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Effects of pretreatment with esmolol and lidocaine on injection pain and rocuronium-induced withdrawal response

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Background/aim: We aimed to compare the effectiveness of esmolol 1 mg/kg and lidocaine 1 mg/kg for injection pain and for the prevention of rocuronium-induced withdrawal response.

Materials and methods: We enrolled a total of 81 patients in the study. Patients were randomly assigned to receive either 10 mL of 0.9% NaCl (Group P), esmolol 1 mg/kg (Group E), or lidocaine 1.0 mg/kg (Group L). A subparalyzing dose of rocuronium 0.05 mg/kg was administered to all patients and its effects were recorded. Anesthesia was induced with intravenous propofol and intravenous rocuronium 0.5 mg/kg in all groups. The withdrawal movements of the patient groups were subsequently graded.

Results: There was a statistically significant difference in overall incidence of pain in group E and L compared to the placebo group after administrating the subparalyzed dose (no pain response: Group E = 81.5%, Group L = 77.8%, Group P = 14.8%) ($P < 0.001$). After intravenous administration of an intubating dose of rocuronium, the esmolol group had a significantly lower incidence of withdrawal movement than the other groups (no response: Group E = 81.5%, Group L = 63%, Group P = 22.2%) ($P < 0.001$).

Conclusion: We found that esmolol significantly attenuates rocuronium-induced withdrawal movement and also reduces pain when used at subparalyzing doses.

Key words: Esmolol, rocuronium, lidocaine, withdrawal movement, injection pain

1. Introduction

Rocuronium is an aminosteroidal nondepolarizing neuromuscular blocking agent with a rapid onset and intermediate duration of action (1). Approximately 50%–80% of rocuronium injections are associated with a withdrawal response during anesthetic induction (2). Furthermore, rocuronium may lead to generalized spontaneous movements, which may increase the risk of reflux of gastric contents and pulmonary aspiration (2). Moreover, several publications have reported severe and distressing symptoms of burning pain following rocuronium injection (3).

Several studies have shown that pretreatment with lidocaine, fentanyl, ondansetron, magnesium sulfate, ketamine, and sodium bicarbonate mixture reduced rocuronium-induced pain (2,4).

Peripheral veins are innerved by polymodal nociceptors (5). Although the mechanism by which rocuronium causes injection pain remains unclear, the activation of C-nociceptors on veins or the triggering of a local quinine cascade by kininogen release are among the most probable causes (6).

Owing to its antiinflammatory effects, lidocaine is used as an adjuvant in multimodal analgesia techniques. Additionally, it inhibits G protein and NMDA-related receptors. Furthermore, systemic lidocaine has been shown to depress spike activities as well as the amplitude and conduction time of both myelinated A-delta and unmyelinated C fibers. While lidocaine is usually regarded as a safe agent, its dose-related side effects on the central nervous system limit its use in anesthesia (7,8).

Esmolol is a cardioselective β_1 adrenergic receptor antagonist. Intraoperative esmolol infusion has frequently been used both as an adjuvant to decrease perioperative opioid consumption and to facilitate fast-track recovery (9,10). In addition, esmolol activates G proteins on the cell membrane and causes a central analgesic effect. Several studies have reported postoperative pain relief following perioperative esmolol use (11).

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In the current study, we aimed to compare the effectiveness of esmolol 1 mg/kg and lidocaine 1 mg/kg on injection pain and on the prevention of rocuronium-induced withdrawal response.

2. Materials and methods

The study was conducted at the Dışkapı Research and Training Hospital between January and March 2013. It was approved by a local research ethics committee (14 December 2012, No. 12) and was registered in ESM 0538 NCT01824758. After obtaining written informed consent from all the patients, we enrolled 81 patients of ASA physical status I–II aged 18–72 years. The patients were scheduled to undergo elective surgery under general anesthesia. Our exclusion criteria included the following: ASA physical status of III or higher, diagnosis with diabetes, BMI of >40, chronic use of beta-adrenergic receptor antagonists, pregnancy, and history of hepatic, renal, or cardiac disease.

We inserted a 20-gauge cannula into the dorsum of the hand and infused 0.9% sodium chloride to the patient. The calculated drug doses were adjusted to a volume of 10 mL with saline solution in Groups P and L (see explanation of groups below). Patients were monitored with standard monitors and the solutions were kept at ambient temperature (20–24 °C).

Patients were randomly assigned to receive 10 mL of 0.9% NaCl in the placebo group (Group P), esmolol 1 mg/kg in the esmolol group (Brevibloc Premixed injection, 10 mg/mL, ready-to-use bags, Baxter Healthcare Corporation, USA) (Group E), or lidocaine 1.0 mg/kg in the lidocaine group (Jetmonal 2% Ampul, 100 mg/5 mL, Adeka, Turkey) (Group L) by using computer-generated random numbers.

