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SHORT COMMUNICATION

Comparison of randomized preemptive dexketoprofen trometamol or placebo tablets to prevent withdrawal movement caused by rocuronium injection

Gözde Bumin Aydın · Reyhan Polat · Julide Ergil · Murat Sayın · Ceyda Özhan Çaparlar

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Abstract Rocuronium is a non-depolarizing neuromuscular blocking agent which is associated with injection pain and induces withdrawal movement of the injected hand or arm or generalized movements of the body after intravenous injection. The aim of this randomized study was to compare the efficacy of pretreatment with oral dexketoprofen trometamol (Arvelles®; Group A) with placebo (Group P) without tourniquet to prevent the withdrawal response caused by rocuronium injection. The study cohort comprised 150 American Society of Anaesthesiologists class I–III patients aged 18–75 years who were scheduled to undergo elective surgery with general anesthesia. The patients response to rocuronium was graded using a 4-point scale [0 = no response; 1 = movement/withdrawal at the wrist only, 2 = movement/withdrawal involving the arm only (elbow/shoulder); 3 = generalized response]. The overall incidence of withdrawal movement after rocuronium injection was significantly lower in Group A (30.1 %) than in Group P (64.6 %) ($p < 0.001$). The incidence of score 0 withdrawal movements was higher in Group A (69.9 %) than in Group P (35.4 %), that of score 1 withdrawal movements was similar between groups (Group A 21.9 %; Group B 26.1 %) ($p = 0.560$) and that of score 2 withdrawal movements was lower in Group A (8.2 %) than in Group P (38.5 %) ($p < 0.001$). There were no score 3 withdrawal movements in either group ($p > 0.05$). These results demonstrate that the preemptive administration of dexketoprofen trometamol can attenuate the degree of withdrawal movements caused by the pain of the rocuronium injection.

Keywords Dexketoprofen trometamol · Rocuronium · Injection pain

G. B. Aydın · R. Polat · J. Ergil · M. Sayın · C. Ö. Çaparlar
Department of Anesthesiology, Ministry of Health Diskapi Yildirim Beyazit Research and Training Hospital, Ankara, Turkey

R. Polat (✉)
Zirvekent 2. etap, C3 blok no 34, Çukurca Birlik mah, Çankaya, Ankara, Turkey
e-mail: r_polat@msn.com

Rocuronium is a non-depolarizing neuromuscular blocking agent with a rapid onset of action that is associated with withdrawal movement of the injected hand or arm and generalized movements of the body due to the pain induced by the injection [1, 2]. Pain caused by the injection of rocuronium is experienced by 75–100 % of patients, although there is no direct complaint or recall of pain due to the patient being in a state of unconsciousness. It is considered most likely that this movement is due to pain at the site of injection [3, 4]. Pretreatment using a lidocaine, fentanyl, rocuronium and sodium bicarbonate mixture has been shown to reduce the pain due to injection of rocuronium [5, 6].

The mechanism of rocuronium pain might be caused by the triggering of a local quinine cascade mediated through the release of kininogen [7]. Prostaglandins improve the action of the products of the quinine cascade on nociceptors present in the vasculature [3]. Non-steroidal anti-inflammatory drugs (NSAIDs) decrease prostaglandin synthesis and abolish quinine cascades [3]. Dexketoprofen is the S(+) enantiomer of ketoprofen, which is a cyclo-oxygenase-1 (COX-1) and COX-2 inhibitor aryl-propionic acid with a good analgesic efficacy and tolerability profile following oral administration [8, 9]. Based on these properties, we hypothesized that this NSAID might be a good choice for preventing this side effect of rocuronium.

The aim of our study was, therefore, to compare the efficacy of pretreatment with oral dexketoprofen trometamol (Arvelles®) with placebo tablets, without tourniquet, for the prevention of the withdrawal response caused by rocuronium injection.

This study [Ref No 6/42, 17.12.2012, ANZCTR (ACTRN12613000432718, Gözde Bumin Aydın, 11 April 2013] was approved by local ethics committee. Written, informed consent was obtained from all 150 patients who comprised the study cohort. These patients were aged 18–75 years, assessed in American Society of Anaesthesiologists (ASA) physical classes I–III and were scheduled to undergo elective surgery with general anesthesia. Patients having difficult venous access on the dorsum of the hand, an allergy to NSAIDs, hepatic renal and gastric disease, a history of peptic ulcer, coagulopathies, chronic pain or pregnancy, those who had used corticosteroids within the last 7 days or anticoagulants within the last month and those who had received analgesics or sedatives within the previous 24 h were excluded from the study. The study was conducted between January and March 2013 at Dışkapı Yıldırım Beyazıt Research and Training Hospital.

