

Can Ephedrine Pretreatment Be Effective in Alleviating Rocuronium Injection Pain?

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Key Words

Ephedrine · Rocuronium · Injection pain

Abstract

Objective: The aim of this randomized, double-blind, placebo-controlled study was to evaluate the effect of ephedrine pretreatment on the intensity of rocuronium injection pain when rocuronium was applied by timing principle and also to compare this effect with lidocaine and placebo. **Subjects and Methods:** 120 American Society of Anesthesiology risk score I–II patients scheduled for elective surgery under general anesthesia were randomized into three groups to receive either 70 µg/kg ephedrine (ephedrine group, n = 40) or 0.5 mg/kg lidocaine (lidocaine group, n = 40) or 5 ml NaCl 0.9% (placebo group, n = 40) as pretreatment. Thirty seconds after pretreatment drugs, rocuronium 0.6 mg/kg was administered by the timing principle and rocuronium injection pain scores were recorded. Twenty seconds after rocuronium administration, anesthesia was induced with thiopental and the patient's trachea was intubated. Hemodynamic parameters and adverse effects were recorded. **Results:** The overall frequency of having pain was 82.5, 52.5 and 22.5% in placebo, ephedrine and lidocaine groups, respectively. Although the frequency of mild and moderate pain scores was higher in the ephedrine group than in the lidocaine group, this difference was not statistically significant (p = 0.032 and p = 0.001, respectively). **Conclusion:** Al-

though not as effective as lidocaine 0.5 mg/kg, 70 µg/kg ephedrine pretreatment was able to alleviate rocuronium injection pain when rocuronium was applied by timing principle.

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Introduction

Rapid sequence intubation is an essential and also a valid method for maintaining airway patency, especially in emergency cases [1]. Rocuronium, the steroidal, intermediate acting, nondepolarizing muscle relaxant with rapid onset time [2–4], is being used as an alternative to succinylcholine for rapid sequence intubation [5]. Different techniques can be used to decrease the effective onset time of rocuronium including priming [6], administration of larger doses [7] or using the timing principle [8]. The timing principle involves giving a single bolus dose of a nondepolarizing neuromuscular blocking agent before the induction agent and then administering the induction agent at the onset of clinical weakness [9]. The purpose of using the timing principle is to reduce the time between induction of anesthesia and muscle relaxation which coincides closely with the peak effect of the muscle relaxant and the intravenous (i.v.) induction agent [8]. Rocuronium is known as a useful muscle relaxant for rapid sequence intubation. However, injection of rocuronium is painful. Even after induc-

Table 1. RIP scores

Degree of pain	Response
None (0)	Negative response to questioning
Mild (1)	Patient reported in response to questioning only, without any behavioral signs
Moderate (2)	Patient 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

tion of anesthesia, hand or limb withdrawal or generalized muscle movements can be seen in 85% of patients administered rocuronium [10, 11]. So using rocuronium by timing principle may probably cause injection pain.

As known, circulatory factors like cardiac output and muscle blood flow may influence the onset time of the neuromuscular blocking agent [12]. Ephedrine, by increasing cardiac output and tissue perfusion, has been shown to reduce the onset time of rocuronium and/or improve intubation conditions [13, 14]. So applying rocuronium by timing principle with ephedrine pretreatment could be useful in rapid sequence intubation. Ephedrine pretreatment has been shown to reduce the incidence and intensity of propofol-induced injection pain [15, 16]. But to date, no study has been conducted to evaluate the effect of ephedrine in alleviating rocuronium injection pain (RIP).

Therefore, in this randomized, double-blind, placebo-controlled study, we aimed to observe the effects of ephedrine pretreatment on alleviating RIP intensity when rocuronium was applied by timing principle during rapid sequence intubation, and compare this effect with lidocaine and placebo.

Subjects and Methods

This study was approved by the Institution's Ethics Committee and each patient gave written informed consent to participate in the study. American Society of Anesthesiology risk score (ASA) I–II patients, aged 18–65 years and scheduled for elective surgical procedures, were included in the study. Exclusion criteria were: increased risk of pulmonary aspiration, neuromuscular disease, hypertension, anticipated difficulty with airway management, receiving analgesics and sedatives, having chronic pain and pregnancy. The patients were informed of the sting pain which could occur at the beginning of anesthesia. They were told that they

would be asked to score the severity of this pain if it occurred. Also they were informed that they might feel weak and might have heavy eyelids, blurred vision or difficulty in swallowing and breathing after the injection of the drug. None of the patients received any analgesics and premedication within 24 h before surgery.

