

## Research Article

# The Effect of Nitrous Oxide on Emergence Agitation in Pediatric Patients under Sevoflurane Anesthesia for Ophthalmic Surgery

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### Abstract

**Objectives:** Nitrous oxide ( $N_2O$ ) is widely used to reduce the consumption of inhalation anesthetics, especially sevoflurane that is one of the most accused risk factor of emergence agitation (EA). The aim of this study was to investigate the impact of  $N_2O$  on EA in pediatrics under sevoflurane anesthesia for ophthalmic surgery.

**Methods:** The patients were classified into two groups: sevoflurane with  $N_2O$  (n=18) and those who received sevoflurane with air (n=18). The two groups were compared each other in terms of basic characteristics, postoperative pain and EA scores. Postoperative pain was measured by Face, Legs, Activity, Cry, and Consolability (FLACC) scale, while EA was assessed with the Pediatric Anesthesia Emergence Delirium (PAED) scale.

**Results:** Thirty-six patients with a mean age of 40.1 months were enrolled in the study. The patients who received sevoflurane with  $N_2O$  and those who received sevoflurane with air were similar in baseline characteristics. There were also no significant differences in all FLACC and PAED scores between the groups.

**Conclusion:**  $N_2O$  had no significant effect on postoperative pain and EA in pediatrics under sevoflurane anesthesia for ophthalmic surgery. Considering the potential adverse effects of  $N_2O$ , this finding is important for more selective use of this anesthetic gas.

**Keywords:** Emergence agitation, nitrous oxide ( $N_2O$ ), pediatric anesthesia

**Cite This Article:** Kilic Y, Bilir A. The Effect of Nitrous Oxide on Emergence Agitation in Pediatric Patients under Sevoflurane Anesthesia for Ophthalmic Surgery. EJMI 2021;5(1):57–61.

Pediatric ophthalmic operations are almost always performed under general anesthesia, using endotracheal tube, laryngeal mask or face mask.<sup>[1]</sup> Emergence agitation (EA), defined as a complex clinical entity characterized by negative behavioral disorders such as crying, thrashing, excitation, incoherence, and disorientation, is common in pediatrics, with an incidence of up to 80%.<sup>[2,3]</sup> Although many risk factors have been demonstrated to date, inhalation anesthetics, particularly sevoflurane, is the most accused

agent for the occurrence of EA.<sup>[3,4]</sup> As known, sevoflurane is frequently used in pediatric anesthesia because of its fast induction and awakening properties, less side effects on airway stimulation and cardiac functions.<sup>[4,5]</sup>

In order to maintain anesthesia depth reducing sevoflurane consumption and contribute to intraoperative hemodynamic stability and postoperative analgesia, nitrous oxide ( $N_2O$ ) has long been used as an adjuvant in pediatric ophthalmic operations.<sup>[6]</sup> Although not clear, it has been shown

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**Submitted Date:** November 12, 2020 **Accepted Date:** December 27, 2020 **Available Online Date:** January 06, 2021

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that N<sub>2</sub>O is associated with decreased risk of postoperative EA by reducing sevoflurane consumption.<sup>[7]</sup> However, increased risk of neurotoxicity, including impaired memory and learning, has been well demonstrated as a potential adverse effect of N<sub>2</sub>O.<sup>[8-10]</sup> In addition, N<sub>2</sub>O may cause megaloblastic crisis or subacute combined degeneration of the spinal cord by inhibiting the activity of vitamin B<sub>12</sub> dependent enzyme.<sup>[11]</sup> Therefore, serious concerns still remain regarding the use of N<sub>2</sub>O in pediatric anesthesia.

In this study, we aimed to evaluate the effect of N<sub>2</sub>O on EA in pediatric patients under sevoflurane anesthesia for ophthalmic surgery.

## Methods

### Patients and Study Design

After approval of Institutional Ethics Committee (decision no: 27, date: 04.02.2020), 36 pediatric patients who underwent elective ophthalmic surgery under general anesthesia at Osmangazi University Hospital were included in the study. Patients' age and gender, procedural data, American Society of Anesthesiologist (ASA) physical status, anesthetic techniques, analgesic medications, and perioperative complications were noted.

