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The Effect of Pretreatment with Thiopental on Reducing Pain Induced by Rocuronium Injection

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We examined whether pretreatment with a small dose of thiopental was effective in reducing pain induced by the intravenous injection of rocuronium. Withdrawal movement was used to assess pain reduction. Ninety patients were randomly assigned to one of two groups: patients in the control group were pretreated with 2 mL saline, and those in the thiopental group were pretreated with 2 mL (50 mg) thiopental. Thiopental 5 mg/kg was injected intravenously. After a loss of consciousness, the upper arm was compressed with a rubber tourniquet, and the pretreatment drugs were administered. Thirty seconds later the tourniquet was removed and 0.6 mg/kg rocuronium was administered. Withdrawal movement was assessed using a four-grade scale: no movement, movement limited to the wrist, to the elbow or to the shoulder. The frequency of withdrawal movement in the group pretreated with thiopental was lower than in the control group (34 vs. 13, $p < 0.05$). We concluded that pretreatment with 2 mL (50 mg) thiopental is effective in reducing pain caused by the intravenous injection of rocuronium.

Key Words: Pain, rocuronium, thiopental

INTRODUCTION

Rocuronium, a derivative of aminosteroid, is a non-depolarizing muscle relaxant with a rapid onset time and has a similar structure to vecuronium.[1,2] While rocuronium is a useful during endotracheal intubation, it induces pain during intravenous (IV) injection. If injected intravenously prior to the loss of consciousness, hot and burning sensations develop, and even if injected after the loss of consciousness by induction agents, a severe withdrawal movement, such as withdrawing the injected hand or arm, may occur due to pain.[3-5] Various studies have attempted to reduce this pain.

Previous studies have shown a reduction in pain to some degree with pretreatment using lidocaine,[6] fentanyl,[7] or an injection of a mixture of rocuronium and sodium bicarbonate.[8,9] Although the pathophysiological mechanism of the pain caused by the IV administration of rocuronium is not clear, it has been reported that the pain may be due to the activation of nociceptors by the osmolality or pH of the solution, or activation by the release of endogenous mediators, such as histamine, kinin, and other substances mediating inflammation.[4,10]

The aim of this study was to evaluate the effects of pretreatment with a small dose of thiopental on pain associated with the IV administration of rocuronium by assessing withdrawal movement.

MATERIALS AND METHODS

This study was performed after obtaining approval from the Ethics Committee at our hospital. The purpose and methods of the study were explained to the patients prior to the experiment and consent was obtained from each patient. This study was performed on 90 patients who were scheduled for elective surgery, who were ASA class I-II, and were between 16 to 69 years old. Patients who had a specific response to thiopental in their medical history, who had a respiratory disease such as asthma or chronic obstructive pulmonary disease, who were pregnant

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women, or who were being treated with analgesic drugs on the day of surgery were excluded from this study. In all patients, an 18-gauge catheter was inserted into a vein on the dorsum of the hand, and an IV infusion of lactated Ringer's solution was started. The patients were premedicated with glycopyrrolate and midazolam 30 minutes before the induction of anesthesia. All patients were monitored with an automatic noninvasive blood pressure measurement, an electrocardiogram, and pulse oximetry.

Patients were randomly divided to one of two groups: the control group (n = 45) pretreated with 2 mL of saline and the thiopental group (n = 45) pretreated with 2 mL (50 mg) of thiopental. After confirming that the IV infusion could be injected without resistance, anesthesia was induced with 2.5% thiopental 5 mg/kg. Just after the loss of consciousness, the route of the IV infusion was occluded by applying a rubber tourniquet at the middle of the forearm. If venous occlusion by the rubber tourniquet was not sufficient, manual compression was also applied. Pretreatment drugs were administered and the tourniquet was released after 30 seconds; IV infusion was applied sufficiently to ensure the removal of residual effects. Then, an intubated dose of 0.6 mg/kg rocuronium was injected intravenously for 5 seconds. The degree of the movement of the patients during the injection was divided into four grades and withdrawal movement was assessed and scored as follows: no movement = 0, movement limited to the hand = 1, movement limited to the forearm including the elbow joint = 2, and movement of the upper arm including the shoulder joint = 3.[11]

Age and weight were compared using the unpaired t-test and gender was compared using the Chi-square test. The risk degree for withdrawal movement was compared using the odds ratio and 95% confidence interval (CI), and withdrawal movements were compared using Fisher's exact test. A p value of less than 0.05 was considered significant.

