

## A comparison of tramadol, sufentanil, meperidine, and lidocaine in prevention of pain due to rocuronium injection

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**Aim:** Alleviation of the pain resulting from injection of rocuronium during anesthesia is still an unsolved problem. We aimed to compare the analgesic effects of sufentanil, tramadol, meperidine, and lidocaine on the pain from injection of rocuronium.

**Materials and methods:** This prospective randomized double-blind study included 200 patients with ASA I–II. After a tourniquet was applied to the forearm, patients received 50 mg of tramadol (group T), 10 µg of sufentanil (group S), 40 mg of meperidine (group M), or 30 mg of lidocaine (group L). The tourniquet was released after 20 s and rocuronium was injected over 10 to 15 s. The patients were asked whether the injection caused pain or not. Side effects were recorded.

**Results:** The incidence of injection pain was highest in group T. Severe pain was most frequently encountered in group S. Lidocaine was the most effective analgesic in alleviating the injection pain while sufentanil was the least effective drug ( $P < 0.05$ ). Erythema was the common side effect at the injection site in group M and arrhythmia was observed in group T.

**Conclusion:** The analgesic effect of meperidine was not significantly superior to that of the other drugs. Lidocaine seemed to be the most effective analgesic drug for minimizing the pain due to rocuronium injection.

**Key words:** Rocuronium, injection pain, opioids, female patients

### 1. Introduction

Rocuronium bromide is a steroidal nondepolarizing neuromuscular blocking agent and is characterized by rapid to intermediate onset of action, depending on dose, and an intermediate duration of action. It is used for precurarization as a priming neuromuscular relaxant agent during induction of anesthesia (1,2). Pain due to injection of rocuronium is a common adverse effect, occurring in 50%–80% of patients (3). Pain accompanied by a burning sensation may be particularly severe (4,5). Shevchenko et al. (6) showed that intravenous (IV) injection of rocuronium might cause significant limb withdrawal or generalized movement in patients even more than with IV propofol, which could be explained by the presence of intense nociception even during anesthesia. Several studies have been designed to determine the effective concentration of fentanyl and lidocaine to efficiently eliminate injection pain caused by propofol and rocuronium (5,7,8). It has been shown that

moderate and severe pain could be treated by tramadol, which is a synthetic analgesic (9). Pang et al. (10) showed that propofol injection pain could be significantly reduced by local anesthetic activity of tramadol and lidocaine. On the other hand, Tsai et al. (11) suggested that the local anesthetic-type effect of tramadol on sciatic nerves of rats was likely to be related to neural conduction blockage. It has been shown that meperidine had a local analgesic effect similar to lidocaine and is more effective than morphine and fentanyl in reducing the pain on propofol injection but its mechanism of action is still unknown (12). To date, various strategies have been drawn up to alleviate discomfort in many studies, but none of them has evaluated the effect of meperidine on rocuronium injection pain. The present study aimed to investigate the effectiveness of 3 commonly used opioids (sufentanil, tramadol, and meperidine) in comparison with lidocaine in minimizing the injection pain due to rocuronium.

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## 2. Materials and methods

After obtaining ethical committee approval and informed consent from patients, 200 female patients between 17 and 71 years of age were included in a prospective randomized double-blind study. All patients with a physical class of American Society of Anesthesiologists (ASA) I or II underwent elective gynecologic surgery. Patients with neurological deficits, thrombophlebitis, chronic pain syndrome, difficult venous access, or clinical conditions that contraindicated the administration of any of the drugs used in the study were excluded. Premedication was not used. After heart rate, noninvasive blood pressure, and pulse oximetry monitoring, a 20-gauge cannula was inserted into the vein on the dorsum of the hand for infusion of the crystalloid solutions and other medications. The dorsal vein of the other hand was also catheterized as an alternative venous access. Mean arterial pressure (MAP) and heart rate (HR) were recorded on arrival at the operating theater (baseline), and before and after endotracheal intubation. A tourniquet was applied to the arm and inflated up to 70 mmHg to keep the drug within the vein. Two hundred patients were randomly assigned to 4 groups of 50 patients each using sealed envelopes with group names. Then the patients randomly received tramadol 50 mg (group T, n = 50), sufentanil 10 µg (group S, n = 50), meperidine 40 mg (group M, n = 50), or lidocaine 30 mg (group L, n = 50) intravenously at ambient operating room temperature (20–22 °C). Physiological saline was added to make the drug solutions up to 3 mL. The tourniquet was released 20 s later and an intubating dose of rocuronium 0.6 mg kg<sup>-1</sup> at room temperature was injected over 10–15 s. Each patient was questioned every 5 s about the presence of any pain or discomfort in the arm by an anesthetist who was unaware of the injected drug. Patients were also observed for signs of limb withdrawal, strong vocal response, grimacing, and crying. Patients' response was evaluated by use of a

