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Research Article

Pretreatment with a Small Dose of Ketamine to Prevent Withdrawal Movement caused by the Rocuronium Injection during Induction

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ABSTRACT

Background & Objectives: Rocuronium causes pain on injection during the induction of anesthesia. This study was carried out to evaluate the efficacy of a small dose of ketamine in managing injection pain and withdrawal movement during induction.

Materials and Methods: This observational study was carried out from August 2022 to November 2022 at Nepal Medical College and Teaching Hospital. The inclusion criteria for the study were ASA I and II. 67 patients (aged 16-65 years) scheduled for elective surgery were included in the study after following the inclusion and exclusion criteria. Then the intravenous ketamine was given without venous occlusion, 30 seconds after followed by rocuronium 0.6 mg/kg intravenous. Then the patient's response to rocuronium injection was recorded on a five-point scale, as well as a change in the vital parameters was collected.

Results: The incidence of pain was significantly less in 49 patients (73.13%), and remaining 18 (26.86%) patients out of 67 patients still had pain after intravenous Ketamine 0.5mg/kg, the incidence was more in the younger patients' groups than older patients' groups. The cause of this incidence was still to find out. The pain score was significantly less in patients receiving ketamine.

Conclusion: We concluded that pretreatment with ketamine 0.5 mg/kg without venous occlusions is effective in decreasing the incidence of pain caused by rocuronium injection

Keywords: ketamine, pain, rocuronium

INTRODUCTION

Rocuronium has gained popularity as a preferred non-depolarizing muscle relaxant for general anesthesia for all age groups due to its rapid onset and intermediate duration of action, effectively replacing succinylcholine [1, 2]. However, Rocuronium causes a burning sensation even after loss of consciousness, spontaneous limb movements, and recalled injection pain. Reports indicate that injection pain and withdrawal movement (IPWM) associated with Rocuronium administration affects 50%-80% of the patient population, which lasts for 10-20 seconds [3,4]. This sudden, spontaneous movement may cause risks of intravenous line dislodgement, pulmonary aspiration, bronchospasm and myocardial infarction [5,6].

Various interventions have been explored to mitigate Rocuronium-induced injection pain and withdrawal movement (IPWM), including non-pharmacological approaches like topical warming or cooling muscle relaxant, and adjusting injection speed [6,7], and pharmacological methods such as opioids, lidocaine, ondansetron, tramadol, magnesium sulfate, and nitrous oxide, with yield conflicting results [8,9]. The mechanism of pain induced by Rocuronium involves activation of polymodal nociceptors in peripheral veins, stimulation of C-nociceptors, and potential release of histamine and tryptase from mast cells, triggering a kinin cascade [10, 11]. Some authors state that Rocuronium is formulated in sodium acetate, sodium chloride, and acetic acid to produce an acidic solution of P^H 3.9-4 [11]. This low P^H value is an extremely unphysiological could be the possible cause of injection pain [12].

Ketamine hydrochloride, a phencyclidine derivative used as an intravenous anesthetic for over three decades, is known to produce dissociative anesthesia, causing emergence reactions, and act as a noncompetitive antagonist on N-methyl-D-aspartate (NMDA) receptors [10,13]. The ketamine possesses analgesic properties at sub-anesthetic doses and serves as a local anesthetic with less impact on cardiorespiratory function compared to other anesthetic agents [14, 15]. Intravenous ketamine pretreatment attenuates injection pain and reduces withdrawal movements by blocking NMDA receptors in the vascular endothelium and central nervous system, thereby raising the central pain threshold [11,16].

This study aimed to evaluate the efficacy of a small dose of intravenous ketamine pretreatment to attenuates injection pain and reduces withdrawal movements during induction of anesthesia with rocuroniun. Although published literature reveals few studies on the topic, our study aims to fill a gap in the existing literature by providing local evidence from Nepal, which has not been specifically included in previous studies.

MATERIALS AND METHODS

After obtaining ethical clearance from Nepal Medical College and Teaching Hospital Institutional Review Committee (IRC No: 11-079/080 dated August 07.2022), the observational study was carried out from August 2022 to November 2022 at Nepal Medical College, Attarkhel, Jorpati. The inclusion criteria for the study were ASA I and II of age 16 to 65 years of either sex and exclusion criteria were patients with a history of neurological deficits, asthma, patients received analgesics or sedatives within 24 hours, allergy to study drugs, muscle

weakness in the upper arm, Obesity (body mass index >35 kg/m^2), coagulation disorder and refusal to participate in the study. For the study purpose patients were assessed for routine pre-anesthetic check-ups and advised to keep nil per oral (NPO) for 4-6 hours, depending upon the type of last food taken, then the patients were admitted a day before in the respective department for surgery. On the day of surgery intravenous line (IV) was secured with an 18 G cannula and Ringer's lactate solution was started without any premedication.

