J Anesth (2013) 27:868–873
DOI 10.1007/s00540-013-1655-z

ORIGINAL ARTICLE

Effect of nitrous oxide inhalation on pain after propofol and rocuronium injection

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Received: 25 November 2012 / Accepted: 5 June 2013 / Published online: 28 August 2013

Abstract
Purpose This prospective, double-blind, placebo-controlled study was designed to determine the efficacy of nitrous oxide (N_2O) in alleviating the pain that followed sequential injection of propofol and rocuronium.
Methods A total of 205 adult patients (age, 18–68 years) received one of the following combinations: NaCl and 100 % O_2 (group C); 0.5 mg/kg lidocaine and 100 % O_2 (group L); NaCl and a mixture of 67 % N_2O/O_2 (group N); or 0.5 mg/kg lidocaine and a mixture of 67 % N_2O/O_2 (group LN). Vein occlusion was released after 1 min, and 5 ml propofol was injected over 10 s. Pain was evaluated on a visually enlarged, laminated, numeric rating (0–10) scale. The remainder of the induction dose of propofol (with a 3-ml bolus of normal saline and 0.6 mg/kg rocuronium) was then injected. The response to the rocuronium injection was assessed with a four-point scale (0–3).
Results The incidence and severity of pain from the propofol injection in groups L, N, and LN were significantly lower than those in group C ($P < 0.001$). Frequency and intensity of the withdrawal response were significantly less in groups N and LN than in groups C and L (no response, $P < 0.001$; severe response, $P < 0.001$).
Conclusions Pretreatment with inhaled N_2O can reduce the pain associated with propofol and rocuronium injection. Moreover, N_2O (with or without lidocaine) is more effective than lidocaine alone in reducing rocuronium-related withdrawal reactions associated with sequential injection of propofol and rocuronium.

Keywords Nitrous oxide · Pain · Propofol · Rocuronium

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Introduction

Propofol is a popular anesthesia induction drug because of its quick onset of action and smooth recovery. Rocuronium is an amino-steroidal, nondepolarizing muscle relaxant with an intermediate duration of effect and a fast onset of action. The major disadvantage of both propofol and rocuronium is the significant pain (or discomfort) associated with injection [1]. Many methods have been used in attempts to prevent the pain associated with the injection of propofol and rocuronium [2–5]. However, not many studies have assessed the effects of nitrous oxide (N_2O) with regard to this pain.

The present study was designed to investigate the effects of N_2O on the pain caused by the injection of propofol and rocuronium.

Materials and methods

After institutional ethics committee approval, informed consent was obtained from 205 patients who had an American Society of Anesthesiologists (ASA) classification of I–II, were aged between 18 and 68 years, and were scheduled to undergo general anesthesia for elective surgery. Patients were excluded if they met any of the following criteria: the regular use of sedatives or analgesics; an allergy to lidocaine; a preexisting movement disorder; preexisting drug abuse; inability to cooperate or give informed consent; any anticipated difficulty in obtaining an airway; thrombophlebitis (or any other pain-causing lesion); the presence of chronic obstructive pulmonary disease (COPD); or any contraindication to the administration of N_2O (e.g., pneumothorax).

