Comparison of the effectiveness of pretreatment by fentanyl and remifentanil on rocuronium induced injection pain

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ABSTRACT

الأهداف: الهدف من هذه الدراسة هو من أجل مقارنة أثر الفنتانيل و ريميفنتانيل كأدوية سابقة للوقاية من ألم الحقن المحرض بالروكرونيوم باستعمال مجموعة التحكم.

الطريقة: في دراسة عشوائية ومزدوجة على مجموعة التحكم و 102 مريضاً تراوحت أعمارهم ما بين 18 و 60 عاماً والذين سيخضعون لعملية جراحية اختيارية تحت التخدير العام وتم تصنيفهم الى مجموعات خطورة (ASA 1) و(ASA 11) قد شملتهم هذه الدراسة (يوليو 2005م الى أبريل 2006م). تم توزيع المرضى عشوائياً الى إحدى المجموعات الثلاثة. المرضى الذين تلقوا 2mL 0.02mg من ريميفنتانيل (n=34)و الذين تلقوا 2mL من فينتانيل (n=34) (0.0mg) والذين تلقوا المحلول الملحي بمقدار 2mL n=34 ، تم حقنهم في 10 ثواني و30 ثانية بعد تلقي الأدوية السابقة. تم إعطاء المرضى (10mg/mL) عبر الوريد من عقار بروميد روكورونيوم في 5 ثوان وتم تقييم الألم بواسطة استعمال جدول النقاط الخمسة.

النتائج: عندما تمت مقارنة الثلاث مجموعات والمكون أعداد المرضى في كل مجموعة 34 مريضاً على ضوء نقاط تقييم الألم، تم تحديد فرقاً إحصائيا ملحوظاً (p=0.02). المجموعات ذات القصور، تبين أن هذا الفرق ناجم عن ريميفنتانيل والمحلول الملحي (p=0.02).

خاتمة: تظهر هذه الدراسة ان الجرعة من ريميفنتانيل بمقدار 0.02 ملجم أكثر فعالية في الأدوية السابقة وذلك بالمقارنة مع تطبيق المحلول الملحي. ولكن، ليس لدى ريميفنتانيل و فينتانيل أولوية لواحد منهما على الآخر وفعالية الفنتانيل هي مساوية للمحلول الملحي في الأدوية السابقة.

Objectives: To compare the efficacy of fentanyl and remifentanil as prodrugs in the prevention of rocuronium injection pain by using a control group.

Methods: In a randomized, double-blinded, controlled study, 102 adult patients aged between 18-60 undergoing elective surgery under general anesthesia and classified into American Society of Anesthesiologists (ASA) I and ASA II risk groups were included in the study. The study was carried out from July 2005 to April 2006 at Dokuz Eylül University, Izmir, Turkey. Unpremedicated patients were randomly allocated to one of 3 groups. Patients received 2 mL (0.02 mg) of remifentanil (n =34), 2 mL of fentanyl 0.1 mg (n=34), and 2 mL of saline (n =34), by injection over 10 seconds. Thirty seconds after prodrug administration, 10 mg (10 mg/mL) intravenous rocuronium bromide was administered over 5 seconds and pain assessment was performed by using a 5-point scale.

Results: When the 3 groups of 34 patients were compared in terms of pain assessment scoring, a statistically significant difference was determined (p=0.02). When the groups were paired, it was seen that this difference resulted from the remifentanil and saline groups (p=0.02).

Conclusion: This study shows that a bolus dose of 0.02 mg of remifentanil is a more effective prodrug administration compared to the application of saline, however, remifentanil and fentanyl have no superiority over one another and the administration of fentanyl is equally effective as saline prodrug administration.

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The pain resulting from the intravenous injection of some anesthetic drugs is a side effect, which is commonly encountered in clinical practice.[1] It is reported that pain on injection of rocuronium, a nondepolarizing muscle relaxant, develops in 50-80% of patients.[2] The mechanism of pain on injection of rocuronium is still not clearly defined. A possible mechanism is the