While patients were waiting for their turn of operation, preoperative vital parameters, including blood pressure (BP), heart rate (HR), and peripheral oxygen saturation (SpO_2), were recorded. Then the patient was transferred to the operating room, all necessary monitors were attached and 0.5mg/kg ketamine was injected 30 seconds before the induction of anesthesia, then propofol 2mg/kg was used for the induction of anesthesia, with assessing loss of consciousness by verbal contact, then rocuronium 0.6mg/kg was injection and observed for any injection pain and withdrawal movement (IPWM) and data were recorded with using withdrawal reflex score [10], and patients were intubated. After completion of data recording, fentanyl 2 mcg/kg was given intravenously for analgesic. At the end of surgery, after gaining spontaneous breathing patient was reversed with the injection of glycopyrrolate 10 mcg/kg, and Neostigmine 40 mcg /kg. Before extubation, the oral cavity was thoroughly cleaned and applied 100% oxygen till the patients were fully awake.

In this study, we used ketamine without applying a tourniquet to know the efficacy of ketamine to attenuate injection pain and withdrawal movement during induction of anesthesia, and observe the change in blood pressure and heart rate before and after induction, as it acts centrally and peripherally. While another explanation suggests that pretreatment with ketamine results deeper level of anesthesia and has action on multiple levels compared to lidocaine. After reviewing various articles, it was decided to carry out research work on the ketamine, assuming that peripheral-acting agents were more effective with using a venous tourniquet and centrally acting drugs have better efficacy without a venous tourniquet [1, 3, 6, 10].

RESULTS

This study was carried out in 67 patients with no significant difference in the Socio-demographic profile between the two age groups (Table 1).

The induction of anesthesia was started with propofol by assessing loss of consciousness and loss of verbal, in the younger age group

Table 1: Socio -demographic profile of patients

Demography	Age groups	
	16- 45 years	46-65 years
Number of pts	30	37
Age (Mean)years	28±2.4	52±3.2
Male	22	20
Female	8	17
Weight(mean kg)	63±2.56	62±1.53
ASA I/II	20/10	20/17

total dose of propofol required was 2.02±1.1 mg/kg, while in the older age group total dose of propofol required was 1.98±1.4 mg/kg to achieve unconsciousness, respectively. The incidence of moderate to

severe movement after administration of rocuronium was 15% in the younger age group of 28±2.4 years, while it was 10% in the older age group of patients, 52±3.2 years. This showed the incidence of pain, and withdrawal movement was less in older patient groups than in the younger age group.

We have investigated the relationship between drug induced pain and hemodynamic variation during the pre-induction and post-induction periods, and found no statistically significant relationship between pre-induction and post-induction ($p>0.05$). The hemodynamic change was recorded at 5-minute intervals for 15 minutes during the preoperative and intraoperative period (Table2). In the first 5 minutes, there was some elevation in HR, and increase in systolic and diastolic blood pressure, the reason behind this was because of rocuronium injection pain, and due to vagolytic or sympathomimetic effects of ketamine, even though ketamine has potent analgesic effect at a sub-anesthetic dose, this analgesic property helpful as multi model analgesia with other analgesic to subside pain during surgery, but no noticeable change was observed in Spo_2. None of the patient has hemodynamic abnormalities that required any intervention. No local signs of erythema, and venous squeal were observed.

The rocuronium injection pain and withdrawal movement (IPWM) were studied and recorded as undetermined responses in 6 patients (8.95 %), no movement in 43 patients (64.17 %), movement in one hand wrist in 10 patients (14.92 %), movement in both hands wrist and shoulder in 6 patients (8.95%) and generalized movement in 2 patients (2.98 %), so that overall patient having pain during rocuronium injection was 18 (26.86%). The maximum number of patients without pain after rocuronium

Table 2: Hemodynamic parameters during preinduction and postinduction

Event	Heart rate/ min	Blood pressure (mmHg)		Spo_2 %
		Systolic	Diastolic	
Pre-induction	86±2.4	116± 2.4	78± 3.2	98± 2.4
Post-induction	94±3.5	130±5.2	87±2.7	97± 4.7

Table 3: Pain assessment by withdrawal reflex score during injection of rocuronium [10]

Score	Events	Observations	No of patients
0	Undetermined	------	6
1	No movement	--------	43
2	Movement at the wrist	Wrist movement	10
3	Movement at both hands' wrist and shoulder	Wrist and shoulder movement at one hand	6
4	Generalize	Wrist, shoulder movement in both hands and legs	2

injection (n=49), with 73.13%, and the remaining 26.86% still have pain even after giving ketamine, indicate that ketamine was not 100% effective (Table3).

