Original Article

Comparison of injection pain in pediatric population; original versus generic rocuronium

ABSTRACT

Background: Rocuronium-induced injection pain causes withdrawal movements. These movements may cause accidental disruption of indwelling needles. Generic rocuronium contains low-acid concentration buffer solution compared with original rocuronium. In animal experiments, it has been suggested that the difference of the buffer solution may alleviate injection pain. The purpose of this study was to identify the difference of injection pain between original and generic rocuronium in pediatric population.

Material and Methods: Patients ranging in age from 1 to 15 years, American Society of Anesthesiologists physical status I or II, undergoing elective surgeries were randomly allocated to two groups; generic rocuronium group (Group R) and original rocuronium (Eslax®) group (Group E). Following anesthetic induction with oxygen, nitrous oxide, and sevoflurane, original or generic rocuronium (1 mg/kg) was administered via intravenous catheter. The difference of vital signs and withdrawal movement associated with rocuronium injection were evaluated.

Results: A total of 64 patients were included in the study. Three patients were excluded. Twenty-nine patients were assigned to Group E and 32 patients to Group R. There was no significant difference in mean arterial pressure and heart rate. No withdrawal movements were observed in both groups.

Conclusion: There was no significant difference in injection pain between original and generic rocuronium under inhalational induction.

Key words: Injection pain; pediatrics; rocuronium

Introduction

Rocuronium is widely used to provide neuromuscular blockade during anesthetic care. Intense pain induced by its intravenous injection is common in the clinical setting.[1] This injection pain causes withdrawal movements and potentially accidental removal of indwelling intravenous cannulas. Although various techniques have been studied to alleviate rocuronium injection pain, there has been no widely accepted method to date. Recently, generic rocuronium with a low-acid concentration buffer solution was introduced to the Japanese market. Jimbo *et al*. suggested after their experiments in rats using electromyography to evaluate a flexor reflex response as the index of vascular pain that the high acid concentration in the original rocuronium buffer solution may be the cause of injection pain, and the newly developed generic rocuronium with a low-acid concentration buffer solution might alleviate the injection pain.[2] To date, however, there

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are no data available regarding the difference in injection pain by the difference of buffer solution of rocuronium. The purpose of the current study was to identify the difference in injection pain between original and generic rocuronium under inhalational induction. This study was conducted as a preliminary study since there has been no data regarding the difference in injection pain by the difference of buffer solution of rocuronium.

Material and Methods

The study was a prospective, randomized, double-blind study in a single institution. The study was approved on 2017/7/21 by the Ethics Committee of Aichi Children's Health and Medical Center (Aichi, Japan) (approval number: 2017024) and registered at University hospital Medicine Information Network (UMIN) (ID: 000028584, reception number: R000032541). Written informed consent was obtained from the parents and assent from the patient when age-appropriate. Since this is a preliminary study, the sample size was chosen based on the previous studies regarding rocuronium-induced injection pain.[3-5] Patients with the American Society of Anesthesiologists (ASA) physical status I or II who were 1--15 years of age undergoing elective surgeries were eligible for inclusion. Patients with allergies to any of the study drugs, neuromuscular disease, and difficult intravenous catheter insertion were excluded. After the enrollment, patients were randomly allocated by computer to either generic rocuronium (Rocuronium: Fuji Pharma Co., Ltd., Tokyo, Japan) group (Group R) or original rocuronium (Eslax®: MSD, Tokyo, Japan) group (Group E).

