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Research Article

Prevention of rocuronium injection pain in paediatrics: Ketamine versus midazolam? A prospective randomized double blind study

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KEYWORDS

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Abstract *Introduction:* Rocuronium bromide is a non-depolarizing muscle relaxant related to mono-quaternary steroid group which is used commonly in general anaesthesia for the facilitation of endotracheal intubation and for maintenance of muscle relaxation. Rocuronium injection pain is a significant drawback with an incidence ranging from 50% to 80% [1,2]. Separation of children from their parents and shifting them to the OT is an everyday problem to paediatric anaesthetists, in our centre; majority of anaesthetists use IV midazolam to solve this problem, some anaesthetists use IV ketamine hydrochloride instead. This randomized, double-blind study was designed to compare the effect of IV ketamine versus IV midazolam in reducing rocuronium injection-related withdrawal movements in paediatric patients.

Methods: Hundred and twenty paediatric patients aged 2–10 years subjected to urologic procedures under general anaesthesia were randomly classified into two groups: the ketamine group in which IV ketamine 1 mg kg^{-1} was given and the midazolam group in which IV midazolam 0.05 mg kg^{-1} was given before shifting the child to the operation room.

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Results: Ketamine showed a highly significant reduction in the incidence of rocuronium injection-related withdrawal movements in paediatric patients (*P*-value 0.000) compared to midazolam which was ineffective.

Conclusion: This study demonstrated that ketamine effectively reduced pain after injection of rocuronium in paediatric patients compared to midazolam which was ineffective, and both ketamine and midazolam resolved peacefully the problem of child-parent separation before shifting to the OR.

1. Introduction

Rocuronium bromide is a non-depolarizing muscle relaxant related to mono-quaternary steroid group which is used commonly in general anaesthesia for facilitation of endotracheal intubation and for maintenance of muscle relaxation. Rocuronium injection pain is a significant drawback with an incidence ranging from 50% to 80% [1,2]. This pain was manifested in conscious patients given a sub-paralysing dose by severe burning sensation and in unconscious patients by withdrawal movements of the injected limb. The underlying mechanism of such pain is unclear; however the significant increase in histamine and tryptase release from mast cells after rocuronium injection and the resultant activation of perivascular nociceptive nerve endings and poly-modal nociceptors in the wall of the peripheral veins may explain rocuronium injection pain [3,4].

Separation of children from their parents and shifting them to the OT is an every day problem to paediatric anaesthetists, in our centre; majority of anaesthetists use IV midazolam to solve this problem, some anaesthetists use IV ketamine hydrochloride instead. This randomized, double-blind study was designed to compare the effect of IV ketamine versus IV midazolam in reducing rocuronium injection-related withdrawal movements in paediatric patients subjected to elective urologic surgeries under general anaesthesia.

2. Methods

This study was conducted in the Urology and Nephrology center/Mansoura University Hospital/Egypt. Both institutional committee approval and an informed consent from each parent were taken. 120 children classified ASA1 and ASA2 (age range 2–10 years) admitted for elective urologic procedures under general anaesthesia were included. Children with known history of allergy to rocuronium bromide, midazoalm, ketamine, and those having either difficult cannulation (more than two trials) or suspected difficult intubation were excluded from the study. Eligible patients were randomly allocated to one of two equal groups (using computer generated-randomized test); ketamine group ($n = 60$) and midazolam group ($n = 60$). EMLA cream was applied for all children on the selected vein on the dorsum of the hand and covered with gauze about 1 h before shifting them to the main OT. In the waiting area of the main OT a 22 G IV cannula was secured followed by IV administration of glycopyrrolate (5 μg kg^{-1}) in addition to midazolam (0.05 mg kg^{-1}) in the midazolam group or ketamine hydrochloride (1 mg kg^{-1}) intravenously. The calculated dose of ketamine and midazolam was diluted with normal saline into 5 ml and given IV slowly by an anaesthetist while the child was being held by his or her parents and once the child was sedated he was placed supine on a trolley in accompaniment with both an anaesthetist and a nurse and shifted rapidly to the operating room (OR).

On arrival to the OR, children were immediately monitored with pulse oximetry, electrocardiograph, and non-invasive arterial blood pressure; meanwhile child was preoxygenated using a transparent face mask connected to Ayer T piece breathing circuit with 100% oxygen. Capnograph was connected after tracheal intubation. Oxygen desaturation defined by a first reading of SpO2 less than 92% was recorded.