activation of nociceptors, receptors that sense pain in the peripheral veins, through the nonphysiological osmolality and pH value of the solution or through the release of endogenous algogenic mediators (mast cell degranulation and protein extravasation) such as histamine and bradykinin.[3] Rocuronium is an isotonic solution with a pH of 4. It has been reported in the literature that acidic solutions (pH≤4) and alkaline solutions (pH≥11) with high osmolality cause injection pain.[4] Many drugs and methods were tested for the prevention of rocuronium injection pain. The efficacy of intravenous local anesthetics (lidocaine), opioids (fentanyl, alfentanil), ondansetron, tramadol, dexmedetomidine, magnesium sulphate, thiopental, ketamine, sodium bicarbonate, and the method of diluting rocuronium with 0.9% sodium chloride (NaCl) in the prevention of rocuronium injection pain were investigated.[5-14] As we reviewed the literature, we determined that the efficiency of remifentanil in the prevention of pain on injection of rocuronium has not been investigated. The aim of this study was to compare the efficacy of fentanyl and remifentanil as prodrugs in the prevention of rocuronium injection pain by using a control group.

Methods. The study was carried out from July 2005 to April 2006 at Dokuz Eylül University, Izmir, Turkey. Ethics Committee approval was obtained from Dokuz Eylul University School of Medicine and all patients gave their informed consent. This prospective, randomized, double-blind, placebo-controlled study was performed on American Society of Anesthesiologists (ASA) I-II patients according to the physical status classification of the ASA.[15] Adult patients aged between 18 and 60 undergoing elective surgery under general anesthesia were enrolled in the study.

Exclusion criteria. Patients who were thought to be susceptible to difficult intubation and patients who might have difficulties in airway control, patients with a body mass index (BMI) of >30 kg/m^2 or patients weighing less than 50 kg, history of chronic pain, severe chronic obstructive pulmonary disease, asthma, reactive airway disease, history of neuropsychiatric and neurological disease, history of allergic reactions against the study drugs, pregnant women, and patients requiring rapid injection, hepatic and renal dysfunction, history of thrombophlebitis, muscle diseases, patients who received analgesic and sedative drugs in the last 24 hours.

The anesthesia circuits were checked, and the gas monitors were calibrated before the study (Narkomed; North American Dräger, Telhord, PA, USA). A thermal blanket was placed on the operating table and set to 37°C. The patients were taken to the operating room and heart rate (HR), non-invasive blood pressure (NIBP), electrocardiogram (ECG) and peripheral oxygen saturation (SpO_2) of the patients were monitored. The basal values [HR, systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and SpO_2 value], age, gender, BMI of the patients were recorded before the induction. A 20-gauge (G) intravenous cannula was inserted into a dorsal hand vein and 0.9% NaCL was infused at a flow rate of 0.1mL.kg^{-1}hr^{-1}. Preoperative medications were not administered as they could affect the results. Preoxygenation was performed through a facemask by applying oxygen for 5 minutes at a flow rate of 6 L/min before the application of prodrugs. After this phase, an anesthesiologist prepared the predetermined amount of drugs at room temperature and the drugs were administered to the patients who were randomly assigned into 3 groups (closed envelope method was used for randomization) over 10 seconds by another anesthesiologist who did not know the content of the drugs he was applying. Narcotic analgesics remifentanil and fentanyl doses were selected in accordance with the literature.[5,7,8,10,16] Group R (n=34) received 2 mL (0.02 mg) remifentanil (Ultiva®, Glaxo Smith Kline Inc, Belgium). Group F (n=34) received 2 mL (0.1 mg) fentanyl (Fentanyl Citrate, Abbott, USA). Group C (n=34) received 2 mL saline (Isotonic Sodium Chloride, Eczacıbası, Turkey). Thirty seconds after prodrug administration, 10 mg (10 mg/mL)[7,12] intravenous rocuronium bromide (Esmeron®, Organon Inc., Holland) was administered over 5 seconds[14] and pain assessment was performed by using a 5-point scale[7,14] (**Table 1**) 10 seconds after the injection. Side effects were recorded. After the assessment, anesthesia was induced with propofol 2 mg.kg^{-1} and rocuronium 0.6 mg.kg^{-1}. After the intubation, the choices for the maintenance of anesthesia were left to the discretion of the anesthesia team in charge.