4-point verbal analogue scale as shown in Table 1. Twenty-five seconds after the administration of rocuronium, 5 mg kg<sup>-1</sup> of thiopental was administered intravenously. The patients were tracheally intubated and anesthesia was maintained with sevoflurane in oxygen/N<sub>2</sub>O. The injection site was checked for any complications such as erythema, swelling, or allergic reactions at the end of operation by an anesthesiologist who did not know which drug had been injected.

Statistical analyses were performed using SPSS 11.0 for Windows. Patients' characteristics and hemodynamic variables were analyzed using one-way ANOVA. Pain scores and side effects were analyzed by the chi-squared test. A P value of 0.05 was considered statistically significant.

## 3. Results

There was no significant difference in terms of demographic data (Table 2). Grades of pain due to injection of rocuronium are presented in Table 3. The incidence of pain in group T was higher than that in group S, whereas the intensity of pain was higher in group S. Pain incidence was 82% (n = 41) in group M. The analgesic effect of meperidine was not significantly superior when compared with the other medications. Lidocaine was the most effective and sufentanil was the least effective drug in the prevention of injection pain due to rocuronium (P < 0.05).

None of the patients suffered from muscle weakness before 30 s. Erythema at the injection site was significantly more common (n = 18; 36%) in group M (P < 0.05). Arrhythmia was observed in 6 (12%) patients in group T (P < 0.05). No complications such as pain, swelling, or allergic reactions were observed at the injection site during the first 24 h following the operation.

**Table 1.** Assessment of pain during injection of rocuronium.

The degree of pain	Response
None (0)	Negative response to questioning
Mild (1)	Pain reported in response to questioning only, without any behavioral signs
Moderate (2)	Pain reported in response to questioning and accompanied by a behavioral sign, or pain reported spontaneously without questioning
Severe (3)	Strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears

**Table 2.** Demographic characteristics of all patients.

	Group T (n = 50)	Group S (n = 50)	Group M (n = 50)	Group L (n = 50)
Age (years)	42.3 ± 11.5 (17–60)	40.1 ± 11.8 (19–68)	38 ± 11.4 (18–56)	40.1 ± 11.4 (20–71)
Height (cm)	160.7 ± 4.9 (150–174)	161.1 ± 5.6 (150–170)	160.2 ± 6.6 (143–175)	161.3 ± 5.7 (150–175)
Weight (kg)	70 ± 13.2 (49–110)	68.7 ± 13.8 (40–103)	69.2 ± 13.2 (45–110)	69.9 ± 14.8 (45–117)
ASA I/II (n)	32/18	35/15	32/18	36/14

All data are expressed as mean ± standard deviation (minimum–maximum) or numbers

**Table 3.** Distributions according to intensity of pain.

	Group T (n = 50)	Group S (n = 50)	Group M (n = 50)	Group L (n = 50)
No pain (0)	3 (6%)	4 (8%)	9 (18%)	21 (42%)*
Mild pain (1)	24 (48%)	10 (20%)	22 (44%)	22 (44%)
Moderate pain (2)	21 (42%)	30 (60%)	19 (38%)	7 (14%)*
Severe pain (3)	2 (4%)	6 (12%)	0 (0%)	0 (0%)

n = number of patients.

\*P < 0.05 versus other groups

**Table 4.** Intraoperative adverse events in all patients.

	Group T (n = 50)	Group S (n = 50)	Group M (n = 50)	Group L (n = 50)
Arrhythmia	6 (12%)*	1 (2%)	1 (2%)	1 (2%)
Flushing	0	0	1 (2%)	1 (2%)
Erythema	0	30 (60%)	19 (38%)	7 (14%)*

n = number of patients.

\*P < 0.05 versus other groups

#### 4. Discussion

In the present study, the analgesic effect of lidocaine was significantly superior compared with the other commonly used opioids in alleviating injection pain due to rocuronium.

