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The Effects Of Nitrous Oxide On Postoperative Pain, Nausea Vomiting and İntraoperative Haemodynamics in Robotic Gynecologic Surgery

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AUTHOR: Dr.Yonca Yanli March 2017

Mehtap Ozdemir[1], Nurten Bakan[1], Murat Haliloglu[2], Yonca Yanli[1*], Nevin, Kurt Celebi[3], Zeynel Abidin Erbesler[4], Tulin Yollu[5]

[1] Department of Anesthesiology and Reanimation, Umraniye Training and Research Hospital, İstanbul,Turkey

[2] Department of Anesthesiology and Reanimation, Marmara University Hospital, Istanbul,Turkey

[3] Department of Anesthesiology and Reanimation, Vize State Hospital, Kırklareli,Turkey

[4] Department of Anesthesiology and Reanimation, Ahi Evran University Hospital, Kırsehir,Turkey [5] Department of Anesthesiology

CORRESPONDENCE AUTHOR

Yonca Yanli
Ümraniye Eğitim ve Araştırma Hastanesi, Anesteziyoloji-Reanimasyon Kliniği, Elmalikent mah, Adem Yavuz Cad. No: 1, Ümraniye, Istanbul, Turkey
Email: **yoncayanli@yahoo.com**

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ABSTRACT

BACKGROUND

n recent years there has been an increase in gynaecological operations performed with robotic surgery. In these procedures, nitrous oxide(N_2O) or air are used together with inhalation anaesthestics. In this study we aimed to compare the effects of O_2/N_2O or O_2/Air on postoperative pain, nausea vomiting (PONV) and intraoperative thermodynamics in robotic surgery.

METHODS

Aged 28-71 years, classified ASA I-II, 58 patients were separated into 2 groups. Following induction, anaesthesia was maintained O_2/Air (Group A) or O_2/N_2O (Group N) with sevoflurane. Heart rate (HR), mean arterial pressure (MAP), Central Venous Pressure (CVP), end tidal carbon dioxide ($ETCO_2$), peripheral oxygen saturation (SpO_2), Aldrete recovery score (ARS), postoperative nausea and vomiting (PONV) and visual analog scale (VAS) were recorded during the operation and postoperative period.

RESULTS

The VAS values were higher in Group N at 5th min and higher in Group A at 150th min ($p<0.05$). In the intragroup analysis, VAS values were significantly lower at 120th, 150th, 180th min compared with 5th, 15th, 30th and 60th min in Group N ($p<0.05$). In Group A, the values at 15th, 30th min was significantly higher than 60th, 120th and 180th min ($p<0.05$). Intraoperative haemodynamic parameters (HR, MAP, CVP) were similar in two groups ($p>0.05$). Intragroup analysis of PONV values were significantly lower at 150th and 180th min compared with both 5th and 30th min in Group N and significantly higher at 5th min compared with 180th min in GroupA($p<0.05$).

CONCLUSION

With regard to acute postoperative analgesia we could not find any significant difference between N_2O and air. Further clinical studies are required to investigate this subject in respect of differences (at 5th min and at 150th min) in the VAS scores.

KEYWORDS

Robotic surgery, Nitrous oxit, General anesthesia, Visual analog scale, Postoperative nausea vomiting

Introduction

Robotic surgery is being used increasingly in gynaecological procedures. The advantages of this surgery are a small incision, 3-dimensional visualisation, minimal blood loss, low levels of postoperative pain and a short hospital stay [1,2]. However, there are conditions which can pose a risk in the application of anaesthesia such as cardiovascular (an increase in central venous pressure, pulmonary artery and pulmonary capillary pressury or severe bradycardia) and pulmonary (an increase in peak airway pressure, plateau pressure and decreased pulmonary compliance) changes created by the steep Trendelenburg position and pneumoperitoneum [3-5]. Also there are circumstances such as, hypothermia and venous gas embolism or subcutaneous emphysema [1,2].

For anaesthesia maintenance in robotic surgery, generally inhalation agents and short-term effect intravenous narcotic analgesics are preferred. Together with inhalation agents O_2/Air is often used and occasionally, O_2/N_2O [6,7]. Nitrous oxide (N_2O) has been used in anaesthesia practice for more than 150 years as anaesthetic and analgesic either alone or together with other anaesthetics. There have been experimental animal and clinical studies which have shown that the analgesic effects of N_2O continues in the postoperative period [8,9]. It has been stated in various studies that N_2O is related to postoperative nausea and vomiting. This has been reported to be related to the ease of penetration of closed areas (eg, intestine, middle ear) of N_2O, the activation of the medullary dopaminergic system and the increase in cerebrospinal opioid peptides [10].