All patients were held nil per as according to guidelines of the ASA. The patients were premedicated with either oral midazolam (0.5 mg/kg, up to 10 mg, 30 min before the induction of anesthesia) or oral diazepam (0.5 mg/kg, up to 10 mg, 1 h before induction of anesthesia) based on the preference of the patient and clinical indication. After transportation to the operating room and application of standard ASA monitors, anesthesia was induced by mask induction with 8% sevoflurane in 4 L/min nitrous oxide and 2 L/min oxygen. After the loss of eyelash reflex and end-tidal sevoflurane above 5%, baseline vital sings including heart rate and noninvasive blood pressure were recorded. Then, a 22- or 24-gauge intravenous cannula was placed in the dorsum of the hand and properly secured. After the arm was placed in neutral position, non-diluted original or generic rocuronium 1 mg/kg was administered via intravenous cannula and flushed with 10 mL of normal saline. Throughout the study period, ventilation was assisted via manual mask ventilation as needed to maintain normocarbia as measured using end-tidal carbon dioxide monitoring. Following rocuronium administration, repeated vital signs were recorded. Withdrawal movement associated with rocuronium injection was also recorded. Withdrawal movement was evaluated by a four-point scale: 0 = no response, 1 = movement at the wrist only, 2 = movement/withdrawal involving the arm only (elbow/shoulder) and 3 = generalized response: Movement/withdrawal in more than one extremity, cough, or breath holding.[3] Withdrawal movement was evaluated by two anesthesiologists who were not involved in the patient care and were blinded to the study agent following the instruction from the study investigator. After the recording of vital signs, fentanyl and/or propofol was administered before tracheal intubation. Following the anesthesia induction, there was no change in the standard anesthetic care including intraoperative anesthetic management and intraoperative monitoring.

Statistical analyses were performed using StatMate IV (ATMS Co., Ltd, Tokyo, Japan). Student's *t*-test was performed for the data of equal variance and Cochran cox test was used for the data of unequal variance. Demographic data (age and weight) between the two groups were analyzed using a non-paired *t*-test while gender distribution was analyzed using a Fisher's exact test. Data are presented as the mean ± standard deviation if normally distributed, median and interquartile range if not normally distributed, and percentage, as appropriate. A *P* value less than 0.05 was considered significant.

Results

Sixty-one of the 64 patients enrolled in this study were included in the final analysis. Three patients were excluded; two patients with involuntary movements due to the high concentration of sevoflurane and 1 patient with tetany due to hyperventilation during spontaneous breathing. Twenty-nine patients were assigned to Group E, and 32 patients were assigned to Group R. The demographic data are presented in Table 1. There was no significant difference in demographic data between the two groups. None of the patients in either group exhibited any withdrawal movement (four-point scale: 0) to the administration of rocuronium. The variables of vital signs are shown in Table 2. Heart rate increased significantly

Table 1: Demographic data

	Group E *n*=30	Group R *n*=34
Sex (M/F)	11/18	15/17
Age (year)	5.1±3.0	5.5±2.8
Height (cm)	106±21	107±17
Weight (kg)	18.8±7.6	18.9±7.2

Data are presented as the mean±standard deviation or number of patients. There were no significant differences between two groups. Group E: EslaxÒ group, Group R: Rocuronium group

Table 2: Mean arterial pressure and heart rate before and after administration of rocuronium

	MAP (mmHg)		HR (bpm)	
	Baseline	After administration of rocuronium	Baseline	After administration of rocuronium
Group E	67.0±9.2	67.9±9.1	122.9±30.0	145.1±21.6*
Group R	63.1±8.3	64.7±9.8	122.3±26.9	142.2±22.4*

Data are presented as the mean ± standard deviation. There were no significant differences in the change of MAP and HR between two groups. MAP: Mean arterial blood pressure (mmHg), HR: Heart rate (bpm), Baseline; before the administration of rocuronium. Group E: Eslax group, Group R: Rocuronium group. *$P<0.05$ compared with baseline value within the group

after administration of original and generic rocuronium within the group compared with the baseline, although the increase of heart rate was not significant between the groups. The size of intravenous cannulas, the time from the start of anesthesia induction to intravenous cannulation and injection of rocuronium, and end-tidal sevoflurane concentration at the recording of baseline vital signs were not statistically different between two groups [Table 3].

Table 3: The size of intravenous cannula, the time from the start of anesthesia induction to intravenous cannulation, injection of rocuronium, and end-tidal sevoflurane concentration at the recording of baseline vital signs

	Group E	Group R
	n=30	n=34
Intravenous cannulation (24/ 22G)	1/28	1/31
Intravenous cannulation (min)	5.7±1.5	5.3±1.1
Injection of rocuronium (min)	6.8±1.6	6.5±1.3
End-tidal sevoflurane concentration (%)	5.9±0.7	5.9±0.5

Data are presented as the mean ± standard deviation. There were no significant differences between two groups

Discussion

This study investigated the difference in injection pain between original and generic rocuronium under inhalational induction. However, none of the patients had withdrawal movements, and there were no significant differences in vital signs before and after injection of rocuronium in two groups.