RESULTS

The demographic characteristics (age, sex, and weight) were not significantly different between the groups (Table 1). Thirty-four of 45 patients (76%) in the control group and 13 of 45 patients (29%) in the thiopental pretreatment group showed withdrawal movement, which indicates that the odds ratio of withdrawal movement in the thiopental pretreatment group was significantly lower than the control group (Odds ratio: 0.131, 95% CI: 0.052-0.335). A comparison of the degree of withdrawal movement showed that the frequency of the each movement of hand, forearm, and upper arm in the thiopental pretreated group was significantly lower than in the control group: 11 vs. 18 (24.5% vs. 40%), 2 vs. 9 (4% vs. 20%), and 0 vs. 7 (0% vs. 16%), respectively (p< 0.05, Table 2). Within 24 hours after surgery, side effects such as pain, edema, and wheals in the injection area were not detected in any patients.

DISCUSSION

When rocuronium is injected intravenously, it causes pain in approximately 50-80% of patients,[3,4] and in unconscious patients, IV injection causes withdrawal movement of the hand, the arm, or the shoulder. Such withdrawal movement may induce pulmonary aspiration in children,[12] cause dislocation or displacement of the IV catheter resulting in difficulty in administrating additional drugs, and induce an emergency situation.

Table 1. Demographic Data

	Control group (n = 45)	Thiopental group (n = 45)
Sex (M/F)	25/20	17/28
Age (yrs)	41 ± 15	43 ± 15
Weight (kg)	61.2 ± 9.4	61.3 ± 9.1

Values are number of patients or mean ± SD. There were no significant differences between groups.

Table 2. Assessment of Withdrawal Movement During the Intravenous Injection of Rocuronium

Groups	No withdrawal movement	Withdrawal movement	Grading of withdrawal movement		
			Wrist	Elbow	Shoulder
Control	11 (24.4%)	34 (75.6%)	18 (40.0%)	9 (20.0%)	7 (15.6%)
Thiopental	32 (71.1%)*	13 (28.9%)*	11 (24.5%)*	2 (4.4%)*	0 (0%)*

Values are numbers of patients.
*$p<0.05$ compared with the control group.

The mechanism by which rocuronium causes pain has not yet been characterized, however, the pain is known to be induced by a low pH[13] or by the release of local mediators such as bradykinin.[4,10] Klement and Arndt 13 reported that IV injections with a pH lower than 4 induce pain, and the lower the pH, the more severe the pain. Rocuronium is a pH 4 isotonic solution[4] and the pain induced by IV injection of this drug has been reduced by injecting of a mix of $NaHCO_3$ and rocuronium. Several studies have reported that the cause of pain induced by IV injections may be a low pH.[8,9] In this study, we initially wanted to compare the effects of an IV injection of a mixture of thiopental and rocuronium (thus neutralizing the acidity) to pretreatment with thiopental on the frequency and severity of pain caused by the IV injection of rocuronium. However, because a mixture of the two drugs forms white precipitates, a study evaluating the mixture of thiopental and rocuronium could not be performed. In the study we conducted examining pretreatment with thiopental, of the 45 control patients pretreated with normal saline prior to the administration of the intubated dose of rocuronium, 16 patients (35.6%) showed severe withdrawal movement including the upper arm or shoulder. However in the 45 experimental patients pretreated with 2 mL (50 mg) thiopental, only 2 patients (4.4%) showed severe withdrawal movement ($p<0.05$). These results show that pretreatment with thiopental reduces pain induced by the IV injection of rocuronium.

Although the mechanism by which pretreatment with thiopental reduces the pain induced by the IV injection of rocuronium is unknown, it can be speculated that the following mechanisms, alone or in combination, are involved. First, the induction dose of thiopental 5 mg/kg may blunt the cognition of pain. However, because the same dose of thiopental was administered to the control group, it is believed that thiopental did not have a significant effect on the results. Although the dose of thiopental administered for pretreatment was small (50 mg), its effect on the frequency and severity of the pain cannot be ruled out. Second, when thiopental is administered as a pretreatment drug it may suppress the local cognition of pain through nociceptors present in the peripheral veins.[14-16] Third, the characteristics of pain from the IV injection of rocuronium appear immediately after the injection and severity decreases with repeated administration, which is similar to the characteristics of pain induced by IV injection of propofol; thus, mediators similar to those involved in the kininogen cascade related to pain induced by IV propofol injections may be involved with the pain associated with rocuronium injections.[4,10] Further, thiopental may block the release of mediators such as bradykinin.[16,17] Finally, concentrations of thiopental remaining on the walls of blood vessels may neutralize rocuronium and thus reduce the pain induced by IV injection.

In conclusion, pretreatment with 2 mL (50 mg) thiopental is considered to be effective in reducing pain induced by the IV injection of rocuronium.

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