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Effect of Sevoflurane-Nitrous Oxide Induction on the Incidence of Rocuronium Injection Pain in Adults

ORIGINAL INVESTIGATION

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ABSTRACT

Objective: This randomized, prospective study was designed to investigate the effect of sevoflurane–nitrous oxide application on the incidence of the hand/arm withdrawal movement caused by rocuronium injection.

Materials and Methods: There were 90 individuals undergoing elective surgery included in the study. After preoxygenation, Group T was given intravenous (i.v.) 5 mg/kg thiopental, Group S was given 7% sevoflurane and 40%/60% air/O2, and Group N was given 7% sevoflurane and 40%/60% N2O/O2 for induction. After the eyelash reflex was lost, 0.6 mg/kg rocuronium was applied intravenously over 5 seconds, and then 2 ml saline was administered. Patients' response to rocuronium injection was graded by using a 4-point scale (0–3). Hemodynamic data were recorded.

Results: After the rocuronium injection, the mean arterial pressure (MAP) and heart rate (HR) values were different between the groups ($p<0.05$). The incidence of withdrawal movements associated with the injection of rocuronium was observed to be 96.7% in Group T (29/30), 73.3% in Group S (22/30), and 13.3% in Group N (4/30). There were significant differences between the groups ($p<0.05$). There were differences between Group T and Group S in terms of MAP and 4-point scale, and between Group N and Group S in terms of MAP, HR, and 4-point scale ($p<0.05$).

Conclusions: Adding nitrous oxide to sevoflurane induction in adults reduces the incidence of withdrawal movements associated with rocuronium injection compared to thiopental induction.

Keywords: Nitrous oxide, pain, rocuronium, sevoflurane

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INTRODUCTION

Rocuronium is a non-depolarizing neuromuscular agent with steroid structure, rapid onset of effect, and moderate effective duration (1). The major disadvantage of intravenous (i.v.) rocuronium injection is severe burning pain in the hand/arm as loss of consciousness occurs, or even after it takes place, causing a withdrawal movement (2). After the rocuronium injection, a withdrawal movement is identified in 50%–80% of adult patients and in 83%–94% of pediatric patients (2-5).

A variety of techniques have been recommended to reduce or prevent rocuronium injection pain. The most popular methods are generally related to various medications; however, there is no method that could fully prevent this pain (2-6). It is stated that rocuronium injection pain may be lessened by applying the inhalation agents immediately after the i.v. induction, or ensuring sufficient depth of anesthesia with inhalation induction (3, 6).

Sevoflurane ensures a rapid anesthesia induction and revival due to a low blood-gas partition coefficient and few negative effects on the cardiovascular system. It does not irritate the airways and is thus frequently chosen for pediatric anesthesia induction (7). Especially in children with the fear of needles and difficulty finding a venous route, sevoflurane induction is commonly used (8, 9). In children, sevoflurane induction is reported to reduce the incidence of withdrawal movements caused by rocuronium 50%–95% (9). Generally, in adults, anesthesia is rapidly and reliably performed with i.v. agents. However, to avoid the effects of i.v. induction such as hypotension, anaphylaxis, apnea and to ensure comfortable induction in patients with the fear of needles and prevent the effect on hemodynamic response in hemodynamically unstable patients, induction with a mask may be chosen (10, 11).

In our study, we researched the effect of sevoflurane–nitrous oxide induction on the incidence of rocuronium injection pain and withdrawal movement in adults.

MATERIALS and METHODS

The study was conducted after receiving permission from our university clinical research ethics committee and informed patient consent. It was a randomized, prospective study that included 90 cases that were, according the American Society of Anesthesiologists (ASA), classified as the I–II risk group, with elective interventions planned under general anesthesia. Exclusion criteria were the following: expected difficult intubation; pregnancy; morbid obesity; known allergic reaction to the study medications; history of neuropsychiatric disease; severe asthma; chronic obstructive pulmonary disease; cardiovascular, hepatic, and renal system diseases; individuals who did not want to cooperate; and individuals reporting problems with the hand/arm. Demographic data were recorded.

