

# Pretreatment with Small-Dose Ketamine Reduces Withdrawal Movements Associated with Injection of Rocuronium in Pediatric Patients

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We evaluated the pretreatment of small-dose of ketamine or normal saline in the reduction of withdrawal movements induced by rocuronium injection. One-hundred pediatric patients (aged 1–6 yr) were randomly assigned into 2 groups. A 22-gauge IV cannula was inserted into the dorsum of the hand, and ketamine 0.2 mg/kg or normal saline was given, followed by a 5 mg/kg thiopental injection 10 s later. IV rocuronium (0.8 mg/kg) was injected over 5 s. The patient's response to rocuronium injection was graded by using a

four-point scale in a double-blinded manner. We observed that the incidence of withdrawal movements was 83% in the saline group and 27% in patients pretreated with ketamine ( $P < 0.05$ ). Some patients in both groups developed skin erythema at the site of injection. We conclude that pretreatment with small-dose ketamine significantly attenuates withdrawal movements associated with IV injection of rocuronium in pediatric patients anesthetized with thiopental.

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**R**ocuronium bromide, a nondepolarizing neuromuscular blocking drug, is characterized by rapid onset with an intermediate duration. When a subparalyzing dose of rocuronium was given IV in awake patients, most of them complained of severe burning pain in their arm (1,2). Even after loss of consciousness from induction drugs, IV rocuronium can still elicit withdrawal of the hand or generalized movements of the body. Although no patient complained of pain or recall after recovery, this withdrawal movement was most likely due to pain at the site of injection (3,4).

Numerous methods have been suggested to attenuate the withdrawal movements related to rocuronium-induced pain (5–9). Two studies showed that small-dose ketamine reduced the pain induced by propofol injection as well as pain from tourniquet inflation (10,11). However, there is no evidence that supports using small-dose ketamine for the reduction of withdrawal movement on injection of rocuronium. This study aimed to determine

whether pretreatment with small-dose ketamine can attenuate the withdrawal movements associated with injection of rocuronium in pediatric patients.

## Methods

The protocol of this study was approved by the Institutional Ethical Committee of the Chang Gung Memorial Hospital, and parental consent was obtained verbally. The study was prospectively conducted on 100 ASA physical status I and II patients, aged 1–6 yr, who were to undergo general anesthesia for elective surgery. We excluded patients who had history of neurological deficits, drug allergy, or asthma, as well as those who had received analgesics or sedatives within the previous 24 hours. On the basis of the randomization table, the study patients were randomized into two groups: IV ketamine 0.2 mg/kg ( $n = 50$ ; diluted into 2 mL of normal saline) and IV saline ( $n = 50$ ; 2 mL). A nurse anesthetist blinded to the study prepared the syringes and the label, which was covered securely. The study was designed to be double-blinded; the investigator who assessed the patient's response was also unaware of the nature of the solution.

No premedication was given before the induction of anesthesia. On arrival in the operation room, patients

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were monitored with electrocardiogram, pulse oximetry, and noninvasive blood pressure. All patients received 70% N<sub>2</sub>O in 30% oxygen via a face mask for anesthetic induction. A 22-gauge cannula was inserted into the dorsum of the hand, and its position was confirmed by a free flow of dextrose/saline infusion by gravity. Pure oxygen was administered until the end-tidal concentration of N<sub>2</sub>O decreased to <5%. Ten seconds after IV injection of ketamine or normal saline at ambient temperature (20°C–22°C), anesthesia was induced with 2.5% sodium thiopental (5 mg/kg). Another 10 s later, rocuronium (0.8 mg/kg IV) was injected through the rubber port of the catheter over 5 s while the IV tubing was clamped above the injection site, followed by a flush with a free flow of 2 mL of dextrose/saline solution. The response of the patients to the injection of rocuronium was assessed with a four-point scale by an independent observer. The score was graded as 1 for no response, 2 for movement at the wrist only, 3 for movement involving the arm only (elbow or shoulder), and 4 for generalized response or movement in more than one extremity. The patients were tracheally intubated with an uncuffed endotracheal tube, and their lungs were mechanically ventilated to maintain normocarbida. Anesthesia was maintained with sevoflurane (inspired concentration of 2%–4%) in oxygen/N<sub>2</sub>O. Patients were also observed for local signs, such as erythema, and venous sequelae (i.e., thrombosis, phlebitis, or thrombophlebitis) of the hand where rocuronium was injected.

To detect a 50% reduction at a significant level of 5% and a probability (power) of 80%, this study required at least 46 patients per group, on the basis of power analysis estimating the incidence of 80% of patients who experience pain or withdrawal movement on injection of rocuronium. Data are presented as mean ± SD. Patients' characteristics were compared by using the unpaired Student's *t*-test. The occurrences of withdrawal movements were analyzed by the  $\chi^2$  test or Fisher's exact test when appropriate. The Mann-Whitney *U*-test was used to compare the four-point scale in relation to withdrawal movements between the groups. Statistical significance was set at a *P* value of <0.05.

