

Effects of Low-Concentration Nitrous Oxide Anesthesia on Patient Anxiety During Cataract Surgery: A Retrospective Cohort Study

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Purpose: We investigated the effects of 30% low-concentration nitrous oxide (N₂O) anesthesia on anxiety, pain, and vital signs and the patient population that would benefit from low-concentration N₂O anesthesia during cataract surgery.

Patients and Methods: Sixty-three patients who underwent cataract surgery due to visual impairment from cataracts were included in this single-center retrospective cohort study conducted at the Ophthalmology Department of Shinseikai Toyama Hospital, Japan. Fifty eyes of 39 patients received a combination of local and N₂O anesthesia (N₂O group), and 30 eyes of 24 patients received local anesthesia without N₂O anesthesia (Air group). The primary outcome measures were visual analogue scale (VAS) scores for patient anxiety, pain, and vital signs. The secondary outcome measures were the patient population.

Results: The change in the VAS scores for anxiety and pain decreased significantly ($p = 0.002$ and $p = 0.014$, respectively) in the N₂O group (-15.6 ± 22.9 and 12.4 ± 14.9 , respectively) compared with that in the Air group (1.2 ± 20.6 and 24.2 ± 22.4 , respectively). The systolic and diastolic blood pressure changes did not significantly differ between both groups ($p = 0.093$ and $p = 0.23$, respectively). The change in heart rate decreased significantly ($p = 0.001$) in the N₂O group (-4.8 ± 4.8 bpm) compared with that in the Air group (-0.6 ± 5.8 bpm). Multivariate analyses demonstrated that the change in anxiety level in the N₂O group correlated significantly with patient age ($p = 0.045$) and preoperative VAS score for anxiety ($p = 0.0001$), whereas the change in anxiety level in the Air group did not correlate with any factor.

Conclusion: Low-concentration N₂O anesthesia showed beneficial effects on intraoperative anxiety and pain during cataract surgery; this may aid the stabilization of intraoperative vital signs. Moreover, low-concentration N₂O anesthesia during cataract surgery could benefit young patients and patients with high levels of preoperative anxiety.

Keywords: cataract surgery, low-concentration nitrous oxide anesthesia, patient anxiety

Introduction

Some patients experience anxiety or fear during cataract surgery under local anesthesia.^{1,2} Surgeons are faced with the challenges of ensuring a successful surgery and reducing patient anxiety during surgery. To date, several techniques for reducing patient anxiety during surgery have been attempted, such as listening to music before and during surgery,^{1,3-5} preoperative patient education,^{6,7} and hand massage or hand-holding before and during surgery.^{8,9}

Recently, Noguchi et al¹⁰ reported that local anesthesia with a low concentration of nitrous oxide (N₂O) could reduce intraoperative patient pain during ptosis surgery. In addition, Noguchi et al¹¹ reported for the first time that low-concentration N₂O anesthesia could reduce intraoperative patient anxiety during cataract surgery. N₂O is a colorless and virtually odorless gas with a faint sweet smell¹² that has both anxiolytic¹³ and analgesic effects.^{14,15} N₂O has low solubility with a high minimum alveolar concentration (MAC) in the brain; the blood partition coefficient (the ratio of N₂O dissolved per gram of brain to that dissolved in 1 mL of blood) was reported to be 1.06,¹⁶ and MAC was 104%.¹⁷ The rapid onset of action of N₂O is associated with rapid recovery. N₂O anesthesia has been used in many disciplines of

medicine, including dentistry, anesthesia, obstetrics, emergency medicine, and pediatrics,^{12,18,19} owing to the relative safety of N₂O anesthesia, with only a few adverse effects reported.^{20,21} However, to date, few reports have evaluated the efficacy of N₂O anesthesia in cataract surgery,¹¹ and the patient population that would benefit from the low-concentration N₂O anesthesia during cataract surgery has not been determined.

In this study, we investigated whether low-concentration N₂O anesthesia reduces patient anxiety and pain during cataract surgery and its effects on vital signs. We also aimed to identify the patient population that would benefit from low-concentration N₂O anesthesia during cataract surgery.