A 20-gauge cannula was placed in the largest vein on the dorsum of the hand without using any local anesthetic agent and i.v. infusion of NaCl 0.9% was started in each patient. The usual monitoring, including electrocardiography, pulse oximeter and non-invasive blood pressure cuff were used and values of all these were recorded at the beginning of the study (baseline), after administration of the test drug, after induction of anesthesia, immediately after intubation and 3 and 5 min after intubation.

The sealed envelope technique was used for randomization. Envelopes which contained information concerning the assigned drug (ephedrine, lidocaine, NaCl 0.9%) were randomly numbered from 1 to 120. Patients consequently received the test drug according to the content of the envelope. An investigator (G.T.) who did not participate in the evaluation of study parameters prepared the test solutions. For the ephedrine group (n = 40) 70 µg/kg ephedrine and for the lidocaine group (n = 40) 0.5 mg/kg lidocaine were diluted with NaCl 0.9% at ambient operating room temperature (20–22°C) to 5 ml. For the placebo group (n = 40), 5 ml NaCl 0.9% was also prepared. This investigator (G.T.) gave the test drug solution to the anesthesiologist who administered the drug. So this anesthesiologist (Z.N.A.) and also the patient were blinded to the group allocation. All parameters during the study were recorded and all interviews were done by this blinded anesthesiologist.

Thirty seconds after injection of the test solution, rocuronium 0.6 mg/kg was administered over 5 s. Patients were asked if they experienced any pain just after rocuronium injection and the scores were recorded as RIP scores, which were assessed according to a 4-point scale [17] (table 1).

During this period, the patients were closely observed for any signs of weakness such as hypoventilation, diplopia and ptosis. Twenty seconds after the administration of rocuronium, anesthesia induction was provided with thiopental sodium (4–6 mg/kg). Anesthesia was maintained with sevoflurane (2% vol) in oxygen/nitrous oxide (40/60%). The lungs were mechanically ventilated to maintain normocarbida. A 20% change in hemodynamic variables from the baseline values was regarded as significant and treated.

All patients were interviewed at 4 and 24 h after surgery and asked, if they felt weak or short of breath, had any discomfort or muscle pain and had experienced awareness of pain during their induction of anesthesia. Any evidence of erythema or venous sequelae during 24 h was recorded.

The primary outcome of this study was to detect the differences in RIP scores. On the basis of power analysis, to detect a 50% reduction in RIP at a significance level of 5% and a power of 80%, sample size required at least 40 patients per group. 120 patients were scheduled for the study and all data were analyzed without dropouts. Data are expressed as mean ± standard deviation or numbers (%). All statistical analyses were done using SPSS for Windows (version 11.0, SPSS Inc., Chicago, Ill., USA). Numerical data (age, weight, height, hemodynamic variables) were analyzed using one-way analysis of variance with post hoc Duncan test; χ^2 test was used for categorical data (gender, ASA status). RIP scores were analyzed by using Kruskal-Wallis test and in the case of significant difference Bonferroni adjusted Mann-Whitney U test was used; $p < 0.05$ was considered significant.

Results

Patient characteristics were comparable in all the groups and are shown in table 2. Tracheal intubation was successful for all the patients. The overall frequencies of having pain were 82.5% in the placebo group, 52.5% in the ephedrine group and 22.5% in the lidocaine group. In the lidocaine group, mild and moderate pain was significantly lower than in the placebo group ($p = 0.032$ and $p = 0.001$, respectively). Although the frequencies of mild and moderate pain were higher in the ephedrine group than in the lidocaine group, this difference was not statistically significant ($p = 0.088$ and $p = 0.201$, respectively). No patient in the lidocaine and ephedrine groups had severe pain. Pain scores are shown in table 3.