Thirty seconds after the administration of the study drug, a subparalyzing dose of 0.05 mg/kg rocuronium (Esmeron, intravenous, 50 mg/5 mL, Merck Sharp Dohme, N.V. Organon, the Netherlands) at room temperature was diluted in 5 mL of normal saline and injected to all the patients within 10 s. After counting another 10 s, a blinded investigator asked the patient if he or she felt any pain in the arm and documented the patient's reactions, if any, such as discomfort, pain, and tears (Table 1). Finally, patients were induced with propofol 2 mg/kg i.v. and rocuronium 0.5 mg/kg i.v. for 10 s. Following the abolition of the eyelash reflex, an investigator blinded to the patient grouping (single-blinded) graded the withdrawal movement as follows: 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 breath-holding (11) (Table 2).

Table 1. Pain assessment during an injection of a subparalyzing dose of rocuronium.

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. Patient assessment of pain during injection of rocuronium.

Pain score	Severity of pain	Patient's response when questioned regarding pain/discomfort
0	None	No pain or discomfort
1	Mild	Mild pain or discomfort
2	Moderate	Moderate pain or discomfort
3	Severe	Pain or discomfort reported spontaneously and described as becoming severe
4	Very severe	Pain or discomfort reported to be very severe and associated with a strong vocal response, hand or arm withdrawal, facial grimacing, or crying

Following muscular relaxation, tracheal intubation was performed and $ETCO_2$ was maintained between 32 and 42 mmHg with a fresh gas flow rate of 4 L/min. Anesthesia was maintained with 50% nitrous oxide in oxygen and sevoflurane to maintain blood pressure and heart rate within 20% of baseline values. We assessed the patients' hands for erythema, thrombophlebitis, and thrombosis, both after injection and 24 h postoperatively.

Sample size estimation was performed using NCSS and PASS 2000 (NCSS LLC, USA) software. We performed a power analysis estimating a frequency of 80% of patients who would experience rocuronium-induced pain or withdrawal movement and found that we required a minimum of 27 patients in each group to detect a 50% reduction at a significance level of 5% and a probability (power) of 80%.

We used SPSS 16.0 for Windows (SPSS Inc., USA) to perform data analysis. While continuous variables were expressed as mean ± standard deviation, categorical data were expressed as n (%). The mean difference in age and weight among groups was compared with the Kruskal–Wallis test. Categorical data were analyzed by Pearson's chi-square test. $P < 0.05$ was considered statistically significant.

3. Results

Eighty-one patients were enrolled in the study. There was no significant difference between the demographic data and ASA status among groups (P = 0.05) (Table 3). There was a statistically significant difference in overall incidence of pain and degree of pain in groups E and L compared to the placebo group after administrating the subparalyzing dose ($P < 0.001$) (Table 4). However, the incidence and degree of pain was similar between groups E and L after administrating the subparalyzing dose (P = 0.735) (Table 4).

The incidence of "no response" withdrawal movement following intravenous administration of the intubating dose of rocuronium was 81.5%, 63%, and 22.2% in the esmolol, lidocaine, and placebo groups, respectively ($P < 0.001$). Generalized movement was not seen in any of the groups (Table 5). We did not observe erythema or venous sequelae in any of the patients during the 24-h follow-up, and no patients reported pain or discomfort.

4. Discussion

In the current study, we demonstrated that esmolol significantly reduces withdrawal movement related to the administration of an intubating dose of rocuronium as compared with placebo and lidocaine groups. Additionally,

Table 3. Demographic data.

	Group E (n = 27)	Group L (n = 27)	Group P (n = 27)	P-value
Age, years*	50 (36–58)	44 (36–52)	47 (34–57)	0.6
Sex, M/F	7/20	5/22	7/20	0.7
Weight, kg	75.88 ± 14.65	81.18 ± 16.14	81.11 ± 12.21	0.3
Height, cm	163.88 ± 6.5	159.92 ± 8.19	162.25 ± 6.75	0.1
ASA physical status, I/II	10/17	14/13	13/14	0.5

*: Median (interquartile range).

Table 4. Severity of pain during the injection of a subparalyzing dose of rocuronium.

Degree of pain	Esmolol group (n = 27)	Lidocaine group (n = 27)	Placebo group (n = 27)	P-value
No pain (0)	22 (81.5%)	21 (77.8%)	4 (14.8%)	P < 0.001
Mild pain (1)	4 (14.8%)	6 (22.2%)	12 (44.4%)	P = 0.039
Moderate pain (2)	1 (3.7%)	0 (0.0%)	5 (18.5%)	P < 0.001
Severe pain (3)	0 (0.0%)	0 (0.0%)	6 (22.2%)	P < 0.001
Yes pain	5 (18.5%) #	6 (22.2%) #	23 (85.2%)	P < 0.01

#: P = 0.735 vs. lidocaine group.

