



Comparison of the Effects of Different Concentrations of Rocuronium on Injection Pain and Hemodynamics Using Isolated Forearm Technique

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Objective: We aimed to evaluate Visual-Analogue-Scale (VAS) scores, hand-withdrawal, rash and skin eruptions after injections of different concentrations of rocuronium in intubation doses in alert patients using the isolated-forearm technique.

Methods: Eighty ASA I-II patients were included in a randomized, controlled, single-blinded study. Two 20 G cannulas were inserted into the dorsum of the left and right hand in each patient. A tourniquet was applied to the left arm and inflated to 50 mm Hg above the patient's systolic blood pressure. Group 1 (n=20) received 2.5 mg mL⁻¹ rocuronium diluted with 0.9% NaCl, Group 2 (n=20) received 5 mg mL⁻¹ rocuronium diluted with 0.9% NaCl, Group 3 (n=20) received 10 mg mL⁻¹ rocuronium and 0.4 mg mL⁻¹ lidocaine mixture, and Group 4 (n=20) received 10 mg mL⁻¹ rocuronium via a cannula on the left hand, provided that a dose of 0.6 mg mL⁻¹ were given to all groups of patients. VAS₀-VAS₆₀ values, hand-withdrawal, rash and skin eruptions were assessed in patients who were administered rocuronium but not under the effects of hypnotic or neuromuscular agents. Hemodynamic values were recorded both before and after the administration of hypnotic-neuromuscular agents.

Results: VAS₀ values were significantly higher in Group 4 when compared to Groups 1, 2 and 3 (p=0.032). No significant difference was observed between VAS₀ and VAS₆₀ values in Groups 1, 2 and 3. In Group 4, VAS₀ values were significantly higher than VAS₆₀ values (p=0.003). No significant difference was observed between groups in terms of side effects and hemodynamic values.

Conclusion: In conclusion, we determined that using rocuronium diluted with 0.9% NaCl was more effective in preventing injection pain than using a rocuronium-lidocaine mixture.

Key Words: Rocuronium, intravenous injection, pain

Introduction

Rocuronium is a steroidal nondepolarizing neuromuscular blocking agent, with similar block onset time as succinylcholine, which is preferred by the anaesthetists because of its rapid effect (1). One of the most frequent complications of rocuronium is injection pain. Even after anaesthesia induction when a state of complete hypnosis is achieved, this pain may lead to hand withdrawal (1-3). The mechanism of pain is not completely known. In order to prevent this side effect, premedication with various drugs before rocuronium injection and application of rocuronium together with drugs such as lidocaine, midazolam and fentanyl had been tested (3-6). Multiple studies evaluated rocuronium-associated pain and hand withdrawal (2, 3, 6).

In our study, using isolated forearm technique, we aimed to evaluate the effects of three different concentrations (10 mg mL⁻¹, 5 mg mL⁻¹, 2.5 mg mL⁻¹) of rocuronium on pain, rash, and skin eruptions and the hemodynamic changes associated with this complication.

Methods

After the approval of the Ethics Committee of İstanbul University Cerrahpaşa Medical School (approval date 03.05.2011 and number 28234), a randomized clinical, prospective, double-blind study was performed in the General Surgery operating theatre, on 80 ASA I-II patients who required general anaesthesia. The study was performed after obtaining the informed consent of the patients.

Exclusion criteria were, known allergies to any anaesthetic agent, dementia, the presence of diseases causing tremor or involuntary movements such as Alzheimers' or Parkinsons' disease and being younger than 18 years of age. Before injection, the patients were informed that the medication used might cause burning sensation in hands. Patients were informed on the Visual Analogue Scale (VAS), and after the drug was administered, they were asked to evaluate pain intensity on VAS. VAS is a horizontal or vertical 10 cm line; anchored by "No Pain" at one end and "Unbearable Pain" at the other. At the same time with patients VAS evaluation, a numeric scale which was produced to evaluate it numerically (7-9).

