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SHORT COMMUNICATION

Superficial venous thrombophlebitis caused by rocuronium

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Abstract Pain is one of the major disadvantages of rocuronium, which is used during induction of anesthesia. Even at subparalyzing doses, 50–100% of patients complain of intense pain. Sudden flexion and withdrawal movement in the wrist or arm have been reported following rocuronium use in many papers. No information about risk factors leading to this withdrawal movement or pain on injection is available and whether this reaction leads to erythema or to venous sequelae (i.e. thrombosis and thrombophlebitis) has not been systematically investigated. However, in both of our cases, visible reactions occurred and both patients were diagnosed with venous superficial thrombophlebitis. Therefore, we believe that rocuronium-related pain may, in part, be because of direct venous injury.

Keywords Rocuronium · Pain · Thrombophlebitis

Introduction

Rocuronium is a monoquaternary aminosteroid neuromuscular blocking agent that first came into use in 1994 [1]. Rapid onset of action is its major advantage and sufficient blockade of the adductor pollicis longus muscle can be achieved in 60–90 s when used at a dose of 0.6 mg/kg [2]. Sudden flexion and withdrawal movement in the wrist or arm have been reported following rocuronium use in many papers [3–5]. Although pain and involuntary movement have been reported in the literature during induction of anesthesia with rocuronium, these two cases are the first in which serious superficial venous thrombophlebitis developed after rocuronium use.

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Case 1

A 24-years-old, male, ASA I patient, who was 173 cm tall and weighed 70 kg, was taken to the operating room for percutaneous nephrolithotomy (PNL) operation under general anesthesia because of renal stone. Preoperative examination of the patient did not reveal a history of known allergy. Intravenous (IV) line was started on the dorsum of the left hand using an 18 G IV cannula and 1000 cc of acetated Ringer's solution (Isolyte S) infusion was started. A priming dose of 25 mg of rocuronium was injected undiluted via the catheter. Patient brought his left arm to flexion right after the injection and complained of burning sensation and pain in the left upper limb. With the exception of a mild erythema around the cubital region, no clinical pathology was detected after the drug administration. Fentanyl (100 mcg) and 1% propofol were given via the same IV cannula for induction of anesthesia. A total of 200 mg propofol had been infused when the eyelash reflex was lost, and increase in erythema in the left upper limb was not observed at that time. The patient was given 25 mg more rocuronium for intubation. As soon as rocuronium was injected, very severe thrombophlebitic reaction developed in the veins, especially, of the cubital region (Fig. 1). Upon observation of this reaction, a second IV line was started on the dorsum of the right hand with an 18 G IV cannula and anesthesia was maintained through this

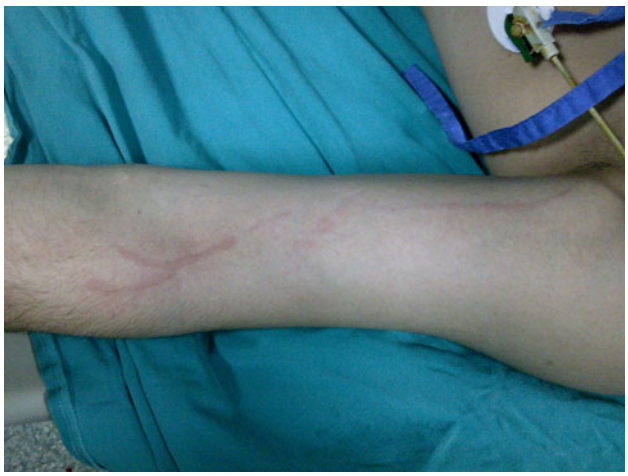

Fig. 1 Severe thrombophlebitic reaction in the veins

second line in the right upper limb. No abnormalities in the patient's hemodynamic data were observed, nor were there any signs of a systemic allergic reaction. Patient was administered 100% oxygen via face mask and SpO_2, measured from the 4th finger of the left hand, was 100%. The patient was intubated with Portex tube ID 8 mm without a problem and controlled respiration was initiated. Further, the patient was injected with 8 mg dexamethasone and 45.5 mg phenyramine via the right arm. Dramatic improvement in the findings was observed 30 min after the first attack. During postoperative examination, the left cubital region had a normal appearance 2 h after the operation and the patient was diagnosed with superficial venous thrombophlebitis. Following uneventful postoperative PACU period, the patient was transferred to the clinic. The next day, patient's left arm was completely remediated, he had no complaints, including pain, and was discharged. During follow-up visit at 1 month, patient reported feeling masses on the arm in which the reaction developed. Palpation of the left arm showed diffuse fibrosis of the veins in which the reaction developed but there was no pain or restriction of movement.