In our knowledge, there are a few clinical studies and case reports about N_2O use and there is no literature comparing N_2O and Air in two different groups in robotic surgery. Moreover, the effects of N_2O has been studied usually on hemodynamics and respiratory parameters.

The primary aim of this study was to investigate whether there is a different effect between O_2/ Air or O_2/ N_2O combination together with sevofluran on postoperative acute pain. The secondary outcomes were the evaluation of the impact of these two combinations on intraoperative haemodynamics and postoperative nausea and vomiting (PONV) during postoperative 24 hour period on patients undergoing robotic gynaecological surgery.

Methods

Approval for the study was granted by the Local Ethics Committee (Ethics committee No: 45, XXXXXXXXXXXXXXX Hospital, XXXXXXX, Turkey, 3 March 2011) and informed consent was obtained from all the patients. The study comprised 58 female patients aged 28-71 years, of ASA I-II status, who were scheduled for robotic gynecological (hysterectomy, myomectomy, tubal reversal and endometriosis) surgery. Exclusion criteria included a history of neurological or psychiatric disease, allergy to propofol, hypersensitivity or intolerance to opioids or sevoflurane and severe pulmonary or cardiovascular system diseases.

Anesthesia monitors were placed prior to induction; an electrocardiographic monitor (ECG), non-invasive blood pressure cuff (NIBP), pulse oximetery (SpO_2). After induction with thiopental sodium 4-6 mg kg^{-1}, vecuronium 0.1 mg kg^{-1}, fentanyl 1 µg kg^{-1}, endotracheal intubation was performed. The patients were separated (using the sealed envelope random number method by the second anaesthetist) into 2 equal (n=29) groups. The first group (Group N) was given O_2 / N_2O (50/50%) and the second group (Group A) O_2/ Air (50/50%). During the maintenance of anesthesia, 1 MAC Et sevoflurane was kept throughout surgery and remifentanil was started initially 0.1 µg kg^{-1} min^{-1} to sustain appropriate heart rate, blood pressure and other clinical signs. Intermittan boluses of vecuronium was given during the operation. When the values of MAP or heart rate increased 20% from baseline; remifentanil infusion was enhanced to 0.2 µg kg^{-1} min^{-1} by titration. Conversly, the values of MAP or heart rate decreased 20% from baseline, ephedrine hydrochloride 10 mg or atropine sulfat 0,5 mg were given respectively. The infusions of remifentanil (Ultiva ^{TM} inj 1 mg vial, GlaxoSmithKline, Belgium) were made with 50 ml injector pump (B.Braun Perfusor Space Syringe Pump, Germany). Pressure Control Ventilation (PCV) was used and respiratory rate and peak inspiratory pressure were adjusted to maintain $ETCO_2$ of 35-40 mmHg. The patients were given Positive End Expirium Pressure (PEEP) +5cmH_2O.

After induction, a radial artery catheter (20G arterial catheter –Bio-flon, Hayrana, India) and a basilic vein catheter (Cavafix Certo 375 B.Braun ,Melsungen, Germany) were placed and both pressure transducers were connected to a monitor (Drager, Infinity Kappa, Telford, PA, USA). Throughout the operation invasive MAP, HR, CVP (Central venous pressure), SpO_2, $ETCO_2$ and airway pressure were measured using a monitor. Blood gases were also analysed during the operation. Urinary catheter was placed and urine output was measured.

Compression stockings were placed on the legs of the patient and position pads were placed on the compression area and the thighs were abducted sufficently to accomodate the robotic system. A warm blanket was placed under the patient during the operation to keep the patients' skin temperature between 34-36 ºC.

The abdominal cavity was insufflated with CO_2 to a pressure of 12 mmHg and the patient was placed in the mild Trendelenburg position then the trocar cannulae were put into place. The patient was then moved slowly into the 45° Trendelenburg position. The surgeon performed the procedure with the da Vinci Robot Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). Intravenous fluids were given to the patients were restricted and intraoperative maintenance fluids were administered at a rate of 3 ml kg^{-1} h^{-1}. Paracetamol 12 mg kg^{-1} and tenocsicam 20 mg flacon IV were given as an analgesic and ondansetron 4 mg IV as an antiemetic after recovering trendelenburg position. At the end of the operation reversal of muscle relaxation was achieved with neostigmine and atropine sulfate.