Patients and Methods

Patients

This retrospective observational study included patients who underwent cataract surgery owing to visual impairment due to cataracts. Each patient received oral and written information regarding the cataract surgery and provided consent before surgery. The study protocol was approved by the Institutional Review Board of Shinseikai Toyama Hospital (reference number: 220,125–2), which adhered to the tenets of the Declaration of Helsinki. We reviewed the medical and ocular histories of patients undergoing cataract surgery between October 12, 2021, and December 23, 2021, in the Department of Ophthalmology of Shinseikai Toyama Hospital (Toyama, Japan).

The inclusion criteria were patients who responded to the questionnaire on anxiety and pain. The patients who could not answer the questionnaire by themselves and had severe cataracts (grades 4 and 5, with nuclei graded according to the Emery–Little classification²²) were excluded from the study.

During the study period, 50 eyes of 39 patients underwent cataract surgery under local anesthesia with N₂O sedation (N₂O group) and met the inclusion criteria. Thirty eyes of 24 patients underwent cataract surgery under local anesthesia without N₂O sedation (Air group) and met the inclusion criteria. Bilateral cataract surgeries were performed one eye at a time with an interval of 1–2 weeks.

N₂O anesthesia was used when the blood pressure (BP) before entering the operating room was higher than 100/60 mmHg, and the initial vital signs after entering the operating room were normal.

Surgical Procedures and N₂O Setting

All the patients received 4% xylocaine eye drop before the procedure. Thirty percent low-concentration N₂O (Oxygen: 2 L/min and N₂O: 1 L/min; total: 3 L/min) inhalation (SAFER-100[®], Nambuk Mednics CO., Ltd, Gyeonggi-do, Korea) with a nasal cannula (SOFTECH[®], Hudson RCI[®], Teleflex Medical, Dublin, Ireland) was administered following initial measurement of the vital signs and continued until the end of the surgery in the N₂O group. All the patients received 2% sub-Tenon's anesthesia (2 mL) at the lower temporal region. Sub-Tenon's anesthesia was performed approximately 2–3 min after the initial vital signs were measured in the operating room. Phacoemulsification was performed using a 2.2-mm single-plane sclerocorneal incision and phacoemulsification system (Centurion[®], Alcon Laboratories, Inc., Fort Worth, TX, USA). All the surgical procedures were performed by two surgeons (H.S. and Y.U., who perform approximately 450 and 500 cataract surgeries per year, respectively). One surgeon (H.S.) performed 45 cataract surgeries (25 eyes of 21 patients in the N₂O group and 20 eyes of 14 patients in the Air group). The other surgeon (Y.U.) performed 35 cataract surgeries (25 eyes of 18 patients in the N₂O group and 10 eyes of 10 patients in the Air group). In this study, the surgical procedures were performed similarly, and classical piano music was played from a CD player during the surgery. In addition, we did not use preoperative sedation drugs in any of the cases.

Assessment of Levels for Anxiety, Pain, and Nausea

Patients reported their anxiety level before anesthesia in the hospital room and immediately following cataract surgery using the 100-mm visual analogue scale (VAS),²³ ranging from 0 to 100, where 0 indicates no anxiety and 100 indicates the maximum level of anxiety. The VAS score was determined by measuring the distance in millimeters from the left end of the line to the point marked by the patient. In the postoperative VAS, patients reported the amount of anxiety perceived during the surgery. The change in the anxiety level was calculated as the intraoperative VAS score for anxiety minus the

preoperative values. After the surgery, the patients answered questions regarding intraoperative pain and nausea using the VAS and were asked whether they had any intraoperative memories as well.

Vital Signs Measurements

Preoperative systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and oxygen saturation (SpO₂) were measured immediately after the surgical chair was positioned in the same position as during the surgery. BP was measured using a cuff-type upper-arm sphygmomanometer (Vismo[®] PVM 2701, NIHON KODEN, Tokyo, Japan), and HR was measured using a two-lead electrocardiogram monitor (Vismo[®] PVM 2701, NIHON KODEN, Tokyo, Japan). SpO₂ was measured on the index finger using a pulse oximeter (Vismo[®] PVM 2701, NIHON KODEN, Tokyo, Japan). Intraoperative BP, HR, and SpO₂ were measured every 5 min until the end of the surgery. We then calculated the mean intraoperative BP, HR, and SpO₂ and used the values for statistical analysis. Changes in the vital signs were calculated as the mean intraoperative values minus the preoperative values. The presence or absence of consciousness was determined by response to the call, and the disappearance of spontaneous breathing was confirmed by the SpO₂ waveform.

