



Original contribution

Rapid injection of rocuronium reduces withdrawal movement on injection[☆]

Yong Cheol Lee MD, PhD (Assistant Professor)^{*},
Young Ho Jang MD, PhD (Assistant Professor), Jin Mo Kim MD, PhD (Professor),
Sang Gyu Lee MD (Resident)

Department of Anesthesiology and Pain Medicine, Keimyung University, School of Medicine,
Joong-gu, Daegu, 700-712, Korea

Received 6 November 2007; revised 20 November 2008; accepted 25 November 2008

Keywords:

Injection pain;
Lidocaine pretreatment;
Rocuronium injection
pain;
Withdrawal movement;
Withdrawal response

Abstract

Study Objective: To test whether rapid injection of rocuronium reduces withdrawal movement on injection.

Design: Randomized, prospective trial.

Setting: Operating room in a university hospital.

Patients: 150 ASA physical status I and II patients aged 18 to 60 years, undergoing general anesthesia.

Interventions: Patients were randomized to three groups. After undergoing anesthesia induction with thiopental sodium, then 5 seconds later receiving a rubber tourniquet applied to the mid-forearm to stop intravenous (IV) flow by gravity, the pretreatment drug was injected. The tourniquet was held for 15 seconds then released, and 1.0 mg/kg of 1% rocuronium was injected IV. Group C patients (n = 50) were pretreated with 0.1 mL/kg of 0.9% NaCl and then injected with rocuronium slowly within 10 seconds. Group L patients (n = 50) were pretreated with 0.1 mL/kg of preservative-free 1% lidocaine and then injected with rocuronium slowly within 10 seconds. Group R patients (n = 50) were pretreated with 0.1 mL/kg of 0.9% NaCl and then rapidly injected with rocuronium within approximately one second (as quickly as possible).

Measurements: After injection of the patient with the study drug, a single anesthesiologist with no knowledge of the study protocol graded each patient's response as follows: 0 = no response; 1 = mild movement limited to the wrist only; 2 = moderate movement involving the elbow and shoulder; and 3 = severe movement involving more than one extremity.

Main Results: Group C had the most intense and frequent withdrawal response. The frequency and intensity of withdrawal movement was significantly less in Groups L and R than Group C. No significant difference in withdrawal response between Groups L and R was noted.

Conclusions: Withdrawal response can be significantly reduced for rocuronium injection without lidocaine pretreatment, simply through rapid injection.

© 2009 Elsevier Inc. All rights reserved.

[☆] Supported by a 2007 Bisa Research Grant from Keimyung University, Daegu, Korea.

^{*} Corresponding author. Tel.: +82 53 250 7193; fax: +82 53 250 7240.
E-mail address: yclee@dsmc.or.kr (Y.C. Lee).

1. Introduction

Rocuronium is a widely used nondepolarizing muscle relaxant of intermediate duration with a rapid onset [1]. Its

injection after induction of anesthesia has often been associated with pain-induced withdrawal movement near the site of injection [2,3], which is commonly reduced by pretreatment with lidocaine. Indeed, pain from rocuronium injection occurs in 50% to 80% of patients [2-5]. Attempts to reduce this adverse effect have included pretreatment or mixing rocuronium with a variety of drugs [3-10]. As far as we can determine, however, there have been no reports of studies of injection speed.

In principle, simply increasing the speed of injection might lessen the pain. Rapid injection would allow the rocuronium to be cleared from the vein and replaced with blood, whereas slow injection prolongs the drug's contact time with the endothelium. Whether rapid injection of rocuronium reduces pain-induced withdrawal movement was determined.

2. Materials and methods

After obtaining Keimyung University Hospital ethics committee approval and patients' informed consent, 150 ASA physical status I and II patients, aged 18-60 years, and undergoing general anesthesia, were enrolled in the study. Patients with neurologic deficits or allergies to thiopental sodium, rocuronium, or lidocaine were excluded from the study.

