Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 80 (2017) 733−736

www.jcma-online.com

Original Article

Pupillary response to nitrous oxide administration in cataract surgery under general anesthesia

Mansoor Masjedi [a], Alireza Ghanbari [b], Hossein Haddad Bakhodaei [a], Tahere Jowkar [a], Vahhab Hosseni [b], Mahnaz Rakhshan [c,*]

[a] *Anesthesiology and Critical Care Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*
[b] *Shiraz University of Medical Sciences, Shiraz, Iran*
[c] *Community Based Psychiatric Research Center, School of Nursing & Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran*

Received July 5, 2016; accepted April 19, 2017

Abstract

Background: Despite recent innovations in cataract surgery, pupillary diameter is one of the most important affecting factors in outcome of this surgery. As cataract surgery is performed ideally when the pupil is sufficiently dilated, anesthesia may contribute significantly in success or failure of this operation. This study was performed to evaluate the effect of nitrous oxide on pupillary diameter in cataract surgery under general anesthesia.

Methods: Forty patients with cataract, scheduled for operation under general anesthesia, were randomly allocated into two groups. After induction of anesthesia, anesthesia was maintained with isoflurane and nitrous oxide − oxygen (60%-40%) in group 1 versus oxygen 100% in group 2. Pupillary diameter, heart rate and blood pressure were monitored and recorded, before induction of anesthesia, just before tracheal intubation, and one and 5 min after laryngoscopy and tracheal intubation.

Results: Statistical analysis of the results using Mann−Whitney test showed no significant difference in pupillary diameter between two the groups.

Conclusion: According to the results of this study, nitrous oxide has no effect on pupillary diameter of patients under general anesthesia, so it could be safety used, in this regard, in ophthalmic operations.

Keywords: Anesthesia; Nitrous oxide; Pupil; Reflex

1. Introduction

The use of modern techniques in cataract surgery in recent years has become increasingly popular. Given that cataract surgery is one of the most common of ophthalmic surgeries, achieving new ways to increase efficiency and reduce the risk of complications is desirable.[1,2]

Despite recent advances in techniques of ophthalmic operation, pupillary size is still one of the important and factors affecting determining final results.[3] Since constricted pupils can impose adverse effects, specifically on cataract surgery, pupillary dilatation has a vital role in its success and outcome.[4,5]

The effects of anesthetics on pupillary diameter are variable. Desflurane and sevoflurane increase but alfentanil and nalbuphine decrease pupillary size during surgery under general anesthesia.[6,7]

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Mahnaz Rakhshan, Community Based Psychiatric Research Center, School of Nursing & Midwifery, Shiraz University of Medical Sciences, Shiraz, Iran.

E-mail addresses: mzrakhshan@ymail.com, rakhshanm@sums.ac.ir (M. Rakhshan).

http://dx.doi.org/10.1016/j.jcma.2017.07.001

Nitrous oxide is one of the oldest and most widely used anesthetics. Its application during anesthesia is common worldwide.[8,9] Nitrous oxide has a linear molecule (N≡N−O) and is a colorless, odorless, and non-flammable gas at standard temperature and pressure. It has no irritant effect on the human respiratory system. This gas is 1.5 times heavier than air and naturally exists in the atmosphere at a concentration of 0.5 ppm. Nitrous oxide is produced normally by heating ammonium nitrate up to 270 °C with substances such as nitric oxide, nitrogen dioxide, chlorine gas, carbon monoxide and nitrogen. Purification of nitrous oxide is a difficult process.[9−12]

Nitrous oxide is one of the weakest anesthetic gases, with minimum alveolar concentration (MAC) of 104%. It means that even with the maximum permitted prescription (70% concentration), it cannot be used as a sole anesthetic. Therefore, it should be used in combination with other anesthetics, inhaled or intravenous, to induce or maintain anesthesia.

Generally, nitrous oxide is known as a weak anesthetic but strong analgesic and facilitates reduction of the required dose of other patent anesthetic drugs.[9,12,13]

Nitrous oxide has a low blood solubility (blood/gas partition coefficient of 0.47) with rapid increase of its relative pressure in blood after administration.[9]

A limited number of studies have evaluated the effect of this gas on human pupillary diameter, with controversial results.[4,14,15] In this research, the effect of nitrous oxide on pupillary diameter in cataract surgery under general anesthesia was investigated.

2. Methods

This study was designed as a prospective, interventional, double blind clinical trial. Considering the standard deviation, appreciable change in pupillary diameter was determined to be 1 mm to achieve 95% confidence interval with 80% test power.

