Effect of Paracetamol Pretreatment on Rocuronium-Induced Injection Pain: A Randomized, Double-Blind, Placebo-Controlled Comparison with Lidocaine

Parasetamol Ön Tedavisinin Roküromyumla İndüklenen Enjeksiyon Ağrısına Etkisi

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Özet

Amaç: İntravenöz yolla verilen parasetamolün roküronyuma bağlı enjeksiyon ağrısı üzerine etkisinin araştırılması amaçlandı. Gereç ve Yöntem: Bu prospektif, randomize, çift-kör, kontrollü çalışmaya genel anestezi altında elektif cerrahi uygulanacak 180 hasta dahil edildi. Hastalara sol el sırtından 20G kanül ile damar yolu açılarak 100 ml/saat hızla Ringer Laktat solüsyonu verildi. Beş dakika sonra infüzyon sonlandırılarak hastanın sol kolu 15 saniye süreyle yerçekimine karşı yüksekte tutuldu. Sol kola pnömotik turnike uygulanarak venöz oklüzyon uygulanırken ön tedavi solüsyonlarından biri (5 mL serum fizyolojik, 40 mg lidokain veya 50 mg parasetamol) 10 saniye sürede enjekte edildi. Ön tedavi solüsyonunun enjeksiyonuna bağlı olarak hastaların hissettiği ağrının yoğunluğu Group C (5 mL serum fizyolojik, n=60), Group L (40 mg lidokain, n=60) ve Group P'de (50 mg parasetamol, n=60) 4-noktalı skala ile. değerlendirildi. İki dakika sonra venöz oklüzyon sonlandırılarak 0.06 mg/kg roküronyum bromide 10 saniyede verildi ve roküronyum enjeksiyonuna bağlı ağrı değerlendirildi. Bulgular: Roküronyum enjeksiyonuna bağlı ağrı insidansı Grup C'de diğer gruplara göre belirgin olarak daha fazla idi (p<0.001). Roküronyum enjeksiyonuna bağlı ağrı insidansı Grup L'de Grup P ve Grup C'ye göre belirgin olarak daha azdı (sırasıyla; p=0.009 ve p<0.001). Ayrıca, Grup P'de roküronyum enjeksiyonuna bağlı ağrı insidansı Grup C'den daha azdı (p=0.002). Tartışma: İntravenöz parasetamol ön tedavisi roküronyum enjeksiyonuna bağlı ağrı insidansının ve yoğunluğunun azaltılmasında etkilidir, fakat bu etki lidokain ön tedavisi kadar belirgin değildir.

Anahtar Kelimeler

Parasetamol; Lidokain; Roküronyum; Enjeksiyon Ağrısı

Abstract

Aim: To compare the effect of intravenous paracetamol on rocuronium-induced injection pain with that of lidocaine. Material and Method: One hundred and eighty patients scheduled for elective surgery under general anesthesia were recruited to this prospective, randomized, double-blinded, placebo-controlled study. A 20-gauge cannula was inserted into a vein on the dorsum of the patient's left hand and lactated Ringer's solution was infused at 100 ml/h. After 5 minutes, infusion was stopped and the left arm of the patient's was elevated for 15 seconds for gravity of venous blood. While venous occlusion was applied to the left upper arm using a pneumatic tourniquet, one of the pretreatment solutions (normal saline 5 mL, lidocaine 40 mg, paracetamol 50 mg) was injected over a period of 10 seconds. The intensity of the pain patients experienced was assessed using a 4-point verbal rating scale in Group C (normal saline 5 mL, n=60), Group L (lidocaine 40 mg, n=60) and Group P (paracetamol 50 mg, n=60). After 2 minutes, the venous occlusion was released and the patients received 0.06 mg/kg rocuronim bromide over 10 seconds and the rocuronim-induced pain was assessed. Results: The overall incidence of rocuronium-induced injection pain was significantly more in Group C than the other groups (p<0.001). The overall incidence of the rocuronium-induced injection pain was significantly less in Group L than in Group P and in Group C (p=0.009 and p<0.001, respectively). Additionally, the overall incidence of the rocuronium-induced injection was less in Group P than the Group C (p=0.002). Discussion: Intravenous pretreatment with paracetamol was effective in reducing the incidence and intensity of rocuronium-induced injection pain, but not as effective as intravenous lidocaine pretreatment.