Ophthalmic Examinations

Axial length was measured in all patients using the OA-2000[®] (Tomey, Nagoya, Japan) before the surgery. The ultrasound and operation times were also evaluated in this study.

Statistical Analysis

A biostatistician (K.M.) performed the statistical analyses using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA). The homogeneity of the variance was analyzed using the F-test. An unpaired *t*-test was used when both groups had equal variance. An unpaired *t*-test with Welch's correction was used when both groups did not assume equal variance. Differences in the categorical data between the two groups were analyzed using Fisher's exact test. All the values were expressed as the mean ± standard deviation. In addition, we also analyzed five factors, namely patient age, sex, first or second eye, preoperative VAS score for anxiety, and surgeon in the N₂O and Air groups, to investigate the patient characteristic affecting the change in anxiety level. This analysis was performed using the multiple linear mixed model, which included the patient's age, sex, first or second eye, preoperative VAS score for anxiety, and surgeon (H.S. or Y.U.) as fixed effects and patients as a random effect. The statistical significance was set at *p*<0.05.

Results

Patient Characteristics

Baseline patient characteristics are summarized in Table 1. No complications were associated with cataract surgery, and no systemic complications, such as excessive hypotension, unconsciousness, or disappearance of spontaneous breathing, were observed in this study.

Table 1 Summary of the Patients' Characteristics Including Vital Signs Before Cataract Surgery

	N ₂ O Group*	Air Group	p-value
No. of eyes	50	30	
Age (years)	73.0 ± 8.2	72.2 ± 4.8	0.55
Sex (male/female)	18/32	10/20	1
Eye (right/left)	26/24	14/16	0.82
Axial length (mm)	23.7 ± 1.4	24.1 ± 1.9	0.4
No. of Emery–Little grade 2 (%) ^a	40 (80)	28 (93.3)	0.19
No. of first eye (%)	25 (50)	16 (53.3)	0.82

(Continued)

Table 1 (Continued).

	N ₂ O Group*	Air Group	p-value
No. of patients on antihypertensive drugs (%)	16 (41.0)	12 (50)	0.60
No. of surgeries (H.S./ Y.U.)	25/25	20/10	0.17
VAS score for anxiety	43.7 ± 21.8	34.2 ± 28.2	0.096
Systolic blood pressure (mmHg)	149.5 ± 21.8	153.3 ± 22.2	0.45
Diastolic blood pressure (mmHg)	78.3 ± 16.3	82.5 ± 10.9	0.18
Heart rate (bpm)	74.0 ± 9.2	75.2 ± 13.7	0.66
Oxygen saturation (%)	97.7 ± 1.4	97.5 ± 1.4	0.66

Notes: *Patients received 30% nitrous oxide (N₂O) anesthesia (Oxygen, 2 L/min; N₂O, 1 L/min; total, 3 L/min). ^aThe rest of the eyes in each group were grade 3 according to the Emery-Little classification. ²² Data are expressed as mean ± standard deviation.

Abbreviations: No, number; VAS, visual analogue scale.

Comparison of the Subjective Measures

The intraoperative VAS score for anxiety did not significantly differ ($p=0.24$) between the N₂O group (28.1 ± 23.6) and the Air group (35.3 ± 30.8) (Figure 1A). However, the change in the VAS score for anxiety was significantly reduced ($p=0.002$) in the N₂O group (-15.6 ± 22.9) compared with the Air group (1.2 ± 20.6) (Figure 1B). In addition, the

