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A Comparison of the Efficacies of Different Pre-treatment Drugs in Resolving the Injection Pain of Rocuronium

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Efficacies of pre-treatment with lidocaine, remifentanil and metoclopramide in the reduction of pain and withdrawal movements induced by rocuronium injection were evaluated. Forty-four adult patients, American Society of Anesthesiologists (ASA) Physical Status I – II, undergoing elective surgery were randomly assigned to four groups. Each patient received intravenously either 10 mg metoclopramide, 50 mg lidocaine, 1 µg/kg remifentanil or 3 ml of 0.9% sodium chloride (control group); followed by occlusion with a tourniquet on the forearm. After 10 s, occlusion stopped and a priming dose of 0.06 mg/kg rocuronium was injected. The patient's response to rocuronium was graded using a four-point scale in a double-blind manner. All groups had significantly lower incidences of pain compared with the control group. After loss of consciousness with sodium thiopental, 0.6 mg/kg rocuronium was administered for intubation and withdrawal movements were assessed. The number of patients in whom withdrawal movements were lowest was in the lidocaine-treated group. Although there was no difference among the study drugs in the prevention of rocuronium-induced pain, lidocaine and remifentanil seemed to be clinically more effective than metoclopramide.

KEY WORDS: Neuromuscular block; Rocuronium; Local anaesthetic; Lidocaine; Remifentanil; Metoclopramide; Pain; Injection

Introduction

Rocuronium bromide, a non-depolarizing neuromuscular blocking drug, is characterized by rapid onset and intermediate duration of effect. It is given in precurarization or priming techniques before the induction of anaesthesia.[1,2] When a subparalysing dose of rocuronium was given intravenously in conscious patients, most of them complained of a severe burning pain in their arm.[3 – 5] As 50 – 80% of patients suffer injection pain, various methods have been recommended for reducing this side-effect.[6,7] Even after loss of consciousness with the use of induction drugs, intravenous rocuronium can still elicit withdrawal of the hand/limb or generalized movements of the body.[3,5,8] The aim of this study was to

examine the incidence of pain and withdrawal movements associated with injection of rocuronium and to evaluate whether prior administration of intravenous lidocaine, metoclopramide or remifentanil decreased the incidence of injection pain in adult patients.

Patients and methods

PATIENTS

Rocuronium, lidocaine, remifentanil and metaclopramide are agents that are frequently used as part of the routine clinical practice of the Department of Anaesthesiology and Reanimation, Faculty of Medicine, Akdeniz University and are administered intravenously in accordance with the clinic's guidelines. For this reason, an application for ethical approval was not made. Patients were informed with regard to the details of the study protocol and informed consent was obtained verbally from all patients. The study was conducted prospectively on American Society of Anesthesiologists (ASA)[9] Physical Status I – II patients who were to undergo general anaesthesia for elective surgery. Patients who had a history of neurological deficits, drug allergy or asthma, and patients who had received analgesics or sedatives within the previous 24 h were excluded.

METHODS

No pre-medication was given before the induction of anaesthesia. On arrival in the operating room, a 22-gauge cannula was placed into a dorsal vein of one hand and normal saline was then infused at the rate of 20 ml/min. Monitoring consisted of lead II electrocardiogram, non-invasive blood pressure measurement and pulse oximetry. An anaesthetist who was not involved in the study prepared the pre-treatment drugs. The study patients were randomly allocated to receive one of four treatments by intravenous injection: 10 mg metoclopramide; 50 mg lidocaine; 1 µg/kg remifentanil; 3 ml of 0.9% sodium chloride (control group), followed by occlusion with a tourniquet on the forearm for 10 s. The patient and the anaesthetist were unaware of the treatment group. Ten seconds after injection of the study drug or saline at ambient temperature (20 – 24 °C), occlusion stopped and a priming dose of 0.06 mg/kg rocuronium was given intravenously. After rocuronium injection, before the patient lost consciousness, pain and burning sensation were determined by an anaesthetist, who was blinded to the treatment group: each patient was questioned every 5 s about the presence of any pain or discomfort in the arm. The pain scale was defined as follows: no pain; mild pain; moderate pain (subjective complaint of a tolerable painful sensation); severe pain (a pain that caused the patient to flex the arm to prevent injection).[7] Burning sensation at the injection site was assessed by asking the patient if this sensation was present or absent.