Rocuronium is a steroidal nondepolarizing muscle relaxant. It has a time of onset from rapid to intermediate depending on the dose and an intermediate duration of action. Moreover, larger doses of rocuronium (up to 2 mg kg<sup>-1</sup>) may be useful for rapid tracheal intubation if succinylcholine is contraindicated (13). The pain related to the administration of rocuronium is a common adverse effect and distressing situation for patients. The exact

mechanism that evokes pain with an intravenous injection of rocuronium is still unknown. Klement et al. (14) showed that acidic and alkaline solutions elicited pain at the pH values of <4 and >11. Rocuronium bromide is an isotonic solution with a pH of 4.0. Injection pain can be explained by the effect of the acidic pH of rocuronium (15). Previous studies showed that pretreatment using lidocaine or fentanyl or an injection of a mixture of rocuronium and sodium bicarbonate was effective in reducing the incidence of pain (15–17). Shevchenko et al. (6) reported that pretreatment with lidocaine and venous occlusion decreased the incidence of withdrawal movements to 46%. It is possible to study the peripheral action of drugs

without the central effect by venous occlusion similar to Bier block (18). Cheong and Wong (15) showed that lidocaine 10 and 30 mg reduced the incidence and severity of rocuronium injection pain but the larger dose was more effective. Akkaya et al. (19) found that lidocaine 30 mg was more effective than ketamine for decreasing the severity of pain and withdrawal movements induced by rocuronium injection. Memis et al. (20) showed that pretreatment with lidocaine by venous occlusion was more effective than with ondansetron, tramadol, or fentanyl and they determined that 30 mg of lidocaine was the most effective dose. Similarly, lidocaine 30 mg was found to be the most effective dose in the present study.

Tramadol is a centrally acting analgesic that inhibits reuptake of serotonin and noradrenalin and this probably explains the mechanism of action. Structurally it is not an opiate but may display some opioid characteristics. Nevertheless, the analgesic effects of tramadol are not completely reversed by opioid antagonists (21). Pang et al. (21,22) demonstrated that IM injection of 25 mg of tramadol had a local anesthetic effect, and, when it was compared with lidocaine, IV injection of tramadol 50 mg prevented injection pain due to propofol. However, in another clinical study, addition of tramadol to levobupivacaine did not improve the block quality (23). It has been suggested that IV injection of tramadol 50 mg reduced the severity of pain due to injection of rocuronium (20). Our study revealed that tramadol 50 mg did not completely eliminate the injection pain of rocuronium.

Joshi and Whitten (5) showed that 100 µg of IV fentanyl and 2 mg of midazolam prevented the pain resulting from the injection of a defasciculating dose of rocuronium in adults. Singh et al. (24) found that the intensity of rocuronium injection pain could be reduced with fentanyl or sufentanil administration in most patients falling into the mild pain group. In our study, sufentanil was the least effective drug.

We used meperidine because no study had been conducted on administration of meperidine to attenuate the pain due to injection of rocuronium. Meperidine,

which has local anesthetic activity, has a molecular weight and pKa similar to lidocaine compared with other opioids (25). Pang et al. (12) showed that meperidine was also effective in reducing the severity of pain resulting from injection of propofol. Jaffe and Rowe (26) reported that only meperidine had local anesthetic effects compared with fentanyl and sufentanil and both sufentanil and fentanyl were not effective in neural conduction of dorsal root axons. We found that the analgesic effect of meperidine was not significantly higher than that of the other agents. Lidocaine 30 mg was the most effective agent in reducing the injection pain due to rocuronium.

Regarding side effects, a few minutes following the injection of meperidine local erythema was observed in 36% (n = 18) of patients but disappeared spontaneously without any medication, which could be explained by histamine release related to meperidine administration. Within the first 24 h following the operation, the injection site was checked for any complications, such as pain, swelling, or allergic reactions, but none were observed. Arrhythmia was observed in 6 (12%) patients in the tramadol group. Wagner et al. (27) reported that preoperative administration of tramadol resulted in an increase in troponin I levels during the postoperative period. That exacerbation could be mediated via serotonergic effects of tramadol and excessive serotonergic activity (serotonin syndrome), causing coronary ischemia (27).

Mencke et al. (28) suggested that female patients reported more pain due to injection of rocuronium than did male patients. Recent reports have shown that women had less tolerance to many types of nociceptive stimuli than men (29,30). In our study, even in the lidocaine group, 58% of the patients suffered from pain, which could be explained by the fact that all of the patients recruited for the study were female.

In conclusion, the analgesic effect of meperidine was not significantly superior to that of the other analgesic agents. Our results showed that lidocaine was the most effective drug, whereas sufentanil was the least effective for alleviating the pain resulting from injection of rocuronium.

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