## Results

The groups did not differ significantly regarding age, weight, or sex (Table 1). One patient in the saline group and two patients in the ketamine group were excluded from the study because they withdrew the hand on injection of pretreated solution or thiopental sodium. The overall incidence of withdrawal movement was 83% in the saline group, compared with 27% in the ketamine group (Table 2; *P* < 0.05). Fewer patients in the ketamine group had generalized movement in more than one extremity in comparison with

**Table 1.** Demographic Data

Variable	Ketamine ( <i>n</i> = 48)	Saline ( <i>n</i> = 49)
Age (yr)	4.0 ± 1.5	4.1 ± 1.6
Weight (kg)	16.1 ± 3.9	17.1 ± 4.4
Height (cm)	97 ± 13.8	99 ± 15.6
Male/female	31/17	33/16

Data are mean ± SD. No statistical difference was found between groups.

**Table 2.** Incidence and Degree of Withdrawal Movements Associated with Rocuronium Injection

Withdrawal movements (four-point scale)	Ketamine ( <i>n</i> = 48)	Saline ( <i>n</i> = 49)
1	35 (73%)*	8 (17%)
2	4 (8%)	5 (10%)
3	5 (10%)*	12 (24%)
4	4 (8%)*	24 (49%)
Overall	13 (27%)*	41 (83%)

Data are number of patients (percentage).

Withdrawal movements: 1 = no response, 2 = movement at the wrist only, 3 = movement involving arm only (elbow or shoulder), and 4 = generalized response or movement in more than one extremity.

\* *P* < 0.05 versus saline (Mann-Whitney *U*-test).

the saline group (8% versus 49%; *P* < 0.05). There was no sex difference in the incidence of withdrawal reactions. Skin erythema was observed on the dorsum of the hand in six patients in the saline group and seven in the ketamine group. No active intervention was required, and all skin erythema was self-limiting. No venous sequelae were observed in any patient during the study period.

## Discussion

In previous studies, the incidence of withdrawal movements or pain caused by the injection of rocuronium was 22% to 84% (5–9). Most of these studies were focused on adult patients; few were on children. Therefore, it is not surprising to note that such generalized movement was seldom seen in pediatric patients (12). However, our results are congruent with another study in which an overall incidence of 84% was reported, with 48% of patients being children and adolescents who developed generalized movement or severe painful responses (5). A more frequent incidence of rocuronium-induced withdrawal reactions in women was reported in another study (13), but we found no sex difference in our pediatric patients. Inadequate sample size, specifically focused on sex differences, was probably one of the confounding factors.

Evidence is still not convincing enough to conclude that withdrawal movements associated with rocuronium would negatively affect patient outcome (13). These authors believed that such a pretreatment or intervention may increase costs without benefit to the

patient and may involve a risk of developing adverse allergic reactions. Unfortunately, we reported on a child who developed pulmonary aspiration secondary to gastric regurgitation caused by generalized spontaneous movements after the injection of rocuronium (14). Pain, emotional stress, and stimulation during the induction of anesthesia induce bronchospasm, asthma, or myocardial ischemia attack (15). Sometimes withdrawal movements can unexpectedly dislodge the venous catheter or cause injury during the induction of anesthesia. Caution should therefore be taken in the prevention of its occurrence. Various preventive methods have been proposed. For instance, pretreatment with midazolam, fentanyl, lidocaine, tramadol, or ondansetron provides protection in the reduction of localized pain (5-9,12,13). However, such protection is incomplete, with a failure rate of 28%-70%.

The exact mechanism of rocuronium-induced localized pain has not been well established. Two possible explanations have been suggested: low pH or the release of local mediators (3,6,16). Although the freshly prepared rocuronium bromide is an isotonic solution with a pH of 4, low pH is unlikely to be the cause, because IV injection of normal saline buffered to a pH of 4 was not associated with pain (4). Another mechanism of rocuronium-induced pain may be the release of local mediators such as histamine that directly irritate the venous nociceptors (17). It should be mentioned that some patients in our study had self-limiting erythema on the skin at the site of injection, suggesting histamine release. However, we could not differentiate in this study whether skin erythema was due to rocuronium or thiopental injection, because both drugs were given in rapid sequence (13). Our finding at least added further suggestion that histamine release was partly involved.

Pretreatment with small-dose ketamine has been demonstrated to reduce pain, without adverse effects, caused by the injection of propofol, as well as ischemic pain from tourniquet inflation (10,11). The activation of *N*-methyl-D-aspartic acid (NMDA) receptors results in an influx of calcium ions, which in turn stimulates the production of nitric oxide (NO) secondary to the activation of NO synthase. NO plays an important role in venous nociception in humans elicited by noxious chemical irritations such as bradykinin, but not by physical stimuli, including cold, heat, and mechanical (18). As a noncompetitive NMDA receptor antagonist, ketamine may attenuate withdrawal movements or pain caused by various chemical irritations through the blockade of NMDA receptor activation either in the vascular endothelium or in the central nervous system (19).

When administered IV for regional anesthesia or epidurally, ketamine can act like local anesthetics, producing analgesia (20-22). This local anesthetic action is also thought to be a possible mechanism by

which ketamine provides an attenuating effect on rocuronium-induced withdrawal movements or pain. Another explanation suggested is that pretreatment with ketamine, followed by thiopental administration, resulted in a deeper level of anesthesia, which could heighten the pain threshold in the central nervous system and thus explains the diminished incidence of withdrawal movements (23).

In conclusion, our results demonstrated that IV injection of rocuronium is frequently associated with withdrawal movements in most patients anesthetized with thiopental. Pretreatment with small-dose ketamine 0.2 mg/kg provides a simple and safe means for reducing the incidence of this withdrawal reaction.

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