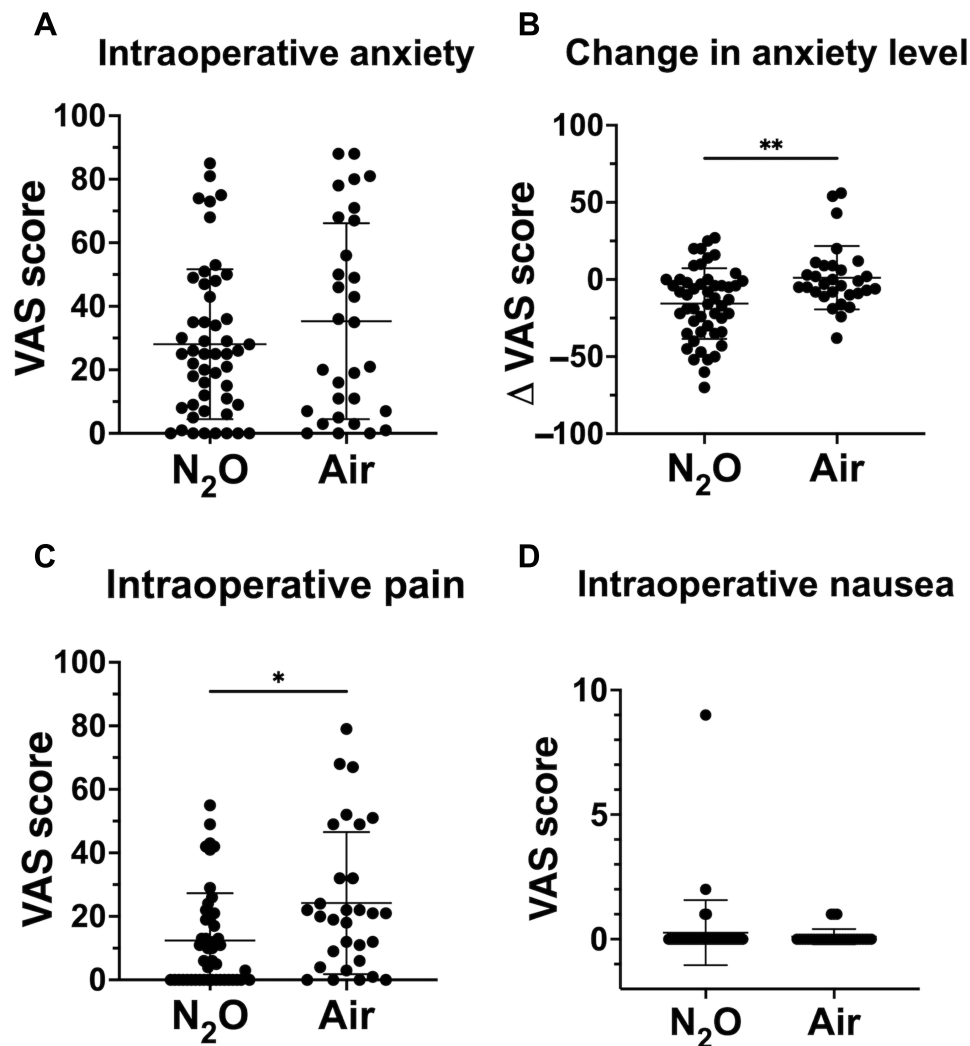


Figure 1 Comparison of intraoperative anxiety (A), change in anxiety level (B), intraoperative pain (C), and intraoperative nausea (D) between the nitrous oxide (N₂O) anesthesia group and the Air group. The change in anxiety level was calculated as the intraoperative visual analogue scale (VAS) score for anxiety minus the preoperative VAS score for anxiety (B). * $p<0.05$. ** $p<0.01$.

intraoperative VAS score for pain was significantly reduced ($p=0.014$) in the N₂O group (12.4 ± 14.9) compared to that in the Air group (24.2 ± 22.4) (Figure 1C). The intraoperative VAS score for nausea did not significantly differ ($p=0.41$) between the N₂O group (0.3 ± 1.3) and the Air group (0.1 ± 0.3) (Figure 1D). Four (4/50, 8%) patients in the N₂O group (with VAS scores of 1, 1, 2, and 9 points) and 3 (3/30, 10%) patients each in the Air group (with a VAS score of 1 point) complained of intraoperative nausea; no severe nausea, which could cause vomiting and affect cataract surgery, was noted. All the patients were fully conscious during surgery.

