Kaohsiung Journal of Medical Sciences (2014) 30, 566–569

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.kjms-online.com

ORIGINAL ARTICLE

The effect of intravenous paracetamol for the prevention of rocuronium injection pain

Sennur Uzun*, **İsmail A. Erden, Ozgur Canbay, Ulku Aypar**

Department of Anesthesiology and Reanimation, Faculty of Medicine, Hacettepe University, Sihhiye, Ankara, Turkey

Received 21 February 2014; accepted 3 July 2014
Available online 22 September 2014

KEYWORDS
Analgesics;
Neuromuscular nondepolarizing agents;
Nonnarcotics;
Paracetamol;
Rocuronium

Abstract Rocuronium is a nondepolarizing neuromuscular blocking agent used in anesthesia induction and is associated with considerable discomfort and burning pain during injection, which is reported to occur in 50–80% of patients. This study was carried out to investigate the effectiveness of intravenous paracetamol pretreatment compared with lidocaine and normal saline to prevent rocuronium injection pain. The study included 150 ASA I–II patients undergoing elective orthopedic, gastrointestinal, and gynecological procedures under general anesthesia. They were allocated into three groups according to pretreatment drugs: lidocaine (40 mg) ($n = 50$), paracetamol ($n = 50$), and normal saline group ($n = 50$). Before anesthesia induction with propofol, all patients were pretreated with rocuronium. The pain caused by the injection was evaluated. Local signs were assessed on the arm at the end of the injection, as well as 24 hours after recovery from anesthesia. There were no patients with blurred speech or vision and there was no respiratory depression in any group after pretreatment with the study drug. The level of pain on injection was statistically lower in those who had received paracetamol compared to normal saline ($p = 0.009$). There were more patients in the saline group with severe pain ($p < 0.001$). Paracetamol relieved the rocuronium injection pain better than normal saline but lidocaine was the best of the three drugs ($p < 0.001$).

Conflicts of interest: All authors declare no conflicts of interest.

* Corresponding author. Department of Anesthesiology and Reanimation, Faculty of Medicine, Hacettepe University, Sihhiye, Turkey.
E-mail address: sennuruzun1@gmail.com (S. Uzun).

http://dx.doi.org/10.1016/j.kjms.2014.08.002

Introduction

Rocuronium is a nondepolarizing neuromuscular blocking agent of rapid onset and intermediate duration of action [1,2]. It is widely used in anesthesia induction and is associated with considerable burning pain during injection, which has been reported to occur in 50–80% of patients [3–8]. The factors affecting the degree of pain are the site of injection, the dose of rocuronium, and pretreatment with midazolam, fentanyl, remifentanil, and lidocaine [9–12].

One hypothesis about the mechanism of pain induced by the intravenous injection of drugs is the stimulation of polymodal nociceptors, leading to the release of endogenous pain mediators such as prostaglandins. This stimulation is thought to be caused by the unphysiological osmolarity or pH of the drug solution [13]. Although the rocuronium preparation is isotonic, it has a pH of 4, which may explain its association with pain on intravenous injection [13].

Animal studies have revealed that the antinociceptive effects of paracetamol reflect a combination of peripheral and central actions resulting from COX-2 inhibition [14,15]. The peripheral action of acetaminophen suggests that intravenous acetaminophen with venous occlusion could decrease rocuronium injection pain. In a recent study, it was demonstrated that paracetamol selectively suppressed peripheral PGE2 release and increased COX-2 gene expression in a clinical model of acute inflammation [16]. In another study, paracetamol showed selectivity for inhibition of the synthesis of prostaglandins and related factors [17]. Although acetaminophen does not inhibit COX enzymes at therapeutic concentrations *in vitro*, it is shown to inhibit a variant of the COX enzymes *in vivo* [18]. In light of these findings, we aimed to investigate the effect of paracetamol on rocuronium injection pain and compare it with lidocaine and normal saline, as there was no study investigating this in the literature.

Materials and methods

After institutional ethics committee approval, written informed consent was obtained from 150 ASA I–II patients undergoing elective orthopedic, gastrointestinal, and gynecological procedures under general anesthesia. The study lasted for 3 months and was carried out in a university hospital.

