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ORIGINAL ARTICLE

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

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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.

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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