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ORIGINAL ARTICLE

Local warming at injection site helps alleviate pain after rocuronium administration

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Abstract
Purpose Various strategies have been proposed to reduce discomfort of pain after rocuronium injection. These studies have shown pretreatment of drugs such as fentanyl and lidocaine to be effective. In a prospective randomized study, we evaluated whether pretreatment with local warming at injection site using an air-warming device could effectively alleviate pain induced by rocuronium.
Methods Ninety patients undergoing spinal surgeries were randomly divided into two groups: group C (control) and group T (treatment). Patients in group T were subjected to warming at 40°C for 1 min prior to injecting 1 ml (10 mg) of rocuronium at the site of venous access. Patients were then assessed for any discomfort and to quantify their discomfort on a 5-point scale.
Results Age, sex, and weight were comparable between the two groups. Pain on rocuronium administration was reported by 88.9% patient in group C versus 66.7% in group T ($p < 0.05$). Severe pain was significantly less in group T (35.6% vs. 8.9%).
Conclusion Application of warmth over the vascular access prior to rocuronium administration effectively reduces injection-related pain.

Keywords Local warming · Rocuronium · Pain

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Introduction

Pain during IV injection makes induction of anesthesia an unpleasant experience for the patient. Rocuronium, a derivative of aminosteroid, is a widely used nondepolarizing muscle relaxant with intermediate duration and a rapid onset of action. Awake patients experience hot and burning sensation when rocuronium is injected IV [1–3]. It is generally accepted that rocuronium is not suitable for use in awake patients, e.g., in a subparalyzing dose before succinylcholine or in priming and should only be administered in deeper planes of anesthesia [3]. However, even when administered after loss of consciousness, a brisk withdrawal reaction of the injected hand or arm [4] or generalized movement of the body occurs, which may dislodge the IV catheter or even cause injury. The associated pain may cause bronchospasm or even lead to pulmonary aspiration [5]. Rocuronium is a better precurarization agent than other neuromuscular drugs for the prevention of succinylcholine-induced fasciculation and myalgia [6]. As it holds a unique place among the nondepolarizing relaxants, continual efforts have been made to alleviate this painful side effect and various strategies have been proposed. Pretreatment or mixing with a variety of drugs such as thiopental, ondansetron, lidocaine, fentanyl, alfentanil, tramadol esmolol, magnesium sulphate, ketamine, antihistaminics, and sodium bicarbonate has been used in an attempt to reduce this pain [7–13]. The analgesic action of heat is mediated by the gate-control theory of pain [14]. It can possibly be an effective method to alleviate rocuronium-induced pain. Based on the above hypothesis, this study was carried out with the aim of evaluating the effect of local warming at the injection site to reduce rocuronium-induced pain.

Materials and methods

This study was performed after obtaining approval from the Institutional Ethics Committee. The purpose and methods were explained to each patient, and written informed consent was obtained. This study was performed on 90 American Society of Anesthesiologists (ASA) physical status I–II patients aged 18–60 years who were scheduled to undergo elective spinal surgery. Patients with a history of chronic pain, neurological deficit, psychiatric illness, substance abuse, alcoholism, and those receiving sedatives and analgesics were excluded from the study. Patients with thin, weak dorsal veins and having difficult venous cannulation were excluded. Patients were informed that they may feel a stinging sensation on administration of a drug at the start of the anesthesia and that they would be asked to score their pain, if any. All patients were premedicated with glycopyrrolate 0.2 mg intramuscularly 1 h before induction. In the operating room, an 18-gauge cannula was placed in the largest vein on the dorsum of the hand without local anesthesia, and an IV infusion of Ringer's lactate was started. All patients were monitored with an electrocardiograph, pulse oximeter, and automatic noninvasive arterial pressure monitor. Blood pressure was measured at 1-min intervals, and heart rate was monitored continuously. Based on computer-generated randomization charts, patients were divided into two groups: group C (control) and group T (treatment). Patients in group T were subjected to warming at 40°C for 1 min at the venous access site with the help of a Bair Hugger (Augustine Medical Inc. Eden Prairie MN, USA) warming device. This was followed by IV administration of 1 ml (10 mg) rocuronium bromide over 2 s. In group C, IV administration of rocuronium 1 ml was not preceded by local warming. Patients were observed and asked immediately if they had any pain in the arm. The response was recorded according to the 5-point scale (Table 1) by an investigator who was blinded to group allocation of the patients. The investigator was called into the operating theater at the time of rocuronium administration after the warming process was over. This was followed by induction of anesthesia with a standard technique. The incidence of pain on rocuronium injection in group C was estimated to be 80%, and after warming (group T), the value was presumed to decrease to 45%. On the basis of power analysis, to achieve a significance level of 5% and power of 90%, this study required at least 44 patients in each group.

Statistical analysis

Age and weight were compared using Student's t test, and gender was compared using the chi-square test. For pain scores, the chi-square test was used to determine the significance of difference between the two groups. A p value <0.05 was considered significant.