A member of the anesthesia team took responsibility for providing anesthesia while a second team member recorded the pain experienced during injection of propofol and rocuronium. The patients were randomly allocated to one of three groups using a computer-generated randomization table: (1) the control group (group C) received 100 % O_2 for 1 min before the injection of 0.5 mg/kg propofol without lidocaine; (2) the lidocaine group (group L) received 100 % O_2 for 1 min before the injection of 0.5 mg/kg propofol with lidocaine; (3) the N_2O group (group N) received 67 % N_2O/O_2 for 1 min before the injection of 0.5 mg/kg propofol without lidocaine. The investigator recording the pain scores was blinded to the drugs given and to the gas mixture administered to the patients (flow meters were covered by cardboard). Fifty additional patients were enrolled to study the combination of lidocaine and N_2O (group LN): the LN group patients were pretreated with lidocaine and received 67 % N_2O/O_2. All patients were allowed to receive 0.07 mg/kg intramuscular midazolam (given 1 h before the induction of anesthesia). Upon arrival at the operating room, patients were instructed to inform the investigator about the amount of pain they experienced by using a 0–10, visually enlarged, laminated, Numeric Rating Scale (NRS-V) [6]. A 20-gauge intravenous (i.v.) cannula was inserted into a vein on the dorsum of the hand, which is more sensitive to pain during injection than other sites, for precise assessment of the drugs injected. Another cannula was placed on the opposite hand for infusion of i.v. fluids. Pulse oximetry, mean arterial pressure, heart rate, electrocardiogram, and bispectral index (BIS) were monitored and recorded at four different times (T0, baseline; T1, after inhalation of N_2O/O_2 or O_2; T2, after propofol injection for an assessment of pain; and T4, before rocuronium injection). All patients received 3 l/min O_2 via nasal prongs before induction of anesthesia. The circuit was primed for 2 min before use (groups C and L received 100 % O_2; group N received 67 % N_2O/O_2). Following elevation of the arm for 15 s, a 70-mmHg tourniquet was applied on the forearm. The patients received either 3 ml isotonic saline or a mixture of 0.5 mg/kg lidocaine diluted with saline to a volume of 3 ml. The study gases (either 6 l/min O_2 or 4 l/min N_2O mixed with 2 l/min O_2) were administrated with a facemask gently held on the patient's face while maintaining an effective seal. Patients were asked to breathe deeply via the facemask for 1 min before induction. The tourniquet was released after 1 min, and 5 ml propofol (10 mg/ml) was injected over 10 s using a handheld stopwatch. The patients were observed and immediately questioned concerning their pain. Responses were charted immediately. The remaining induction dose of propofol, as well as a 3-ml saline bolus and 0.6 mg/kg rocuronium, were injected over 10 s. The response of the patients to the injection of rocuronium was assessed with a 4-point scale by an investigator. The score was graded as 0 for no response; 1 for movement at the wrist only; 2 for movement involving the arm only (elbow or shoulder); and 3 for a generalized response or movement in more than one extremity, including reactions such as discomfort and pain. All patients received 100 % O_2 after assessment of the injection pain. After tracheal intubation, anesthesia was maintained with a mixture of O_2 and room air plus sevoflurane. Within the first 24 h after the operation, the injection site was checked by an anesthesiologist (who did not know which drug had been administered) for any complications such as pain, swelling, or signs of an allergic reaction.

For continuous variables and ordinal variables, the one-way analysis of variance (ANOVA) or the Kruskal–Wallis test (or repeated-measures ANOVA) was used. The results are given as means ± standard deviations (SD) or the number (percentage) of patients, as appropriate. For categorical variables, the Chi-square test was used, and the results are given as a number (percentage) of patients. Multiple testing was performed using the Mann–Whitney *U* test or the Pearson Chi-square test, as appropriate. For all analyses, two-tailed $P < 0.05$ was considered statistically significant. Sample sizes of 50 subjects per group were sufficient to provide an 80 % probability (power) of detecting a real difference of 25 % based on a Chi-square test.

Results

A total of 205 patients were initially recruited into the study. Three patients were excluded because of difficulty with venous cannulation on the dorsum of the hand. Two patients in group N could not complete the study (one developed excitement and laughing and the other was

Table 1 Patient characteristics

	C ($n = 50$)	L ($n = 50$)	N ($n = 50$)	LN ($n = 50$)	P value
Age (years)	38.32 ± 15.73[a]	35.52 ± 15.57[a]	41.86 ± 15.67[ab]	47.26 ± 13.97[b]	0.002
Gender (M/F)	25/25	20/30	29/21	20/30	0.206
Weight (kg)	62.8 ± 11.1	61.3 ± 13.3	63.9 ± 12.6	63.2 ± 10.8	0.725
Height (cm)	165.4 ± 8.5	165.7 ± 9.6	165.6 ± 9.5	163.3 ± 7.6	0.460
ASA (I/II)	33/17	35/15	34/16	31/19	0.853