ASA scores 3 or 4, significant hepatic, renal, cardiac, or respiratory disease, developmental or mental delay, and allergy to study medications were the exclusion criteria. The patients were classified into two groups; patients who received sevoflurane with N<sub>2</sub>O (Group 1) and those who received sevoflurane with air (Group 2). The two groups were then compared each other in terms of basic characteristics, pain and agitation scores.

### Anesthesia Management

Fasting time was set at least six hours before surgery. Patients were not given any premedication. A 4-point scale, called as separation score, just after the separation of patients from parents and before entering the operating room was recorded: 1=excellent (separates easily), 2=good (not clinging, whimpers, calms with reassurance), 3=fair (not clinging, cries, will not calm or quiet), and 4=poor (crying, clinging to parent). A separation score of 1-2 was considered satisfactory, whereas a score of 3-4 was considered unsatisfactory.<sup>[12]</sup>

Standard monitoring included five-lead electrocardiogram, noninvasive blood pressure, pulse oximetry, and inspiratory/expiratory gas concentrations. Anesthesia was induced with intravenous (IV) administration of propofol (2-4 mg/kg) + remifentanyl (0.5-1 mcg/kg) + lidocaine (0.5 mg/kg) following mask ventilation with inhalation sevoflurane (8-5-3%) in 4 L/min oxygen and N<sub>2</sub>O (50%-50%) or air

(50%-50%). Airway control was provided by laryngeal mask or face mask. Anesthesia was maintained with sevoflurane (2-3%) in 4 L/min of a mixture of 50% N<sub>2</sub>O and O<sub>2</sub> in Group 1, and with sevoflurane (2-3%) in 4 L/min of a mixture of 50% O<sub>2</sub> and air in Group 2. IV remifentanyl was administered when the heart rate (HR) exceeded 20% of the basal value. IV paracetamol (10 mg/kg) was given in prolonged operations.

HR, mean arterial pressure, oxygen saturation, and end-tidal carbon dioxide were monitored continuously during the procedure. Time of awakening (from end of surgery to getting out of the operating room) were recorded. All patients were followed up for at least 30 minutes at the recovery room, and their modified Aldrete scores (MAS) were calculated at every five minutes. They were transferred to inpatient clinic when their MAS achieved nine. The time of MAS to reach nine was also noted.

### Evaluation of Postoperative Pain and EA Status

Postoperative pain level was measured by Face, Legs, Activity, Cry, and Consolability (FLACC) scale, scores ranging from 0 to 10.<sup>[13]</sup> Maximum FLACC score of  $\geq 4$  meant that pain was present. EA was assessed with the Pediatric Anesthesia Emergence Delirium (PAED) scale, which consists of five psychometric items describing emergence behavior, scores ranging from 0 to 20.<sup>[14]</sup> Maximum PAED score  $\geq 12$  was accepted as having emergence delirium (ED). Pain and EA scores were measured at 5<sup>th</sup>, 10<sup>th</sup>, 15<sup>th</sup>, and 20<sup>th</sup> minutes in the recovery room.

### Statistical Analysis

A power analysis based on a previous article<sup>[15]</sup> showed that a sample size of 28 patients was required to achieve a power of 80% with a significant level of 5% for evaluating the difference of PAED scores between the two groups. Data analysis was done using the standard version of statistical package for social science (SPSS 23.0, IL-Chicago-USA). Descriptive analyses were presented as number/percentage for categorical variables, and mean $\pm$ SD/percentages for continuous variables. Chi-square, Mann Whitney U, and Fisher's exact tests were used to assess the differences between the groups. P value less than 0.05 was accepted as significance level.

## Results

Thirty six children with a mean age of 40.1 (3-144) months were enrolled in the study. There were 17 (47.2%) males and 19 (52.8%) females. All patients underwent ophthalmic surgery under sevoflurane anesthesia using laryngeal mask (25, 69.4%) or face mask (11, 30.6%). The anesthetic medications were all standard in the study population. The patients were classified as: children who received sevo-

flurane plus N<sub>2</sub>O (Group 1, n=18) and those who received sevoflurane plus air (Group 2, n=18). All surgical procedures were successfully completed. Only one patient developed laryngospasm which was treated by simple medications. No death was observed in the study population. Basic characteristics were presented in Table 1.

