

Effect of pretreatment with palonosetron on withdrawal movement associated with rocuronium injection

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Background: The main disadvantage of rocuronium is the pain associated with vascular injection. We evaluated the efficacy of palonosetron for reducing pain after rocuronium injection.

Methods: Eighty patients scheduled for elective surgery were randomly divided into two groups: Group C (normal saline 1.5 ml, n = 40) and Group P (palonosetron 0.075 mg, n = 40). Anesthesia was induced with thiopental 5 mg/kg and the test drug was injected over 10 seconds. Thirty seconds after the injection of the test drug, rocuronium 0.6 mg/kg was injected over 30 seconds and the response was recorded. Injection pain was graded using a 4-point scale. The grade was 0 points for no movement, 1 point for wrist movement, 2 points for elbow or shoulder movement, and 3 points for whole body movement. Mean arterial pressure and heart rate were recorded on arrival in the operating room and before and 30 seconds after rocuronium injection.

Results: There was no significant difference in the grade 1 response between the two groups; however, the grade 2 and 3 responses in Group P were 5 (12.5%) and 4 (10%), respectively, which were significantly lower than in Group C, with 13 (32.5%) responses for each grade. There were no significant differences in hemodynamic changes within each group. However, the difference in mean arterial pressure before and after the injection of rocuronium was significantly larger in Group C compared to Group P.

Conclusions: Pretreatment with palonosetron 0.075 mg reduced the incidence and severity of withdrawal movement after rocuronium administration. (Korean J Anesthesiol 2014; 66: 23-27)

Key Words: Injections, Pain, Palonosetron, Rocuronium.

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Introduction

Rocuronium, which has been used increasingly in various procedures, is a nondepolarizing neuromuscular blocker in the aminosteroid series with a fast onset and medium duration [1,2]. However, it has been reported that 50–80% of patients who receive rocuronium complain of burning intravenous injection pain and show withdrawal movement in their arm or whole body [3,4]. This pain-induced withdrawal reflex can dislodge the intravenous catheter and make it difficult to inject the medication. This problem, in turn, makes prompt endotracheal intubation difficult and may cause unnecessary changes in the vital signs and pulmonary aspiration of infants [5].

There are reports that preliminary injection of opioids [6], lidocaine [7-10], ketamine [11], or ondansetron [9] is effective in reducing intravenous injection pain from rocuronium.

Among these, ondansetron is a 5-hydroxytryptamine-3 (5-HT₃) receptor antagonist that is used mainly to prevent postoperative nausea and vomiting (PONV); in addition, administering it before intravenous injection of rocuronium has been reported to relieve pain [9]. This effect occurs because ondansetron has a mechanism similar to that of local anesthetics in blocking the sodium channel. Palonosetron, a recently introduced second-generation 5-HT₃ receptor antagonist, has a stronger affinity and longer half-life and duration compared to the first-generation drugs ondansetron [12], dolasetron and granisetron [13-16].

However, there have been no reports on whether palonosetron has an effect on intravenous injection pain from rocuronium and the resulting withdrawal reflex.

Hence, the authors used palonosetron as premedication when inducing general anesthesia to investigate whether it is effective in reducing intravenous injection pain from rocuronium.

Materials and Methods

Among adult patients scheduled for elective surgery, 80 patients (20–70 years old) of American Society of Anesthesiologists physical status classification I or II were selected as subjects. The purpose and methods of the research were sufficiently explained to them and informed consent was obtained from the patients and their guardians. Approval was also obtained from the Institutional Review Board of the hospital. Patients those who had been administered an analgesic or sedative on the day of the surgery were excluded, along with patients whose periphery veins were difficult to secure, patients with an allergic reaction to local anesthetics, patients with chronic pain, and pregnant patients.

The subjects were randomly divided into two groups, the normal saline group (Group C, n = 40) and the palonosetron group (Group P, n = 40). On the day of the surgery, a 20-gauge intravenous catheter was used to secure the intravenous line in

the antecubital vein, and lactated Ringer's solution was instilled. Thirty minutes before surgery, glycopyrrolate 0.2 mg was given as premedication by intramuscular injection. After subjects arrived in the operating room, noninvasive blood pressure, electrocardiogram, and pulse oximetry were monitored.

