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Effects of Pretreatment with Lidocaine or Ketamine on Injection Pain and Withdrawal Movements of Rocuronium

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Aims: The incidence and severity of pain on injection of rocuronium and its pretreatment with saline, lidocaine or ketamine were evaluated.

Materials and Methods: One hundred and twenty patients were randomized into three groups to receive intravenous (i.v.) lidocaine 30 mg (Group Lidocaine, n=40), ketamine 0.5 mg/kg (Group Ketamine, n=40) or saline 2 ml (Group Saline, n=40). Thirty seconds after the pretreatment drug, intubation dose of rocuronium (0.6 mg/kg) was injected by i.v. route in 5 seconds. The pain and the withdrawal movements were assessed by a five-point and a four-point scale, respectively. Six hours after anesthesia, patients were asked whether they recalled pain in the arm during induction of anesthesia.

Results: The incidence of pain response after rocuronium injection (grade 2 or more) was 82.5%, 12.5% and 62.5% in saline, lidocaine and ketamine groups, respectively. The median pain score in Group Lidocaine was significantly lower than those of groups Ketamine and Saline ($P < 0.001$). The incidence of withdrawal movements was 32.5%, 2.5% and 15% in the saline, lidocaine and ketamine groups, respectively. The median withdrawal movement score was significantly lower only in Group Lidocaine compared to Group Saline ($P=0.011$). There was no difference in reported pain or withdrawal movements between men and women.

Conclusions: For decreasing the severity of pain and withdrawal movements induced by rocuronium injection, lidocaine is more effective when compared with ketamine.

Key Words: Rocuronium, injection pain, withdrawal movement, lidocaine, ketamine

Rocuronium'a Bağlı Enjeksiyon Ağrısı ve Kol Çekme Hareketine Lidokain ve Ketamin ile Ön Tedavinin Etkileri

Amaç: Salin, lidokain ve ketamin ile ön tedavinin rocuronium enjeksiyon ağrısınının sıklığı ve şiddetine olan etkileri incelendi.

Yöntem ve Gereç: Genel anestezi uygulanacak olan 120 hasta randomize olarak intravenöz (i.v.) 30 mg lidokain (Grup lidokain, n=40), 0.5 mg/kg ketamin (Grup ketamin, n=40) veya 2 ml salin (Grup salin, n=40) verilmek üzere üç gruba ayrıldı. Ön tedavi ilacından 30 saniye sonra entübasyon dozunda rocuronium (0.6 mg/kg) 5 saniyede i.v. olarak verildi. Ağrı ve kol çekme hareketleri sırasıyla beş nokta ve dört nokta skalaları ile değerlendirildi. Anesteziden 6 saat sonra hastalarda anestezi indüksiyonu sırasındaki ağrı sorgulandı.

Bulgular: Rocuronium enjeksiyonu sonrasında ağrı cevabının (evre 2 ya da daha fazla) sıklığı salin, lidokain ve ketamin gruplarında sırasıyla % 82.5, % 12.5 ve % 62.5 olarak gözlendi. Lidokain grubundaki median ağrı skoru ketamin ve salin gruplarına kıyasla anlamlı düşük bulundu ($P < 0.001$). Kol çekme hareketinin sıklığı salin, lidokain ve ketamin gruplarında sırasıyla % 32.5, % 2.5 ve % 15 olarak tespit edildi. Median kol çekme hareketi skoru lidokain grubunda salin grubuna kıyasla anlamlı düşük bulundu ($P = 0.011$). Ağrı ve kol çekme hareketi değerlendirildiğinde kadın ve erkek cinsiyet arasında fark gözlenmedi.

Sonuç: Rocuronium enjeksiyonuna bağlı ağrının şiddetinin azaltılmasında ve kol çekme hareketinin giderilmesinde lidokain ketamin'e kıyasla daha etkili bir ajandır.

