ORIGINAL ARTICLE

Comparison of lidocaine and a combination of lidocaine and ketorolac pretreatment on withdrawal movement induced by rocuronium injection

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ABSTRACT

Introduction: Rocuronium is a widely used monoquaternary aminosteroid nondepolarizing muscle relaxant of intermediate duration with a rapid onset to achieve optimal conditions for endotracheal intubations. The injection of rocuronium bromide during induction of anesthesia has often been associated with pain-induced withdrawal movement near the site of injection. It has been hypothesized that addition of ketorolac and Lidocaine in combination as pretreatment drugs among patients undergoing general anesthesia with rocuronium injection provides a better control of withdrawal movements in comparison to patients who receive only lidocaine. The objective of this study was to compare the efficacy of pretreatment of combination of ketorolac and Lidocaine and Lidocaine alone in the frequency of withdrawal movement associated with rocuronium injection in peripheral veins during intubation.

Methodology: This study was conducted on 90 patients undergoing elective surgeries under general anesthesia in operation theater complex of our hospital. Patients were randomly divided in group A and B by lottery method. Group A received 20 mg lidocaine IV prior to rocuronium. Group B received lidocaine 20 mg and ketorolac 10 mg IV. General anesthesia was administered by induction via 5 mg/kg thiopental sodium in a separate peripheral intravenous line. Withdrawal movements were observed as mild, moderate and severe, and recorded on a well-structured performa. Efficacy was defined as no withdrawal movement on injecting rocuronium.

Results: The differences in age and gender of patients were not significant in both groups and these were not associated with efficacy of treatment in the groups. However ASA status of the patients was significantly associated with efficacy of treatment groups.

In Group-A 27(60%) and in Group-B 36(80%) patients had no withdrawal movement while mild movement was observed in 12(26.7%) patients in Group-A, and in 7(15.6%) patients in Group-B. Moderate movement was seen in 6(13.3%) patients in Group-A, and in 2(4.4%) patients in Group-B. The number of patients who had withdrawal movement was 18(40%) vs. 9(20%) in Group-A and Group-B respectively ($p = 0.0384$).

The criterion of efficacy was fulfilled by 27(60%) Group-A patients, compared to 36(80%) patients in Group-B.

Conclusion: Results of this study showed that combination of intravenous lidocaine and ketorolac prior to rocuronium injection is more effective that lidocaine alone for preventing withdrawal movements for general anesthesia.

Key words: Withdrawal movement; Ketorolac; Lidocaine; Rocuronium; Intubation; General anesthesia; Efficacy

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INTRODUCTION

Rocuronium is a widely used nondepolarizing muscle relaxant known for its rapid onset of action and intermediate duration of action[1]. Rocuronium is indicated in adult and pediatric population to facilitate tracheal intubation during routine sequence induction and to provide skeletal muscle relaxation during surgery. In adults rocuronium is also used to facilitate tracheal intubation during rapid sequence induction (RSI) and as an adjunct in the intensive care unit for short term use. ED_{50} for rocuronium bromide has been estimated to be 0.3 mg/kg and dose for tracheal intubation ranges from 0.6 to 1.0 mg/kg for adults and pediatric patients.

During rapid sequence induction of anesthesia pain on injection[2-4] has been reported especially when the patient has not yet completely lost consciousness and particularly when propofol[1, 5] is used as the induction agent. In clinical studies, pain on injection has been noted in 75-100% of the patients who underwent rapid sequence induction of anesthesia with propofol and fewer patients experienced pain who underwent rapid sequence induction of anesthesia with fentanyl[2] and thiopental.

Mechanism for pain on injection and subsequent withdrawal movement has been ascribed to the release of local kinin from endohelial cells of peripheral veins. Prostaglandins seem to have enhancing effects on kinin cascade and therefore implicated for the pain experienced by the patients.

Ketorolac belongs to nonsteroidal anti-inflammatory group of analgesics (NSAID) which act via inhibition of prostaglandin synthetase and lidocaine is a local anesthetic agent, also categorized as a membrane stabilizing drug which reversibly decreases the rate of depolarization and repolarization of excitable membranes including nociceptors. Ketorolac acts to directly inhibit the local mediators which are hypothesized to be involved in the rocuronium-induced withdrawal movement while Lidocaine acts to inhibit sodium channels and prevents transmission of painful inplulses[3,4].