Values are mean ± SD or number of patients, as appropriate. No significant differences between the three groups were noted except age. Group C, NaCl in 100 % O_2; group L, 0.5 mg/kg lidocaine in 100 % O_2; group N, NaCl in 67 % N_2O/O_2; group LN, 0.5 mg/kg lidocaine in 67 % N_2O/O_2

Table 2 Incidence of pain and Numeric Rating Scale (NRS-V) associated with propofol injection

	Group				P value
	C ($n = 50$)	L ($n = 50$)	N ($n = 50$)	LN ($n = 50$)	
Pain					
No	12 (24.0)	39 (78.0)*	33 (66.0)*	47 (94.0)*,‡	<0.001
Yes	38 (76.0)	11 (22.0)*	17 (34.0)*	3 (6.0)*,‡	
NRS-V	5.02 ± 3.30	1.12 ± 1.83*	2.02 ± 2.68*	0.18 ± 0.83*,†,‡	<0.001

Values are number (percentage) of patients

NRS-V, a 0–10 visually enlarged laminated Numeric Rating Scale; group C, NaCl in 100 % O_2; group L, 0.5 mg/kg lidocaine in 100 % O_2; group N, NaCl in 67 % N_2O/O_2; group LN, 0.5 mg/kg lidocaine in 67 % N_2O/O_2

* $P < 0.001$ compared with group C

† $P < 0.05$ compared with group L

‡ $P < 0.001$ compared with group N

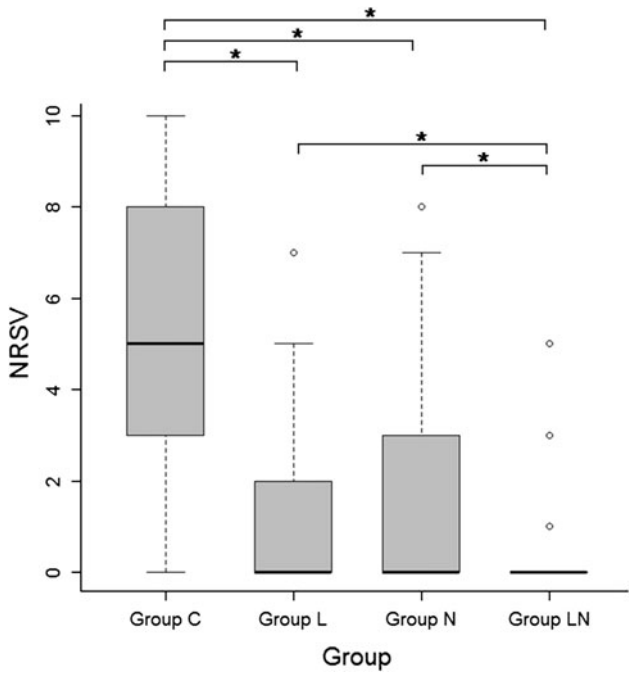

Fig. 1 Pain on injection of propofol using a Numeric Rating Scale (NRS-V) with 0 = no pain to 10 = worst pain imaginable. *$P < 0.001$ was taken as a significant value. *NRS-V*, 0–10 visually enlarged laminated Numeric Rating Scale

oversedated). There were no significant differences in demographic characteristics among the groups, except for age (Table 1).

The incidence of pain during propofol injection in group L (22 %), group N (34 %), and group LN (6 %) was significantly lower when compared with that in group C (76 %) ($P < 0.001$; Table 2). A greater number of patients in group N experienced pain than in group L; however, the difference was not statistically significant ($P = 0.181$). The NRS-V scores after propofol injection were also significantly lower in group L, group N, and group LN than in group C ($P < 0.001$; Fig. 1). Statistically, there were differences with respect to both the incidence and severity of pain during propofol injection in group LN compared to those in group L and group N ($P < 0.001$).