The anesthesia recovery profile was evaluated with the Aldrete Recovery Score [11] at 5, 15, 30, 60, 120, 150, 180th minutes postoperatively. VAS (Visual Analog Score) was used for pain assesment in the recovery room at the same time with the Aldrete Recovery Score and in the ward until 24th hour. Tramadol 1mg kg^{-1} was performed when VAS ≥ 4 in recovery room or in the ward (besides routine analgesic treatment) . The severity of postoperative nausea was rated by the patient on a verbal rating scale (0=none, 1= little, 2=mild, 3=bad, 4= worse, frequent vomiting) and recorded as a patient number. Ondansetron 4 mg IV as a rescue antiemetic was administered when vomiting occured or if requested by the patient. A record was made of the total number of patients who were administered antiemetics and analgesics in recovery room and ward.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007&PASS (Power analysis and sample size) 2008 Statistical Software (Kaysville, Utah, USA) were used for the statistical analysis. As a result of power analysis applied, for delta 1,7 and standart deviation 2, assuming an α level of 0.05 and power of 0.80, a minimum of 22 patients in each group were required to detect a mean difference in VAS between the two groups. Besides the descriptive statistical methods (mean, standard deviation) in the evaluation of study data repeated measures ANOVA was used for review of the observed changes in quantitative data depend on time. Student's t-test was used in the comparison between the groups of parameters showing normal distribution and the Mann-Whitney u test was used for parameters not showing normal distribution. Friedman test was used to examine the time dependent changes observed in nonparametric quantitative data in groups and Wilcoxon Signed Rank test with Bonferroni correction was used as a post hoc tests. For comparison of categorical variables Chi–Square test was used (where available Fisher Exact test). A value of $p<0.05$ was accepted as statistically significant.

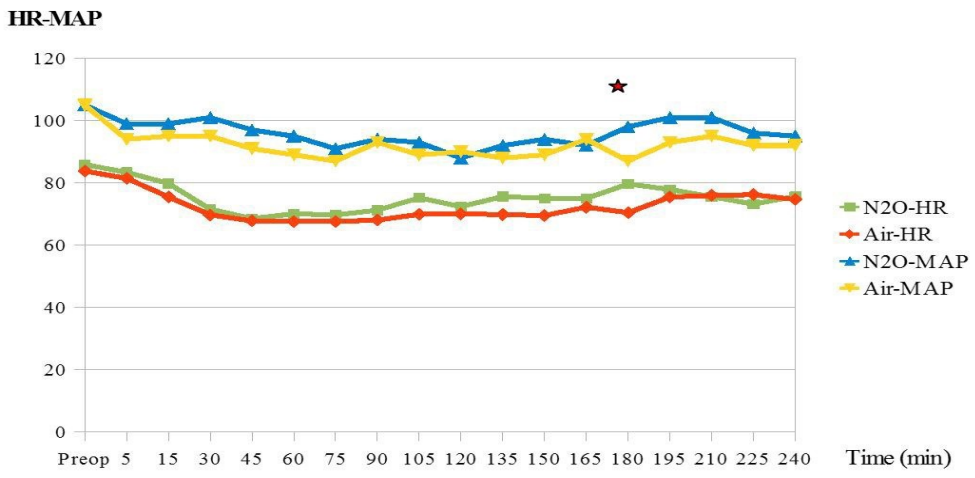

Figure1: Heart Rate and Mean Arterial Pressure Values between the groups (* p<0.05)

Results:

No difference was determined between the two groups in respect of the patient age, BMI, anaesthesia and insufflation time ($p>0.05$) (Table 1). Number of types of surgery was listed in table 2.

Table 1: Demographic values, anaesthesia and insufflation times between the groups

	Group N (n=29)	Group A (n=29)	*p*
Age (year)	46.62±9.57	46.79±12.66	*0.954**
BMI	27.43±4.15	27.40±4.00	*0.975**
Anesthesia time (min)	183,79±56,69	191,38±41,40	*0,889***
Insufflation time (min)	160±52,21	161,38±41,53	*0,777***

**Student t test, ** Mann Whitney u test,*

Table 2: Numbers of types of surgery according to groups.