Table 5. Withdrawal reactions associated with the intravenous administration of an intubating dose of rocuronium.

Degree of withdrawal reactions	Esmolol group (n = 27)	Lidocaine group (n = 27)	Placebo group (n = 27)	P-value
No response (1)	22 (81.5%)	17 (63.0%)	6 (22.2%)	P < 0.001
Wrist (2)	4 (14.8%)	9 (33.3%)	11 (40.7%)	P = 0.09
Elbow/shoulder (3)	1 (3.7%)	1 (3.7%)	10 (37.0%)	P < 0.001
Generalized response (4)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
Yes response (total)	5 (18.5%) #	10 (37.0%) #	21 (77.8%)	P < 0.05

Values are presented as numbers (percentages).
#: P < 0.05 vs. lidocaine group.

esmolol equally attenuated pain and withdrawal movement as did lidocaine following the administration of a subparalyzing dose of rocuronium.

Although rocuronium is regarded as an ideal nondepolarizing neuromuscular blocker owing to its fast onset of action (12), 50%–80% of patients report rocuronium-induced burning pain (13). Peripheral veins are innervated by polymodal nociceptors, which are thought to mediate the injection response of certain anesthetics. Blunk et al. (8) demonstrated that the direct activation of C-nociceptors could be mediating the burning sensation caused by aminosteroidal neuromuscular blocking drugs. Lidocaine, which is an amide derivative with analgesic, anesthetic, and antiinflammatory effects, is known to be the most effective agent in relieving rocuronium-induced pain. This presumed analgesic effect is thought to be related to sodium channel blockage, G protein-related receptor inhibition, and NMDA receptor inhibition (9).

Mencke et al. reported a 33% incidence of pain in patients who received a precurarization (0.03 mg/kg in 5 mL of saline) dose of rocuronium (14). Yavascaoglu et al. (5) reported a 63% incidence of pain in patients who received a higher subparalyzing dose of rocuronium (0.05 mg/kg in 5 mL of saline) following 0.5 mg/kg esmolol and 0.5 mg/kg lidocaine. In the current study, 85% of patients who received a rocuronium dose of 0.05 mg/kg in 5 mL of saline experienced injection pain, and a similar rate of patients in groups E and L reported attenuation of pain. The fact that patients in groups E and L achieved a higher rate of analgesic effect may be explained by our use of a higher dosage of esmolol (1 mg/kg) and lidocaine (1 mg/kg) compared to Yavascaoglu et al.

Rocuronium-induced withdrawal movements may primarily cause displacement of the venous catheter and may lead to pulmonary aspiration of gastric contents. They may even induce bronchospasm, asthma, or myocardial infarction (15,16). Several drugs, such as lidocaine, tramadol, fentanyl, ondansetron, remifentanil, and a mixture of sodium bicarbonate and rocuronium, have been previously assessed for their potential to reduce rocuronium-induced injection pain (13,17–19).

Cheong and Wong compared the use of 10 mg and 30 mg of lidocaine pretreatment in adult patients and found that although 30 mg was more effective, both significantly reduced the incidence and severity of rocuronium-induced pain (20). Yavascaoglu et al. similarly demonstrated that i.v. lidocaine administration significantly reduced the rate of patients experiencing rocuronium-induced injection pain as compared with the placebo (5). The use of lidocaine, however, is associated with several side effects such as coughing, chest rigidity, hypotension, bradycardia, and anaphylaxis (15). Salman et al. compared the analgesic effects of esmolol 10 mg and lidocaine 40 mg following propofol infusion and found that, although the dose was lower, esmolol provided better analgesia than lidocaine (21).

Esmolol is an ultrashort-acting, cardioselective beta-1 receptor antagonist. It is a moderate lipophilic drug and takes part in central adrenergic activation. Additionally, it is effective in blunting adrenergic responses related to several perioperative stimuli such as the application of a laryngoscope, intraoperative events, and tracheal extubation (10). Esmolol-associated postoperative analgesia has been attributed to several mechanisms. Functional MRI studies have demonstrated hippocampal activation following anxiety, emotional stress, and fear. The hippocampus is estimated to participate in nociception induced by at least some of the NMDA receptors, and the activation of hippocampal beta adrenergic receptors is thought to influence nociception. By blocking these receptors, we may attenuate nociceptive processing and relieve pain (22).

A limitation of this study is the lack of pH and osmolality analysis of solutions (saline, esmolol/saline, and lidocaine). Further studies performing these analyses on all patients may help elucidate the cause of injection pain.

In the current study, we observed that withdrawal movements and hemodynamic effects were significantly attenuated by esmolol 1 mg/kg. Although esmolol may cause hypotension and bradycardia, we did not observe any side effect or negative hemodynamic signs associated with its use. In conclusion, we found that esmolol significantly attenuates rocuronium-induced withdrawal movement and also reduces pain when used at subparalyzing doses.

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