The patient was transferred to the operating room, and two 20-gauge cannulas were placed at the back of the patient's right and left hands at one attempt without causing any hematoma and 4 mL kg⁻¹ of 0.9% NaCl infusion was started from the right hand. Age, weight and gender of the patients were recorded, and as a standard procedure ECG, SpO₂, non-invasive arterial pressure monitoring was performed (Datex Ohmeda S/5 Avance) in the operating room. Patients were randomized into 4 groups. Group 1 (n=20) received 2.5 mg mL⁻¹ rocuronium diluted with 0.9% NaCl, Group 2 (n=20) received 5 mg mL⁻¹ rocuronium diluted with 0.9% NaCl, Group 3 (n=20) received a mixture of 10 mg mL⁻¹ rocuronium and 0.4 mg mL⁻¹ lidocaine, and Group 4 (n=20) received 10 mg mL⁻¹ rocuronium, providing a total dose of 0.6 mg kg⁻¹ in all groups. No analgesics were administered before rocuronium application. Drugs were prepared in 20 mL syringes by an anaesthetist other than the anaesthetist who would administer the drug. In order to provide double blind testing, the syringes were covered with a non-transparent foil in order to keep the anaesthetist who administered the drug, unaware about the concentration and content of the drug.

In order to prevent the systemic effects of rocuronium, the tourniquet at the left arm of the patient, was inflated 50 mmHg above the systolic arterial pressure. Left forearm circulation was isolated from the systemic circulation. Before administration of the hypnotic agent, rocuronium prepared according to the patient's group, was administered from the cannula at the back of the left hand. VAS scores at 0 (VAS₀) and 60 seconds (VAS₆₀) of injection, and hand withdrawal and rash at the injection site developed in this period were recorded. After that, induction of anaesthesia was carried out, with 2 mg kg⁻¹ propofol and 2 µg kg⁻¹ fentanyl, administered from the intravenous cannula in the other forearm vein. After hypnosis was induced, tourniquet was released and rocuronium entered into the systemic circulation. Intubation was performed after 90 seconds. Hemodynamic parameters (systolic arterial pressure: SAP, diastolic arterial pressure: DAP, mean arterial pressure: MAP, heart rate: HR) were recorded before and after rocuronium administration. Anaesthesia was maintained with 1-2% sevoflurane in 40% oxygen/air mixture.

Statistical analysis

Number Cruncher Statistical System (NCSS) 2007& Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA) program was used in the statistical analysis of data. Parametric data were expressed as mean±SD, nonparametric data as median and range (min-max) and categorical data as frequencies and rates. Variance analysis was used for the comparison of variables showing normal distribution and paired t test was used in the comparison of two dependent groups. Comparisons between variables with non-normal distribution were performed using the Kruskal Wallis test and Mann-Whitney U test, and Wilcoxon-signed rank test was used to compare two dependent groups. In comparison of variance between the groups, percentage change from baseline (%) was taken into consideration for hemodynamic variables and difference score

from baseline was taken for VAS scores. Comparison of categorical data between the groups was performed with chi-square test. Side effects were compared using Fisher Exact Test and Yates Test. The significance level was set at p<0.05.

Results

No significant difference was found between the groups regarding demographic data and ASA scores (Table 1).

Heart rate, SAP, MAP and DAP values measured before and after rocuronium administration were similar in all groups (Table 2). Comparisons made in the groups showed no significant difference in MAP values before and after rocuronium administration in Group 1, 3 and 4; however, MAP values before rocuronium administration was significantly higher in comparison to MAP values after rocuronium administration in Group 2 (p=0.046).

Inter-group comparisons revealed that VAS₀ scores of the patients in Group 1 were significantly lower than that of Group 2, 3 and 4 (p=0.032).

Intra-group comparisons in Group 1, 2 and 3 revealed significant difference between VAS₀ and VAS₆₀ scores; however, VAS₀ scores of Group 4 were significantly higher in comparison to VAS₆₀ scores (p=0.003, Table 3). No significant differences were found between VAS₀ and VAS₆₀ scores in Groups 2, 3 and 4.

Hand withdrawal was observed in 15% (n=3) of the patients in Group 1, in 30% (n=6) of the patients in Group 2, in 25% (n=5) of the patients in Group 3 and in 35% (n=7) of the patients in Group 4 (Table 4).

There was no difference between the groups regarding hand withdrawal rates. While rash developed in 15% (n=3) of cases in Group 1, rash rates were 15% (n=3), 10% (n=2) and 15% (n=3) in Group 2, Group 3 and Group 4, respectively. No significant difference was determined between the groups regarding the percentage of patients with rash-skin eruptions.

Discussion

The pathophysiological mechanism of rocuronium-associated injection pain is still not completely understood. Unphysiological osmolality or pH-induced nociceptor activation, and release of endogenous mediators such as histamine and bradykinin can be mentioned among the causes of this side effect (10). The onset of pain immediately after injection and pain limited to the arm where rocuronium is injected suggests that the drug induces pain via direct irritation of peripheral veins (11-13). Administration of various different drugs such as local anaesthetics, opioids, sodium bicarbonate and ondansetron, at the same time or before rocuronium administration have been tried in the attempts to prevent injection pain (4, 14-16).