None of the patients were premedicated and standard monitoring was performed. A 20-gauge cannula was placed by the same anesthesiologist preoperatively in the largest vein on the dorsum of the hand without local anesthesia, and the infusion of Ringer Lactate solution was started. Using a computer-generated randomized table, patients were randomly assigned to receive either oral placebo (starch) tablets (Group P) or oral 25-mg dexketoprofen trometamol tablets from one investigator (Arvelles®; İbrahim Etem Ulagay, Istanbul, Turkey) (Group A) 30 min before induction with one sip of water. After 3 min of preoxygenation, 2.5 % thiopental sodium 5 mg/kg was injected for induction. When the verbal response and the eyelash reflex were abolished and after a 20- to 30-s pause, rocuronium (Esmeron®; intravenous 50 mg/5 ml; Merck Sharp Dohme, Organon, Oss, The Netherlands) 0.6 mg/kg was injected over a 5-s interval and intravenous fluid was continuously administered for 10 s. While rocuronium was being injected, the withdrawal movement was graded by an investigator who was blinded to patient group (single blinded) using a 4-point scale, with a score of 0 = no response, 1 = movement/withdrawal at the wrist only, 2 = movement/withdrawal involving the arm only (elbow/shoulder) and 3 = generalized response with movement/withdrawal in more than one extremity, cough or holding of breath [3].

A total sample size of at least 124 (62 per group) cases was required to detect at least a 26.4 % difference between groups with a power of 85 % at the 5 % significance level. The difference of 26.4 % was taken from literature [1]. Assuming a dropout rate of 20 % we decided to enroll 75 cases to each group. Sample size estimation was performed using NCSS and PASS 2000 software (NCSS LLC, Kaysville, UT). Data analysis was performed by using SPSS for Windows, ver. 11.5 (SPSS, Chicago, IL). Continuous variables were shown as the mean ± standard deviation (SD); otherwise, the number of cases and percentages were used for categorical data. The mean differences in age and weight between groups were compared using Student's t test. Categorical data were analyzed by Pearson's chi square test. A p value of <0.05 was considered to be statistically significant.

Of the 138 patients eligible for entry, 12 were dismissed for various reasons. We therefore did achieve the required sample size (62) and concluded the study. There was no significant difference between the groups with respect to demographic variables and ASA status (Table 1).

Table 1 Demographic variables and American Society of Anaesthesiologists scores of study groups

Demographic variables	Group P (n = 65)	Group A (n =73)	p value
Age (years)	54.8 ± 14.1	51.1 ± 14.7	0.136
Mean age (years)	29–85	28–84	
Weight (kg)	74.7 ± 9.7	76.2 ± 8.9	0.345
ASA			0.148
I	31 (47.7 %)	44 (60.3 %)	
II	22 (33.8 %)	23 (31.5 %)	
III	12 (18.5 %)	6 (8.2 %)	

Patients were randomly assigned to receive either oral placebo (starch) tablets (Group P) or oral 25-mg dexketoprofen trometamol tablets (Arvelles®; İbrahim Etem Ulagay, Istanbul, Turkey) (Group A)

$p < 0.05$

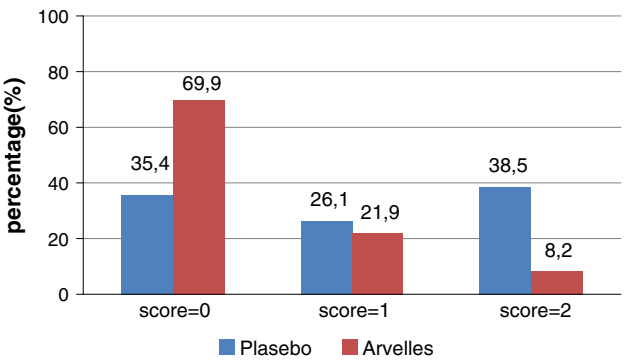

Fig. 1 Pain scores of groups. Pain was graded on a 4-point scale, with a score of 0 = no response, 1 = movement/withdrawal at the wrist only, 2 = movement/withdrawal involving the arm only (elbow/shoulder) and 3 = generalized response with movement/withdrawal in more than one extremity, cough or holding of breath