All subjects were given 0.07 mg/kg midazolam intramuscularly as premedication 45 minutes before the surgery. In the operating room, the subjects were monitored for electrocardiogram (ECG), non-invasive blood pressure, heart rate (HR), peripheral oxygen saturation, end-tidal carbon dioxide ($EtCO_2$), and inspired and expired sevoflurane concentration (FIsev and ETsev, respectively) (Drager Medical Systems inc. Fabius® GS Premium USA). The subjects had a 20-gauge cannula inserted into the largest vein on the back of the non-dominant hand and had 0.9% saline infusion started at 5 mg/kg/hr. One person on the study team was assigned to the anesthesia management, while a person without information about the research was assigned to evaluate the rocuronium pain and withdrawal movement. After the subjects were informed about the study, they were randomly divided into three groups via the closed-envelope method. Patients were then fitted for mask size. A good fit was defined as no air leak around an occluded mask on maximal forced expiration. All subjects were instructed on the performance of a vital capacity breath. The subjects were given 6 L/min O_2 through a face mask, and preoxygenation begun. For anesthesia induction, the thiopental group (Group T, n=30) was administered 2.5% concentration i.v. 5 mg/kg dose. The other two groups were administered inhalation induction. In the sevoflurane group (Group S, n=30), the vaporizer was opened at 7% concentration with the carrier gas air/O_2=40%/60%, while in the sevoflurane–nitrous oxide group (Group N, n=30), the vaporizer was set at 7%, and N_2O/O_2=40%/60% was administered for anesthesia induction via the tidal respiration technique. In the three groups after the anesthesia induction begun, the eyelash reflex was assessed every 5 seconds. After the eyelash reflex was lost, the serum set was clamped, and 0.6 mg/kg rocuronium was administered intravenously over 5 seconds, and then 2 ml saline was applied. At the moment the eyelash reflex was lost, and after rocuronium injections, FIsev and ETsev values were recorded. The 4-point scale after the rocuronium injection (score 0=no motion; 1=wrist movement; 2=movement in one arm [elbow or shoulder]; 3=widespread movement in one or more extremities) was used to evaluate the physical response of subjects by an individual with no information about the research, and this value was recorded. Respiration frequency was set to ensure $EtCO_2$:35–45 mmHg. The study ended after evaluation of the hand/arm pain and the withdrawal movement caused by rocuronium injection.

The hemodynamic data in all groups before induction (T_1), after the eyelash reflex loss (T_2), and after the rocuronium injection (T_3) and $EtCO_2$ values, FIsev–ETsev concentrations, and findings due to inhalation induction such as cough, breath holding, excitator motion, laryngospasm, and desaturation were recorded.

Power analysis: Previous studies determined that there was no motion response after rocuronium injection in only 18% of adults (12). For 80% power and 0.05 alpha error, to determine a 30% reduction in motion response linked to rocuronium injection, we determined that one group should include at least 29 cases. Considering possible data loss, we planned that each group include 30 cases.

Statistical analysis

The statistical packet program 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Results are given as mean±standard deviation (mean±SD) for continuous values, and frequency (n) and percentage (%) for frequency data. For continuous variables such as age, height, weight, and hemodynamic data, the analysis of normality used the Kolmogorov-Smirnov test. Analysis of continuous variables such as age, height, weight, and hemodynamic data was completed with the one-way analysis of variance (ANOVA) test and post-hoc Tukey analysis. An analysis of data determining frequency used the chi-square test. Statistically significant difference was accepted with $p<0.05$ value.

RESULTS

There was no difference between the groups in terms of demographic characteristics and ASA scores ($p>0.05$) (Table 1). Comparison of MAP in the groups at control and after the eyelash reflex loss found no statistically significant difference ($p>0.05$). After the rocuronium injection, there was a statistical difference in MAP values between the groups ($p<0.05$) (Table 2). Comparison of the groups found a statistically significant difference in HR values measured after the rocuronium injection ($p<0.05$) (Table 3). The incidence of withdrawal movement caused by rocuronium was 96.7% in Group T (29/30), 73.3% in Group S (22/30), and 13.3% in Group N (4/30). The incidence of widespread motion in one extremity (Score 3) was 43.3% (13/30), 10% (3/30), and 0% (0/30), respectively. There were significant differences between the groups ($p<0.05$) (Table 4). There was no difference between the inhalation induction groups in terms of $EtCO_2$ values and FIsev–ETsev con-

Table 1. Demographic characteristics and ASA scores in the groups

	Group T (n=30)	Group S (n=30)	Group N (n=30)	p
Sex (F/M)	19/11	16/14	16/14	0.665
Age (years)	39.4±14.2	36.7±13	44.7±10	0.065
Height (cm)	165.4±8.3	167.07±6.9	166.9±8.2	0.679
Body weight (kg)	77.0±14	69.2±14	74.2±13.7	0.072
ASA (I/II)	16/14	11/19	11/19	0.365

Group T: thiopental group; Group S: sevoflurane group; Group N: sevoflurane–nitrous oxide group; F: female; M: male; ASA: American Society of Anesthesiologists
Values are mean±SD or number of patients.