It has been hypothesized that lidocaine and ketorolac when used alone or in combination reduced the withdrawal movement after rocuronium injection in patients undergoing anesthesia. Above stated effect has been studied at established centers of the developed world as Jeon Y et al. observed the frequency of the movements with lidocaine alone (34.3%)[1], ketorolac alone (40%)[1], and found that it was significantly less with the combination of the two (8.6%)[1].

This study aimed to compare the response of local subjects to pretreatment with combination of ketorolac and lidocaine and lidocaine alone[4,6,7] to reduce withdrawal movements associated with rocuronium injection in peripheral veins in a tertiary care hospital of Rawalpindi, Pakistan. Rocuronium has recently gained popularity for both emergency and elective procedures in this region of the world and this study aims to ascertain response of the local population to the potentially distressing effect of rocuronium Bromide injection and simple but effective methods to abolish the above mentioned responses.

METHODOLOGY

After the approval of ethical committee of the institution, a total of 90 patients were enrolled in this study who were admitted elective patients. Patients were divided in two groups of 45 each by non-probability consecutive sampling. This study was carried out as randomized control trial at Operation Theater Complex, of our hospital, from August 2015 till February 2016. Patients included in the study were ASA I-II aged 20-60 years from either gender scheduled for elective surgery under general anesthesia. Patients with difficult venous access, concomitant co-morbid conditions like diabetes mellitus, hypertension, malignancy, pulmonary, hepatic or renal diseases were excluded. Patients with contraindications for using NSAIDS or Lidocaine (allergic reactions/ hypersensitivity) and those already taking opioid analgesic, long term NSAIDS/COX-2 inhibitors or other pain killers were also not included for this study.

After approval from hospital ethical committee, 90 patients were recruited according to selection criteria. All patients were assessed a day before surgery (at least 8 hours before surgery as preoperative anesthesia fitness procedure) and written informed consent was taken. Patients were prepared by overnight fasting. Patients were randomly divided in group A and B by lottery method. Group A received 20 mg lidocaine IV prior to rocuronium. Group B received 20 mg lidocaine and 10 mg ketorolac IV. Intravascular access with two 18G cannulae was established in the pre-operative room before arriving in the operation theater. After arrival in Operation theater, monitoring including electrocardiography, pulse oximeter, noninvasive blood pressure was attached and base line heart

rate and blood pressure was noted. Patients was pre-oxygenated for 3 minutes via face mask and General anesthesia was administered with either 20 mg lidocaine alone or a combination of 20 mg lidocaine and 10 mg ketorolac with a tourniquet and released after 2 minutes, followed by induction via 5 mg/kg Thiopental sodium in the separate intravenous line. After abolishment of eyelash reflex 0.6 mg/kg rocuronium was injected over 10 seconds[3,5,6] for intubation in the intravenous line from which pretreatment agents were given. An observer who was blinded to the patient group assignment observed withdrawal movement which was scored as 1 (no movement of the upper extremity or a part of it, in which injection has been given), 2 (mild movement- movement of the WRIST of the upper extremity in which the injection had been given) 3 (moderate movement- elbows and shoulders of the upper extremity in which the injection had been given) and 4 (generalized body movements). After intubation anesthesia was maintained with 60% Nitrous oxide, 40% Oxygen and 0.8-1.2% Isoflurane. Injection rocuronium 1/4th of the induction dose was repeated to maintain muscle relaxation. Vitals monitoring and appropriate interventions was done accordingly at regular intervals of 3 minutes. At the end of surgery, patients were extubated and were shifted to the post-anesthesia care unit (PACU).

Data analysis: Data was collected on a structured Performa and SPSS version 10 was used to analyze data. Effect modifiers like age, gender and ASA grade was controlled by stratification. Post stratification Chi Sqaure test was applied keeping P-value less than 0.05 as significant.

RESULTS

In Group-A 27(60%) and in Group-B 36(80%) patients had no movement. While mild movement was observed in 12(26.7%) patients in Group-A and 7(15.6%) patients in Group-B. Moderate movement was seen in 6(13.3%) patients in Group-A and 2(4.4%) patients in Group-B (Table-1). There were 18(40%) patients in Group-A and 9(20%) patients in Group-B who had withdrawal movement (Table-2). In both treatment groups the dependent variable or efficacy was defined in terms of no withdrawal movement. In Group-A efficacy was observed in 27(60%) patients while in Group-B efficacy was seen in 36(80%) patients (Table-3). Efficacy of treatment was also seen in relation to the age groups of patients. In age group 20-30 years there were 5(41.7%) patients in Group-A and 9(75%) in Group-B who were observed with no withdrawal movements. In age group 31-40 years there were 21(65.5%) patients in Group-A and 24(82.8%) patients in Group-B who were observed with no withdrawal movements and in patients who were >40 years 1(100%) patient in Group-A and 3(75%) in Group-B were observed with no withdrawal movements. According to p-value no statistical significant association was seen for efficacy and