Anahtar Sözcükler: Rocuronium, enjeksiyon ağrısı, kol çekme hareketi, lidokain, ketamin

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Introduction

Rocuronium bromide is a steroidal nondepolarizing neuromuscular blocking drug characterized by rapid onset with an intermediate duration (1). When rocuronium was given intravenously (i.v.) in awake patients, most of them complained of severe burning pain in their arm (2). Even after loss of consciousness from induction drugs, i.v. injection

of rocuronium can still elicit withdrawal of hand or generalized movement of the body. There are several reports of sudden flexion and withdrawal movements of the wrist or arm to which rocuronium was administered (3,4). Pretreatment with ondansetron (5), fentanyl (6), lidocaine (7), tramadol (8), and ketamine (9) has been used with the aim of reducing this pain and the withdrawal movements. Unfortunately, the failure rate of these pretreatments in adults is between 7% and 35%.

To the best of our knowledge, no other study has yet compared the effect of lidocaine and ketamine on rocuronium injection pain and withdrawal movements. The purpose of this study was to evaluate efficacy of pretreatment with i.v. lidocaine and ketamine on preventing the pain and withdrawal movements associated with rocuronium administration in awake patients.

Materials and Methods

After obtaining approval from the Institutional Ethics Committee and informed consent, 120 American Association of Anesthesiologists (ASA) I-II patients, aged 20-60 years and undergoing elective orthopedic and general surgical procedures requiring general anesthesia, were enrolled in this double-blind, randomized study. No premedication was given. Patients with diabetes mellitus, operation time longer than 3 hours (h) or shorter than 1 h, known allergy, neurological or psychiatric disorders, long-term analgesic treatment, thrombophlebitis, or with poor dorsal hand veins were excluded.

In the operating room, a 20-gauge cannula was placed in a vein on the dorsum of the hand, and i.v. infusion of 0.9% NaCl was started. Standard monitoring was used. All the solutions were at ambient temperature (20-24ºC) and the calculated drug doses were adjusted to a volume of 2 ml with saline solution. Patients were allocated randomly to one of three groups: Group Lidocaine (n=40) received 30 mg 2% lidocaine, Group Ketamine (n=40) received 0.5 mg/kg ketamine and Group Saline (n=40) received saline. Study drugs were administered in a double-blind fashion, and syringes were prepared by an investigator who did not participate in the evaluation of injection pain. The induction regimen was standardized as follows: The study drug (lidocaine, ketamine or saline) according to the patient's group assignment was injected and then i.v. saline infusion was ceased. Thirty seconds after the pretreatment drug, intubation dose of rocuronium (0.6 mg/kg) was injected by i.v. route in 5 seconds. The patients were asked during this period if they had any pain at the injection site. Patients who responded positively were asked to rank their pain on a five-point scale (6) (Table 1). Withdrawal movements were also assessed and scored as follows: no movements = 0, movement limited to hand = 1, movement limited to the forearm including the elbow joint = 2, and movement of the upper arm including the shoulder joint = 3 (7). After the administration of rocuronium, Na-thiopental was administered until loss of consciousness, and anesthesia proceeded as planned. Six hours after anesthesia, patients were asked whether they recalled pain in the arm during induction of anesthesia, and the intensity of the pain was again evaluated according to a five-point scale (Table 2).

Statistical analysis was performed with the SPSS package version 11.5. While descriptive statistics were expressed as means ±SD for continuous data, original data were shown as median (min-max). Mean age, height and weight were evaluated by one-way ANOVA. The differences among groups regarding medians were

Table 1. Patient characteristics (Mean±SD).

	Saline group (n=40)	Lidocaine group (n=40)	Ketamine group (n=40)	P
Age (yr)	38.5 ± 9.5	37.7 ± 10.0	37.0 ± 12.1	0.825[a]
Sex (M/F)	19 / 21	19 / 21	21 /19	0.875[b]
Height (cm)	167.5 ± 7.8	167.5 ± 6.6	169.9 ± 8.4	0.288[a]
Weight (kg)	72.9 ± 11.1	72.5 ± 10.8	76.7 ± 11.2	0.173[a]

No statistical difference was found between groups.
[a] One-way ANOVA
[b] Pearson chi-square test.

Table 2. Patient assessment of pain during injection of rocuronium.

Pain score	Severity of pain	Patient's response when questioned regarding pain/discomfort
0	None	No pain or discomfort
1	Mild	Mild pain or discomfort
2	Moderate	Moderate pain or discomfort
3	Severe	Pain or discomfort reported spontaneously and described as becoming severe
4	Very severe	Pain or discomfort reported to be very severe and associated with a strong vocal response, hand or arm withdrawal, facial grimacing, or crying

compared by Kruskal–Wallis test. When the P-value from Kruskal-Wallis test statistics was statistically significant, multiple tests were used. Comparisons for categorical variables were performed using X^2 test. P<0.05 was considered as statistically significant.