Patients with chronic pain syndromes, neurological deficits, thrombophlebitis, difficult venous access and estimated difficult airway, patients with paracetamol and local anesthetic allergies, and those who had taken an analgesic within the previous 24 h were excluded. Subjects were randomly allocated to one of three groups by a computer-generated randomized number in a sealed envelope. The test solutions were prepared in identical syringes by another investigator and covered, therefore the investigator who assessed the patient's response was unaware of the group.

Patients were monitored with an electrocardiogram, pulse oximetry, and noninvasive blood pressure measurement. A 20-gauge cannula was inserted into the dorsum of the hand and lactated Ringer's infusion was infused. Lactated Ringer's infusion was stopped and the arm with the intravenous line was elevated for 20 seconds for gravity to drain the venous blood. Noninvasive blood pressure measurement using a pneumatic tourniquet inflated to 70 mmHg was used to occlude the venous drainage of the upper arm while elevated. After lowering the arm, patients were pretreated with one of the pretreatment solutions; 40 mg lidocaine diluted to 5 mL (Group I), 50 mg intravenous paracetamol (5 mL, 10 mg/mL) (Group II) or 5 mL normal saline (Group III). After 2 minutes stasis, the tourniquet was released and 0.6 mg/kg of 1% rocuronium at room temperature was injected over 10 seconds. An independent blinded anesthetist asked whether the patient had any pain on the dorsum of the hand and evaluated the pain score as 0–3 (0: no pain, 1: mild pain, 2: moderate, and 3: severe pain, in accordance with the scale advocated by McCrirrick and Hunter [19], Table 1) during the injection of the pretreatment drug and rocuronium. Immediately after the evaluation of the pain, general anesthesia was induced with propofol and fentanyl. The anesthesia was continued with an appropriate technique at the discretion of the attending anesthetist.

Signs of neuromuscular blockage effects, such as impaired speech, blurred vision, or respiratory depression were recorded. Local signs such as erythema and redness on the arm where rocuronium was injected were assessed at the end of the injection as well as 24 hours after recovery from anesthesia [20].

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS 9.05 for Windows; SPSS Inc. Chicago, IL, USA). Based on the estimated incidence of 80%, a power analysis indicated that a sample size of 50 patients per group was sufficient to have 80% power (type II error $\beta = 0.2$) to detect 50% difference in the incidence of pain among three groups at 95% significance level (type I error $\alpha = 0.05$). Patient characteristics were analyzed using one-way ANOVA and Chi-square tests. The Kruskal-Wallis test was used for the incidence of rocuronium injection pain. Statistical significance was defined as $p < 0.05$.

Table 1 Assessment of pain [14].

Pain score	Degree of pain	Response
0	None	Negative response to questioning
1	Mild	Pain reported in response to questioning only without any behavioral signs
2	Moderate	Pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning
3	Severe	Strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears

Table 2 Mean baseline data (± standard deviation).

	Lidocaine ($n = 50$)	Paracetamol ($n = 50$)	Normal saline ($n = 50$)
Age, y	41.8 ± 13.9	42.7 ± 11.9	41.7 ± 13.3
Body weight, kg	73.3 ± 14.5	68.7 ± 14.9	71 ± 12.2
Sex, M/F	20/30	21/29	21/29

Results

There were no differences between the three groups in respect to age, body weight, and sex distribution (Table 2). There were no patients with impaired speech or blurred vision or respiratory depression in any group after the pretreatment drug injection.

The overall incidence of rocuronium injection pain in the three groups is shown in Table 3. The incidence of severe pain related to pretreatment drug injection was 2% in the lidocaine group, whereas there were no patients with severe pain in the intravenous paracetamol and normal saline groups. Thirty-eight patients (76%) in the lidocaine group, 45 patients (90%) in the intravenous paracetamol group and 46 patients (92%) in the normal saline group had no pain on pretreatment drug injection. There was a statistically significant difference between the lidocaine and normal saline groups ($p = 0.024$).

During the first 24 hours after the operation, there were no complications such as redness, tenderness, pain, or allergic reaction at the injection site.

