Brief Communication

Fentanyl or ketamine pre-treatment to prevent withdrawal response to rocuronium

INTRODUCTION

Rocuronium bromide, a steroidal non-depolarising neuromuscular blocking drug, is characterised by rapid onset and intermediate duration of action. However, it is associated with severe burning pain on injection, and withdrawal response even after loss of consciousness following induction of anaesthesia.[1] Pre-treatment with peripherally acting drugs, for example, lignocaine, ondansetron, tramadol[2] and centrally acting agents such as opioids,[3] nitrous oxide[4] and ketamine[5] to reduce rocuronium-induced pain have yielded conflicting results.

We conducted a study to compare the efficacy of intravenous (IV) fentanyl with IV ketamine, as pre-treatment, without the use of venous tourniquet, for prevention of withdrawal response associated with rocuronium injection.

METHODS

This prospective, randomised, double-blind study was performed after approval from the Institutional Ethics Committee. After obtaining informed consent, 105 patients aged between 18 and 60 years, American Society of Anesthesiologists' Physical Status I or II, undergoing elective surgical procedures requiring general anaesthesia were randomly allocated to three groups using computer-generated randomised numbers in sealed envelopes. Patients in the Control group received 5 mL of normal saline (n = 35), those in the fentanyl group received 2 μg/kg fentanyl (diluted to 5 mL with normal saline, n = 35) and patients in the ketamine group received 0.5 mg/kg ketamine (diluted to 5 mL with normal saline, n = 35). Patients with a history of hypertension, convulsions, neurological disorders, difficult IV access or clinical conditions that contraindicate the administration of any drugs used in the study were excluded from the study. Two 18-gauge IV lines were secured without the use of local anaesthetic agents, with one line dedicated only for injecting study drugs and rocuronium. All syringes were prepared by another investigator and covered so that the investigator who assessed the patient's response was unaware of the nature of the study drug. All patients were pre-oxygenated and premedicated with midazolam 0.03 mg/kg IV on arrival in operation theatre. Study drug was administered through the dedicated line with free flow of IV fluid. After 2 min, through the other IV line, anaesthesia was induced by thiopentone sodium (2.5%) 5 mg/kg IV until loss of consciousness, as assessed by standard clinical criteria (no verbal response and loss of eyelash reflex as end point) and after confirming adequate ventilation, 0.6 mg/kg rocuronium IV was given through the dedicated line.

Patient's response was graded by the following scale:[6] grade 1 = no response; Grade 2 = movement at the wrist only; Grade 3 = movement/withdrawal involving arm only (elbow/shoulder); Grade 4 = generalised response, movement/withdrawal in more than one extremity, cough or breath holding. (Grade 1 signifies no withdrawal response. Grade ≥2 signifies withdrawal response). General anaesthesia was continued till the end of procedure at the discretion of the attending anaesthesiologist.

Statistical analysis was performed using the SPSS (IBM SPSS Statistics for Windows, Version 20.0 Armonk, NY: IBM Corp.) package. Sample size was calculated from the data in the study by Shevchenko *et al*. The projected rate of withdrawal movements (response >2) in the control group was 84%. The expected reduction in the ketamine and fentanyl groups was 17% and 8%, respectively. For an 80% power of study at 95% significance level, by a statistical method for proportion, a sample size of 29 was obtained in each group. We enrolled 35 patients in each group to compensate for a possible loss of data. Chi-square test and Mid-P exact test were used to compare the incidence of withdrawal response in the three groups.

RESULTS

Demographic characteristics (age, weight and sex) amongst the three groups were comparable. The incidence of withdrawal response after rocuronium injection (grade ≥2) was 97.1%, 80% and 54.3% in control, fentanyl and ketamine groups, respectively [Table 1]. The incidence of withdrawal response in the fentanyl and ketamine groups was less frequent compared with the control group (P < 0.001),

Table 1: Comparison of withdrawal response associated with rocuronium between three groups

Grade of withdrawal response	Control (%)	Fentanyl (%)	Ketamine (%)
1	1 (2.9)	7 (20)	16 (45.7)
≥2	34 (97.1)	28 (80)	19 (54.3)

Table 2: The incidence of withdrawal response in the ketamine group compared with fentanyl group

Grade of withdrawal response	Fentanyl (*n*=35)	Ketamine (*n*=35)	Test applied	*P*
1	7	16	Chi-square test	0.022
≥2	28	19		

with ketamine group being most effective ($P = 0.022$) [Table 2].

DISCUSSION

Peripheral veins are innervated with polymodal nociceptors which mediate the response to injection of certain anaesthetics that cause pain. Furthermore, the allogeneic effect of aminosteroidal neuromuscular blocking drugs could be attributed to direct activation of C-nociceptors.[7] Rocuronium bromide is formulated with sodium acetate, sodium chloride and acetic acid to produce a solution of pH 3.98. The low pH could be the possible cause of pain as formulations of extremely unphysiological osmolalities or pH values cause pain on injection.[8]

Fentanyl in this study was administered 2 min before induction followed by rocuronium so that adequate time was given for the onset of the analgesic effect, as the effect-site concentration peaks at 3–4 min.[3] Similarly, ketamine (0.5 mg/kg IV) was also administered 2 min before induction, as its onset of action is 30 s and it reaches peak effect at 1–4 min. In this study, ketamine was more effective than fentanyl in attenuating pain on rocuronium administration.

Studies in which venous tourniquet was used, peripherally acting agents were more effective[2] whereas, when venous tourniquet was not used, centrally acting drugs had a better efficacy.[3] In our study, the venous occlusion technique was not used under the assumption that fentanyl and ketamine reduce rocuronium injection pain through central analgesic effect. Fentanyl acts on opioid receptors that are found in the dorsal root ganglia and the central terminal of primary afferent nerves. Ketamine hydrochloride is a non-competitive antagonist of N-methyl-D-aspartate (NMDA) receptor and has analgesic properties in subanaesthetic doses.[9] Thus, ketamine attenuates pain through the blockade of NMDA receptor activation in the vascular endothelium and in the central nervous system. Pre-treatment with ketamine can also heighten the pain threshold in the central nervous system. As ketamine has actions on multiple levels as compared to fentanyl, we assume it must be the reason for ketamine being more effective than fentanyl in attenuating the withdrawal response of rocuronium injection pain.

Our study has some limitations. Ketamine may have an action on NMDA receptors in the vascular endothelium. Furthermore, opioid receptors have been identified in the peripheral sensory nerve terminals. In this case, pre-treatment with the above drugs in conjunction with application of tourniquet may also have a role in attenuating rocuronium-induced pain.

During the study, there was no evidence of adverse reaction or side effects. Ketamine has very well-known side effects such as sedation, nystagmus and hallucinations. However, we did not observe these in our patients.

CONCLUSION

Ketamine is more effective than fentanyl in attenuating withdrawal response to rocuronium injection.

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Conflicts of interest
There are no conflicts of interest.

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