Incidence and grade of withdrawal movements are listed in Table 3. Incidence of pain during rocuronium injections was significantly less in group N and group LN than in group C and group L. No patients had a withdrawal score of 3 (severe response) in group N and group LN. The incidence and severity of pain were lower in group N than in group LN; however, the difference was not statistically significant ($P = 0.054$).

There was no difference in BIS among the groups except for a recorded BIS of 2 in group LN (Table 4, Fig. 2). There was a decreasing trend based on time intervals in

Table 3 Incidence and characteristics of withdrawal movement associated with injection of rocuronium

Group	Withdrawal movement			
	0	1	2	3
C ($n = 50$)	14 (28)	5 (10)	9 (18)	22 (44)
L ($n = 50$)	20 (40)	5 (10)	8 (16)	17 (34)
N ($n = 50$)*,†	41 (82)	8 (16)	1 (2)	0 (0)
LN ($n = 50$)*,†	33 (66)	12 (24)	5 (10)	0 (0)

Values are numbers of patients (% incidence)

Group C, NaCl in 100 % O_2; group L, 0.5 mg/kg lidocaine in 100 % O_2; group N, NaCl in 67 % N_2O/O_2; group LN, 0.5 mg/kg lidocaine in 67 % N_2O/O_2

* $P < 0.001$ compared with group C

† $P < 0.001$ compared with group L

BIS values. Other values, such as hemodynamic values and SpO_2 levels, did not differ among the four groups. There were no venous complications (such as pain or swelling) in any of the patients during 24 h after the injection. There were also no differences in the incidence of adverse effects associated with N_2O (such as nausea and vomiting) among the groups.

Discussion

Propofol and rocuronium are often used for induction of general anesthesia in a sequence. The combination of these two agents covers many of the characteristics of an ideal anesthetic agent in clinical practice. However, pain during injection is a common problem and can be very distressing to patients.

The mechanism of the pain associated with the injection of propofol and rocuronium remains unclear. The injection

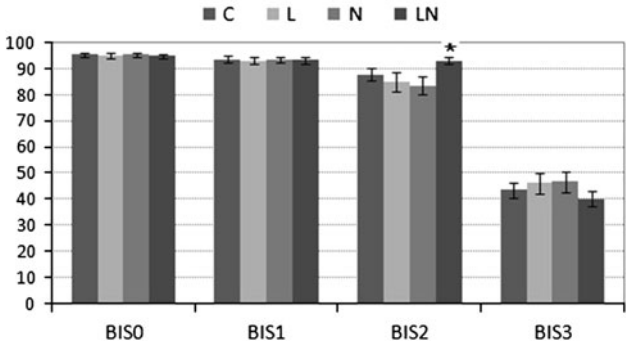

Fig. 2 The comparison with bispectral index (BIS) values at 0, 1, 2, and 3 among groups. *I bars*, SE; *asterisks*, significant between-group differences ($P < 0.05$). *P* values were calculated by repeated-measures analysis of variance using the Sheffé adjustment for multiple comparisons. *BIS 0* baseline, *BIS 1* after inhalation of N_2O/O_2 or O_2, *BIS 2* after assessment of pain on propofol injection, *BIS 3* before rocuronium injection

pain of propofol may be caused by direct irritation of the vessels and/or indirect effects via the kinin cascade [7, 8]. Withdrawal movement and/or pain from the injection of rocuronium may be caused by the activation of nociceptors by the osmolality or pH of the solution or via the release of endogenous mediators associated with inflammation, such as histamine and/or bradykinin [9–11]. This study demonstrated a significant decrease in the incidence and severity of pain during propofol injection when patients were pretreated with lidocaine, N_2O, or both (compared with the control group). These results are similar to the results of previous studies [3, 12–14]. The incidence of pain during propofol injection was reduced by 6 % with the combination of lidocaine and N_2O, which may be the result of the local analgesic effect of lidocaine, in conjunction with effect of the tourniquet, and/or the opioid-like effect of N_2O. Interestingly, this study demonstrated