Table 1: Response grade (severity of movement) in treatment groups [n (%)]

Response	Group-A (n=45)	Group-B (n=45)
None	27(60)	36(80)
Mild	12(26.7)	7(15.6)
Moderate	6(13.3)	2(4.4)
Sever	0(0)	0(0)

Table 2: Withdrawal movement in treatment groups [n (%)]

Withdrawal	Group-A (n = 45)	Group-B (n = 45)	*Chi-Square Test*	p-value
Yes	18(40)	9(20)	4.286	0.0384
No	27(60)	36(80)		

Table 3: Efficacy in treatment groups

Efficacy	Group-A (n = 45)	Group-B (n = 45)	*Chi-Square Test*	p-value
Yes	27(60)	36(80)	4.286	0.0384
No	18(40)	9(20)		

age group of patients. Among male patients efficacy was seen in 2(40%) patients in Group-A and 2(100%) patients in Group-B. While among female efficacy was seen in 25(62.5%) female in Group-A and 34(79.1%) in Group-B. No statistically significant association was seen between gender of the patients and efficacy of treatment. It was observed that patients whose ASA grade was 1 among them efficacy of treatment was significantly associated with treatment groups, Group-A: 61.8% and Group-B:84.4% (p = 0.039) respectively. However, in ASA grade 2 patients, the efficacy was not significantly associated with ASA grade, e.g. Group-A 54.5% and Group-B 69.2% (p = 0.459) respectively. In Group-A mean age of patients was 33.48 ± 6.75 and in Group-B mean age of patients was 34.55 ± 6.17 years. In Group-A there were 5(11.1%) male and 40(88.9%) female while in Group-B there were 2(4.4%) male and 43(95.6%) female patients. In Group-A when patients were assessed for ASA status there were 34(75.6%) patients who were on ASA-1 and 11(24.4%) were on ASA-2 grade. While in Group-B there were 32 (71.1%) patients whose ASA grade was 1 and 13(28.9%) patients ASA Grade was 2.

DISCUSSION

Rocuronium bromide has been recently gaining popularity in various secondary and tertiary care hospitals across Pakistan for its favorable properties of rapid onset and relatively prolonged duration of action required for muscle relaxation during surgery. The authors studied the effects of rocuronium bromide injection on local population at a tertiary care hospital in Rawalpindi as most of the research has been carried out in the well-established centers in the West and developed countries. Rocuronium-induced injection pain or withdrawal movement (IPWM) is well known and its incidence varies between 50 and 80 %.[8,9,10] Severe and burning pain occurred sometimes during rocuronium injection.[9,11] In anesthetized patients, injection pain may cause withdrawal movement of the arm, which may extend to a generalized movement presumably secondary to its injection pain.[9,11,12] The withdrawal movements occur more frequently in young patients. Extreme movements during induction can cause injury, and pulmonary aspiration due to gastric regurgitation has been reported in children.[8] Even after loss of consciousness during the induction of anesthesia, rocuronium causes localized or generalized movements in 84% of patients[9]. Numerous strategies have been proposed for decreasing the pain associated with rocuronium injection. The most popular strategies involve pretreatment with drugs, such as lidocaine, although no method is completely satisfactory.

In this study it was observed that combination of lidocaine and ketorolac prior to rocuronium injection was more effective in prevention of withdrawal movements as compared to lidocaine alone. i.e. lidocaine: 40% vs. lidocaine + ketorolac: 20%. Age and gender was not significantly associated with efficacy of treatment groups. However ASA-1 status was significantly associated with efficacy of treatment groups.

Younghoon Jeon in his study compared the efficacy of lidocaine, ketorolac, and the 2 in combination as pretreatment for the prevention of rocuronium-induced withdrawal movement. As per his findings the incidence of moderate to severe withdrawal movements was 14.3% with lidocaine, 17.2% with ketorolac, and 2.9% with lidocaine/ketorolac combination, as compared to 45.7% with the placebo. There was no significant difference in withdrawal movement between the lidocaine group and the ketorolac group.[1] Results of this study are consistent with the results reported by Younghoon Jeon which shows that combination of lidocaine and ketorolac is more effective in the prevention of withdrawal movement prior to rocuronium injection.