Keywords

Paracetamol; Lidocaine; Rocuronium; Injection Pain

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Introduction

Rocuronium bromide is a neuromuscular blocker which has an aminosteroidal structure. It is established that it can be caused a burning pain in 50-80% of patients of both awake and anesthetized patients [1-4]. Due to the fact that it has the fastest onset of the action among the nondepolarizing muscle relaxants it is used in anesthesia practice as an alternative to succinylcholine when rapid tracheal intubation is required [1-4]. Additionally, using the ''timing principle'', with rocuronium being given before the induction agent, it was reported similar intubating conditions to succinylcholine at 45 seconds and 1 minute after induction of anesthesia [5]. The use of lidocaine to reduce the rocuronium-induced injection pain was reported in several studies [6-9].

Recently, the use of paracetamol (acetaminophen) was shown to reduce propofol-induced injection pain [10]. Although the cause and mechanism of the rocuronium-induced injection pain were unknown, the characteristics of this pain are similar to the propofol-induced injection pain [3]. The pain appears immediately during intravenous (i.v.) administration, duration of pain is short and intensity of pain decreases with subsequent injections [3]. In this randomized, double-blind, placebo-controlled prospective study, we aimed to compare the effect of i.v. paracetamol on rocuronium-induced injection pain with that of lidocaine.

Material and Method

After obtaining approval from the Institutional Ethics Committee and informed consent, 180 patients aged 18-65 years, American Society of Anesthesiology (ASA) I-II, undergoing elective surgery under general anesthesia were recruited to this prospective, randomized, double-blinded, placebo-controlled study. The patients with chronic pain syndromes, neurological deficits, vascular diseases, difficult venous access, infection on the dorsum of their left hands, habituation to analgesics, sedatives or anti-anxiety drugs and the patients who have a history of allergic reaction to the study drugs and who received analgesics or sedative drugs within the 24 hours before surgery were excluded from the study. Patients were randomly allocated one of three groups of 60 each using a table of random numbers: Group C (placebo) received normal saline 5 mL, Group L (Lidocaine) received 40 mg of lidocaine (Aritmal® 2%; Biosel, Istanbul) diluted to 5 mL with normal saline, Group P (Paracetamol) received 50 mg (5 mL) of paracetamol (Perfalgan®, Bristol-Myers Squibb, France). Identical syringes containing study drugs were prepared and labeled by an anesthetist not involved to study.

None of the patients was premedicated before entering the operating room. On arrival at operating room, a 20-gauge cannula was inserted into a vein on the dorsum of the patient's left hand and lactated Ringer's solution was infused at 100 ml/h. Monitoring consisted of pulse oximetry, electrocardiography, non-invasive blood pressure was applied (Datex-Ohmeda, Cardiocap 5, Helsinki, Finland). After 5 minutes, infusion of lactated Ringer's solution was stopped and the left arm of the patient's was elevated for 15 seconds for gravity of venous blood. While venous occlusion was applied to the left upper arm using a pneumatic tourniquet (pressure inflated to 70 mmHg), one of the pretreatment solutions was injected by an investigator who was unaware of group assignments over a period of 10 seconds. The intensity of the pain patients experienced was assessed by the same investigator using a 4-point verbal rating scale [7, 10-12]. (Table 1). None of the patients were informed about which pretreatment solution was used. After 2 minutes, the venous occlusion was released and the patients received 0.06 mg/kg rocuronim bromide (Esmeron®, Organon, Holland) was injected over 10 seconds. After the assessment of the rocuronim-induced pain using 4-point verbal scale, induction of anesthesia was continued with the i.v. 2.5% thiopental sodium 5 mg/kg followed by the remainder of calculated dose of rocuronium bromide to facilitate endotracheal intubation. Then, anesthesia was maintained by using 50% N2O/O2 and sevoflurane. An i.v. access obtained on the dorsum of the right hand was used for the crystalloid infusion and other medications. The injection site was checked for any complications, such as pain, swelling, or allergic reaction during the operation and after the first 24 hours of the operation.

Table 1. Four-point verbal rating scale for assessment of the injection pain

Pain Score	Degree of Pain	Response
	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 verbal response or response accompanied by facial grimacing, arm withdrawal, or tears.

A power study was conducted based on similar previous studies. Assuming that the prevalence of rocuronium-induced injection pain is 70% and that this would be reduced to 35% after the use of pretreatment solution, with $\alpha = 0.05$ and $\beta = 0.95$, 59 patients need to be included in each group. Therefore we include 60 patients in each group.

Data were analyzed using the SPSS 11.5 (SPSS Inc. Software, Chicago, Illinois, USA) statistical software. The demographic data of the patients were analyzed using one-way analysis of variance and x2 test. The incidence of the pain due to the injection of pretreatment solutions and rocuronium bromide was assessed using x2 test. All data were presented as mean (±SD) or number (percentage) of patients. A p value less than 0.05 was considered statistically significant.