The mechanism of rocuronium-induced pain is unclear. Acidic or alkaline solution with high osmolality is known to cause injection pain.[6] Rocuronium is an isotonic solution with a pH value of 4. While normal saline is also buffered to pH 4, it does not cause injection pain. It has also been assumed that pain on rocuronium injection occurs as a result of the release of local mediators, such as kinins, stimulating the venous nociceptors.[7] There have been several studies exploring the way of alleviating rocuronium injection pain. Tuncali *et al*. reported after investigating in awake patients that injection pain was eliminated when original rocuronium was diluted to 0.5 mg/mL with normal saline.[8] Another method was to neutralize original rocuronium to pH 7.4 by adding sodium bicarbonate prior to administration.[9] However, these methods require the preparation of a dosing solution prior to administration and possibly cause the confusion. Administration rocuronium following high dose bolus of remifentanil (1 mcg/kg) or fentanyl (1.5 mcg/kg) was also examined. However, high dose bolus of these agents could induce the adverse events such as cough, breath holding, and chest rigidity.[10] Although various techniques have been studied to alleviate rocuronium injection pain, there has been no widely accepted method to date.

In a rat model monitored by electromyogram, injection pain was reported to increase with the increase of the acid concentration in the buffer solution rather than the type of the acid (acetate buffer, citrate buffer, citrate/phosphate buffer, or glycine/hydrochloric acid buffer).[2] Generic rocuronium was developed using a low-acid concentration buffer as compared with original rocuronium (original: 0.15 M acetate buffer, generic: 0.03 M glycine/phosphate buffer). It was advertised that newly invented generic rocuronium with low-acid concentration buffer eliminated the injection pain. However, there has been no data available regarding the injection pain of generic rocuronium in human subjects. Thus, we investigated it in the clinical settings in pediatric population.

There are some differences in anesthesia induction between pediatrics and adults. Firstly, inhalational induction via mask is generally selected in pediatric patients to relieve the stress on insertion of intravenous line, while rapid induction via intravenous line is common in adult patients.[11] Although withdrawal movements on injection of rocuronium may be observed more frequently in rapid induction, we decided to induce by inhalational induction before intravenous line insertion as it was standard practice in this age group of children. Yun Chan Na *et al*. reported that there was a time-dependent decrease in the incidence of withdrawal movements on injection of rocuronium during the anesthesia induction with sevoflurane, and end-tidal sevoflurane concentration of 5.5 ± 0.7% with 67% of nitrous oxide completely prevented withdrawal movement.[12] In the current study, the intravenous line was inserted after slow induction with sevoflurane. Injection of rocuronium was approximately

6 min after the initiation of anesthesia induction with the end-tidal sevoflurane concentration of 5.9% in both groups. This might affect the result of our study that no withdrawal movement was observed on injection of rocuronium.

Secondly, in small children, the intravenous line is often inserted in the dorsum of the opposite side of the dominant hand. The site where intravenous line is inserted is affected by multiple factors including the surgical site, dominant hand, postoperative early ambulation, and other medical conditions such as paralysis and skin damage. There was a report that administration via a large vein (e.g., antecubital vein) instead of via small vessels in hand significantly reduced injection pain of rocuronium.[13] In this study, we standardized to insert intravenous catheter in the back of the hand based on our standard practice and to minimize the effect of administration site on injection pain. The increase of heart rate and blood pressure may not necessarily reflect the injection pain. There have been controversial reports regarding hemodynamic effects of rocuronium. Shorten *et al*. stated after investigating during thiopentone, fentanyl, nitrous oxide anesthesia in elderly patients that the use of rocuronium did not result in a clinically significant change in heart rate, blood pressure, or plasma concentration of noradrenaline and adrenaline.[14] Gursoy *et al*. also reported rocuronium did not significantly increase the heart rate in isolated rat atria under identical experimental condition. However, they suggested rocuronium had positive inotropic effects via direct stimulation of beta receptors.[15]

The limitation of the study was that there was some impact from sevoflurane on the study results since the study agent was administered following anesthetic induction with oxygen, nitrous oxide, and sevoflurane. However, since inhalational induction via mask is a standard practice in this age group of children, we designed the current study with inhalational induction as a real clinical setting.[11]

In conclusion, there was neither statistically nor clinically significant difference in injection pain between original and generic rocuronium under inhalational induction.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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