Kyo S. Kim determined the technique which prevents the withdrawal associated with rocuronium administration in adults and children. The incidence of no movement after rocuronium was 96% in L-O, 46% in L-F, 26% in C-O, and 18% in C-F in adult and 96% in S, 58% in L, and 8% in P in children. Withdrawal after rocuronium can be eliminated by the pretreatment of lidocaine during the occlusion of the IV flow in adults and addition of sodium bicarbonate in children.[15]

Kyo used different other drugs with combination for the prevention of withdrawal movement. But he also reported that when lidocaine used with combination it is more effective.

Taylan Akkaya and his colleagues determined the incidence and severity of pain on injection of rocuronium and its pretreatment with saline, lidocaine or ketamine were evaluated. The incidence of withdrawal movements was 32.5%, 2.5% and 15% in the saline, lidocaine and ketamine groups, respectively. The median withdrawal movement score was significantly lower only in Group Lidocaine compared to Group Saline

(p-value=0.011). There was no difference in reported pain or withdrawal movements between men and women[16] . Taylan separately compared lidocaine and ketamine and reported that incidence of withdrawal movement was less with lidocaine. However in this study combination of both these drugs lidocaine and ketorolac gives much effective cover for withdrawal movement prior to rocuronium.

Ki Tae Jung in his study compared the preventive effect of lidocaine, ketamine, and remifentanil on the withdrawal response of rocuronium. His findings showed that incidence of withdrawal response was significantly lower in lidocaine group (Group L) (20%), ketamine group (Group K) (30%), and remifentanil group (Group R) (0%), than normal saline group (Group N) (87%). Severe withdrawal response was observed in 5 of the 30 patients (17%) in Group L, and in 9 of the 30 patients (30%) in Group K. There was no severe withdrawal response in Group R. Mean blood pressure and heart rate were significantly decreased in Group R compared to other groups.[17]

Huang et al. demonstrated that pretreatment with 10 mg ketorolac with venous occlusion for 2 min reduced the propofol injection pain. They compared the retention time under venous occlusion and commented that sufficiently long venous occlusion (120 s, but not 30 or 60 s) played a significant role in reducing this pain.[18]

Indeed, experimental data suggest that ketorolac produces analgesia, mainly peripherally, by reducing sensitizing prostaglandins, although some NSAIDs also have a central action.[19-21] Ketorolac improved the tourniquet tolerance and quality of postoperative analgesia when it was combined with lidocaine as intravenous regional anesthesia.[22,23] Studies indicate that 20 mg of ketorolac is effective in intravenous regional anesthesia without adverse effects, implying that a larger dose may increase the risk of local complications.[24]

One short coming relevant to the use of rocuronium bromide pertains to unavailability of sugammadex in local market, a cyclodextrin which has been established as the reversal of steroid-based neuromuscular blockers including vecuronium and rocuronium[25], limiting the use of rocuronium as an alternative of succinylcholine in anticipated difficult airway situations warranting rapid sequence intubations. Succinylcholine is still the drug of choice for difficult airway management involving emergency and non-emergency surgeries in our institution because of reversal of its effects with in span of a few minutes despite an array of adverse effects such as such as hyperkalemia, myalgia, and rhabdomyolysis. Rocuronium bromide provides the anesthesiologists of our resource-constrained country an opportunity to avoid the oft-feared complications of succinylcholine injection, provided sugammadex becomes widely available across the secondary and tertiary care setups.

Besides lidocaine, several other drugs such as ondansetron, magnesium sulfate, sodium bicarbonate, fentanyl, and remifentanil are effective in reducing pain on rocuronium injection, but pretreatment of lidocaine or other drugs before rocuronium prolongs the time between anesthesia induction and neuromuscular block administration. In addition, most of these drugs can, even in rare cases, induce adverse effects such as allergic reaction, bradycardia, and hypotension.

Since this study was carried out on patients in whom RSI was not indicated and elective procedures were to be performed in non-emergent, non-stressful controlled environment, more studies and case reports are expected in the future to establish protocols for this promising drug in RSI situations. Rocuronium bromide heralds a new era, perhaps marking an end to the reign of succinylcholine in in-hospital and field settings for airway management

CONCLUSION

Results of this study showed that combination of Intravenous lidocaine and ketorolac prior to rocuronium injection is more effective than lidocaine alone for preventing withdrawal movements. Based on these results it is now clear that combination of both these drugs can effectively eliminate withdrawal movement. It is recommended that combination of these drugs should be used as pretreatment for rocuronium administration.

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