Results

The data from all 120 patients were analyzed without dropouts. The demographic data are summarized in Table 2. There was no difference in patient characteristics between the three groups in terms of age, sex distribution, body weight or height.

The incidence of pain response after rocuronium injection (grade 2 or more) was 82.5%, 12.5%, and 62.5% in saline, lidocaine and ketamine groups, respectively (Table 3). The saline group produced the most intense pain response, with the median pain score of 4 (min: 0, max: 4). In this group, 57.5% of the patients reported very severe pain and only 5% of the patients had no pain.

In the lidocaine group, injection of 30 mg lidocaine significantly reduced the incidence and intensity of pain compared to saline and ketamine groups (P<0.001); in this group, 12.5% of the patients complained of pain and the median pain score reduced to 1 (min: 0, max: 4). Only 1 (2.5%) patient in this group had very severe pain.

Ketamine 0.5 mg/kg injection decreased the intensity of pain to 2 (min: 0, max: 4) and this was statistically significant compared to the saline group (P = 0.007). While 13 (32.5%) patients had very severe pain, 10 (25 %) patients had no pain.

The incidence of withdrawal movements after rocuronium injection was 32.5%, 2.5% and 15% in the saline, lidocaine and ketamine groups, respectively (Table 4). The median withdrawal movement was significantly lower only in the lidocaine group [0 (min: 0, max: 1)] compared to the saline group [0 (min: 0, max: 2)] (P = 0.011). None of the patients showed severe withdrawal reaction and only 3 patients (7.5%) in saline group showed grade 2 withdrawal movements.

At the postoperative evaluation, pain score was significantly reduced both in Group Lidocaine [1 (min: 0, max: 4)] and Group Ketamine [2 (min: 0, max: 4)] when compared with Group Saline [4 (min: 0, max: 4)] (P <

Table 3. Incidence of pain on injection with rocuronium.

Pain scores	Saline group (n=40)	Lidocaine group (n=40)	Ketamine group (n=40)
0	2(5%)	16(40%)	10(25%)
1	5(12.5%)	19(47.5%)	5(12.5%)
2	5(12.5%)	3(7.5%)	7(17.5%)
3	5(12.5%)	1(2.5%)	5(12.5%)
4	23(57.5%)	1(2.5%)	13(32.5%)
Pain score 2 or more	33(82.5%)	5(12.5%)*#	25(62.5%)**

*P < 0.01 vs. saline group.
**P = 0.45 vs. saline group.
#P < 0.01 vs. ketamine group.

Table 4. Incidence of withdrawal movements.

Withdrawal movements	Saline group (n=40)	Lidocaine group (n=40)	Ketamine group (n=40)
0	27(67.5%)	39(97.5%)	34(85%)
1	10(25%)	1(2.5%)	6(15%)
2	3(7.5%)	0	0
3	0	0	0
1 or more	13(32.5%)	1(2.5%)*	6(15%)

*P < 0.001vs. saline group.

0.001, P=0.003; respectively). Group Lidocaine also had significantly lower pain scores than Group Ketamine (P < 0.002) (Figure).

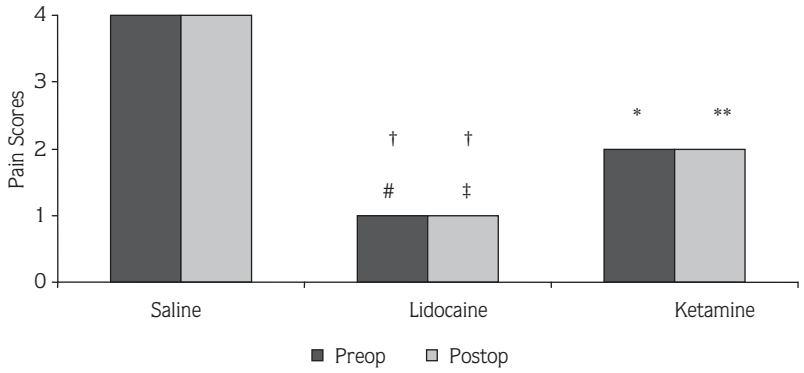
There was no difference in reported pain or withdrawal movements between men and women.