Comparison of the Objective Measures

Intraoperative SBP was significantly lower ($p=0.046$) in the N₂O group (147.6 ± 17.9 mmHg) than in the Air group (156.1 ± 18.4 mmHg) (Figure 2A). However, the change in SBP did not significantly differ ($p=0.093$) between the N₂O group (-1.9 ± 12.0 mmHg) and the Air group (2.8 ± 11.6 mmHg) (Figure 2B). Intraoperative DBP was significantly lower ($p=0.016$) in the N₂O group (76.2 ± 12.6 mmHg) than in the Air group (82.9 ± 9.6 mmHg) as well (Figure 2C). However, the change in the DBP did not significantly differ ($p=0.23$) between the N₂O group (-2.1 ± 11.0 mmHg) and the Air group (0.4 ± 7.0 mmHg) (Figure 2D). Intraoperative HR and the change in HR significantly decreased ($p=0.047$ and $p=0.001$, respectively) in the

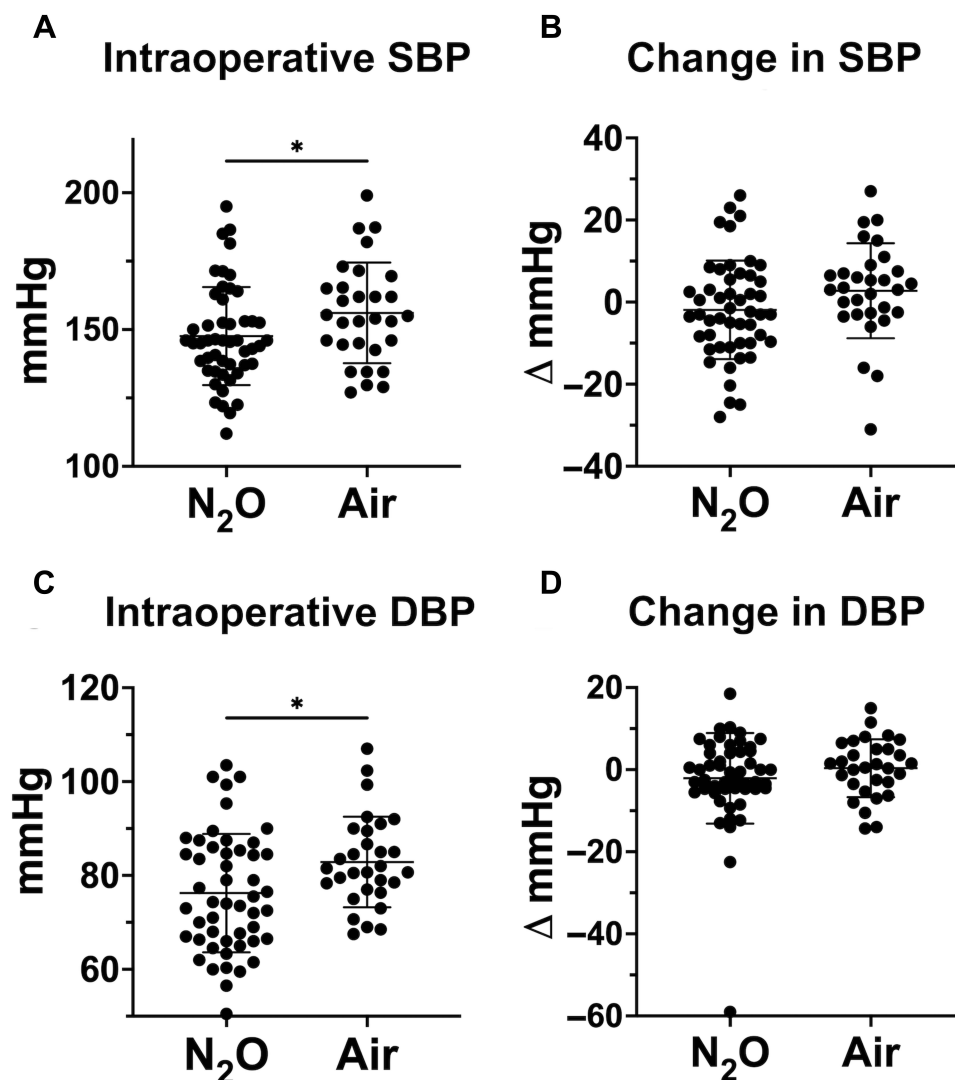


Figure 2 Comparison of intraoperative systolic blood pressure (SBP) (A), change in SBP (B), intraoperative diastolic blood pressure (DBP) (C), and change in DBP (D) between the nitrous oxide (N₂O) anesthesia group and the Air group. The changes in SBP and DBP were calculated as the mean intraoperative SBP and DBP values minus the preoperative SBP and DBP values, respectively (B and D). * $p < 0.05$.

N₂O group (69.2±8.4 bpm and -4.8±4.8 bpm) compared to that in the Air group (74.6±13.2 bpm and -0.6±5.8 bpm) (Figure 3A and B). Intraoperative SpO₂ and the change in SpO₂ significantly increased ($p<0.001$ and $p<0.001$, respectively) in the N₂O group (99.3±0.7% and 1.6±1.4%) compared to that in the Air group (97.5±1.4% and -0.03±0.7%) (Figure 3C and D).

Factors Affecting the Change in Anxiety Level Using the Multiple Linear Mixed Model

The results of the multivariate analyses for the change in anxiety level are shown in Table 2. The change in anxiety level in the N₂O group significantly correlated with patient age (adjusted coefficient: 0.79, 95% confidence interval (CI): 0.018–1.6, $p=0.045$) and preoperative VAS score for anxiety (adjusted coefficient: -0.55, 95% CI: -0.82– -0.29, $p=0.0001$). Meanwhile, the change in anxiety level in the Air group did not correlate with any of the factors.

Surgical Procedures

The ultrasound time and operation time did not significantly differ between the N₂O group and the Air group (28.5±10.6 s and 24±10.9 s, $p=0.075$; 487.4±118.7 s and 519.2±101.8 s, $p=0.23$, respectively).