Both groups were subjected to the same anaesthetic management; diluted thiopental (1.25%) 3 mg kg^{-1} was given intravenously then followed by an IV injection of rocuronium bromide 1 mg kg^{-1} in approximately 30 seconds to facilitate tracheal intubation. All children were intubated successfully after 90 seconds with an appropriate sized endotracheal tube followed by an IV administration of fentanyl (1 μg kg^{-1}). Children were mechanically ventilated with air enriched oxygen using a low-flow closed circuit. After induction of anaesthesia, the child was placed in lateral position and a lumbar epidural analgesia with a ''single shot'' injection of a mixture of isobaric bupivacaine 0.25% (0.8 mg kg^{-1}) and fentanyl (0.6 μg kg^{-1}) was injected into lumbar 4–5 or 3–4 epidural spaces in order to achieve both intraoperative and postoperative analgesia. Anaesthesia was maintained with isoflurane in a concentration of approximately 1% and air-enriched oxygen, increments of rocuronium were given to maintain muscle relaxation, at the end of surgery both atropine and neostigmine were administered for reversal of muscle relaxant and all children were extubated and shifted uneventfully to post-anaesthesia care unit.

To achieve study blindness, one of the anaesthetists (OR anaesthetist) gave premedication; glycopyrrolate and ketamine/midazolam according to group randomization kept with him, this anaesthetist prepared induction agents and rocuronium according to the study protocol. A second anaesthetist who was oblivious to group assignment injected both induction agent and rocuronium and assessed rocuronium injection pain objectively using the following withdrawal scale (Table 1).

Table 1 Grading of withdrawal response [5].

Degree of movement	Patient response
1	No response withdrawal
2	Movement at wrist only
3	Movement/ withdrawal involving arm only
4	Generalized response – withdrawal movement in more than one extremity, cough, or breath holding

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 17). Based on previous investigations which reported an incidence of rocuronium injection between 50% and 80% [1,2] and assuming an average of 60% is the predicted incidence of the current study, to detect 50% reduction in the incidence of rocuronium injection pain at two-sided significance level 0.050 and 90% power, it was calculated that a minimum of 58 patients was required in each study group. Normally distributed numerical data were presented by their mean and standard deviation (SD), while in-between group differences were compared parametrically using the independent-samples Student *t*-test. Non-normally distributed numerical data were presented as absolute number (percent or range), while inter-group differences were compared non-parametrically using the Mann–Whitney *U* test. Significance level was set at $P < 0.050$.

3. Results

In this study 5 patients in the ketamine group and 6 in the midazolam group were rejected from the study because of either difficult cannulation or cannulation in a vein away from the dorsum of the hand. Rejected patients were replaced according to the group randomization. The group's demographic data did not significantly differ (Table 2). The incidence of rocuronium withdrawal movements associated with rocuronium injection in the ketamine group was 3.3% compared to 81.7% in the midazolam group ($P = 0.000$). The incidence of (grade 2) withdrawal movements in the ketamine group was 3.3 compared to 23.3% in the midazolam group. Ketamine group showed 0% in the incidence of withdrawal movement grades-3 or -4 while the incidence of the movement grade-3 and -4 in the midazolam group was 31.7% and 26.7%, respectively (Table 3).

Table 2 Demographic data.

Variable	Ketamine group ($n = 60$)	Midazolam group ($n = 60$)
Age (years)	6.2 (1.7) 2–10	5.9 (1.8) 2–10
Weight (kg)	23 (0.5) 14–38	24 (0.4) 16–41
Gender (M/F)	48/12	51/9

Age and weight data are represented by mean (SD) range, while gender is represented by absolute number, M = male, F = female and n = number.

Table 3 Incidence and grade of withdrawal movement associated with rocuronium injection in ketamine and midazolam groups.

Withdrawal movements (4-point scale)	Ketamine ($n = 60$)	Midazolam ($n = 60$)
1	58 (96.7%)	11 (18.3%)
2	2 (3.3%)	14 (23.3%)
3	0 (0%)	19 (31.7%)
4	0 (0%)	16 (26.7%)
Overall incidence of pain	3.3%*	81.7%

Data are number of patients (%).
Withdrawal movements: 1 = no response, 2 = movement at wrist only, 3 = movement involving arm only (elbow and shoulder), 4 = generalized movements in more than one extremity.
* *P*-value < 0.050 versus midazolam group (Mann–Whitney *U* test).

4. Discussion

In this study, we found that a bolus dose of IV ketamine (1 mg kg^{-1}) significantly prevented the withdrawal movements associated with rocuronium injection when compared with IV midazolam (0.05 mg kg^{-1}) in children subjected to elective urologic surgical interventions under general anaesthesia.