	Group N	%	Group A	%
Hysterectomy	10	34,5	11	37,9
Myomectomy	9	31,0	9	31,0
Endomeriozis	4	13,8	4	13,8
Tubal reversal	6	20,7	5	17,3
Total	29	100	29	100

HR values were similar in both groups at all measured times (p>0.05) (Figure 1). In the post-hoc analysis; HR values were significantly lower at 60th min and 120th min compared with 1st min and at 60th min compared with 5th min in Group N (p<0.05). In Group A, the decrease of HR values was significant at all times compared with 1st min and 5th min (p<0.05).

MAP (high in Group N at 180 mins only) were similar in both groups at all measured times (p>0.05)(Figure 1). In the post-hoc analysis; MAP values were significantly lower at 60th min and 120th min compared with 1st min in Group N and at 30th min and 60th min compared with 1st min in Group A (p<0.05).

No difference was determined between the two groups in respect of CVP values, before and after insufflation and at the trendelenburg positions. In the post-hoc analysis CVP values were significantly higher after insufflation and at all trendelenburg positions compared with before insufflation in both two groups (p<0.01).

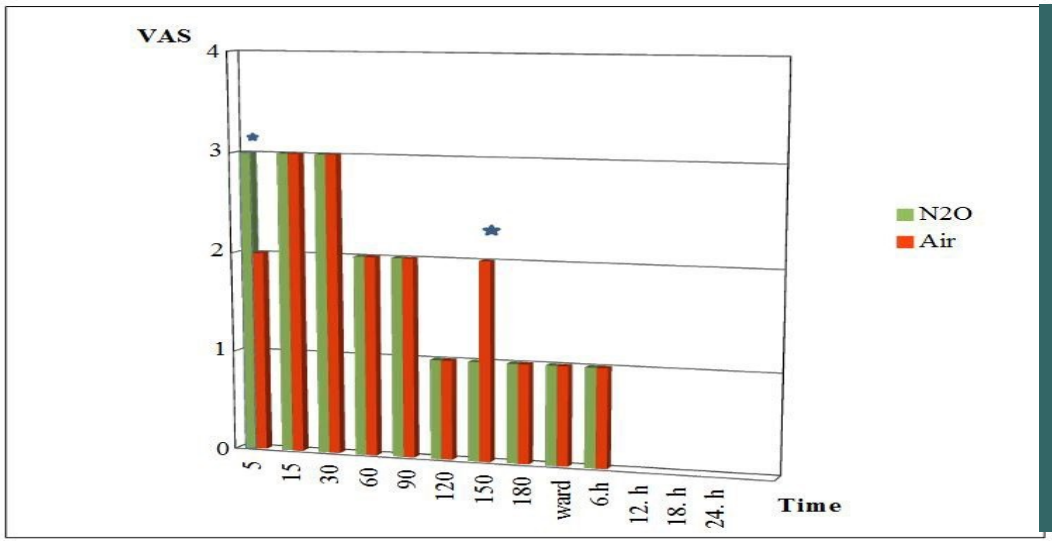

Figure 2: Visual Analog Scale Values (The time was recorded as a minute after extubation until 180th minute and as an hour after the patients were sent to the ward) (h:hour) (* p<0.05)

SpO_2, $ETCO_2$ values and airway pressures were not different in both groups at all measured times (p>0.05). Total urine amounts were similar in Group N and Group A (p<0.05).

There was no difference about the remifentanil usage between Group N (1557,41±486,05) and Group A (1729,7241±494,83) intraoperatively ($p>0.05$). VAS scores were higher in Group N at 5th min and in Group A at 150th min ($p<0.05$), but were similar at all other times in the recovery room ($p>0.05$) (Figure 2). In the ward, there was no difference between the groups ($p>0.05$). In the intragroup analysis, VAS values were significantly lower at 120th, 150th, 180th min compared with 5th, 15th, 30th and 60th min in Group N, in the recovery room ($p<0.05$). In Group A, the values at 15th,30th min was significantly higher compared with 60th, 120th and 180th min ($p<0.05$). In the ward, there was significant decrease at all measured times in both Group N and Group A ($p<0.05$). Tramadolar consumption (mg) was similar between the two groups in recovery room (69±66 for Group N, 65,5±67 for Group A) and in ward (48,3±68,8 for Group N, 55,2±68,6 for Group A) ($p>0.05$). Analgesics was administered to 17 patients in the recovery room and to 11 patients in the ward in Group N, and to 16 patients in the recovery room and 13 patients in the ward in Group A. The total number of analgesics were given to the patients were not different between two groups ($p>0.05$) (Table 3). Other than this all measured VAS values were < 3 in two groups.

