

## Comparing palonosetron and lignocaine pretreatment with venous occlusion on reducing rocuronium associated withdrawal movements. A double blinded randomized control trial

Kamal Kajal<sup>1</sup>, Jesto kurian<sup>2</sup>, Ishwar Bhukkal<sup>3</sup>, Amarjyoti Hazarika<sup>4,\*</sup>, Shiv Lal Soni<sup>5</sup>

<sup>1,4,5</sup>Assistant Professor, <sup>2</sup>Senior Resident, <sup>3</sup>Professor, Dept. of Anaesthesia and Intensive Care, M.D. Postgraduate Institute of Medical Education and Research, Chandigarh, India.

**\*Corresponding Author:**

Email: amarjyoti28@rediffmail.com

### Abstract

**Introduction:** Use of rocuronium has been associated with withdrawal movements of injected arm during its administration. Our study is to compare the effectiveness of palonosetron vs. lignocaine pretreatment with venous occlusion on reducing withdrawal movements associated with rocuronium injection.

**Materials and Methods:** This prospective randomized double blind trial includes 150 patients aged between 18 and 65 years undergoing elective day-care surgeries. Patients were randomly divided into 3 groups of 50 patients each with assistance from computer generated random number table. Group P received palonosetron 0.75mg, Group L received Lignocaine 30 mg and Group S received Normal saline as pretreatment. The degree of withdrawal of limb was graded on four-point scale. Haemodynamic changes namely HR and MAP following administration of study drugs and complications following administration of the study drugs like urticaria, wheal and rash were also monitored.

**Results:** Overall incidence of rocuronium induced withdrawal movements was significantly more in-group S (84%) than other study groups ( $p < 0.001$ ). Their incidence was significantly less in group P (6%) than in group L (25%) and group S (84%);  $p$  value  $< 0.001$  and  $< 0.001$  respectively. Additionally, significantly less withdrawal movements were observed in-group L when compared to group S ( $p < 0.001$ ). Statistically significant higher HR ( $p$  value  $< 0.001$ ) and MAP (0.001) values were observed in-group S. They were comparable in group L and group P.

**Conclusion:** Study demonstrated that palonosetron pretreatment and venous occlusion has reduced rocuronium induced withdrawal movements more effectively than lignocaine.

**Keywords:** Palonosetron, Rocuronium, Withdrawal movements, Lignocaine.

### Introduction

Rocuronium is a non-depolarizing neuromuscular blocking agent that resembles structurally to vecuronium. Typical distinguishing features are fast onset and intermediate duration of action.<sup>1</sup> It is frequently used for routine endotracheal intubation and for rapid sequence induction in situations where succinylcholine is contraindicated.<sup>2</sup> Despite its safe side effect profile, it induces pain at the injection site and withdrawal responses of the injected arm during its administration. Reported incidences of injection pain and withdrawal movements with rocuronium are in ranges of 50-80%<sup>3-5</sup> and 63-84%<sup>6-7</sup> respectively. It can be given as a precurarisation,<sup>8</sup> or priming technique<sup>9</sup> before induction of anesthesia. If injected intravenously prior to loss of consciousness as in priming technique, hot and burning sensations occur over the injected site.<sup>5</sup> Vigorous withdrawal movements such as withdrawing the injected hand or arm may occur even after loss of consciousness and sometimes even generalized movements may occur due to pain. These untoward withdrawal movements may cause accidental displacement of IV catheter causing difficulty in administering additional drugs.<sup>6-7</sup> Pain following IV injection often leads on to sympathetic stimulation and resultant tachycardia<sup>10</sup> and often these generalized movements are responsible to cause the reflux of gastric contents, which may predispose to pulmonary

aspiration.<sup>11</sup> The underlying pathophysiologic mechanism of the withdrawal movements by intravenous injection of rocuronium remains elusive. It has been reported that pain may be the contributed factor and various attributing factors may be the activation of nociceptors,<sup>12</sup> osmolality and acidic pH of the solution<sup>13</sup> or some have implicated the release of inflammatory mediators such as histamines, kinins and other substances during its administration.<sup>4</sup> Several methods have been suggested to mitigate these withdrawal movements that includes pretreatment using lidocaine,<sup>7-14</sup> fentanyl,<sup>15</sup> remifentanyl,<sup>10</sup> alfentanil,<sup>16</sup> sodium bicarbonate,<sup>16,17</sup> ketamine,<sup>18,19</sup> ketorolac<sup>20</sup> and paracetamol.<sup>21</sup> Priming technique<sup>9</sup> and local warming of injection site<sup>22</sup> has also been shown to be effective 5HT<sub>3</sub> antagonists, like ondansetron (OND) are extensively used as an antiemetic drugs for treatment of postoperative nausea and vomiting.<sup>23</sup> Animal experiments has shown that ondansetron curtailed nociceptive responses of dorsal horn neurons when delivered intrathecally by modifying the 5-HT<sub>3</sub> nociceptive receptors.<sup>24</sup> It has Na<sup>+</sup> channel blocking action as studied on rat brain neuron<sup>25</sup> and has  $\mu$  opioid receptors agonistic action.<sup>26</sup> Probably, because of the multifaceted action as 5HT<sub>3</sub> antagonism,  $\mu$  opioid agonist and Na<sup>+</sup> channel blocking, it was hypothesized that OND can alleviate pain and prevent the withdrawal movements produced by rocuronium injection.<sup>24-26</sup>