All patients were premedicated with 0.1 mg/kg of midazolam orally and 0.2 mg glycopyrrolate intramuscularly one hour before anesthesia induction. On patient arrival in the operating room, routine noninvasive monitoring was established and a 20-gauge intravenous (IV) catheter with a three-way stopcock attached was placed on the dorsum of the patient's hand. Free flow of lactated Ringer's IV fluid was confirmed.

Each group of patients underwent IV induction of anesthesia using 5 mg/kg of 2.0% thiopental sodium, followed by free flow of IV. Five seconds later, a rubber tourniquet was applied to the mid-forearm to stop the IV flow by gravity, and the pretreatment drug was injected. The tourniquet was maintained for 15 seconds and then released, and 1.0 mg/kg of rocuronium IV was injected. All study drugs were injected into a three-way stopcock directly connected to the IV catheter.

Patients were randomized to three groups via a table of computer-generated numbers. Group C patients (control group; $n = 50$) were pretreated with 0.1 mL/kg of 0.9% NaCl and then slowly injected with 1.0 mg/kg of rocuronium within 10 seconds. Group L patients (lidocaine group; $n = 50$) were pretreated with 0.1 mL/kg of preservative-free 1% lidocaine and then slowly injected with 1.0 mg/kg of rocuronium within 10 seconds. Group R patients (rapid-injection group; $n = 50$) were pretreated with 0.1 mL/kg of 0.9% NaCl and then rapidly injected with 1.0 mg/kg of rocuronium within approximately one second (as quickly as possible).

Table 1 Assessment of withdrawal movement on injection of rocuronium

Withdrawal score	Severity of withdrawal	Patient's response
0	None	None
1	Mild	Mild movement, limited to the wrist
2	Moderate	Moderate movement involving the elbow and shoulder
3	Severe	Severe movement involving more than one extremity

After injection of the study drug, a single anesthesiologist with no knowledge of the study protocol graded each patient's response, according to Table 1. After injection of the study drugs, the study was terminated. Then an opioid was used and the anesthetic was continued at the discretion of the attending anesthesiologist. We assessed erythema, thrombosis, and phlebitis of the vein by noting skin redness, vein hardness, and tenderness on vein palpation in the injected hand and arm immediately after injection, at one hour, and 24 hours after injection.

Demographic data were compared by one-way analysis of variance, and frequency of movement (response) was assessed by chi-square test. A P -value < 0.05 was considered statistically significant.

3. Results

There were no significant differences in demographic characteristics among groups regarding age, gender, body weight, or height (Table 2).

Fig. 1 shows the distribution of responses among the three groups. Group C had the most intense and frequent withdrawal response. Frequency and intensity of withdrawal response were significantly less in Groups L and R than Group C. There were significantly fewer withdrawal scores of 0 (no response) in Group C than Groups L and R ($P = 0.0001$ and 0.001 , respectively) and significantly more withdrawal scores of 2 (moderate response) in Group C than Groups L and R ($P = 0.004$ and 0.019 , respectively). Total frequency of response was significantly higher in

Table 2 Demographic characteristics

Group (n)	Age (yrs)	Gender (M/F)	Weight (kg)	Height (cm)
C (50)	41.0 \pm 13.3	19/31	61.2 \pm 9.9	164.8 \pm 8.5
L (50)	41.7 \pm 11.3	21/29	63.7 \pm 10.7	165.1 \pm 9.3
R (50)	43.4 \pm 12.0	18/32	59.8 \pm 9.6	162.5 \pm 8.0

Values are presented as means \pm SD. No statistical significance was found among groups. Group C was pretreated with NaCl, then slowly injected with rocuronium. Group L was pretreated with lidocaine, then slowly injected with rocuronium. Group R was pretreated with NaCl, then rapidly injected with rocuronium.