The patients who received sevoflurane plus N<sub>2</sub>O and those who received sevoflurane plus air were similar in baseline characteristics including age, gender, ASA status, separation score, rescue remifentanil use, and time of awakening (p>0.05) (Table 2).

The two patient groups were then compared each other in terms of FLACC scores, PAED scores, and MASs, at 5<sup>th</sup>, 10<sup>th</sup>, and 15<sup>th</sup> minutes in the recovery room (Table 3). Statistically, there were no significant differences in all scores between the groups (p>0.05). The time of MAS to reach 9 was also similar between group 1 and group 2 (p=0.055).

## Discussion

In the present study, EA during the early postoperative period was observed in nine patients, consistent with the literature.<sup>[2,3,16]</sup> Postoperative EA or delirium is an important problem for both anesthesiologists and surgeons, especially when prolonged. In addition to the self-harming of the child, it can lead to various problems such as prolonged hospitalization and increased healthcare costs related to need of additional medications.<sup>[5,17]</sup> Among all pediatric surgeries, ophthalmologic procedures were determined as more risky operations for the development of EA.<sup>[18]</sup> As known, ophthalmologic operations are often short and performed under sevoflurane anesthesia due to its safe profile. Despite its potential side effects on hematologic and neurocognitive systems, N<sub>2</sub>O is primarily preferred as an adjuvant in routine pediatric anesthesia practice because

it decreases possible complications related to sevoflurane and incidence of postoperative EA by reducing the need for administration of this anesthetic agent. However, N<sub>2</sub>O is not a fully safe anesthetic agent, and many questions are still raised with its use. To the best of our knowledge, there are only two clinical studies investigated the potential role of N<sub>2</sub>O on reducing the incidence of EA in pediatric patients receiving sevoflurane anesthesia.<sup>[6,7]</sup>

**Table 2.** Comparison of baseline characteristics between the groups

Characteristics	Group 1 (n=18)	Group 2 (n=18)	p
Age (year)	43.1±47.4 (3-144)	37.6±30.7 (8-120)	0.424
Gender (Female/Male), n (%)	10 (55.6)/8 (44.4)	9 (50)/9 (50)	1.000
ASA status, n (%)			1.000
ASA 1	15 (83.3)	16 (88.9)	
ASA 2	3 (16.7)	2 (11.1)	
Rescue remifentanil use, n (%)	6 (33.3)	3 (16.7)	0.443
Separation score, n (%)			0.237
Satisfactory (score 1-2)	10 (55.6)	11 (61.1)	
Unsatisfactory (score 3-4)	4 (22.2)	4 (22.2)	
Missing	4 (22.2)	3 (16.6)	
Time of awakening (minute)	6.6±1.6 (4-10)	6.3±2.7 (3-11.5)	0.166
Complication, n (%)	1 (5.6)	0	1.000

Data are presented as mean±Standard deviation for age and time of awakening; n (%) for other variables.

**Table 3.** Comparison of FLACC scores, PAED scores, and MASs between the groups

	Group 1 (n=18)	Group 2 (n=18)	p
FLACC 5	1.5±2.5 (0-6)	0.5±1.5 (0-6)	0.335
FLACC10	2.8±4.2 (0-14)	0.9±2 (0-6)	0.281
FLACC15	4.9±4.2 (0-16)	2.9±2.3 (0-8)	0.128
PAED5	3.7±5.7 (0-16)	1.2±4.3 (0-18)	0.245
PAED10	7±6.4 (0-18)	2.8±4.7 (0-12)	0.069
PAED15	10±6.2 (0-20)	7.2±6.5 (0-20)	0.230
MAS5	6.5±3.4 (0-18)	5.3±1.8 (0-7)	0.252
MAS10	6.9±2.5 (0-10)	6.8±1.4 (4-9)	0.669
MAS15	8.8±0.9 (7-10)	8.3±1.5 (6-10)	0.520
Time of MAS to reach 9 (minute)	14.6±4.1 (10-25)	18±6.6 (5-30)	0.055

Data are presented as mean±Standard deviation (minimum–maximum). MAS: Modified aldrete scores; FLACC: Face, legs, activity, cry, and consolability; PAED: Pediatric anesthesia emergence delirium.