After induction of anaesthesia with intravenous 5 mg/kg sodium thiopental and the subsequent loss of consciousness, 0.6 mg/kg rocuronium was administered intravenously to facilitate tracheal intubation. An anaesthetist who was not involved in the study prepared the pre-treatment drugs and looked for withdrawal movements. Patients were also observed for local signs, such as erythema and venous sequelae (i.e. thrombosis, phlebitis or thrombophlebitis) of the hand where rocuronium was injected.

The patient's lungs were ventilated mechanically to maintain normocapnia and anaesthesia was maintained with nitrous oxide (50%) and sevoflurane (1.0 – 2.0%, end tidal).

STATISTICAL ANALYSIS

Values are expressed as mean ± (standard deviation) SD. The incidence of pain and occurrences of withdrawal movements were analysed using the χ^2 test or Fisher's exact test as appropriate. *P*-values < 0.05 were considered to be statistically significant.

Results

Forty-four patients were randomly allocated to the four groups (n = 11 per group). The groups were similar with respect to demographic characteristics ($P > 0.05$) (Table 1). The results of pain assessments, grading of pain and burning sensation during injection of rocuronium are shown in Table 2.

TABLE 1:
Demographic data for 44 patients in a study to compare the efficacy of pre-treatment with 10 mg metoclopramide, 50 mg lidocaine, 1 µg/kg remifentanil or 3 ml of 0.9% sodium chloride (control) in resolving the pain associated with intravenous injection of rocuronium[a]

	Metoclopramide group (n = 11)	Lidocaine group (n = 11)	Remifentanil group (n = 11)	Control group (n = 11)
Age (years)	41.00 ± 11.84	42.81 ± 11.05	65.63 ± 15.22	42.54 ± 17.67
Gender (male/female)	6/5	5/6	7/4	3/8
Weight (kg)	67.36 ± 8.11	76.63 ± 13.76	68.18 ± 7.82	68.72 ± 7.84
Anaesthesia time (min)	97.27 ± 45.40	85.90 ± 32.00	115.90 ± 44.26	87.00 ± 7.28
Operation time (min)	78.63 ± 45.11	75.00 ± 27.83	100.45 ± 42.57	73.72 ± 8.00

Data are number of patients or mean ± SD.
[a]A priming dose of 0.06 mg/kg rocuronium was administered intravenously 10 s after injection of the study drug or saline (control). After induction of anaesthesia with 5 mg/kg sodium thiopental intravenously and loss of consciousness, 0.6 mg/kg rocuronium was administered intravenously to facilitate tracheal intubation.

TABLE 2:
Grading of pain and burning sensation during intravenous injection of 0.06 mg/kg rocuronium after pre-treatment with 10 mg metoclopramide, 50 mg lidocaine, 1 µg/kg remifentanil or 3 ml of 0.9% sodium chloride (control)

	Metoclopramide group (n = 11)	Lidocaine group (n = 11)	Remifentanil group (n = 11)	Control group (n = 11)
No pain	8	11	10	3
Mild pain	3	0	0	2
Moderate pain[a]	0	0	1	3
Severe pain[b]	0	0	0	3
Total with pain	3[d]	0[d]	1[d]	8
Burning sensation[c]	5	1[e]	7	9

Data are number of patients.
[a]Moderate pain, subjective complaint of a tolerable painful sensation.
[b]Severe pain, pain that caused the patient to flex the arm to prevent injection.
[c]Burning sensation was assessed by asking the patient whether it was present or absent.
[d]$P < 0.05$ versus the control group.
[e]$P < 0.05$ versus the remifentanil and control groups.

The incidence of pain of any degree on intravenous injection of 0.06 mg/kg rocuronium was 72.7% (8 of 11 patients) in the control group, 27.3% (3 of 11 patients) in the metoclopramide-treated group, 0% (0 of 11 patients) in the lidocaine-treated group and 9.1% (1 of 11 patients) in the remifentanil-treated group ($P < 0.05$ for each treatment group versus the control group).