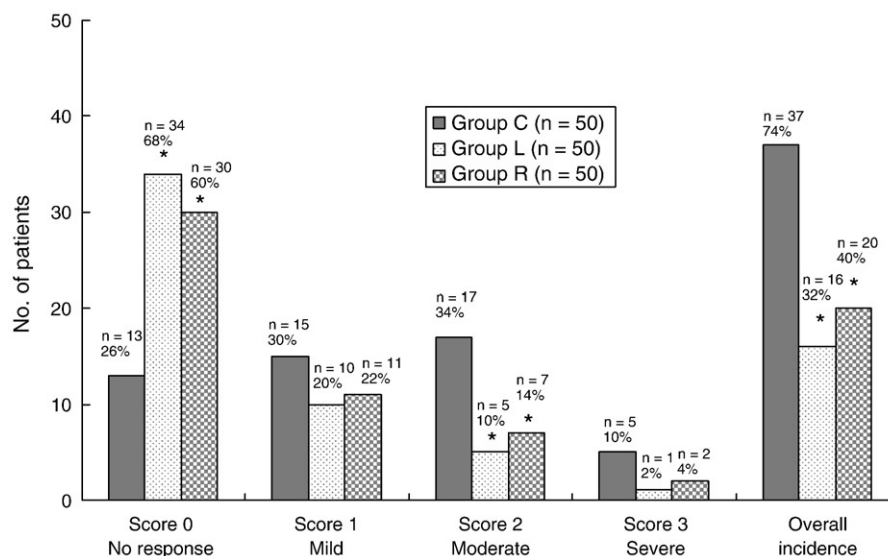


Fig. 1 Distribution of withdrawal scores according to severity of withdrawal movement and overall frequency of movement among groups. Group C was pretreated with NaCl and then slowly injected with rocuronium. Group L was pretreated with lidocaine and then slowly injected with rocuronium. Group R was pretreated with NaCl and then rapidly injected with rocuronium. * $P < 0.05$ vs. Group C.

Group C than in Groups L and R ($P = 0.0001$ and 0.001 , respectively). There was no significant difference in withdrawal response between Groups L and R.

There were no venous sequelae of erythema, thrombosis, or phlebitis in any patient during the 24 hours after the injection of rocuronium.

4. Discussion

Pain on rocuronium injection is an undesirable side effect for which the pathophysiologic mechanisms are still unclear. Possible causes include nociceptor activation by the nonphysiologic osmolality or pH of the solution and release of endogenous mediators such as histamine and bradykinin [11,12]. However, the absence of perivenous edema, erythema, and thrombophlebitis after injection renders these possibilities unlikely. Indeed, direct irritation of peripheral veins seems likely, because pain-induced movement appears immediately during injection and is usually limited to the arm in which the drug is infused. Peripheral veins are innervated with polymodal nociceptors [13] that mediate the response to injection of certain anesthetics that cause pain.

Over the last 10 years, a variety of drugs have been used in an attempt to ameliorate this adverse effect. Shevchenko et al. [3] reported that pain on rocuronium injection can be alleviated in children by pretreatment with IV lidocaine. Memiş et al. [9] concluded that ondansetron, lidocaine, tramadol, and fentanyl decrease the intensity of injection pain, with lidocaine being the most effective. Cheong and Wong [4] evaluated the effect of two different doses of

lidocaine on the frequency of injection pain and found that both 10 and 30 mg of IV lidocaine, given before the administration of rocuronium, significantly reduced the frequency and severity of injection pain, and that the larger dose was more effective. Tuncali et al. [14] introduced the dilution method, showing that the dilution of rocuronium to one mg/mL significantly reduced pain frequency and intensity compared with a 10 mg/mL dose. Moreover, dilution of rocuronium to 0.5 mg/mL with 0.9% NaCl completely prevented injection pain.

Besides lidocaine, several other drugs such as ondansetron [8,9], magnesium sulfate [10], sodium bicarbonate [10,15], fentanyl [16,17], and remifentanyl [18,19] are effective in reducing pain on rocuronium injection, but pretreatment of lidocaine or other drugs before rocuronium prolongs the time between anesthesia induction and neuromuscular block administration. In addition, most of these drugs can, even in rare cases, induce adverse effects such as allergic reaction, bradycardia, and hypotension.