Forty patients with cataract, 50−80 years old, American Society of Anesthesiologists Physical Status (ASAPS) 1 or 2 were enrolled in the study after their consent was obtained. They were randomly allocated in two groups, 20 patients per group, on the basis of the rightmost odd or even number of their file number.

Exclusion criteria were: patients with obesity (BMI > 30), blood pressure above 160/90 mmHg, glaucoma, pseudo exfoliation pupillary adhesions, optical trauma, clear corneal opacity (leucoma), diabetes and endotracheal intubation lasting more than 30 s.

All patients received the same method to induce dilation of pupils half an hour prior to induction of anesthesia, with 4−5 drops of homatropine and phenylephrine 5%, every 5 min, for three times. Pressure on the panctum and lacrimal sac was applied for 15 s after application of each drop. Then, patients were taken to the operating room and standard monitoring (non-invasive blood pressure, electrocardiogram, pulse oxymetry and capnography) were applied. Premedication, 0.03 mg/kg intravenous midazolam and 2 μ/kg of fentanyl, was given to all patients, then 5 mg/kg pentothal and 0.6 mg/kg atracurium were administered respectively for induction of anesthesia and muscle relaxation. This was followed by endotracheal intubation 3 min later. Anesthesia was maintained with isoflurane plus 40% oxygen and 60% nitrous oxide in the first group and 100% oxygen in the second group with preservation of normocapnia and normoxia.

Pupillary diameter was measured by pupillometer (Colvard Pupillometer, OASIS, United States) at four time points: before anesthesia induction, before endotracheal intubation, and one and five minutes after intubation. The blood pressure and heart rate were recorded at each time. Collected data were analyzed by SPSS 16 statistical software. Demographic findings were investigated and compared by Mann−Whitney test.

3. Results

Patients' demographic characteristics are shown in Table 1. As can be seen, there were no significant differences between the mean age and sex of the patients (Table 1). As Table 2 indicates, the average blood pressures at all time points were compared between the two groups and showed no statistically significant difference ($P > 0.05$) (Table 2).

In Table 3, comparison of the average heart rate between both groups is shown and indicates no statistically significant difference (Table 3).

Table 4 demonstrates the comparison of the mean pupillary diameter of groups 1 and 2 at four studied time points. Statistical analysis revealed no significant difference ($P > 0.05$).

Table 5 shows changes in mean pupillary diameter from the 1st to 3rd and 4th time points (respectively one and 5 min after endotracheal intubation). No statistically significant differences were noted ($P > 0.05$).

Mann−Whitney test was used to compare the results.

All patients had a favorable condition after surgery. No case of vomiting or cardiovascular or respiratory complication was observed, and all of them achieved a favorable level of consciousness within 15 min after the surgery.

4. Discussion

> "Because human pupillary size is under control of the sympathetic and parasympathetic systems, therefore, drugs that affect the autonomic nervous system have the ability to affect the pupillary diameter".[4]

Many studies indicate that nitrous oxide activates the sympathetic nervous system.[4,16−18] Fukunaga, using direct recording of visceral nerve activity in cats anesthetized with 9% halothane, found that after adding 70% nitrous oxide to the inhaled gas, the sympathetic activity increased 13%. Ebert

Table 1
Characteristics of patients undergoing cataract surgery under general anesthesia using nitrous oxide according to age and sex.

Group	Age mean (y)	Male	Female
Nitrous oxide	64.2	13	7
Without nitrous oxide	64.3	12	8

Table 2
A comparison of mean arterial blood pressure in patients undergoing cataract surgery under general anesthesia with or without nitrous oxide at four studied time points.

Studied time points	Group 1 (anesthesia with nitrous oxide)	Group 2 (anesthesia without nitrous oxide)	*P*
Before anesthesia	107.8 ± 8.1	106.1 ± 10.5	0.64
Before tracheal intubation	94 ± 20.1	95.3 ± 24.3	0.98
One minute after tracheal intubation	111.2 ± 16.5	108.1 ± 19.3	0.73
Five minutes after tracheal intubation	95.4 ± 18.3	97.4 ± 17.9	0.71

Table 3
A comparison of the average heart rate of patients undergoing cataract surgery under general anesthesia with or without nitrous oxide at four studied time points.