Table 2. Comparison of MAP between groups

	Group T (n=30)	Group S (n=30)	Group N (n=30)	p
T_1 MAP	100.5±11.9	96.1±13.1	103.2±14.8	0.123
T_2 MAP	87.5±10.7	83.03±11	85.9±13.3	0.317
T_3 MAP	113.7±22.9	85.6±17*	87.7±18.7*	<0.001

Group T: thiopental group; Group S: sevoflurane group; group N: sevoflurane–nitrous oxide group; T_1 MAP: mean arterial pressure before induction; T_2 MAP: mean arterial pressure after loss of eyelash reflex; T_3 MAP: mean arterial pressure after rocuronium injection
*=compared with group T

Table 3. Comparison of HR between groups

	Group T (n=30)	Group S (n=30)	Group N (n=30)	p
T_1 HR	81.7±14.0	79.9±15.2	84.1±20.0	0.600
T_2 HR	86.1±10.7	81.6±15.7	85.2±20.9	0.511
T_3 HR	92.2±13.5	86.3±12.2	83.2±14.4*	0.035

Group T: thiopental group; Group S: sevoflurane group; Group N: sevoflurane–nitrous oxide group;T_1 HR: heart rate before induction; T_2 HR: heart rate after loss of eyelash reflex; T_3 HR: heart rate after rocuronium injection
*=compared with group T

Table 4. Incidence of withdrawal movement associated with rocuronium (%)

	Group T (n=30)&#	Group S (n=30)&*	Group N (n=30)*#
0 (No movement)	1 (3.3%)	8 (26.7%)	26 (86.7%)
1 (Only wrist movement)	4 (13.3%)	5 (16.6%)	0 (0%)
2 (Only arm (elbow or shoulder) movement)	12 (40%)	14 (46.7%)	4 (13.3%)
3 (Widespread movement in single extremity)	13 (43.3%)	3 (10%)	0 (0%)

Group T: thiopental group; Group S: sevoflurane group; Group N: sevoflurane–nitrous oxide group; *=p<0.05, compared with Group T; #=p<0.05, compared with group S; &=p<0.05, compared with group N, chi square test

centrations after the eyelash reflex loss and rocuronium injection (p>0.05). After anesthesia induction, complications such as desaturation, laryngospasm, increased secretions, cough, and breath holding were not observed in any case.

DISCUSSION

In our study, sevoflurane induction reduced withdrawal movements caused by rocuronium injection in adults, and we concluded that adding nitrous oxide to sevoflurane induction increased analgesia and that it may reduce withdrawal movements.

Pain and emotional stress during anesthesia induction may cause dangerous situations such as myocardial ischemia, asthma, bronchospasm, pulmonary aspiration due to gastric regurgitation, and pulling of the i.v. catheter out of place (13, 14).

Many medications used in anesthetic practice such as propofol, thiopental, and rocuronium are known to cause i.v. injection pain. The primary mechanism responsible for this pain is not fully known, but it is thought to be due to activation of chemonociceptors in the peripheral vein walls (15, 16). Klement et al. (17) showed that medications with non-physiological osmolality or pH values have more incidence of pain with greater severity (>1 osmol/kg, pH<4 and pH>11). Pain starts immediately after the injection, and as it is limited to the injection arm, it is thought that the pain is caused by direct irritation of the venous wall. Blunk et al. (16) concluded that medications with low pH did not play a role in pain, but that pain was caused by direct activation of cutaneous C nociceptors by aminosteroid structure muscle relaxants. Borgeat et al. (18) determined that locally released mediators may play a role in the pain mechanism as the pain lasts a short time and severity reduces or disappears with repeated injections. As there is no erythema in the tissue surrounding the injection site, the histamine release does not play a role in this reaction; however, they reported that other mediators such as kininogen may be responsible.

To reduce the pain and withdrawal movement related to rocuronium injection, many medications and methods have been attempted, and a variety of conclusions have been reached. Some of these include ondansetron, lidocaine, tramadol, opioids, esmolol, thiopental, magnesium sulfate, sodium bicarbonate, diphenhydramine, and dexmedetomidine administration (6, 19).