The frequency and intensity of withdrawal movements were significantly lower in the lidocaine group than the control group. In addition, rapid injection of rocuronium also reduced both frequency and intensity of withdrawal movements and was as effective as lidocaine pretreatment.

Acknowledgments

We thank S.H. Kim, MD, for grading study participants' responses, and Katharine O'Moore-Klopf, for providing editorial assistance.

References

- [1] Silverman DG, Mirakhor RK. Nondepolarizing relaxants of the 1990s. In: Silverman DG, editor. *Neuromuscular block in perioperative and intensive care*. Philadelphia: J.B. Lippincott; 1994. p. 204-10.
- [2] Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? *Br J Anaesth* 1997;79:382-3.
- [3] Shevchenko Y, Jocsion JC, McRae VA, et al. The use of lidocaine for preventing the withdrawal associated with the injection of rocuronium in children and adolescents. *Anesth Analg* 1999;88:746-8.
- [4] Cheong KF, Wong WH. Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment. *Br J Anaesth* 2000;84:106-7.
- [5] Steegers MA, Robertson EN. Pain on injection of rocuronium bromide. *Anesth Analg* 1996;83:203.
- [6] Joshi GP, Whitten CW. Pain on injection of rocuronium bromide. *Anesth Analg* 1997;84:228.
- [7] Ruetsch YA, Borgeat A. Withdrawal movements associated with the injection of rocuronium. *Anesth Analg* 2000;90:227-8.
- [8] Reddy MS, Chen FG, Ng HP. Effect of ondansetron pretreatment on pain after rocuronium and propofol injection: a randomised, double-blind controlled comparison with lidocaine. *Anaesthesia* 2001;56:902-5.
- [9] Memiş D, Turan A, Karamanlioğlu B, Süt N, Pamukçu Z. The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol, and fentanyl. *Anesth Analg* 2002;94:1517-20.
- [10] Turan A, Memiş D, Karamanlioğlu B, Süt N, Pamukçu Z. The prevention of pain from injection of rocuronium by magnesium sulphate, lignocaine, sodium bicarbonate and alfentanil. *Anaesth Intensive Care* 2003;31:277-81.
- [11] Klement W, Arndt JO. Pain on I.V. injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. *Br J Anaesth* 1991;66:189-95.
- [12] Lockey D, Coleman P. Pain during injection of rocuronium bromide. *Anaesthesia* 1995;50:474.
- [13] Arndt JO, Klement W. Pain evoked by polymodal stimulation of hand veins in humans. *J Physiol* 1991;440:467-78.
- [14] Tuncali B, Karci A, Tuncali BE, et al. Dilution of rocuronium to 0.5 mg/mL with 0.9% NaCl eliminates the pain during intravenous injection in awake patients. *Anesth Analg* 2004;99:740-3.
- [15] Chiarella AB, Jolly DT, Huston CM, Clanachan AS. Comparison of four strategies to reduce the pain associated with intravenous administration of rocuronium. *Br J Anaesth* 2003;90:377-9.
- [16] Ahmad N, Choy CY, Aris EA, Balan S. Preventing the withdrawal response associated with rocuronium injection: a comparison of fentanyl with lidocaine. *Anesth Analg* 2005;100:987-90.
- [17] Borgeat A, Kwiatkowski D, Ruetsch YA. Spontaneous movements associated with rocuronium injection: the effects of prior administration of fentanyl. *J Clin Anesth* 1997;9:650-2.
- [18] Oh AY, Seo KS, Goo EK, Park YO, Kim SJ, Kim JH. Prevention of withdrawal movement associated with injection of rocuronium in children: comparison of remifentanyl, alfentanil and fentanyl. *Acta Anaesthesiol Scand* 2007;51:1190-3.
- [19] Kim JY, Kim JY, Kim YB, Kwak HJ. Pretreatment with remifentanyl to prevent withdrawal after rocuronium in children. *Br J Anaesth* 2007;98:120-3.