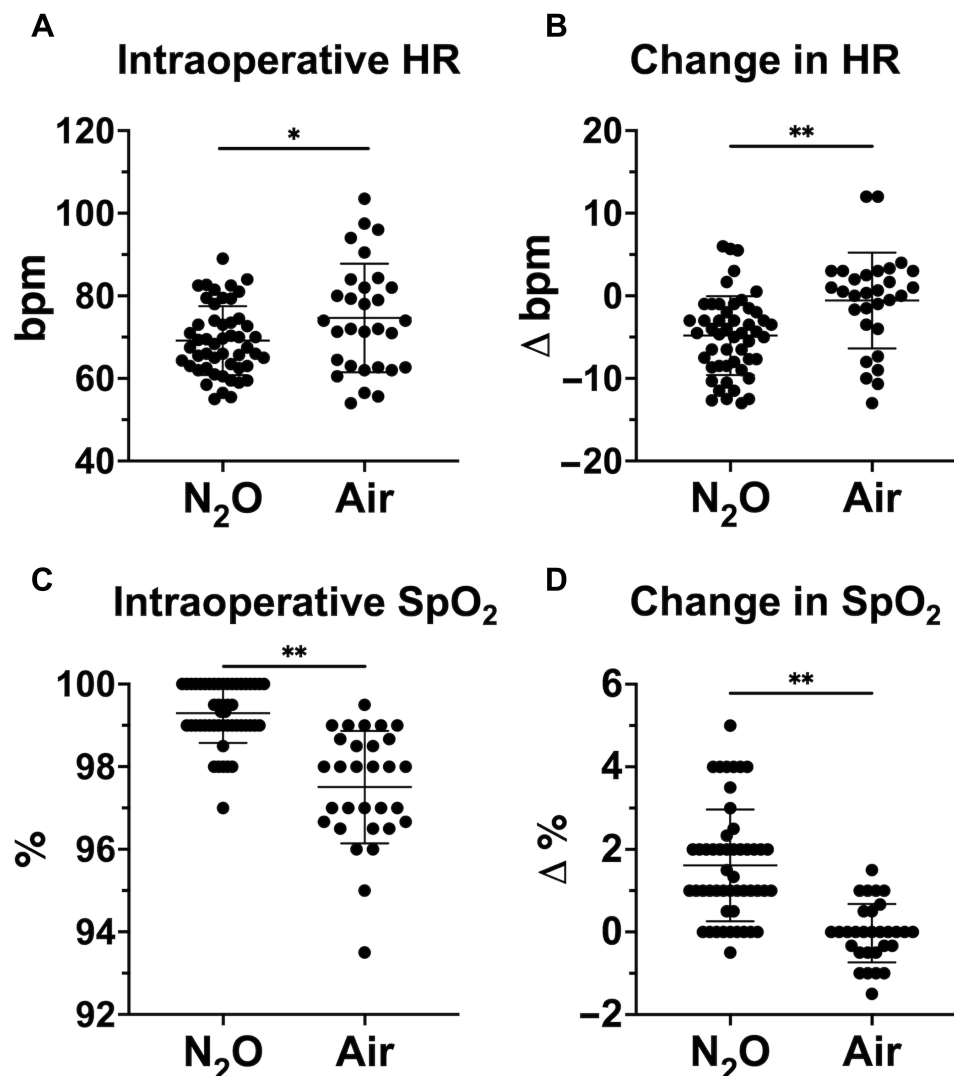


Figure 3 Comparison of intraoperative heart rate (HR) (A), change in HR (B), intraoperative oxygen saturation (SpO₂) (C), and change in the SpO₂ (D) between the nitrous oxide (N₂O) anesthesia group and the Air group. The changes in HR and SpO₂ were calculated as the mean intraoperative HR and SpO₂ values minus the preoperative HR and SpO₂ values, respectively (B and D). * $p<0.05$. ** $p<0.01$.

Table 2 Factors Affecting the Change in the Anxiety Level in the Multivariate Analyses Using the Linear Mixed Model

Parameters	N ₂ O Group			Air Group		
	Adjusted Coefficient	95% CI	p value	Adjusted Coefficient	95% CI	p value
Age (years)	0.79	0.018 to 1.6	0.045	-0.28	-2.3 to 1.7	0.78
Sex (female)	3.1	-9.6 to 15.7	0.63	8.6	-10.5 to 27.7	0.36
Second eye	-10.8	-22.2 to 0.64	0.064	1.3	-16.5 to 19.1	0.88
Preoperative VAS score for anxiety	-0.55	-0.82 to -0.29	0.0001	-0.21	-0.55 to 0.13	0.21
Surgeon (Y.U.)	-0.43	-11.9 to 11.0	0.94	-0.11	-20.4 to 20.2	0.99

Abbreviations: CI, confidence interval; N₂O, nitrous oxide; VAS, visual analogue scale.

Discussion

In this study, we demonstrated that the application of low-concentration N₂O anesthesia significantly reduced patient anxiety and pain during cataract surgery. Moreover, N₂O anesthesia significantly, but not excessively, decreased intraoperative SBP and DBP in the enrolled patients. The change in the HR significantly decreased under N₂O anesthesia but did not result in bradycardia. These findings suggest that using low-concentration N₂O anesthesia in cataract surgery may help reduce intraoperative patient anxiety and pain, which may help stabilize intraoperative vital signs. Moreover, multivariate analyses demonstrated that changes in anxiety level in the N₂O group significantly correlated with patient age and preoperative VAS score for anxiety. This suggests that low-concentration N₂O anesthesia during cataract surgery could be more advantageous for young patients and patients with high preoperative anxiety.

Our results demonstrated that the intraoperative anxiety score was lower in the N₂O group (28.1±23.6) than in the Air group (35.3±30.8); however, it did not differ significantly ($p=0.24$). This could be attributed to the sample size.¹¹ Meanwhile, our study demonstrated that the change in the anxiety level decreased significantly ($p=0.002$) in the N₂O group (-15.6±22.9) compared with that in the Air group (1.2±20.6), which may suggest that low-concentration N₂O anesthesia is useful in reducing intraoperative anxiety.