The mean arterial pressure (MAP) and heart rate (HR) values are shown in figures 1 and 2. Baseline values of MAP and HR were comparable among groups. MAPs after test drug and after induction were higher in the ephedrine group than in the lidocaine and placebo groups ($p = 0.017$ and $p = 0.032$, respectively). HR values after the test drug, after induction and after intubation were higher in the ephedrine group than in the lidocaine and placebo groups ($p = 0.017$, $p = 0.027$, $p = 0.037$, respectively). Although these differences were statistically significant, they were not clinically important and became comparable in the three groups after a short time interval. No patient presented with arrhythmias and none was treated for MAP or HR changes.

None of the patients complained of weakness, shortness of breath or discomfort before induction of anesthesia. None of the patients had muscle pain, erythema or venous sequelae during a 24-hour follow-up. No patient recalled any pain or discomfort and no one experienced awareness of pain.

Discussion

This study demonstrated that, applying rocuronium by timing principle, ephedrine pretreatment significantly reduced RIP compared to placebo, but ephedrine was not as effective as lidocaine. In anesthetic practice, rocuronium can be preferred as a nondepolarizing neuromuscular blocking agent alternative to succinylcholine in rapid sequence intubation [5]. To decrease the effective onset time of rocuronium, the timing principle can be used which does not affect the onset time of rocuronium but instead induces muscle relaxation and induction of anesthesia simultaneously [6–9]. But RIP is a common, distressing and

Table 2. Patient characteristics in groups

	Ephedrine (n = 40)	Lidocaine (n = 40)	Placebo (n = 40)
Age, years	41.6 ± 8.8	42.2 ± 12.0	40.5 ± 13.4
Weight, kg	73.2 ± 11.8	70.8 ± 14.3	69.1 ± 14.7
Height, cm	167.9 ± 9.8	166.8 ± 10.2	169.7 ± 8.2
Gender, M/F	16/24	17/23	14/26
ASA, I/II	22/18	20/20	19/21

Table 3. Pain scores during rocuronium injection in groups

Pain scores	Ephedrine (n = 40)	Lidocaine (n = 40)	Placebo (n = 40)
0 (none)	19 (47.5) ^{a, c}	31 (77.5)	7 (17.5) ^b
1 (mild)	16 (40)	8 (20)	18 (45) ^a
2 (moderate)	5 (12.5)	1 (2.5)	12 (30) ^b
3 (severe)	0 (0)	0 (0)	3 (7.5)
Any pain	21 (52.5) ^{a, c}	9 (22.5)	33 (82.5) ^b
Median pain score, range	1 (0–2)	0 (0–2)	1 (0–3)
Mean pain score ± SD	0.65 ± 0.7	0.25 ± 0.5	1.27 ± 0.9

Number of patients with percentage in parentheses unless indicated otherwise.

^a $p < 0.05$ vs. lidocaine. ^b $p < 0.01$ vs. lidocaine. ^c $p < 0.05$ vs. placebo.

serious pain that makes the patient's arm sting, especially when rocuronium is injected prior to loss of consciousness [2, 18–20]. Although the pathophysiologic mechanism of this pain is still not clear, it may be due to nociceptor activation, by the osmolality or pH of the solution or activation of histamine-kinin-like endogenous inflammatory mediators [2, 21]. Withdrawal movements due to rocuronium injection may negatively affect patient outcome. Due to pain and emotional stress during anesthesia, bronchospasm, asthma or myocardial infarction can be induced [22]. Pretreatment or mixing with a variety of drugs such as opioids, lidocaine, midazolam, esmolol, thiopental, metoclopramide, bicarbonate, ondansetron, tramadol or techniques like dilution with NaCl 0.9% were studied before, in which lidocaine [2, 11, 23–25], esmolol [2], bicarbonate [16], medication or dilution with NaCl 0.9% [26] were found effective for decreasing RIP. Lidocaine is the most studied agent and was found to be very effective in decreasing RIP [2, 11, 23–25]. In this study we decided to evaluate the effect of ephedrine, which was not studied before, and compare it with lidocaine.