Discussion

In this study, it was demonstrated that intravenous paracetamol was effective in preventing rocuronium injection pain during anesthesia induction compared with normal saline but was not better than lidocaine. The injection pain can be attenuated by pretreatment with intravenous lidocaine [7,8,21]. Cheong and Wong compared the influence of two doses of lidocaine pretreatment (10 mg and 30 mg, 10 seconds after pretreatment) in adult patients and found that both significantly reduced the incidence and severity of the pain, and that larger doses were more effective [8]. Previous studies have shown that the incidence of rocuronium injection pain was 7% with 30 mg lidocaine, 37% with 10 mg lidocaine and 77% with saline pretreatment [8]. Ahmad et al. found an incidence of 30% with 40 mg lidocaine and 57% with saline pretreatment without tourniquet technique and with an interval of 2 minutes between lidocaine and rocuronium injection [10]. We have selected the same dose as in the previous study with venous occlusion and gravity drainage technique. Another reason for the lidocaine dose was to enable the double blindness of the study, as 5 mL lidocaine is equivalent to 40 mg (0.8%). In our study, 40 mg intravenous lidocaine produced a statistically significant reduction in the incidence of pain compared with saline ($p = 0.009$). The proportion of patients with no pain was 48%. This is the first study showing the effect of intravenous paracetamol in the prevention of rocuronium injection pain using the venous occlusion method.

The incidence of pain during the injection related to pretreatment drugs has to be considered when choosing the pretreatment drug. Mild pain during intravenous pretreatment with paracetamol was 10%, as compared with 24% for lidocaine and 8% for saline groups in this study. Paracetamol caused less pain during pretreatment compared with lidocaine ($p = 0.009$). This is an advantage over lidocaine. Trying to treat the painful state with a painful drug is not rational. The perfect technique does not yet exist but the best method seems to be lidocaine pretreatment as it demonstrates more potent pain relief.

The mechanism of rocuronium injection pain is still unclear. Peripheral veins are innervated with nociceptors that mediate the response to the injection of certain anesthetics that cause pain [13]. Recently, it was concluded that the algogenic effect of aminosteroidal neuromuscular-blocking drugs could be attributed to a direct activation of C-nociceptors. Rocuronium injection increases bradykinin concentrations in the skin, and the algogenic effect of rocuronium may result from direct activation of C-nociceptors with concomitant release of the calcitonin gene-related peptide and prostaglandin E2 [21]. Another mechanism of pain after rocuronium injection may be the release of local mediators such as histamine and kinins. Lack of erythema and warmth in the surrounding tissue after injection, however, makes histamine release unlikely [22].

Venous occlusion allows the study of the peripheral action of drugs without a central effect, similar to a Bier block [23]. It is a technique that has been used for the pretreatment of rocuronium injection pain [7,24]. It is suitable for studying the peripheral action of pretreatment drugs as in our study. The use of lidocaine for the prevention of pain caused by the injection of some anesthetic drugs is well established in the literature [8].

Table 3 Pain assessment of patients after pretreatment and rocuronium.

Degree of pain	After pretreatment			After rocuronium		
	Lidocaine	Paracetamol	Normal saline	Lidocaine	Paracetamol	Normal saline
0 (none)	38 (76%)	45 (90%)	46 (92%)	24 (48%)[a]	11 (22%)[c]	1 (2%)
1 (mild)	8 (16%)[b]	5 (10%)	4 (8%)	17 (34%)	22 (44%)[c]	10 (20%)
2 (moderate)	3 (6%)[b]	0 (0%)	0 (0%)	6 (12%)[a]	14 (28%)	16 (32%)
3 (severe)	1 (2%)[b]	0 (0%)	0 (0%)	3 (6%)	3 (6%)[c]	23 (46%)

[a] $p = 0.009$, lidocaine group vs. paracetamol group.
[b] $p = 0.024$, lidocaine group vs. normal saline group.
[c] $p < 0.001$, paracetamol group vs. normal saline group.

We evaluated the degree of pain using the scale advocated by McCrirrick and Hunter graded between 0 and 3 [19]. This verbal rating scale has been used in several reports to assess the intensity of rocuronium injection pain [22,24]. We questioned the patients when they were awake. Because the patients were not asleep, the evaluation result is more accurate.

Limitation

There was no rescue medicine to alleviate the injection pain of the patients in saline group. This was a weakness of the study.