Park et al. (20) used a venous occlusion technique with tourniquet, and patients in the thiopental group were induced with 2 ml (50 mg) thiopental, whereas the control group was induced with 2 ml saline and i.v. 5 mg/kg thiopental and found that the arm pull incidence was low in the thiopental group and that a low dose (50 mg) of thiopental was more effective to reduce rocuronium injection pain. Although there is no clear information on how thiopental administration reduces rocuronium injection pain, they determined that the alkaline thiopental solution remaining in the vein may neutralize rocuronium, that subanesthetic doses of thiopental may inhibit perception of pain or thiopental causes an increase in venous dilatation and permeability preventing release of bradykinin, thus reducing pain. Shevchenko et al. (3) used a manual occlusion technique and stated that the redistribution of thiopental in the time between the i.v. thiopental induction and rocuronium injection may reduce the hypnotic effect and cause rocuronium injection pain, that anesthetic depth should be ensured before the rocuronium injection, and that using inhalation anesthesia immediately after the i.v. induction or inhalation induction with sufficient anesthetic depth may reduce the injection pain.

Na et al. (21) compared the efficacy of sevoflurane, remifentanil and sevoflurane - remifentanil combination to prevent withdrawal movements due to rocuronium and found no significant difference; however, they observed that the combined use had a lower incidence of withdrawal movement. They determined that the administration of remifentanil as premedication ensured a better

hemodynamic stability and, at the same time, increased the pain threshold and anesthesia depth, reducing the incidence of withdrawal movement.

Nitrous oxide (N_2O) is widely used in anesthetic practice for analgesia as it is cheap, easy to use, and has relatively few side effects. A variety of studies have determined that N_2O, a centrally effective sedative and analgesic agent, reduced severity and incidence of propofol and rocuronium injection pain (6, 22-24).

Sharma et al. (24) in random patients given 100% O_2 and 50% N_2O/O_2 for 3 min before induction observed that after the anesthesia induction, 30 patients (90%) in the N_2O/O_2 group and 15 patients (37.5%) in the O_2 group had a pain score of zero and the withdrawal movement was observed in 6 (15%) and 18 (45%) patients, respectively. They determined that N_2O/O_2 inhalation was a simple and effective method to reduce the severity and incidence of rocuronium injection pain.

In our study, the incidence of withdrawal movement associated with rocuronium was 96.7% in Group T, 73.3% in Group S, and 13.3% in Group N, with the incidence of widespread motion in a single extremity (Score 3) 43.3%, (13/30), 10% (3/30), and 0% (0/30), respectively. There were differences between the groups. The low pain incidence and pain score values in the inhalation induction groups support previous studies on this topic. In the thiopental group, we consider the high incidence of withdrawal movements (4-point scale) may be linked to the hyperalgesic effect of thiopental. The incidence in the thiopental group is higher than in other studies with rocuronium, supporting a response to hyperalgesia.

Mask induction provides advantages for patients with apnea, anaphylaxis, hypotension, and the fear of needles. Sevoflurane has minimal cardiac effect, rapid onset of effect and tolerable smell, making it an agent of choice for inhalation induction (7). Different from other inhalation agents, as N_2O stimulates the sympathetic nervous system, there is a slight increase in myocardial depression and MAP instead of a decrease (25). The use of sevoflurane and N_2O for anesthesia induction is common. Some studies have stated that different concentrations (4%, 6%, and 8%) of sevoflurane induction are well tolerated by patients, it is practical and reliable, ensures hemodynamic stability, and is an alternative induction method to i.v. induction, especially for the patient group with unstable hemodynamics (11, 26, 27).

In our study, we used 7% sevoflurane with tidal respiration technique, and we did not encounter any problems in terms of patient compliance, complications, and hemodynamics.

Muscle relaxants that affect muscarinic and nicotinic receptors outside the neuromuscular junction may cause hemodynamic changes like hypertension and tachycardia, and additionally vasodilatation, hypotension, and compensatory tachycardia may occur as a result of histamine release caused by these agents (28). In studies, it was stated that an increase in HR and blood pressure after the rocuronium injection may be explained by vagolytic or sympathomimetic effects, and that these reactions may cause injection pain (2, 29).

In our study, in the thiopental group after the rocuronium injection, there was a significant increase observed in the MAP and HR values compared to the inhalation induction groups. Especially for patients who do not have stable hemodynamics, we believe induction with the sevoflurane–nitrous oxide combination may suppress increases in the HR and blood pressure that may develop due to the rocuronium injection pain.

CONCLUSION

Adding nitrous oxide to sevoflurane induction in adults will reduce the incidence of withdrawal movements associated with the rocuronium injection compared to the thiopental induction, and we believe it ensures a better hemodynamic stability in the early period after induction.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Bülent Ecevit University Faculty of Medicine.

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

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: GK., VH., IÖT. Performed the experiments or case: GK., AÇ., ÖP., DO. Analyzed the data: VH., HA. Wrote the paper: GK., VH., HA., IÖT. All authors have read and approved the final manuscript

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