Studied time points	Group 1 (anesthesia with nitrous oxide)	Group 2 (anesthesia without nitrous oxide)	*P*
Before anesthesia	78.3 ± 10.7	73.6 ± 7.9	0.18
Before tracheal intubation	75.5 ± 10.8	77.4 ± 8.9	0.39
One minute after tracheal intubation	82.5 ± 8.6	81.5 ± 13.7	0.77
Five minutes after tracheal intubation	73.3 ± 8.8	77.1 ± 13.3	0.35

Table 4
A comparison of pupillary diameter in patients undergoing cataract surgery under general anesthesia with or without nitrous oxide at four studied time points.

Studied time points	Group 1 (anesthesia with nitrous oxide)	Group 2 (anesthesia without nitrous oxide)	*P*
Before anesthesia	6.7 ± 0.92	6.1 ± 1.21	0.1
Before tracheal intubation	6.3 ± 1.03	5.85 ± 1.18	0.2
One minute after tracheal intubation	6.4 ± 1.09	5.7 ± 1.30	0.08
Five minutes after tracheal intubation	6.4 ± 0.99	5.75 ± 1.33	0.08

Table 5
A comparison of changes in pupillary diameter in patients undergoing cataract surgery under general anesthesia with or without nitrous oxide between time point 1 and time points 3 and 4.

Phase	Group 1 (anesthesia with nitrous oxide)	Group 2 (anesthesia without nitrous oxide)	*P*
1 and 3	0.80 ± 0.3	0.59 ± 0.4	0.67
1 and 4	0.80 ± 0.3	0.48 ± 0.35	0.88

reported that 40% nitrous oxide resulted in an increase of sympathetic activity in skeletal muscle nerves in healthy volunteers. Sellgren et al. reported similar results. Increased sympathetic activity following nitrous oxide administration is probably the cause of relative cardiovascular stability when "NO_2" is used along with other anesthetic drugs with suppressive effects on the sympathetic system. However, the mechanism of increase of sympathetic activity by nitrous oxide is unknown.[18]

As mentioned earlier, not many studies have been conducted on the possible effects of nitrous oxide on the size of human pupil.[4] Smith and colleagues, showed that adding nitrous oxide to halothane-oxygen in humans, increased pupillary diameter,[18] not matching our result. In another study on the role of fentanyl, clonidine and nitrous oxide on dilated pupils due to of anesthesia with desflurane, it was found that fentanyl and clonidine decrease mydriasis and nitrous oxide increase the mydriasis during anesthesia.[14] Another study evaluated the effect of nitrous oxide on dogs' pupillary diameter. Twenty dogs were anesthetized in each of two groups with 10 mg/kg of propofol. Then, to maintain anesthesia in one group desflurane with 100% oxygen and in the other group, desflurane plus 70% of nitrous oxide and 30% oxygen was used. Finally, they found that pupillary diameter in nitrous oxide group, unlike the other group was not significantly decreased.[4] In contrast, in a study evaluating pupillary diameter upon painful stimulation, nitrous oxide reduced pupillary dilation in response to painful stimulation.[16] In addition, several other studies noted that nitrous oxide causes suppression of pupillary reflection to light and led to a little reduction in pupillary diameter, perhaps the effect of this drug on the opioid receptors.[15,19,20]

The results of the present study also indicate a slight and intangible decrease in the pupillary diameter following the use of nitrous oxide and in fact nitrous oxide results in the maintenance of pupillary diameter in a suitable range for cataract surgery. According to the fact that the main role of nitrous oxide in anesthesia is to reduce the opioid dose and by considering the fixed role of opioids in reduction of pupillary diameter, it seems that addiction of nitrous oxide may results in better condition for cataract surgery rather the opioids alone. Although, there is a need for more research in this field.

We didn't interfere with routine application of pre-op ophthalmic drops because we were to evaluate the effect of N_2O in real situation. Although our results indicate mild reduction in pupillary diameter but it should be considered as a disturbing factor.

In conclusion, nitrous oxide could safely be used in general anesthesia for ophthalmologic operations regarding is negligible effect on pupillary diameter.

The present study may have some important clinical implications such as:

1) In any situation when there is limitation or contraindication to consumption of ophthalmic drops (e.g. closed angle glaucoma, eye trauma, corneal transplant) one should know if NO_2 have any effect on pupillary diameter.
2) Generalizing our result, if there is any change in pupillary diameter in surgeries under general anesthesia and one is going to find out the causes, it may be helpful to know whether NO_2 is a contributor or not.
3) With ever-growing number of ophthalmologic examinations under anesthesia (EUA) and the need to return to

daily activities as soon as possible, consumption of mydriatic drugs is limited, and so the effect of NO_2 on pupillary diameter is very important and should be delineated.