Results

There were no statistically significant differences among groups regarding the demographic data (Table 2).

Table 2. Demographic data of the patients

	Grup L (Lidokaine) (n=60)	Grup P (Paracetamol) (n=60)	Grup C (Control) (n=60)	P value
Age (years)	39.27±11.81	36.45±12.94	35.58±11.92	0.232
Height (cm)	166.61± 7.34	166.06±7.64	169.28±7.57	0.46
Weight (kg)	76.46± 14.72	70.93±15.82	74.95±14.99	0.122
Gender (Female/Male)	30/30	33/27	23/37	0.172

All data were presented as mean±SD or number of the patients.

The data regarding to intensity and incidence of the pain during the injection of pretreatment solutions were statistically different among all groups (p = 0.047) (Table 3). The overall incidence

Table 3. The intensity and incidence of pain during injection of pretreatment solutions.

Pain score	Group L (Lidokaine) (n=60)	Group P (Paracetamol) (n=60)	Group C (Control) (n=60)
0	46 (76.7%)	54 (90.0%)	45 (75.0%)
1	8 (13.3%)	6 (10.0%)	9 (15.0%)
2	6 (10.0%)	0 (0%)	6 (10.0%)
3	0 (0%)	0 (0%)	0 (0%)
Overall incidence (1+2+3)	14 (23.3%)*	6 (10.0%)†	15 (25.0%)**

Data were presented as number of patients (percentages).
*p=0.016 compared with Group
†p=0.024 compared with Group C
**p=0.471 compared with Group L

of pain during i.v. injection of pretreatment with paracetamol was 10%, compared with 23.3% and 25% in each of the lidocaine and control groups, respectively (P=0.047). The intensity and incidence of the pain during the injection of pretreatment solutions were significantly lower in Group P than in Group L and Group C (p=0.016, p=0.024; respectively). Additionally, there were no statistically significant difference between Group L and Group C (p=0.471).

The overall incidence of rocuronium-induced injection pain was significantly more in Group C than the other study groups (p < 0.001). The overall incidence of the rocuronium-induced injection pain was significantly less in the Group L than in the Group P and in the Group C (p = 0.009 and p < 0.001, respectively). Additionally, the overall incidence of the rocuronium-induced injection pain was significantly less in the Group P than the Group C (p = 0.002) (Table 4).

Table 4. The intensity and incidence of rocuronium-induced injection pain

Pain score	Group L (Lidokaine) (n=60)	Group P (Paracetamol) (n=60)	Group C (Control) (n=60)
0	51(85.0%)	35(58.3%)	19(31.7%)
1	6(1.%)	13(21.7%)	15(25.0%)
2	3(5.0%)	12(20%)	9(15.0%)
3	0(0%)	0(0%)	17(28.3%)
Overall incidence (1+2+3)	9(15.0%)*†	24(41.7%)**	41(68.3%)

Data were presented as number of patients (percentages).
*p=0.009 compared with Group P
†p=0.001 compared with Group C
**p=0.002 compared with Group C

The complications due to the i.v. injection of the study drugs, such as pain, swelling, or allergic reaction were not observed during the operation and after the first 24 hours of the operation in any of the groups.

Discussion

The rocuronium-induced injection pain has been described as a burning sensation and it can be occur in both awake and anesthetized patients [1-4, 9]. Borgeat et al. reported at eight of ten awake patients who received 10 mg rocuronium complained of a burning pain during the i.v. injection [3]. Moorthy and Dierdorf observed severe burning pain with the injection of rocuronium when it was given as a priming dose before the i.v. induction of anesthesia to awake patients [1].

The mechanism of rocuronium-induced pain is unknown. Peripheral veins are innervated with polymodal nociceoptors which mediate pain responses to injected drugs [13]. Because rocuronium bromide is formulated with sodium acetate, sodium chloride, acetic acid, it has a relatively low pH of 4. Although Klement and Arndt showed that the low pH values of i.v. agents may have been cause of injection pain, the absence of perivenous edema and/or thrombophlebitis argue such a relationship [14]. Additionally, a study reported by Borgeat and Kwiatowski demonstrated that patients receiving i.v. saline adjusted to pH 4 reported no pain [3]. They demonstrated that administration of rocuronim bromide was associated with severe burning pain on injection which lasted for 10-20 seconds and the withdrawal movements were observed simultaneously during i.v. injection of rocuronium. They also reported that the rocuronium-induced pain was decreased during a subsequent second administration of the drug [3].