The overall incidence (score 0–3) of withdrawal movement after rocuronium injection was significantly lower in Group A (30.1 %) than in Group P (64.6 %) ($p < 0.001$). The incidence of score 0 withdrawal movements was higher in Group A (69.9 %) than in Group P (35.4 %), that of score 1 withdrawal movements was similar between groups (Group A 21.9 %, Group P 26.1 %) ($p = 0.560$) and that of score 2 withdrawal movements was lower in Group A (8.2 %) than in Group P (38.5 %) ($p < 0.001$). There were no score 3 withdrawal movements in either group ($p > 0.05$) (Fig. 1).

The results of our study demonstrate that pretreatment with 25-mg dexketoprofen trometamol (Arvelles®) tablets reduces the incidence of withdrawal movements related to the pain caused by the injection of rocuronium. Rocuronium is a preferred non-depolarizing neuromuscular blocker because of its fast onset of action [9]. The incidence of a burning pain among patients due to the injection of rocuronium is as high as 50–80 % [10]. Pain or withdrawal movements caused by the injection of rocuronium can potentially cause pulmonary aspiration secondary to gastric regurgitation, induce bronchospasm, asthma or myocardial ischemia attack and/or cause displacement of the venous route [11, 12]. A number of theories have been proposed to explain the mechanism of this pain, including nociceptor activation caused by the osmolarity or acidic pH of the solution or activation of endogenous mediators (kinin, bradykinin, histamine and other inflammatory mediators) [3, 5, 10]. Klement and Arndt [13] reported that pain gets worse with decreasing pH. However, Borgeat and Kwiatkowski [7] demonstrated that patients who received 0.9 % NaCl adjusted to pH 4.0 had no pain. Tuncali et al. [14] showed that the injection of an undiluted solution of rocuronium caused significantly more pain than the injection of a diluted solution, although the osmolarity of these two solutions was the same. The results of these two studies are inconsistent with the theories of pain due to rocuronium injection. Borgeat and Kwiatkowski [7] suggested that pain due to the injection of rocuronium might be caused by the activation of the quinine cascade because the duration of pain is short and pain decreases when rocuronium is injected for the second time [4].

Pretreatments with lidocaine, tramadol, fentanyl, ondansetron, remifentanil and sodium bicarbonate and a rocuronium mixture have been studied to reduce this pain [10, 15–17]. Lidocaine was found to be the most effective treatment to reduce the pain due to the injection of rocuronium [18]. However, lidocaine pretreatment may induce possible side-effects, such as anaphylaxis, coughing, chest rigidity, hypotension and bradycardia [11]. Because of the need to use tourniquet, some treatments are not effective and have limited practical use. For venous occlusion, only the peripheral action of drugs without a central effect could be studied [3].

Ketorolac pretreatment has been found to reduce withdrawal movements due to its inhibition of the quinine cascade through the COX pathway, just like our study drug. Jeon et al. [3] demonstrated that the effects of ketorolac are caused through the suppression of prostaglandin synthesis, such as the action of dexketoprofen trometamol [8]. Huang et al. [19] also used ketorolac for reducing propofol pain, and kerorolac has a similar mechanism as rocuronium.

In our study we evaluated the effectiveness of preemptive oral dexketoprofen trometamol (Arvelles®) in patients with pain due to the injection of rocuronium. Dexketoprofen is the S(+) enantiomer of the racemic compound of ketoprofen. Racemic ketoprofen is an analgesic, anti-inflammatory agent and is the most potent in vitro inhibitor of prostaglandin synthesis [20]. Dexketoprofen trometamol is a very potent analgesic and very active in the central nervous system at the spinal cord level in nociception [20]. Our patients received the tablet 30 min before the induction of anesthesia as the plasma peak concentration and the half life of the drug are about 30 min and 4–6 h, respectively.

In conclusion, our results demonstrate that preemptive administration of dexketoprofen trometamol (Arvelles®) can attenuate the degree of withdrawal movements caused by pain due to the injection of rocuronium.

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