Table 4 BIS values at 0, 1, 2, and 3 among groups

	BIS			
	0	1	2	3
Group C	95.40 ± 2.976	93.52 ± 4.595	87.78 ± 9.237	43.62 ± 10.832
Group L	94.78 ± 3.765	92.96 ± 4.886	85.04 ± 13.536	46.20 ± 13.985
Group N	95.26 ± 3.122	93.34 ± 4.029	83.46 ± 12.911	46.70 ± 14.401
Group LN	94.80 ± 3.071	93.24 ± 4.547	92.92 ± 4.776*	40.26 ± 10.734
Total	95.06 ± 3.236	93.27 ± 4.495¶	87.30 ± 11.215¶,†	44.20 ± 12.769¶,†,‡

Values are mean ± SD

* $P < 0.05$ compared with groups C, L, and N

BIS 0, baseline; BIS 1, after inhalation of N_2O/O_2 or O_2; BIS 2, after assessment of pain on propofol injection; BIS 3, before rocuronium injection

¶ $P < 0.05$ compared with BIS0

† $P < 0.001$ compared with BIS1

‡ $P < 0.001$ compared with BIS2

that preventive effects with respect to withdrawal movements were more pronounced with N_2O than with lidocaine. Several studies have reported that pretreatment with N_2O may reduce the incidence and severity of injection pain [14–16]. Lidocaine has been the drug most frequently used in this regard, and it has been shown to also be effective in reducing pain during rocuronium injections [5, 17–19]. It is important to note that the incidence of pain was closely related to the interval between the administration of lidocaine and rocuronium (30 %, 120 s vs. 7 %, 10 s) [4, 18]. In our study, the time interval may have been too long (139.24 ± 20.78 s). Therefore, N_2O (which has opioid-like effects) produced a superior result compared to lidocaine for prevention of pain during rocuronium injection in this study.

Self-report scales of pain intensity can be affected by the vigilance status of the patient [6]. The BIS values were monitored to assess level of consciousness. Among all groups, there was no difference in BIS values after the inhalation of a mixture of N_2O/O_2 compared to O_2 alone (BIS 1). The mean BIS value was >90 (93.27 ± 4.495). The NRS-V, which is the most feasible and discriminative self-reporting scale for measuring pain intensity, was used to assess pain [6]. It is a very intuitive method for pain assessment, even in slightly sedated patients. The short duration of inhalation (60 s) may have been responsible for the reduction in the incidence of possible adverse effects (such as hypoxia, excitement, nausea, restlessness), with the exception of two patients: one who was oversedated and another who experienced laughing and excitement. All the patients were also administered 0.3 mg ramosetron/hydrochloride at the end of the surgical operation, which may have been responsible for the finding that there were no significant differences in the incidence of nausea and vomiting among the groups.

This study has several limitations. The main limitation is the application of higher concentration of N_2O than other studies (67 % vs. 50 %) to prevent the pain caused by propofol injection. Two patients had to be excluded because of the apparent pharmacological effect of N_2O. We cannot exclude the possibility that the level of consciousness in all the patients who were in group N and group LN may be affected by N_2O even though the BIS value was over 90. Second, we could not adopt a procedure for random allocation (because group LN was added for further evaluation of the effects of N_2O). As a consequence, there was a difference in the age of the patients in group LN compared with the other groups. Because the age was significantly higher in group LN, we performed additional analysis using logistic regression that adjusted for age. However, the corrected result was the same as the previous result. Third, we tested two drugs in a sequence. We cannot completely rule out the possibility that propofol (which was administered first) might interfere with the results of withdrawal movement during the subsequent injection of rocuronium. However, because the same protocol was applied when evaluating the effects of injection pain in all groups, it is unlikely that the protocol sequence altered the results.

In conclusion, we found that pretreatment with inhaled N_2O is an easy and effective technique for reduction of pain experienced during the combined injection of propofol and rocuronium. In addition, we found that when induction of anesthesia is performed with propofol and rocuronium in a sequence, N_2O (with or without lidocaine) is more effective than lidocaine alone in reducing withdrawal reactions during rocuronium injections.

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