After loss of consciousness, the number of patients in whom withdrawal movements were observed on intravenous injection of 0.6 mg/kg rocuronium was 6 (54.5%) in the control group, 3 (27.3%) in the metoclopramide-treated group, 1 (9.1%) in the lidocaine-treated group and 3 (27.3%) in the remifentanil-treated group ($P < 0.05$ for each treatment group versus the control group).

No erythema or any change of the skin surrounding the point of injection or the arm was observed.

Discussion

The principal stimulus that evokes pain on intravenous injection of some agents used as supplements for anaesthesia is still unknown. Although the relationship between intravenous osmolality and pain intensity has not been examined systematically, the incidence of pain seems to increase at osmolalities greater than 1 osmol/kg.[10] The exact mechanism of rocuronium-induced localized pain has not been established, but it has been reported that the pain may be due to the activation of nociceptors by the osmolality or pH of the solution, or activation by the release of endogenous mediators, such as histamine, kinin and other substances mediating inflammation.[8,11] Freshly prepared rocuronium bromide is an isotonic solution with a pH of 4; low pH is unlikely to be the cause of pain, because intravenous injection of normal saline buffered to a pH of 4 was not associated with pain.[10] The pain associated with propofol and rocuronium is similar: it appears immediately during administration, its duration is short and its intensity decreases with subsequent injections.[12] Factors such as local distension of the vein, reduction of buffering by flowing blood and longer exposure time of rocuronium to the vessel wall have been associated with an increase in pain on injection of propofol, and may have a similar relevance for rocuronium. It is reported that the similarity of movements of the arm observed in anaesthetized patients is the direct consequence of pain associated with the administration of rocuronium.[13]

Previous studies have shown a reduction in pain to some degree with pre-treatment using lidocaine,[6] fentanyl[8] or an injection of a mixture of rocuronium and sodium bicarbonate.[7,14] Mahajan *et al.*[15] reported that ketamine pre-treatment, at a dose of 20 mg, significantly reduced the pain associated with the injection of rocuronium in adults. In that study, the incidence of pain in the control group (78%) was significantly higher than in the ketamine 10 mg and ketamine 20 mg groups (40% and 12%, respectively). Memis *et al.*[16] reported that ondansetron, lidocaine, tramadol and fentanyl were effective in reducing pain caused by the intravenous injection of rocuronium. Lidocaine was the most effective and fentanyl the least effective. Cheong and Wong[6] assessed the incidence of pain on injection of rocuronium and whether it was reduced by pre-treatment with intravenous lidocaine. They found that 37% of patients pre-treated with 10 mg lidocaine had pain on injection of rocuronium compared with 77% of patients who received saline pre-treatment and 7% of patients who were pre-treated with 30 mg lidocaine.

In the present study, all the groups receiving a study drug had significantly

lower incidences of pain compared with the control group. No erythema or any change in the skin surrounding the point of injection or the arm was observed.

Even after induction of anaesthesia with propofol or pentothal, rocuronium causes hand or limb withdrawal or generalized movements in 85% of patients, suggesting the presence of intense nociception even under anaesthesia.[14] In the present study, the incidence of withdrawal movements was significantly lower for the study drugs than for the control treatment. In this study, lidocaine was the most effective agent in decreasing the incidence of withdrawal movements on injection of an intubation dose of rocuronium.

Although there was no statistically significant difference among the lidocaine-, metoclopramide- and remifentanil-treated groups in preventing rocuronium-induced pain, lidocaine and remifentanil seemed to be more effective clinically than metoclopramide (when we evaluated the pain scores, none of the patients in the lidocaine group complained of pain and only one patient in the remifentanil group complained of pain, which was scored as moderate pain).

It was concluded that pre-treatment with lidocaine attenuates withdrawal movements associated with intravenous injection of rocuronium in patients anaesthetized with sodium thiopental. Although the number of patients in this study was low, routine pre-treatment with lidocaine can be recommended for the prevention of pain associated with the injection of rocuronium.

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Conflicts of interest

No conflicts of interest were declared in relation to this article.

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