Results

All 90 patients completed the study. Demographic data (age, sex, and weight) were comparable between groups (Table 2). Overall pain frequency was 88.9% in group C and 66.7% in group T (Table 3). The difference was found to be significant ($p = 0.01$). Pain intensity (Table 4) varied significantly between the two groups ($p = 0.007$). There were significantly more patients with severe pain (pain score 3 and 4) in group C ($p = 0.002$). The mean pain score in group T was significantly less compared with group C (2.04 ± 1.04 vs. 3.02 ± 1.28; $p = 0.0002$). No patient developed any complications due to local warming.

Discussion

The occurrence of pain after IV administration of rocuronium has been reported in about 50–80% of patients [1, 3]. Despite such a common occurrence, no single drug or technique has been uniformly incorporated into clinical practice to alleviate this pain. Various preventive methods have been suggested, but none is completely satisfactory, and failure rates are as high as 28–70% [7–9, 11]. The pathophysiological mechanisms leading to this adverse effect are still unclear. Rocuronium is supplied as an isotonic solution of pH 4, and pain is known to be induced by

Table 1 Pain scoring

Pain score	Pain severity	Patient response
0	None	No pain or discomfort reported when questioned
1	Mild	Pain or discomfort reported by the patient to be mild when questioned
2	Moderate	Pain or discomfort reported by the patient to be moderate when questioned
3	Severe	Pain or discomfort reported spontaneously by the patient stated to be severe
4	Very severe	Pain or discomfort associated with a strong vocal response, hand or arm withdrawal, facial grimacing or crying, and reported to be very severe

Table 2 Patient characteristics (number, mean ± standard deviation)

Variable	Group C ($n = 45$)	Group T ($n = 45$)	p value
Age (years)	38.4 ± 12.6	43 ± 12.7	0.091
Sex (M/F)	37/8	35/10	0.598
Weight (kg)	61.8 ± 9.4	62.7 ± 7.5	0.595

Table 3 Comparison of patients with or without pain in the two groups

	Group C ($n = 45$)	Group T ($n = 45$)
No pain	5 (11.1%)	15 (33.3%)
Pain	40 (88.9%)	30 (66.7%)

$p = 0.01$

Table 4 Distribution of patients according to pain intensity

Pain score	Group	
	Group C ($n = 45$)	Group T ($n = 45$)
0	5 (11.1%)	15 (33.3%)
1	13 (28.9%)	19 (42.2%)
2	11 (24.4%)	7 (15.6%)
3	8 (17.8%)	2 (4.4%)
4	8 (17.8%)	2 (4.4%)

$p = 0.007$

low pH injections [15]. However, absence of pain in patients receiving IV saline adjusted to pH 4 is inconsistent with this hypothesis [3]. It has been advocated that the allogenic effect can be attributed to a direct activation of C-nociceptors by osmolality or pH of the solution or activation by release of endogenous mediators such as histamine, kinin, and other substances mediating inflammation [15, 16].

The efficacy and stability of the mixed drug solutions should be evaluated before clinical application because, once mixed, they may become unstable [17] or may be precipitated. In addition, in the presence of other adjuvant treatment, they may lose efficacy and/or potency. Greater pain may solely be due to greater nociception stimulation by the colder solution. On this basis, heating local anesthetic solutions to body temperature has been suggested as a way of reducing pain associated with subcutaneous injection [18]. Rocuronium bromide has to be stored in a refrigerator at 2–8°C (36–46°F); otherwise, it loses potency. Hence, temptation to heat the agent to body temperature to study the warming effect on pain has been ruled out. Instead, local warming being a simple and safe method to attempt to reduce pain was chosen.

The mechanism of pain relief from topical heat treatment involves the gate control theory of pain [14]. Heat applied externally increases the temperature of the skin and deep tissue, thereby stimulating thermoreceptors—special temperature-sensitive nerve endings [19]. These receptors initiate afferent nerve signals that inhibit transmission of nociceptive signals through the spinal cord to higher nerve centers for pain recognition. Moreover, superficial heat has been reported to elevate nociceptive threshold [20].

Pain may be significantly influenced indirectly via local vasomotor effects and increased blood flow. The physiological response to heat therapy includes increased local blood flow and metabolism, thus helping to clear the region of exacerbating metabolites and chemical mediators of inflammation, such as prostaglandins. For optimal biophysical effects, a 3–4°C increase in surface temperature is required [21]. The Bair Hugger device is a forced-air warming system that provides heat by convective mechanism. Research shows that heat applied directly to the skin at 40°C increases muscle-tissue temperature by at least 1°C at a depth ranging from 2.0 to 3.8 cm below the surface of the skin [22] and thus can stimulate thermoreceptors to gate the pain pathway. However, surface temperature at injection site was not measured in this study.

In our study, 33.3% of patients did not experience pain after application of local warming, whereas 42.2% of patients complained of mild pain. It seems the intensity of pain was definitely reduced, with most patients experiencing no to mild pain. Thus, local warming at the injection site is a cost-effective and safe method to decrease rocuronium-induced pain.

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