Table 3: Analgesic uses in recovery room. Patient number (%)

	Recovery Room		Ward		Total
Group	N_2O	Air	N_2O	Air	
Analgesic (-)	12 (41,4)	13 (44,8)	18 (62,1)	16 (55,2)	59 (50,9)
Analgesic (+)	17 (58,6)	16 (55,2)	11 (37,9)	13 (44,8)	57 (49,1)
*P	*0,908*		*0,524*		

**Ki-Kare test*

The postoperative nausea and vomiting (PONV) scores were similar in both groups either in recovery room or in the ward ($p>0.05$). In post-hoc analysis; The PONV values were significantly lower at 150th and 180th min compared with 5th, 15th, and 30th min in Group N ($p<0.05$). The values at 5th and 15th significantly higher compared with 180th min in Group A ($p<0.05$). In the ward, there was no difference for the PONV scores between two groups ($p>0.05$). There was no significant difference between the groups in the number of patients who required antiemetic (8 patients in the recovery room, 7 patients in the ward in Group N, 13 patients in the recovery room, 8 patients in the ward in Group A) ($p>0.05$)(Table 4). 2 patients in Group N and 3 patients in Group A had vomiting in the recovery room ($p>0.05$). None of the patients had vomiting in the ward.

Table4: Antiemetic uses in recovery room.Patient number (%)

	Recovery Room		Ward		Total
Group	N2O	Air	N2O	Air	
Antiemetic (-)	21 (72,4)	16 (55,2)	22 (75,9)	21 (72,4)	80 (69,6)
Antiemetic (+)	8 (27,6)	13 (44,8)	7 (24,1)	8 (27,6)	35 (30,4)
*P	***0,145***		***0,708***		

**Ki-Kare test*

There was no difference in the Aldrete Recovery Scores at the all measured times ($p>0.05$).

Discussion:

In the present study, the difference related to VAS scores between the groups were significant only at 5th min and 150th min. Hemodynamic changes were similar in either N_2O or Air groups in robotic surgery. PONV was found to be similar both of N_2O and Air groups along with 24 hours.

Robotic surgery is often applied in gynaecological procedures and it has been reported to make a positive contribution to results [2]. General anaesthesia is often preferred in cases of robotic surgery. Together with inhalation agents, O_2/Air or O_2/N_2O are used. N_2O causes relatively potent analgesic/antinociceptive effects and weak anesthetic/hypnotic effects in humans. The addition of N_2O to general anesthesia, reduces the requirement of other analgesic and anesthetic agents [12].

Postoperative pain is known to be a factor which reduces patient comfort and delays healing. While nitrous oxide is often used for pain relief in normal vaginal delivery and dental procedures, during surgery it is combined with anaesthetic agents. It has been reported in experimental animal studies that the supraspinal opioid receptors are activated through the corticotropine releasing factor of N_2O [13]. Thus, an interaction occurs between N_2O and exogenous opioids. In rats anaesthetised with isoflurane, N_2O has been shown to decrease the MAC-sparing effect of morphine [14]. In another rat study, the NMDA receptor antagonist activity shown by N_2O was seen to prevent hyperalgesia induced by opioids [8]. Therefore in a clinical study by Echeverria et al, they were shown that intraoperative 70% N_2O administration significantly reduced postoperative opioid induced hyperalgesia in patients after septorhinoplasty operation [15]. A subgroup follow-up analysis of Enigma trial showed that intraoperative nitrous oxide administration was associated with a reduced risk of chronic postsurgical pain [16]. Also the preventive analgesic effect of N_2O has been suggested by a previous Enigma trial subgroup analysis after major surgery [9]. In another study postoperative VAS scores were found to be similar in patient groups using and not using N_2O in outpatient gynaecology surgical procedures [17]. In the current study, the effects of N_2O were evaluated on postoperative pain in patients undergoing gynaecological robotic surgery with a minimal incision. In the first 24 hours postoperatively, the VAS values in the N_2O group were higher at 5^{th} minute and the median value was 5. In the Air group, at 150^{th} minute the VAS values were higher than N_2O group but the median value was 2. At all other measured times the VAS values of the two groups were similar. That the postoperative pain level was higher in the N_2O group immediately after surgery was thought to be due to high abdominal pressure associated with that type of surgery having been further increased after the distribution of N_2O into closed areas. The higher VAS values at 15^{th}, 30^{th} min in both two groups were thought to be the result of diminishing effect of anesthesia and the patient's feeling of pain in the awakening period. Also a similar number of patients in both groups required additional analgesia.

