine-induced emergence agitation[21]. However, the current study is the first double blinded RCT testing pre-emergence intravenous midazolam effects on agitation following nasal surgery in adults, to the best of our knowledge.

Despite the lack of similar studies in the literature, especially in adults undergoing nasal surgery, our results are in keeping with the results of some cohorts[10,11,12]. Sherwin et al.[10] studied the midazolam effect on recovery agitation following ketamine sedation in pediatric procedures, and demonstrated that midazolam didn't have beneficial effects. Similarly, Mamuda et al.[11] also demonstrated no positive effects of midazolam 0.5 mg.kg-1 oral premedication in reduction of emergence agitation following pediatric surgery. Furthermore, Ozcan et al.[12] demonstrated that neither ketamine nor midazolam reduced emergence agitation in children who received sevoflurane anaesthesia with caudal block for lower abdominal and groin surgical procedures.

On the other hand, our results are in contrast to some cohorts[9,13,17-20]. All of these studies were conducted on children who received sevoflurane anaesthesia with variable regimens of midazolam, they showed that midazolam significantly reduced the incidence and severity of emergence agitation following different surgical procedures, such as; cataract, strabismus, dental, penile and scrotal surgical procedures. In fact, our study is directed to adults undergoing nasal surgery, and it is well known that this kind of surgery is associated with a higher risk of emergence agitation as compared to other surgical procedures, this could be related to airway manipulation and residual blood in the naso- and oropharynx. This major difference between our study and the above mentioned ones could, at least, partially explain the different results.

Fang et al.[14] conducted a network meta-analysis on the Efficacy of dexmedetomidine, midazolam, ketamine, propofol, and fentanyl for the prevention of sevoflurane induced emergence agitation in children. They demonstrated that all these medications are associated with significantly reduced incidence of emergence agitation when compared to placebo.

We think that the well structured methodology of our RCT represents an essential strength point for the validity of our results; this was reflected by using the exact anaesthetic technique, equipments and medications by the same anaesthetist for the whole study's population. However, the fact that patients undergoing airway surgery are better to be extubated when fully awake, to avoid complications such as; laryngospasm and subsequent hypoxia, could increase the risk of agitation. As a result, this could be a limitation factor for our study. Anyway, this technique, extubation when fully awake, was adapted for all studied patients.

In conclusion, although midazolam was associated with a lower incidence of agitation following nasal surgery, it wasn't statistically significant. Longer surgical duration was the most important risk factor for agitation following nasal surgery.

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