Anesthesia was induced by intravenous injection of thiopental 5 mg/kg over 10 seconds, and loss of consciousness was checked by the loss of the palpebral reflex and response to oral commands. An anesthesiologist who was blinded to the prepared medication injected normal saline 1.5 ml in Group C and palonosetron 0.075 mg in Group P for 10 seconds for each group. Normal saline 3 ml was further injected to administer the remaining medication in the fluid line. Thirty seconds after the injection of the medication, rocuronium 0.6 mg/kg was slowly injected for 30 seconds.

Patients' subsequent withdrawal reflex was evaluated by another anesthesiologist using 4 grades based on Borgeat and Kwiatkowski [4]. The grade was 0 points for no movement, 1 point for wrist movement, 2 points for movement of the elbow or shoulder, and 3 points for whole body movement. The baseline for vital signs was checked after arriving in the operating room; vital signs were measured again before injecting the rocuronium and again 30 seconds after completing the injection of rocuronium. The subjects were observed for 24 hours after the end of the anesthesia to check for headache, dizziness, constipation, and diarrhea, which are known complications of 5-HT₃ receptor antagonists.

Ki et al. [17] reported that 85% of patients that received normal saline and 55% of those that were administered ondansetron experienced pain on rocuronium injection. When we considered similar results for our study, the number of subjects needed for a significance level of 0.05 and a test power of 80% was 36 subjects for each group. By also considering the failure rate, the group size was set at 40. SAS 9.2 (SAS Institute Inc, Cary, NC, USA) was used for the statistical analysis. Height and weight were analyzed with the student's t-test; sex, ASA status and withdrawal response were analyzed with the chi-square test; and hemodynamic changes were analyzed using one-way repeated measures ANOVA and the independent t-test. The results were considered statistically significant when the P value was less than 0.05.

Results

There were no statistically significant differences in patient age, weight, and height in each group (Table 1). The withdrawal reflex occurred in 35 out of 40 (87.5%) patients in Group C, and in only 18 out of 40 (45%) patients in Group P. Therefore, there was a significant difference (P < 0.0001). There was no significant difference in the grade 1 response between the two groups, but the grade 2 and 3 responses in Group P were 5 (12.5%) and

4 (10%), respectively, which were significantly lower than Group C, where there were 13 (32.5%) responses for each grade (Table 2).

There were no significant differences in the mean arterial pressure and heart rate within each group. However, the difference in mean arterial pressure before and after the injection of rocuronium was significantly larger in Group C compared to Group P ($P = 0.0034$) (Table 3). The number needed to treat (NNT) was 3 (95% confidence interval 1.6–4.2). The heart rate increased in both groups before and after the injection of rocuronium, but the change was not significant (Table 3). There were no patients who experienced headache, dizziness, constipation, or diarrhea.

Discussion

In this study, there was no significant difference in the grade 1 response between the two groups, but the grade 2 and 3 responses in Group P were 5 (12.5%) and 4 (10%), respectively, which were significantly lower compared to Group C, where there were 13 (32.5%) responses for each of those grades.

Intravenously injected rocuronium causes burning pain in approximately 50–80% of patients and the pain continues for approximately 10–20 seconds immediately after the injection [3,4]. The precise mechanism for this pain has not yet been elucidated and only a few hypotheses exist. Klement and Arndt [18] reported that pain result when a solution with a pH of 4 or lower, or 11 or higher, is injected into the blood vessel. Under this reasoning, rocuronium causes pain because it has a solution pH of 4. How-

ever, in Borgeat et al. [6], vecuronium did not cause intravenous injection pain despite also having a pH of 4; therefore, it can be presumed that pH is not directly related to pain. In addition, severe pain appears immediately after intravenous injection but is not long in duration and when continuous injection is performed, the degree of pain decreases compared to the initial injection. This characteristic is similar to the intravenous injection pain of propofol and may be related to a local mediator, such as the kinin cascade. Blunk et al. [19] reported that injection pain might result from the direct activation of C-nociceptor rather than from a correlation between the release of a local mediator and pain.

Several drugs have been investigated to prevent or reduce pain and the withdrawal reflex that occurs after the administration of rocuronium. In a study by Cheong and Wong [10], premedication with 10 mg and 30 mg of lidocaine resulted in pain frequencies of 37% and 7%, respectively, which were significantly lower than in the control group. Reddy et al. [20] premedicated with ondansetron and lidocaine; while both drugs significantly reduced pain, the effect of lidocaine was better. Although ondansetron had a smaller effect than lidocaine, it was effective in preventing the intravenous injection pain of rocuronium considering that it is a first-generation 5-HT₃ antagonist usually used for the prevention of PONV. With intravenous lidocaine 30 mg, given 10 seconds before the injection of rocuronium, the NNT was 2 [21]. In this experiment, the NNT for intravenous palonosetron was 3.