DISCUSSION

We have analyzed the efficacy of ketamine to prevent the withdrawal movement during the rocuronium. Pain during intravenous injection of rocuronium is a common distressing side effect [6,10,11], and causes withdrawal movement of the arm which can create secondary injury or pulmonary aspiration due to gastric regurgitation and dislodgement of the intravenous line [12]. The mechanisms of pain during rocuronium injection are not clear. However, the primary cause of injection pain and withdrawal movement may be due to the formulation of rocuronium with sodium acetate, sodium chloride, and acetic acid to produce a solution of p^H 3.98. This low p^H formulation is extremely unphysiological and could be the possible cause of pain [11], or the irritation of local and peripheral polymodal nociceptors, and the allogeneic effect of amino-steroidal neuromuscular blocking drugs that directly activate the C-nociceptors in the veins [9].

Ketamine is a phencyclidine derivative hypnotic agent with strong analgesic properties and acts on N-methyl-D- aspartate (NMDA) receptors as a non-competitive antagonist and agonist on opioid μ receptor in the central nervous system, and has local analgesic properties on peripheral vascular endothelium in sub-anesthetic doses [10]. As ketamine acts on multiple sites, we assume it must be more effective than other drugs to attenuate the withdrawal response of rocuronium injection during intravenous administration [17, 18]. This study was carried out without venous tourniquet, as ketamine has better efficacy without tourniquet to acts locally and centrally, by acting on opioid receptors, that are found in the dorsal root ganglia, and the central terminal of primary afferent nerve terminals to produce analgesic effect [8], but peripherally acting agents were more effective with venous tourniquet [19]. Pre-treatment with ketamine also increases the pain threshold in the central nervous system.

The study conducted by the KT Jung et al 2014, concluded that the incidence of withdrawal response after rocuronium administration was different with various dose of pretreatment ketamine used, when ketamine 0.2 mg/kg was used the incidence of pain and withdrawal was 27% and 40% when 0.5 mg/kg ketamine was used respectively [21]. Whereas in our study, pretreatment with ketamine 0.5 mg/kg showed that the incidence of undetermined movement was 8.95% and no movement was 64.1%, so the total undetermined and no movement patients were 73 %. The higher result in our study may be due to the additive response of undetermined and no moment response. Similarly, the study conducted by Chang and colleagues 2005 [19] showed that the incidence of pain was significantly less in patients (55%) receiving ketamine 0.3 mg/kg than in patients receiving saline (85%) with $P<0.05$. However, no difference was found between ketamine 0.1 mg/kg, 0.2 mg/kg, and saline groups. Whereas, in our study, 6 patients (8.95 %) out of 67 patients had undetermined movement and 43 patients (64.1%) out of 67 patients showed no movement at all; so the total undetermined and no movement patients were 49 (73 %). This was statistically significant ($P< 0.05$), and it hints that ketamine might have a significant role in reducing the pain induced

by rocuronium, as we have used 0.5mg/kg ketamine. This may be because of the central and peripheral action of ketamine on pain receptors and the potent analgesic effect of ketamine in sub-anesthetic doses [20]. However, we did not observe a significant increase in blood pressure or heart rate compared to the control, and psychomimetic reactions in our patients. In the first 5 minutes, there was some elevation in HR, and increase in systolic and diastolic blood pressure, the reason behind this was because of rocuronium injection pain, and due to vagolytic or sympathomimetic effects of ketamine, even though ketamine has potent analgesic effect at a sub-anesthetic dose, which was also stated by Hirota and Lambert [17], this analgesic property helpful as multi model analgesia with other analgesic to subside pain during surgery, but no noticeable We think that this was due to the low dose of ketamine (0.5 mg/kg).

CONCLUSION

We concluded that ketamine was effective for decreasing the incidence and severity of rocuronium injection pain and withdrawal movements. As Ketamine has an analgesic property in sub-anesthetic doses during intravenous anesthesia. We recommend using ketamine while inducing with rocuronium. Further studies in this clinical context should be considered to validate the result, and use of ketamine during induction.

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