Conclusion

In conclusion, we demonstrated that intravenous paracetamol (50 mg) is effective in decreasing the intensity of rocuronium injection pain compared to lidocaine but is not as effective as lidocaine and it does not cause any injection pain by itself. This result leads us to believe that the mechanism of rocuronium pain is very closely related to the release of local mediators and that acute inflammation is revealed by intravenous paracetamol.

Acknowledgments

The funding for the study was supported by the anesthesia department of the university.

References

[1] Feldman SA. Rocuronium-onset times and intubating conditions. Eur J Anaesthesiol (Suppl) 1994;9:49—52.
[2] Sieber TJ, Zbinden AM, Curatolo M, Shorten GD. Tracheal intubation with rocuronium using the 'Timing Principle'. Anesth Analg 1998;86:1137—40.
[3] Borgeat A, Kwiatowski D. Spontaneous movements associated with rocuronium: is pain on injection the cause? Br J Anaesth 1997;79:382—3.
[4] Moorthy SS, Dierdorf SF. Pain on injection of rocuronium bromide. Anesth Analg 1995;80:1067.
[5] Lockey D, Coleman P. Pain during injection of rocuronium bromide. Anesthesia 1995;50:474.
[6] Steegers MAH, Robertson EN. Pain on injection of rocuronium bromide. Anesth Analg 1996;83:203.
[7] Shevchenko Y, Jocson JC, McRae VA, Stayer SA, Schwartz SE, Rehman M, 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.
[8] Cheong KF, Wong WH. Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment. Br J Anaesth 2000;84:106—7.
[9] Joshi GP, Whitten CW. Pain on injection of rocuronium bromide. Anesth Analg 1997;84:228.
[10] Ahmad N, Choy CY, Aris EA, Balan SB. Preventing the withdrawal response associated with rocuronium injection: a comparison of fentanyl with lidocaine. Anesth Analg 2005;100:987—90.
[11] 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.
[12] Kim KS, Kim YS, Jeon WJ, Yeom JH. Prevention of withdrawal associated with the injection of rocuronium in adults and children. J Clin Anesth 2006;18:334—8.
[13] Kelment W, Arndt JO. Pain on i.v. injection of some anesthetic agents is evoked by the unphysiological osmolarity or pH of their formulations. Br J Anaesth 1991;66:189—95.
[14] Abbott FV, Hellemans KG. Phenacetin, acetaminophen and dipyrone: analgesic and rewarding effects. Behav Brain Res 2000;112:177—86.
[15] Hinz B, Cheremina O, Brune K. Acetaminophen (paracetamol) is a selective cyclooxygenase-2 inhibitor in man. FASEB J 2008;22:383—90.
[16] Lee YS, Kim H, Brahim JS, Rowan J, Lee G, Dionne RA. Acetaminophen selectively suppresses peripheral prostaglandin E2 release and increases COX-2 gene expression in a clinical model of acute inflammation. Pain 2007;129:279—86.
[17] Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of paracetamol: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. Inflammopharmacology 2013;21:201—32.
[18] Simmons DL, Botting RM, Robertson PM, Madsen ML, Vane JR. Induction of an acetaminophen-sensitive cyclooxygenase with reduced sensitivity to nonsteroid antiinflammatory drugs. Proc Natl Acad Sci USA 1999;96:3275—80.
[19] McCrirrick A, Hunter S. Pain on injection of propofol: the effect of injectate temperature. Anaesthesia 1990;45:443—4.
[20] Zacharias M, Clarke SJ, Dundee JW, Johnston SB. Venous sequelae following etomidate. Br J Anaesth 1979;51:779—83.
[21] Blunk JA, Seifert F, Schmelz M, Reeh PW, Koppert W. Injection pain of rocuronium and vecuronium is evoked by direct activation of nociceptive nerve endings. Eur J Anaesthesiol 2003;20:245—53.
[22] Reddy MS, Chem FG, Ng HP. Effect of ondansetron pretreatment on pain after rocuronium and propofol injection: a randomised, double-blind controlled comparison with lidocaine. Anaesthesia 2001;56:879—905.
[23] Koppert W, Sittl R, Schmelz M. The Bier block as an experimental tool to differentiate peripheral and central effects of analgesics on people. Schmerz 2000;14:69—76.
[24] Memis D, Turan A, Karamanlioglu 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.