In our study, using isolated forearm technique, we aimed to evaluate the effects of three different concentrations (10 mg mL⁻¹, 5 mg mL⁻¹,

Table 1. Demographic data

	Group 1	Group 2	Group 3	Group 4	p
Age (years); mean±SD	45.30±6.70	48.20±8.21	46.10±7.20	48.60±6.40	0.492
Weight (kg); mean±SD	66±7.20	68±9.10	68±7.50	65±6.40	0.761
Gender (M/F); n	9/11	8/12	10/10	11/9	0.801
Mean±SD: Mean±Standard deviation					

Table 2. Hemodynamic data (Mean±SD)

	Group 1 Mean±SD	Group 2 Mean±SD	Group 3 Mean±SD	Group 4 Mean±SD	p
SAP before rocuronium	139.50±27.07	134.00±23.42	135.00±24.08	131.55±26.86	0.795
SAP after rocuronium	129.20±27.00	125.00±24.62	127.70±29.32	126.35±24.68	0.797
*p	0.197	0.202	0.147	0.437	
MAP before rocuronium	102.15±18.14	97.75±13.75	99.60±12.20	95.80±16.13	0.595
MAP after rocuronium	94.85±16.35	91.20±15.00	94.95±18.71	92.50±19.73	0.882
p	0.085	0.046	0.539	0.525	
DAP before rocuronium	81.65±9.00	78.20±13.75	79.75±8.97	76.80±8.19	0.478
DAP after rocuronium	82.95±19.69	82.25±19.94	81.65±18.45	77.40±13.76	0.760
*p	0.763	0.439	0.568	0.849	
HR before rocuronium	81.85±13.60	80.70±12.74	85.70±16.32	86.25±18.10	0.581
HR after rocuronium	83.90±12.40	77.10±12.39	84.45±14.88	86.05±18.23	0.234
*p	0.457	0.184	0.358	0.917	

Mean±SD: Mean±Standard deviation. SAP: systolic arterial pressure; MAP: Mean arterial pressure; DAP: diastolic arterial pressure; HR: heart rate * p<0.05

Table 3. Visual Analogue Scale (VAS) scores (Mean±SD)

	Group 2 Mean±SD	Group 3 Mean±SD	Group 4 Mean±SD	Significance (p) [†]	Significance (p) [*]	
VAS ₀	4.50 (0-10)	5.0 (0-10)	5.0 (0-10)	7 (0-10)	0.032*	Gr 1- 2 0.039* Gr 1- 3 0.013* Gr 1- 4 0.017* Gr 2- 3 0.305 Gr 2- 4 0.601 Gr 3-4 0.744
VAS ₆₀	4.0 (0-10)	6.0 (0-10)	5.0 (0-10)	4 (0-10)	0.443	
*p	0.421	0.975	0.670	0.003**		
	VAS ₀ -VAS ₆₀ Median (Min-Max)	VAS ₀ -VAS ₆₀ Median (Min-Max)	VAS ₀ -VAS ₆₀ Median (Min-Max)	VAS ₀ -VAS ₆₀ Median (Min-Max)		
Difference	0 (-6-5)	0 (-3-8)	0 (-5-5)	1.5 (-1-10)	0.039*	Gr 1- 2 0.010* Gr 1- 3 0.064 Gr 1- 4 0.020* Gr 2- 3 0.443 Gr 2- 4 0.540 Gr 3-4 0.849

[†]Kruskal Wallis variance analysis test. ^{*}Wilcoxon signed rank test ^oMann-Whitney U test. *p<0.05. **p<0.01 Difference: VAS₀ -VAS₆₀ ; Min: Minimum; Max: Maximum

2.5 mg mL⁻¹) of rocuronium on pain, rash, and skin eruptions and the hemodynamic changes associated with this complication.

Memiş et al (15), in their study, which compared the efficacy of ondansetron, lidocaine, tramadol and fentanyl, showed that, among these drugs, the most effective drug in reducing pain was lidocaine.

Tuncali et al (10), diluted 0.06 mg kg⁻¹ rocuronium in different concentrations with 0.9% NaCl, and examined injection pain at 5 seconds of injection, before the effects of neuromuscular blocker agent started. They concluded that rocuronium diluted at a concentration of 0.5 mg mL⁻¹ led to a significant decrease in injection pain compared to the other groups.