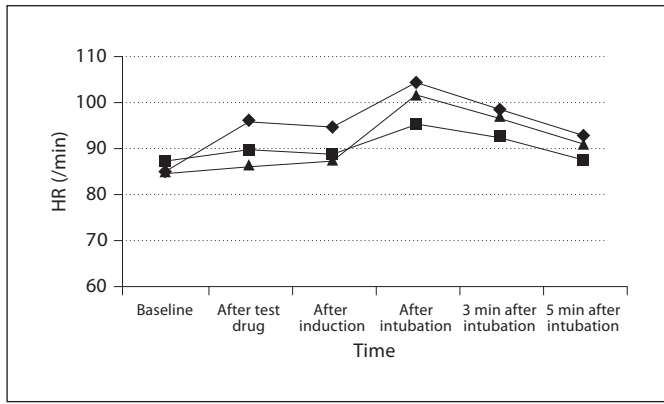


Fig. 1. HR in groups. ■ = Lidocaine; ◆ = ephedrine; ▲ = placebo.

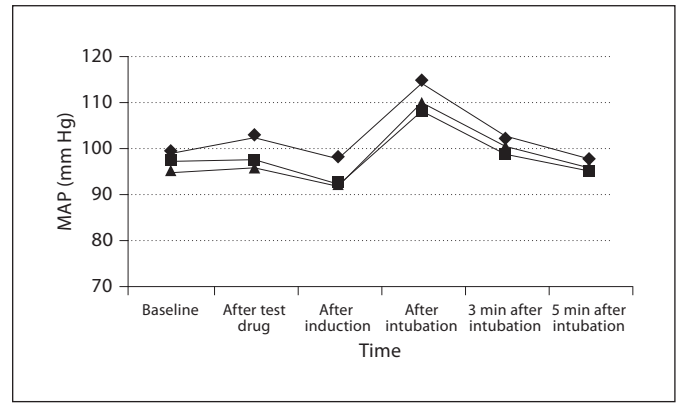


Fig. 2. MAP in groups. ■ = Lidocaine; ◆ = ephedrine; ▲ = placebo.

Ephedrine has no known analgesic effect. But some possible mechanisms were suggested for it to induce analgesia. Bradykinin was reported to inhibit norepinephrine efflux from sympathetic nerve terminals innervating canine mesenteric and pulmonary arteries, so it was suggested that endogenous norepinephrine released by ephedrine might reduce the effect of bradykinin [16]. Also Tekol et al. [27] reported the enhancement of analgesic effects of opioids by ephedrine both experimentally and clinically. The alpha adrenergic stimulating action of ephedrine may play a role in this intervention. It was shown that spinal administration of norepinephrine produces or enhances analgesia in man and in experimental animals.

It is postulated that pain associated with propofol and rocuronium is similar: it appears immediately during administration, its duration is short and its intensity decreases with subsequent injections [23]. The effect of ephedrine on propofol injection pain was studied before and different results were reported. Ephedrine pretreatment was found effective in a study by Austin and Parke [15] in which 30 mg ephedrine to 20 ml of 1% propofol was used. In the study by Cheong et al. [16], 30 and 70 µg/kg ephedrine pretreatment was found to be effective against propofol injection pain. However, 70 µg/kg ephedrine was reported as ineffective in the prevention of propofol injection pain in the study by Ozkocak et al. [28]. In our study we decided to use ephedrine at a dose of 70 µg/kg, which was found effective against propofol injection pain without producing significant adverse hemodynamic effects [16]. Similar to previous studies [11, 24–26], we observed RIP in 82.5% of our patients without

pretreatment. In our study, lidocaine was found more effective than ephedrine for alleviating RIP, similar to studies by Memis et al. [24] and Cheong and Wong [11] in which rocuronium was also applied by timing principle. RIP was prevented in 47.5% of patients when ephedrine pretreatment was applied. Although this percentage was not as high as lidocaine pretreatment (77.5%), it was better than placebo (17.5%).

Generally when the timing principle is used, clinical weakness can be seen before loss of consciousness, leading to a potential risk for the patient to experience discomfort during the induction. However, in our study, no patient complained of weakness or shortness of breath before induction of anesthesia and none complained of any muscle pain, awareness or discomfort during the 24-hour follow-up. Although MAP and HR values during induction increased in the ephedrine group, these increments were temporary and returned to baseline levels within a short time interval. Pretreatment with ephedrine can prevent hypotension after induction of anesthesia as was the case in our study; we observed this effect of ephedrine also. No patient needed any treatment for hemodynamic changes.

Conclusion

Although not as effective as lidocaine (0.5 mg/kg), ephedrine pretreatment with 70 µg/kg was effective in alleviating RIP, when rocuronium was applied by timing principle during rapid sequence intubation.

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