In this study, we also investigated the patient characteristics affecting the change in anxiety level in the N₂O and Air groups. Table 2 shows that the change in the anxiety level in the N₂O group positively correlated with the patients' age (adjusted coefficient: 0.79, $p=0.045$) and negatively correlated with the preoperative VAS score for anxiety (adjusted coefficient: -0.55, $p=0.0001$). These results suggest that N₂O anesthesia is more effective in reducing intraoperative anxiety in young patients and patients with high preoperative anxiety.

The intraoperative pain score was significantly lower ($p=0.014$) in the N₂O group (12.4±14.9) than in the Air group (24.2±22.4). The analgesic effect of N₂O suggests that 30% N₂O is equivalent to 10–15 mg morphine.²⁴ Meanwhile, a previous study did not observe a significant reduction in intraoperative pain score.¹¹ This could be due to the duration of N₂O anesthesia; in fact, the operation time was longer in this study (approximately 8 min) than in the previous report (approximately 5 min).¹¹ Further studies with a large number of cases are warranted to elucidate the analgesic effect of low-concentration N₂O anesthesia in cataract surgery.

A previous study suggested that the level of patient-perceived anxiety and pain could differ between the first and second cataract eye surgery.²⁵ In addition, the outcome could also be affected by the fact that different surgeons performed the surgeries. Considering these, we analyzed the data using a linear mixed model for statistical comparisons, which was adjusted for the group (N₂O or Air), surgeon (H.S. or Y.U.), and first or second eye as fixed effects and patients as a random effect. The results demonstrated that anxiety levels were significantly reduced (adjusted coefficient: -16.4, 95% CI: -26.8– -6.0, $p=0.0025$) in the N₂O group as compared to the Air group. The intraoperative pain score was significantly lower (adjusted coefficient: -12.7, 95% CI: -21.1– -4.3, $p=0.0036$) in the N₂O group than that in the Air group. Thus, we believe that the results of our study are valid.

No significant adverse effects of low-concentration N₂O anesthesia were observed in this study. Vital signs, including BP, HR, and SpO₂, were stable in each group during cataract surgery, and no disorientation was noted on low-

concentration N₂O. Although further studies are warranted to elucidate the safety of N₂O anesthesia in ophthalmic surgery, our results suggest that N₂O anesthesia could be effective in other ophthalmic surgeries such as vitreous, glaucoma, and ptosis surgeries.¹⁰ These surgeries generally take longer and sometimes cause more patient anxiety and pain than cataract surgery. Meanwhile, N₂O has the potential to escape into the dead space and brings an increase in the intraocular gas bubble size, resulting in a subsequent rise in intraocular pressure.^{26–28} Although conscious sedation is generally safer than general sedation,²⁹ we should be aware of the possibility of expansion of the intraocular gas caused by N₂O, which may result in severe and permanent visual loss.

This study had several limitations. First, a sampling bias inherent to its retrospective nature and relatively small sample size cannot be excluded. Although using low-concentration N₂O anesthesia significantly reduced patient anxiety and pain during cataract surgery, additional studies with a larger number of patients are warranted to determine the efficacy of low-concentration N₂O anesthesia in cataract surgery. Second, this study was conducted at a single center. Although the use of low-concentration N₂O anesthesia significantly reduced patient anxiety, as reported by a previous study,¹¹ it may be necessary to confirm our findings at another medical center. Finally, although vital signs were stable under low-concentration N₂O anesthesia in cataract surgery,¹¹ prospective studies with a larger number of cases are warranted to evaluate the safety of N₂O.

Conclusion

Our results suggest that low-concentration N₂O anesthesia may reduce patient anxiety and pain, which may stabilize the vital signs during cataract surgery. Moreover, low-concentration N₂O anesthesia during cataract surgery could be particularly advantageous for young patients and patients with high levels of preoperative anxiety.

Abbreviations

BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, heart rate; MAC, minimum alveolar concentration; N₂O, nitrous oxide; SBP, systolic blood pressure; SpO₂, oxygen saturation; VAS, visual analogue scale.

Data Sharing Statement

The datasets used in this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Shinseikai Toyama Hospital, Toyama, Japan (reference number: 220125-2). Informed consent was obtained from all the patients involved in the study.

Acknowledgments

We want to thank Editage (www.editage.com) for English language editing.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Disclosure

The authors have no conflicts of interest to declare.

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