It has been said that the tendency of N_2O to stimulate the sympathetic nerve system may cause the cardiovascular effects [10]. In previous studies, it has been reported that N_2O has shown effects on cardiovascular contractility such as minimal increase, decrease or no change [18-20]. In the study of Henry et al [21], the cardiovascular effect of 20%, 40%, 60% concentrations of N_2O were investigated in both spontaneously hypertensive rat and normotensive Wister-Kyoto counterpart. The decreases in systolic blood pressure and heart rate were found greater with increasing concentration of N_2O. In literature one clinical report has stated that the use of a high concentration (60%) of N_2O at the beginning caused cardiovascular stimulation was reduced with gas inhalation which continued for a long time [18]. In a study by Turan et al [22], while intraoperative MAP and HR values were found to be similar in patients on whom N_2O was used and not used, a difference was seen in the Enigma study [23]. However, the percentages of N_2O used in the two studies were different, with approximately 70% in the Enigma study and 55% in the Turan et al study. In the current study, the haemodynamic data (MAP, HR and CVP) of the patients who were administered 50% N_2O together with O_2 were within normal limits and similar to the data of the group where N_2O was not used. This result was seen to be consistent with other studies showing that haemodynamic stability (normal range MAP and HR) had been achieved with the use of N_2O at a concentration below 60%. The progressive time dependent decreases in MAP and HR values were considered the result of prolonged anesthesia in both two groups. The values of CVP increased after insufflation and trendelenburg position in both two groups as expected in robotic surgery. These values were returned normal ranges after recovering trendelenburg position at the end of surgery. For the reasons described above, we thought that the use of N_2O did not create additional haemodynamic changes in robotic surgery.

Postoperative nausea and vomiting is an important complication of anaesthesia with incidence ranging from 10% to 79% [24]. In literature, it has been defined by patients as an undesired and frustrating postoperative complication [25]. In addition to studies showing that N_2O increases postoperative nausea and vomiting [26-28], there are also studies showing that it has no effect [17,29,30].The effective prophylaxis and treatment would be diminish the risk of PONV [31]. Furthermore another meta-analysis show that the influence of N_2O on PONV, with its relative risk approximately 1.4, is relatively low [32]. Also, Apfel et al [33], pointed out the main cause of early (0-2 h) PONV is the use of volatile anesthetics rather than N_2O.

In the current study, postoperative nausea and vomiting was found to be similar in two groups, along with 24 hours. The reduction of postoperative nausea and vomiting from 150^{th}-180^{th} min in both two groups was thought to be the the result of diminishing effect of volatile anesthetics rather than N_2O, as mentioned previous study [33].

Therefore, in line with previous studies [17,30] it can be considered that N_2O does not increase postoperative nausea and vomiting.

Several studies suggest that, EEG-derived monitoring index values respond paradoxically to N_2O application. These values indicate arousal rather than increased depth of anesthesia after N_2O application. Therefore EEG-derived monitoring index values responding to N_2O, associated with either underestimation or overestimation of anesthesia depth [34]. To avoid this evaluation complexity we did not use EEG-derived monitoring index. In our study, we controlled anaesthesia depth by haemodynamic monitorization.

The missing part of our study is the lack of neuromuscular monitoring. Owing to the patient's whole body is covered with sterile drapes and the robot's large mass is positioned on the patient, the neuromuscular monitoring could not be possible.

Conclusion:

In this study, N_2O was applied in operations using robotic surgery features. There was no significant difference between N_2O and air concerning acute postoperative analgesia. No complications were encountered due to the use of N_2O, either in intraoperative haemodynamic status or in respect of postoperative nausea and vomiting. There is a need for further clinical prospective studies to ascertain whether or not there is any significant difference in acute postoperative pain scores of the patients administered with N_2O or air.

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Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of XXXXXXXX Training And Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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