Chiarella et al. (17), in their study, administered a precurarization dose of 10 mg rocuronium to four different groups of patients, in combina-

tion with 2% lidocaine, 100 µgr fentanyl, 8.4% sodium bicarbonate and 0.9% NaCl, respectively; they found that pain was significantly lower in lidocaine and sodium bicarbonate treated groups, and was significantly higher in 0.9% NaCl and fentanyl treated groups in comparison to the other groups. This finding was attributed to the pH of rocuronium, and the low dilution effects of fentanyl and 0.9% NaCl (17).

In our literature search, the single study that evaluated injection pain using full dose (dose used to perform intubation during induction) rocuronium, was the study performed by Turan and colleagues (4). In that study, lidocaine, 0.9% NaCl, magnesium sulphate, sodium bicarbonate and alfentanil was administered under tourniquet control, then after 30 seconds the tourniquet was deflated and 0.6 mg kg⁻¹ of rocuronium was administered, and pain was evaluated. They concluded that, pain was significantly higher in the group treated with alfentanil when compared to the other groups.

Table 4. Side effects observed after injection (patient number)

	Withdrawal n (%)	Rash n (%)
Group 1	3 (15.0)	3 (15.0)
Group 2	6 (30.0)	3 (15.0)
Group 3	5 (25.0)	2 (10.0)
Group 4	7 (35.0)	3 (15.0)
Fisher Exact Test		

In our study, different from all the above-mentioned studies, administration of intubation dose rocuronium, from the distal of the tourniquet, prevented the development of unwanted side effects, and pain evaluation could be performed without the influence of any hypnotic or sedative drugs. In our study, no significant difference was found between the rocuronium-lidocaine mixture group and the groups that were treated with rocuronium diluted with 0.9% NaCl in terms of VAS₀ scores after rocuronium injection. VAS values were found to be significantly higher after pure rocuronium injection. This difference disappears at 60 seconds of injection and no significant difference was observed between the groups. This finding may aid in the understanding of the pathophysiology of pain.

Tuncali et al. (10) showed that pain was significantly decreased during the injection of 0.5⁻¹ mg mL⁻¹ rocuronium diluted in 0.9% NaCl. However, the disadvantage of this dilution is that the required total drug volume in intubation doses can increase to such high levels as 100 mL in an individual weighing 80 kg. It has a low usage potential in practice. We think that dilution with % 0.9 NaCl is safer than diluting with lidocaine as the VAS scores in diluted group were significantly lower.

Mencke et al. (18), reported the percentage of hand withdrawal approximately 22% after pure rocuronium injection. Withdrawal rates after injection were between 15 and 35% in our study. These rates are similar with the rates reported in the literature (12-28%) (15, 18). The fact that no significant difference was observed in hand withdrawal rates between lidocaine and 0.9% NaCl groups during or after injection support our opinion that 0.9% NaCl use should be preferred. In our literature search, we were not able to find any information about the rate of rash and skin eruptions after rocuronium injection. In our study, there was no significant difference between the groups.

Yörükoğlu et al. (19) evaluated the intubating conditions and hemodynamic changes associated with rocuronium and succinylcholine, after 2 mg kg⁻¹ propofol induction. In that study, no significant difference was found in the HR values of patients, who were given 1.5 mg kg⁻¹ lidocaine plus rocuronium. The HR values of patients without lidocaine administration were increased. The reason for that is the attenuated hemodynamic stress response against lidocaine intubation. In our study, there was no significant difference in inter- and intra-group comparisons, before and after rocuronium administration, regarding HR, SAP and DAP values. Intra-group comparisons revealed that MAP values before rocuronium administration were significantly higher compared to MAP measured after rocuronium use in Group 2. Although this difference was statistically significant, it was not within the range of clinically significant levels. Different rocuronium concentrations had similar effects on hemodynamic conditions.

Conclusion

We found that the use of rocuronium at a concentration of 2.5 mg mL⁻¹ diluted in 0.9% NaCl is much more effective than using lidocaine-rocuronium mixture in the management of rocuronium-induced injection pain.

Conflict of Interest

No conflict of interest was declared by the authors.

Peer-review: Externally peer-reviewed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul University Cerrahpaşa School of Medicine (03.05.2011, 28234)

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

Author Contributions

Concept - E.E.; Design - E.E., G.M.K., G.K.; Supervision - F.A., G.K.; Data Collection and/or Processing - Y.T., E.E., B.E., Ç.A.T., Ö.Ö.Ç.; Analysis and/or Interpretation - E.E., G.M., F.A.; Literature Review - E.E., B.E.; Writer - E.E., G.M.K.; Critical Review - Y.T., G.K., F.A.; Other - Ö.Ö.Ç.

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