Statistical evaluation. When the difference between the groups was considered as 0.5, predicted sample size for a significance level of 0.05 (α= 0.05) and a statistical power of 0.80 was 102 patients. The data on a total of 102 patients assigned into the 3 groups (n=34) were loaded into the SPSS v13.0 software. Continuous variables were summarized as mean ± standard deviation (SD). When the mean values of 2 groups were compared, student's-t test was used and chi-square test was used in the comparison of the categorical data. One-way ANOVA procedure was applied when comparing multiple groups. The homogeneity of the variables was controlled with Levene test. When a difference was present, Tukey's post-hoc test was used for the differences between the groups. Pearson's simple correlation analysis was used in analyzing the

Table 1- Pain assessment scoring.[7,14]

Pain score	Response	Pain severity
0	When asked, the patient reports no pain and feeling of disturbance	No pain
1	When asked, the patient reports mild pain and feeling of disturbance	Mild
2	When asked, the patient reports moderate pain and feeling of disturbance	Moderate
3	The patient spontaneously reports that he/she feels severe pain or feeling of disturbance	Severe
4	The face of the patient is wrinkled with pain, the patient withdraws his/her arm and loudly states that he/she feels severe pain	Very Severe

Table 2 - The characteristics of the groups and pain assessment scoring.

Number of patients	Remifentanil (n=34)	Fentanil (n=34)	Saline (n=34)	*P* value
Gender (F/M)	21/13	22/12	21/13	0.96
Age (years)	40.59 ± 10.96	45.03 ± 11.06	43.94 ± 10.65	0.22
BMI (kg/m^2)	24.85 ± 4.22	26.3 ± 3.5	26.14 ± 3.74	0.24
PAS	1.74 ± 1.39	1.97 ± 1.19	2.56 ± 1.16	0.02

Data are means ± SD, BMI - body mass index, PAS - pain assessment scoring. When the 3 groups were compared in terms of PAS, a statistically significant difference was determined (p=0.02)

relation between pain assessment scoring (PAS) and various parameters. For all tests, p<0.05 was considered significant.

Results. A total of 102 patients (64 M/38 F; 43.2± 0.9 years) were included in the study group. The patients were assigned to 3 groups. In each group, the same number of patients was present (n=34). The gender, BMI, age of the patients in these groups (**Table 2**) and MAP (Group R 93.26±22.8 mm Hg, Group F 95.53±11.4 mm Hg, Group S 88.3±11.2 mm Hg) were statistically similar (p>0.05). When the 3 groups were compared in terms of PAS, a statistically significant difference was determined (p=0.02) (**Table 2**). This difference resulted from the remifentanil and saline groups. In the remaining prodrug comparisons (fentanyl versus control and remifentanil versus fentanyl), a significant difference was not observed in terms of PAS (p=0.9 and p=0.7). When the patients who had pain (PAS=1, 2, 3, 4) and those with no pain (PAS=0) were compared according to the prodrug administration, a statistically significant difference was observed between the groups (p=0.012). When the groups were compared with each other, it was seen that this difference originated from the remifentanil group (remifentanil-fentanyl, p=0.046, remifentanil-control, p=0.016, fentanyl-control, p=0.915).

Discussion. The primary mechanism responsible for the pain on intravenous injection of certain anesthetic drugs is still not adequately defined.[4] Peripheral veins are innervated with polymodal nociceptors.[1] It is thought that the pain that occurs after the intravenous injection of certain drugs results from the activation of peripheral vascular chemonociceptors.[3] Rocuronium, an aminosteroid muscle relaxant, often causes spontaneous withdrawal movements of the arm when it is injected into an arm vein. This movement possibly results from the burning pain in the region injection. As a result of the pain, an increase in heart rate and sometimes in blood pressure may be seen.[3] It was reported that rocuronium, when administered to awake patients at subparalyzing doses (priming principle), caused a feeling of disturbance and pain in 50-80% of patients.[2] In our study, rocuronium was administered to awake patients prior to induction of a hypnotic and premedications as they could affect the results. Thus, we were able to evaluate the direct effects of the drugs that we used on the rocuronium injection pain. The severity and the incidence of the pain on injection of rocuronium may be affected by the dose of rocuronium and the drugs used with the region (such as midazolam, opioids, and lidocaine) also the diameter and of the vein, where the drug is applied.[8] In a study on rocuronium administered through an antecubital

fossa vein by a 22G intravenous cannula, rocuronium 0.6 mg/kg was administered right after the injection of propofol at an induction dose and mild pain was determined only in 2 of the 20 patients included in the study.[1] Ahmad et al,[5] assessed pain in patients to whom rocuronium 0.6 mg/kg was administered right after the induction of thiopental through the dorsal hand veins and/or the cephalic vein using an 18G intravenous cannula and did not determine a statistically significant difference between the veins in terms of spontaneous withdrawal movements of the arm. To determine the severity and incidence of rocuronium injection pain and the efficiency of prodrug administration, we used a 20G intravenous cannula and injected the drug through the veins on the nondominant dorsal hand.[9,10,12,14,16-18] The dose of the administered rocuronium may affect the severity and incidence of the pain on injection of rocuronium,[8] thus, we administered rocuronium 10 mg to all patients in 5 seconds.