**Table 1.** Baseline characteristics of the study population (n=36)

Characteristics	n (%)
Age (year)	40.1±39.5 (3-144)
Gender (Female/Male)	19 (52.8)/17 (47.2)
ASA status	
ASA 1	31 (86.1)
ASA 2	5 (13.9)
Airway instrument	
LMA	25 (69.4)
FM	11 (30.6)
Complication	1 (2.7)

Data are presented as mean±Standard deviation for age; n (%) for other variables. LMA: Laryngeal mask airway; FM: Face mask; ASA: American Society of Anesthesiologist.

Shibata and colleagues investigated the effectiveness of N<sub>2</sub>O administration on reducing sevoflurane concentration at awakening and suppressing postanesthetic agitation.<sup>[7]</sup> Their hypothesis based on the idea that agitation may be attributed to residual sevoflurane and administration of N<sub>2</sub>O during washout of sevoflurane may improve postanesthetic recovery. Although only twenty patients were enrolled in that study, the results obtained from their study also supported their hypothesis. Actually, N<sub>2</sub>O is most often used for reducing the amount of sevoflurane concentration, and therefore is expected to decrease the incidence of EA. However, there is insufficient evidence for such effect of N<sub>2</sub>O in the literature. The results obtained from our study also did not support that kind of effect regarding N<sub>2</sub>O use.

In another study by Park et al.,<sup>[6]</sup> the patients who received sevoflurane with N<sub>2</sub>O was compared with those who received sevoflurane alone. The authors did not find any differences in pain scores, incidence of EA, or need of rescue fentanyl between the groups, similar to our study. Although that study had similar methodology with our study in general, there were also several differences that could affect the results. First of all, the study was conducted in patients who underwent adenotonsillectomy. However, type of surgery cannot be a significant difference for the occurrence of EA because both ophthalmologic and otorhinolarynx related operations were recognized as most risky surgeries for this entity. The authors, on the other hand, used thiopental sodium in anesthesia induction while propofol was the induction agent in our study. The previous studies showed that propofol was more effective in reducing the incidence of EA compared with thiopental sodium.<sup>[19,20]</sup> Additionally, the authors prescribed pre-emptive ketorolac, an effective analgesic agent, to all patients, which might affect the pain and agitation status of the patients. Moreover, all patients were premedicated with atropine in the mentioned study. As known, atropine is a competitive antagonist of acetylcholine receptors that potentially modulate the central nervous system, and may evoke potent psychotropic effects, such as characteristic delirium-like situations with cognitive disorders, altered mood, and hallucinations.<sup>[21]</sup> Therefore, premedication with atropine might have affected the agitation status of the patients. In our study, we did not give any premedication to the patients in order to prevent potential effects of premedication drugs on pain or agitation status, and to provide homogeneity between the patient groups. Despite the differences, the results that showed no significant effect of N<sub>2</sub>O on postoperative pain and EA is important for more selective use of this gas.

## Conclusion

The present study showed that N<sub>2</sub>O had no significant negative or positive effect on postoperative pain status and EA in pediatric patients under sevoflurane anesthesia for ophthalmic surgery, in comparison with air. Considering the potential adverse effects of N<sub>2</sub>O, this finding is important for more selective use of this anesthetic gas in pediatric patients.

## Limitations

Several limitations of the present study should be noted. First, it was conducted in a single center, which may limit the generalizability of the statistical results. The relatively small number of patient groups may be another limitation, which makes it difficult to interpret subgroup findings. Considering that there are few studies on the effect of N<sub>2</sub>O on EA, the results obtained from the study may provide significant scientific contribution to the literature.

## Disclosures

**Acknowledgement:** We would like to thank all of the ophthalmic surgeons who in the performance of the surgical procedures, for their collaboration.

**Ethics Committee Approval:** The study protocol was approved by Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee with 04/02/2020 dated and 27 numbered decision.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

**Authorship Contributions:** Concept – Y.K., A.B.; Design – Y.K., A.B.; Supervision – Y.K., A.B.; Materials – Y.K.; Data collection &/or processing – Y.K.; Analysis and/or interpretation – Y.K.; Literature search – Y.K.; Writing – Y.K.; Critical review – Y.K., A.B.

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