Because of the short duration of the pain and marked decrease or absence of pain with subsequent injections, the release of local mediators such as histamine and kinins can be suggested as another possible causative mechanism of the rocuronium-induced injection pain. The lack of erythema, edema and increased warmth in the surrounding tissue of injection site excludes the histamine release. Other mediators such as a kininogen cascade may be involved similar to propofol-induced injection pain. The characteristic of the pain of these i.v. agents are also similar with short duration and decreasing intensity of the pain with subsequent injections. Rocuronium injections 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 (PG) E2 [15]. It was reported that the analgesic effect of paracetamol reflect central and peripheral actions [16]. Paracetamol selectively suppresses peripheral PGE2 release and increases cyclooxygenase-2 (COX-2) gene expression [17]. In addition, Hintz et al. reported that paracetamol inhibits COX-2 activity in human blood cells and suppresses PGE2 generation in human blood monocytes [18]. Canbay et al. reported that paracetamol pretreatment was effective in reducing the propofol-induced injection pain like lidocaine. They found the overall incidence of propofol-induced injection pain was 64%, 22% and 8% in control, acetaminophen and lidocaine groups, respectively. And they suggested that this analgesic effect might be related with the effects of paracetamol on the release of COX-2 and PGE2 [10]. In this study, we also used 40 mg of lidocaine and 50 mg of paracetamol to compare the effect of paracetamol on rocuronium-induced injection pain with lidocaine and placebo. We found that paracetamol was effective in reducing the incidence and intensity of rocuronium-induced injection pain, but not as effective as lidocaine. The overall incidence of pain was 68.3%, 41.7% and 15% in Group C, Group P and Group L, respectively. Severe pain was observed 28.3% of the patients of Group C, and was not observed any of the patients of Group P and of the Group L. Because of the greater

incidence of pain observed in this study than observed by Canbay et al., we concluded that rocuronium-induced injection pain and propofol-induced injection pain are mediated by different mechanisms at least partly.

In another study reported by Jeon et al., the overall incidence of rocuronium-induced injection pain was found as 74.4%, 35.0% and 30.8% in control, paracetamol and lidocaine groups, respectively. They found that pretreatment with 50 mg of paracetamol was as effective as 40 mg of lidocaine on the control of rocuronium-induced withdrawal movement [11]. The different results which were reported by Jeon et al. and our study can be explained by the difference of the i.v. administration time of rocuronium. While we were not administer any anesthetic drug before the i.v. injection of rocuronium, they administered rocuronium after loss of consciousness which was maintained by the i.v. injection of 2.5% thiopental sodium 5 mg/kg. In this situation, the induction dose of thiopental 5 mg/kg might blunt the cognition of pain. And systemic analgesic effect of paracetamol might be contributed to its local analgesic effect.

The overall incidence of pain during i.v. injection of pretreatment with paracetamol was 10% when it was compared with 23.3% and 25% that were observed in each of the lidocaine and control groups, respectively. Pretreatment with i.v. paracetamol produced mild pain in 10% of patients. Pretreatment with lidocaine produced mild pain in 13.3% and moderate pain in 10% of the patients. When we evaluated the pretreatment pain in saline group, there was mild pain in 15% and moderate pain in 10% of the patients. That was to mean, i.v. acetaminophen caused less pretreatment pain with respect to lidocaine and control groups This results were similar with the results reported by Canbay et al. and also unexpectedly high in our study [10].

The results of this study were compatible with the previous placebo-controlled studies investigated the rocuronium-induced injection pain using tourniquet technique with 40 mg of lidocaine [6, 11, 19]. We preferred using the tourniquet technique because venous occlusion allows study of the peripheral action of drugs without a central effect, similar to a Bier block [20]. Lidocaine reversibly blocks peripheral pathways by blocking excitable membranes and it was shown that its effect on rocuronium-induced injection pain is dose dependent [8]. In this study, lidocaine pretreatment decreased the overall pain incidence to 15.0% and severe pain was not observed any of the patients of the pretreated with 40 mg of lidocaine.

Some of the previous studies reported that rocuronium-induced injection pain was more seen in females than males [21-23]. Because the patient distribution regarding the gender was similar in three groups, we did not think that our results were complicated by the gender difference.

In conclusion, i.v. pretreatment with paracetamol was effective in reducing the incidence and intensity of rocuronium-induced injection pain, but not as effective as i.v. lidocaine pretreatment.

Competing interests

The authors declare that they have no competing interests.

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