Case 2

A 47-years-old, female ASA II patient, who was 162 cm tall and weighed 92 kg, had general anesthesia when she underwent surgery for gastro-esophageal regurgitation. Preoperative examination of the patient revealed asthma. Intravenous line was started over the medial aspect of the left forearm using an 18 G IV cannula and 1000 cc of acetated Ringer's solution (Isolyte S) infusion was started. For induction of anesthesia, 100 mcg fentanyl and 200 mg propofol were used. When hypnosis was achieved, 50 mg rocuronium was given upon confirmation of spontaneous respiration with a mask. Redness along the brachial vein was noted immediately after rocuronium administration. Besides the reaction in the patient's left arm, there were no reactions in other parts of her body. No alterations in hemodynamic data were observed. An IV line was introduced on the dorsum of the right hand when no changes in the patient's condition were confirmed, 8 mg dexamethasone and 45.5 mg phenyramine were given, and the operation continued. Erythema disappeared 25 min later and the operation was terminated uneventfully. The patient did not have any complaints during examination the following day. Because of a history of asthma, tryptase and eosinophilic cationic protein were measured to rule out anaphylactic reaction and were found to be normal. The patient was diagnosed with venous superficial thrombophlebitis.

Pain is one of the major disadvantages of rocuronium, which is used during induction of anesthesia [3, 5, 6]. Even at subparalyzing doses, 50–100% of patients complain of intense pain [3, 6, 7]. The exact mechanisms through which rocuronium causes pain have not been elucidated. Release of a localized mediator [3, 4] or direct activation of C-nociceptors [8] has been proposed as a possible cause. However, in both of our cases, visible reactions occurred and both patients were diagnosed with venous superficial thrombophlebitis. Therefore, we believe that rocuronium-related pain may, in part, be because of direct venous injury.

Absence of a visible reaction in all patients with pain and withdrawal movement as a result of rocuronium use does not necessarily rule out direct injury. In our first case, even though the drug was administered via the dorsal hand veins, most severe reaction was observed in the antecubital region where veins are most superficial beneath the skin. However, during examination at the 1 month follow-up visit, fibrosis was noted along the course of the veins of the upper limb, extending proximally from the dorsum of the hand. In our second case, the reaction developed in the brachial region where the subcutaneous veins were most superficial. That the reaction observed in the second case was less intense can be explained by the fact that body mass index and, therefore, subcutaneous fat tissue in the second patient was higher than the first. Pain and withdrawal movement as a result of rocuronium use may be attributed to venous injury. We believe that this injury is not visible when it is in deep veins or when there is excessive subcutaneous fat tissue. An opioid was used before rocuronium in our second case as well, and skin changes in response to venous injury were observed despite lack of pain and withdrawal movements. This suggested that opioid use prevents pain and withdrawal movements but has no effect on venous injury.

Probable mechanisms of thrombophlebitis development due to rocuronium use may include reduced pH, higher

osmolality, and local tissue damage [9–11]. Rocuronium isotonicity is obtained by using sodium chloride and pH 4 by adding acetic acid or sodium hydroxide. It has already been shown that pH 4 or less may lead to pain [9]. Past studies have shown that the low pH of rocuronium can be neutralized by 8.4% sodium bicarbonate ($NaHCO_3$) and that no pain or venous damage occurred subsequent to injection [10, 11]. Another probable reason for thrombophlebitis may be the higher osmolality of the agent used. However, this theory does not apply to rocuronium, because an osmolality value of 201 ± 5 mOsm/kg for rocuronium resulted in pain in the study by Kim et al. [10] whereas an osmolality of 872 ± 8 mOsm/kg for the mixture of rocuronium and 8.4% $NaHCO_3$ did not result in any pain. Another possible mechanism for development of thrombophlebitis in association with rocuronium may be the local tissue damage. It has been demonstrated that rocuronium is associated with localized mediator release [3, 4]. In addition, as in the case of propofol use, rocuronium may result in activation of the kallikrein–kinin system in plasma with subsequent generation of bradykinin that acts locally to dilate the vein and increase its permeability [12]. We believe that further studies are needed for a better understanding of mechanisms of thrombophlebitis development in association with rocuronium use.

In conclusion, our cases are the first in which patients developed severe venous superficial thrombophlebitis after rocuronium use. One possible mechanism of pain and withdrawal movements after use of rocuronium for induction of anesthesia could be venous superficial thrombophlebitis. These two cases highlight the importance of anesthesiologists being careful when rocuronium is used for anesthesia induction and raise serious questions regarding the safety of rocuronium.

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