The rapid onset (60–90 s) of rocuronium bromide at a dose of 0.9–1.2 mg kg^{-1} expands its use to be used in rapid-sequence intubation situations replacing succinylcholine [6] in addition to its routine use to maintain muscle relaxation during general anaesthesia. Unfortunately the high incidence of rocuronium injection pain is a major drawback of this muscle relaxant agent.

Rocuronium injection pain seems a minor problem that does not need a lot of attention from anaesthesia society, however, the reported pulmonary aspiration secondary to gastric regurgitation caused by generalized spontaneous movements after the injection of rocuronium [7], increased the risk of venous catheter dislodgment which is sometimes considered a major problem specially in case of difficult cannulation like in an obese child, in addition to the pain-related stress response that can induce bronchospasm , tachycardia and hypertension [8].

All the above makes rocuronium injection pain a considerable problem especially in paediatrics that deserves our attention to expand the ways for its solution.

Drugs like lidocaine [9], ondansetron [10], sodium bicarbonate and magnesium sulphate [11], also fentanyl and alfentanil [10–12] and the dilutional effect of normal saline [13] were used for alleviation of this pain.

Lidocaine and opioids (mainly fentanyl) are probably the most commonly studied drugs to minimize rocuronium injection pain, mixing rocuronium with lidocaine gave rise to a debate regarding its effect in reducing rocuronium injection pain, some reported minimal effect and others reported a significant effect in this aspect [9,11].

The pretreatment administration with opioids like fentanyl and alfentanil [10–12], was seen as a simple and effective method to decrease rocuronium injection pain, however Chiarella et al. [14] found that mixing 100 μg fentanyl with rocuronium was comparable to mixing normal saline with rocuronium and both resulted in minimal reduction of rocuronium injection pain which was postulated as a dilutional effect. In their study Chiarella et al. [14] found that despite both midazolam 1 mg and 100 μg fentanyl premedication was given to all patients, the rocuronium injection pain was high reaching 66%. Ahmed et al. [11] compared lidocaine and fentanyl pretreatment using tourniquet and found both were effective, on the other hand, Memiş et al. [10] compared ondanosteron, lidocaine, tramadol and fentanyl with normal saline and reported that all were effective in different degrees and lidocaine was the

most effective and whereas fentanyl was the least. Sindh et al. [15] studied compared the pretreatment effect of fentanyl, sufentanil, lidocaine with normal saline on rocuronium injection pain and found that the incidence of pain after injection of fentanyl, sufentanil and normal saline was comparable and lidocaine significantly reduced rocuronium injection pain which agree with the result of Chiarella et al. [14].

In contrast to the debate around opioid like fentanyl and sufentanil, Choi et al. [16], found remifentanil in a dose of ($1\ \mu g\ kg^{-1}$) decreased the incidence of rocuronium related withdrawal movements from 70% in the saline group to 0% in the remifentanil group.

Ketamine and midazolam alone or in combination are the most commonly used drugs to separate children peacefully from their parents before shifting them to the OR, up to our knowledge no study compared the efficacy of ketamine versus miadazolam in reducing rocuronium injection pain or midazolam effect on the reduction of pain.

Ketamine is an intravenous dissociative anaesthetic agent related to phencyclidine group which works by antagonizing N-methyl D-aspartate (NMDA) receptors, its analgesic effect has become a piece of fact. Midazolam is one of the benzodiazepines which are used commonly for the purpose of sedation, amnesia and induction of anaesthesia thorough binding to benzodiazepine receptor in the cerebral cortex [17].

Liou et al. [18] found that a small dose of ketamine ($0.2\ mg\ kg^{-1}$) reduced the incidence of withdrawal movement in paediatric patients from 83% in the saline group to 27% in the ketamine group after injection of rocuronium. Ketamine was used by Mahajan et al. [19] and they reported its efficacy in reducing rocuronium injection pain. The higher reduction in the incidence of rocuronium injection pain compared to both Liou and Mahajan studies could be explained by the higher dose of ketamine in the current study.

On the other hand midazolam was ineffective, however, up to our knowledge there is lack of data about the effect of midazolam on rocuronium injection pain in paediatrics.

In conclusion, this study demonstrated that ketamine effectively reduced pain after injection of rocuronium in paediatric patients compared to midazolam which was ineffective. Both ketamine and midazolam resolved peacefully the problem of child-parent separation before shifting to the OR without violence or serious disorders; however, ketamine could be a better option compared to midazolam in paediatric patients planned to be given rocuronium bromide for the purpose of muscle relaxation otherwise there is a contraindication to its use.

This study has some limitations including the absence of placebo or control group which was obligatory for the purpose of peaceful child-parent separation, absence of data about the haemodynamic impacts of both ketamine and midazolam especially on blood pressure and heart rate is another limitation of this study.

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