References

1. Hayashi K, Hayashi H. Pupil size before and after phacoemulsification in nondiabetic and diabetic patients. *J Cataract Refract Surg* 2004;**30**:2543−50.
2. Narvaez J, Kronberg BP, Park H, Zumwalt JR, Wong B, Bacon G, et al. Pupil dilation using a standard cataract surgery regimen alone or with atropine 1.0% pretreatment: prospective comparative evaluation. *J Cataract Refract Surg* 2010;**36**:563−7.
3. Anaraki AN, Akrami A, Motamed N, Seydali E. Effect of fentanyl versus buprenorphine on the pupil size in phacoemulsification cataract surgery. *Saudi J Anaesth* 2012;**6**:268−72.
4. Almeida DE, Nishimori CT, Oria AP, Paula DP, Nunes N, Laus JL. Effects of nitrous oxide on IOP and pupillary diameter in dogs anesthetized with varying concentrations of desflurane. *Vet Ophthalmol* 2008;**11**:170−6.
5. Ong-Tone L, Bell A. Pupil size with and without adrenaline with diclofenac use before cataract surgery. *J Cataract Refract Surg* 2009;**35**:1396−400.
6. Huybrechts I, Barvais L, Ducart A, Engelman E, Schmartz D, Koch M. Assessment of thoracic epidural analgesia during general anesthesia using pupillary reflex dilation: a preliminary study. *J Cardiothorac Vasc Anesth* 2006;**20**:664−7.
7. el Messiry S, Chiou GC. Interaction between nalbuphine and alfentanil on intraocular pressure and pupil size of conscious rabbits. *Ophthalmic Res* 1989;**21**:134−40.
8. Gilani SM, Sofi K. Is nitrous oxide necessary for general anaesthesia? *J Ayub Med Coll Abbottabad* 2008;**20**:149−52.
9. Sanders RD, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. *Anesthesiology* 2008;**109**:707−22.
10. Hopkins PM. Nitrous oxide: a unique drug of continuing importance for anaesthesia. *Best Pract Res Clin Anaesthesiol* 2005;**19**:381−9.
11. O'Sullivan I, Benger J. Nitrous oxide in emergency medicine. *Emerg Med J* 2003;**20**:214−7.
12. Stoelting RK, Hillier SC. *Pharmacology and physiology in anesthetic practice*. Lippincott Williams & Wilkins; 2012.
13. Mathews DM, Gaba V, Zaku B, Neuman GG. Can remifentanil replace nitrous oxide during anesthesia for ambulatory orthopedic surgery with desflurane and fentanyl? *Anesth Analg* 2008;**106**:101−8.
14. Larson MD, Berry PD, May J, Bjorksten A, Sessler DI. Latency of pupillary reflex dilation during general anesthesia. *J Appl Physiol (1985)* 2004;**97**:725−30.
15. Eilers H, Larson MD. The effect of ketamine and nitrous oxide on the human pupillary light reflex during general anesthesia. *Auton Neurosci* 2010;**152**:108−14.
16. Oka S, Chapman CR, Kim B, Nakajima I, Shimizu O, Oi Y. Pupil dilation response to noxious stimulation: effect of varying nitrous oxide concentration. *Clin Neurophysiol* 2007;**118**:2016−24.
17. Niwa H, Tanimoto A, Sugimura M, Morimoto Y, Hanamoto H. Cardiovascular effects of epinephrine under sedation with nitrous oxide, propofol, or midazolam. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;**102**:e1−9.
18. Pac-Soo CK, Wang C, Ma D, Chakrabarti MK, Whitwam JG. Vagally mediated sympathoexcitation and central depression by desflurane in rabbits. *Br J Anaesth* 2000;**84**:777−82.
19. Fujinaga M, Doone R, Davies MF, Maze M. Nitrous oxide lacks the antinociceptive effect on the tail flick test in newborn rats. *Anesth Analg* 2000;**91**:6−10.
20. Ghanbari A, Farid Z, Askarian M, Rahimi A, Haddad Bakhodaei H, Jowkar T, et al. A comparative study on the effect of inhaled anesthetics on alkaline phosphatase and alanine aminotransferase serum level in nursing team and operating room personnel. *Biomed Res India* 2017;**28**:e1−5.