Shevchenko et al[19] determined that lidocaine administered at a dose of 0.1 mg/kg after the induction with a hypnotic agent decreased the spontaneous withdrawal movements resulting from pain. Cheong and Wong[2] compared the effectiveness of lidocaine 10 mg and 30 mg before the injection of rocuronium at the dose of 0.6 mg/kg in awake patients and concluded that lidocaine 30 mg was more effective in preventing the rocuronium injection pain and the increase in the dose of lidocaine was correlated with a decrease in the incidence of pain. In 2 studies, Memis et al[10,11] compared the efficacy of opioids and the efficacy of various drugs with different pharmacological structures in preventing rocuronium injection pain. They investigated the efficacy of ondansetron, lidocaine, tramadol, and fentanyl in the prevention of rocuronium injection pain and determined that these drugs were all effective in the prevention of pain, while the most effective drug in the prevention of injection pain was lidocaine. They also investigated the efficacy of magnesium sulphate, lidocaine, sodium bicarbonate and alfentanil in the prevention of rocuronium injection pain and determined that magnesium sulphate and sodium bicarbonate were the most effective drugs in preventing pain on rocuronium injection. Joshi and Whitten[8] reported that the administration of midazolam 2 mg and 100 µg fentanyl as prodrugs before the injection of rocuronium 0.06 mg/kg was an effective method in preventing the rocuronium injection pain. Similarly, Borgeat et al[6] showed that the administration of 2 µg/kg fentanyl as a prodrug was effective in the prevention of pain on rocuronium injection. In a study conducted by Ahmad et al[5] the effectiveness of the administration of 100 µg fentanyl was compared with that of lidocaine 40 mg and it was determined that fentanyl was more effective. In our study, we compared the effectiveness of remifentanil, an opioid that was not previously used for the prevention of rocuronium injection pain, with that of fentanyl, which is also an opioid by using a control group. We preferred to use remifentanil at the dose of 0.02 mg, which was found to be effective in the prevention of propofol injection pain in the study of Iyilikçi et al.[16] We did not prefer to use the higher bolus doses of remifentanil since this might have caused respiratory depression. As for fentanyl, a bolus dose of 0.1 mg, which was found to be effective in many studies, was used in the study.[5,8] When the control and remifentanil groups were compared, we concluded that remifentanil effectively prevented pain and as we compared the fentanyl and control groups, we did not determine a statistically significant difference between the 2 groups in terms of the prevention of rocuronium injection pain. Additionally, a statistically significant difference was not observed between the remifentanil and fentanyl groups in terms of the effectiveness of the 2 drugs in the prevention of rocuronium injection pain.

The findings of the 2 studies,[5,8] which determined that a bolus dose of fentanyl 0.1 mg/kg was effective in preventing rocuronium injection pain were not consistent with our findings. We did not determine a difference between the fentanyl group and the control group. Ahmad et al[5] administered midazolam 2 mg to the patients before the injection of fentanyl 0.1 mg. Similarly, Joshi and Whitten[8] used midazolam 2 mg together with fentanyl 0.1 mg. In our study, we did not use premedication since this might have affected the results. Thus, according to our result, fentanyl 0.1 mg as a prodrug may not be effective when compared to the control group in the studies mentioned above. Additionally, another possible cause may be that rocuronium was administered at the dose of 0.06 mg/kg in these studies while it was used at the dose of 10 mg for all patients in our study.

In conclusion, this study shows that a bolus dose of 0.02 mg of remifentanil is a more effective prodrug compared to the application of saline, however, remifentanil and fentanyl have to superiority over and another and the administration of fentanyl is equally effective as saline. According to this result, we believe that further studies on the prevention of rocuronium injection pain comparing remifentanil with other opioids at various doses and with larger groups should be conducted and using a large vein and diluting rocuronium with saline may be a cheaper and easier method for the prevention of rocuronium injection pain.

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Statistics

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