Discussion

In the present study, the effect of pretreatment with lidocaine or ketamine on injection pain and withdrawal movements of rocuronium was compared and it was shown that both lidocaine and ketamine decreased the severity of pain caused by i.v. rocuronium injection. Moreover, lidocaine decreased the incidence of pain and prevented withdrawal movements associated with i.v. rocuronium injection more effectively than ketamine.

Pain and the occurrence of sudden flexion and withdrawal movements of the wrist and arm (3-5,8-10) are common on injection of rocuronium. When rocuronium was injected in subparalyzing doses, 50-80% of the patients reported a severe, burning pain (9). Peripheral veins are innervated with polymodal nociceptors (11), which mediate the response to the injection of certain anesthetics that cause pain. Blunk et al. (12) concluded that the algogenic effect of amino-steroidal neuromuscular blocking drugs could be attributed to a direct activation of C-nociceptors.

Rocuronium bromide is formulated with sodium acetate, sodium chloride, or acetic acid to produce a solution of pH 4; Lockey and Coleman (13) postulated that the low pH was a possible cause of pain on injection. However, Borgeat and Kwiatkowski (3) speculated that



† Statistically significant compared to saline group (P<0.001).

Statistically significant compared to ketamine group (P<0.001).

‡ Statistically significant compared to ketamine gr oup (P=0.002).

* Statistically significant compared to saline grou p (P=0.007).

** Statistically significant compared to saline gro up (P=0.003).

Figure. Evaluation of intensity of pain.

local release of mediators might be implicated because of the short duration of the pain and the marked decrease or absence of pain during a second administration.

Various methods have been proposed and compared to find the most effective treatment to prevent the occurrence of injection pain and withdrawal movements caused by rocuronium (4,5,7,10,14-16). The present study was designed since no study to date has compared the effects of lidocaine and ketamine pretreatments for this purpose.

Cheong and Wong (4) compared whether pretreatment with lidocaine 10 mg or 30 mg i.v. decreased the incidence and severity of injection pain on rocuronium, and found that 30 mg was more effective. Based on their results we used 30 mg lidocaine in our study.

Mahajan et al. (16) reported that 20 mg ketamine pretreatment significantly reduced the pain associated with the injection of rocuronium in adults. Ketamine hydrochloride is a noncompetitive antagonist of N-methyl-D aspartate (NMDA) receptor and has analgesic properties in subanesthetic doses (17,18). Thus, 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). Another explanation suggested is that pretreatment with ketamine could heighten the pain threshold in the central nervous system and thus explain the diminished incidence of withdrawal movements (20). Besides these beneficial effects, ketamine has very well-known side effects such as sedation, nystagmus, and hallucination. However, we did not observe these side effects of ketamine in our patients. We think that this may depend on the duration of the operation.

In their study, Ozkocak et al. (21) found that 0.5 mg/kg i.v. ketamine pretreatment was effective on reducing the injection pain of propofol. In this study, ketamine 0.5 mg/kg was compared with 30 mg lidocaine for the reduction of injection pain.

Our study showed that both lidocaine and ketamine reduced the severity of pain caused by rocuronium injection; yet the reduction in the incidence and severity of pain was more pronounced in the lidocaine than the ketamine group. Moreover, it was observed that the incidence of withdrawal movements was reduced in both lidocaine and ketamine groups, but only the decrease in the lidocaine group was statistically significant when compared with the saline group.

The major limitation of our study is that we did not have data regarding neuromuscular blockage characteristics of the study drugs. As both lidocaine and ketamine could affect the neuromuscular blockage level, data in this regard would have made the results more meaningful.

In the present study, the relation between rocuronium-induced pain and withdrawal movements and gender was also analyzed. Even though Mencke et al. (10) showed that women reported more pain than men, we could not find a gender-related difference in this study.

In our study, we concluded that lidocaine was more effective than ketamine for decreasing the incidence and severity of rocuronium injection pain and withdrawal movements. For decreasing pain severity, ketamine was shown to be comparable with lidocaine.

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