Table 1. Demographic Data

| | Group C (n = 40) | Group P (n = 40) |
|-------------|---------------------|---------------------|
| Sex (M/F) | 13/27 | 10/30 |
| Age (yr) | 49.0 ± 14.1 | 49.4 ± 15.2 |
| Height (cm) | 162.0 ± 7.8 | 159.8 ± 8.3 |
| Weight (kg) | 60.0 ± 9.1 | 61.7 ± 11.5 |
| ASA (I/II) | 27/13 | 29/11 |

Values are the mean ± SD or number of patients. There was no difference between the groups. Group C: normal saline 1.5 ml, Group P: palonosetron 0.075 mg. ASA: American Society of Anesthesiologists.

Table 2. Incidence and Severity of Withdrawal Response on Injection of Rocuronium

| Grade of withdrawal | Group C (n = 40) | Group P (n = 40) |
|--|---------------------|---------------------|
| 0 | 5 (12.5) | 22 (55.0)* |
| 1 | 9 (22.5) | 9 (22.5) |
| 2 | 13 (32.5) | 5 (12.5)* |
| 3 | 13 (32.5) | 4 (10.0)* |
| Overall incidence of withdrawal movement | 35 (87.5) | 18 (45.0)* |

Values are presented as the number of patients (percentage). Group C: normal saline 1.5 ml, Group P: palonosetron 0.075 mg. * $P < 0.05$ compared with group C.

Table 3. Mean Arterial Pressure and Heart Rate

| | Group | Baseline | Before rocuronium injection | 30 seconds after rocuronium injection |
|----------------|------------|-------------|-----------------------------|---------------------------------------|
| MAP (mmHg) | C (n = 40) | 95.9 ± 11.9 | 93.5 ± 14.7 | 102.9 ± 13.3 |
| | P (n = 40) | 99.9 ± 13.6 | 97.5 ± 15.9 | 98.3 ± 15.7* |
| HR (beats/min) | C (n = 40) | 77.3 ± 13.2 | 81.9 ± 13.7 | 90.3 ± 12.7 |
| | P (n = 40) | 80.4 ± 14.2 | 83.3 ± 13.1 | 88.8 ± 14.3 |

Values are the mean ± SD. No significant differences were noted between the groups. MAP: mean arterial pressure, HR: heart rate, baseline, on arrival in the operating room. Group C: normal saline 1.5 ml, Group P: palonosetron 0.075 mg. * $P = 0.0034$ for the difference between baseline and 30 seconds after rocuronium injection of group P compared with group C.

According to Ye et al. [22], subcutaneous injection of ondansetron has a local anesthetic effect 15 times stronger than lidocaine. Lidocaine, known to be the most effective drug in preventing intravenous injection pain from propofol or rocuronium, has a structural formula that combines hydrophobic and hydrophilic structures. The hydrophilic structure is a tertiary or secondary amine structure, while the hydrophobic structure is aromatic. The 5-HT₃ antagonist does not have this aromatic structure but it has a similar effect as a local anesthetic. It is known that the periphery 5-HT₃ antagonist has this effect by interacting with the nociceptor pathway and blocking the sodium channel, and in animal experiments, it reduces the pain response of the dorsal root ganglion when injected into the intrathecal. Wijngaarden et al. [23] reported that the 5-HT₃ antagonist combines with μ receptors in humans to function as the working agent, and the peripheral 5-HT₃ receptors interact with the nociceptor pathway resulting in the 5-HT₃ antagonist having an analgesic effect.

Through this analgesic effect, premedication with palonosetron reduced the intravenous injection pain of rocuronium and the subsequent withdrawal reflex. Hemodynamic changes such as mean arterial pressure and heart rate also showed a larger increase in the control group compared to the palonosetron group; thus, there seems to be less stimulation from pain when using palonosetron premedication.

There are some limitations to this study. First, we did not clarify by what mechanism palonosetron reduces the pain from intravenous injection of rocuronium. Further study will be required to reveal whether palonosetron has local anesthetic effect or has an effect on the central pain control mechanism. Second, in this study, we used the same dose of palonosetron. Further research is warranted to evaluate the dose-response effect of palonosetron.

In conclusion, premedication with palonosetron to prevent PONV also has an effect on decreasing withdrawal movement induced by injection pain from rocuronium.

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