Palonosetron is a second generation 5HT<sub>3</sub> antagonist. It has more affinity for 5HT<sub>3</sub> receptors.<sup>27</sup> so, it has more antiemetic potential and a longer duration of action (40h) than ondansetron. It has less side-effects compared to first generation 5HT<sub>3</sub> antagonist.<sup>28</sup> There has been various studies comparing the effect of ondansetron on withdrawal movements caused by rocuronium injection,<sup>29, 30</sup> but there is dearth of studies with palonosetron pretreatment on withdrawal movements caused by rocuronium injection. Hence, it was hypothesized that palonosetron pretreatment with venous occlusion may be better alternative than ondansetron for rocuronium-induced withdrawal movements. The primary objective of our study was to compare the effectiveness of palonosetron vs. lignocaine pretreatment with venous occlusion on decreasing withdrawal movements associated with rocuronium injection. Secondary objectives were to compare the haemodynamic changes namely HR and MAP following administration of study drugs and complications following administration of the study drugs like urticaria, wheal and rash were also monitored.

### Materials and Methods

This prospective, randomized controlled double-blinded clinical trial was carried out "between" July 2012–September 2013. The study obtained an approval from the local Institution Research and Ethics Committee and written informed consent was obtained from all the patients. We enrolled 150 patients aged between 18 and 65 years undergoing elective day-care surgeries belonging to ASA class 1 or 2. Patients with known allergic to the study drugs, history of migraine, pregnant patients and patients who were treated with analgesic or sedatives 24 hours prior to surgery were omitted from the study. Patients were randomly divided into 3 groups of 50 patients each with the assistance of computer generated random number table. Group P received palonosetron .075mg (1.5ml) with normal saline 0.5 ml, Group L received Lignocaine 30 mg (1.5ml) with normal saline 0.5 ml and Group S received Normal saline 2ml as pretreatment. Code assignments of 3 study groups were retained in sealed envelopes. One envelope was selected for each patient by anesthesiologists not involved in the study and same had prepared the pretreatment drug. All pretreatment drugs were injected as 2 ml volume. The investigator and the patient involved in the study were unaware of the contents of the syringe. After applying routine monitoring devices and obtaining baseline hemodynamic parameters, an 18 G cannula was inserted on the dorsum of the non-dominant hand for delivery of study drugs. Another cannula was placed on the other hand for infusion of IV fluids and delivery of other drugs. A non-invasive blood pressure cuff was applied on the non-dominant (study) arm. Anesthesia was established with thiopental 5mg/kg after

confirming that the IV infusion could be injected without resistance. Immediately after the loss of consciousness (absent eye lash reflexes), the opposite limb was occluded. Using venous-stasis mode of the monitor set at 60-70 mmHg, venous occlusion was done. Subsequently, patients received the pretreatment drugs over a period of 5-10 seconds according to the group allocation. The venous stasis was released 60 seconds after the administration of the pretreatment drugs. Subsequently, an intubating dose of 0.6mg/kg rocuronium was given intravenously over 5 seconds in the study arm. The amount of withdrawal movement of the patients during injection was assessed and scored as follows: (Table 1).<sup>18</sup>

**Table 1: Four point scale**

Grade	Response
0	No movement
1	Movement limited to hand
2	Movement limited to forearm including elbow joint
3	Movement of upper arm including shoulder joint

Analgesics were given on the opposite arm intravenously, after assessing the study arm for any withdrawal response for 30 seconds. Trachea was secured and anesthesia was maintained with inhalational anesthetics and muscle relaxants. The intraoperative hemodynamics of the patient like non-invasive blood pressure (NIBP), pulse oximetry (SpO<sub>2</sub>), end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) were monitored pre-induction, post induction, pre-intubation and till 10 minutes post-intubation for this study. But the standard hemodynamic monitoring was done throughout the procedure. The injection site where the study drug was given was assessed for pain, edema and wheal or flare response till 24 hours by an anesthesiologist who was unaware of the nature of the drug administered.

### Statistical Analysis

Statistical analyses were accomplished using SPSS version 12.5 (SPSS Inc., Chicago, IL, USA). Considering the incidence of withdrawal movements with rocuronium injection as 70% from the previous studies,<sup>6,7</sup> to detect a 40% difference in the incidence of withdrawal movement on rocuronium injection at a significant level of 5% and a power of 90%, 30 patients per group were required. So, we studied 50 patients in each group. Data was presented as mean ± SD or number of patients. Patients' characteristics such as age, height, weight, hemodynamic parameters were compared with one-way ANOVA with Bonferroni's correction. Kruskal-Wallis test was used for comparison of withdrawal movements.

Results obtained were considered statistically significant when  $p$  value  $< 0.05$ .

## Results

All the patients met the inclusion criteria and were taken in study. (Fig .1)

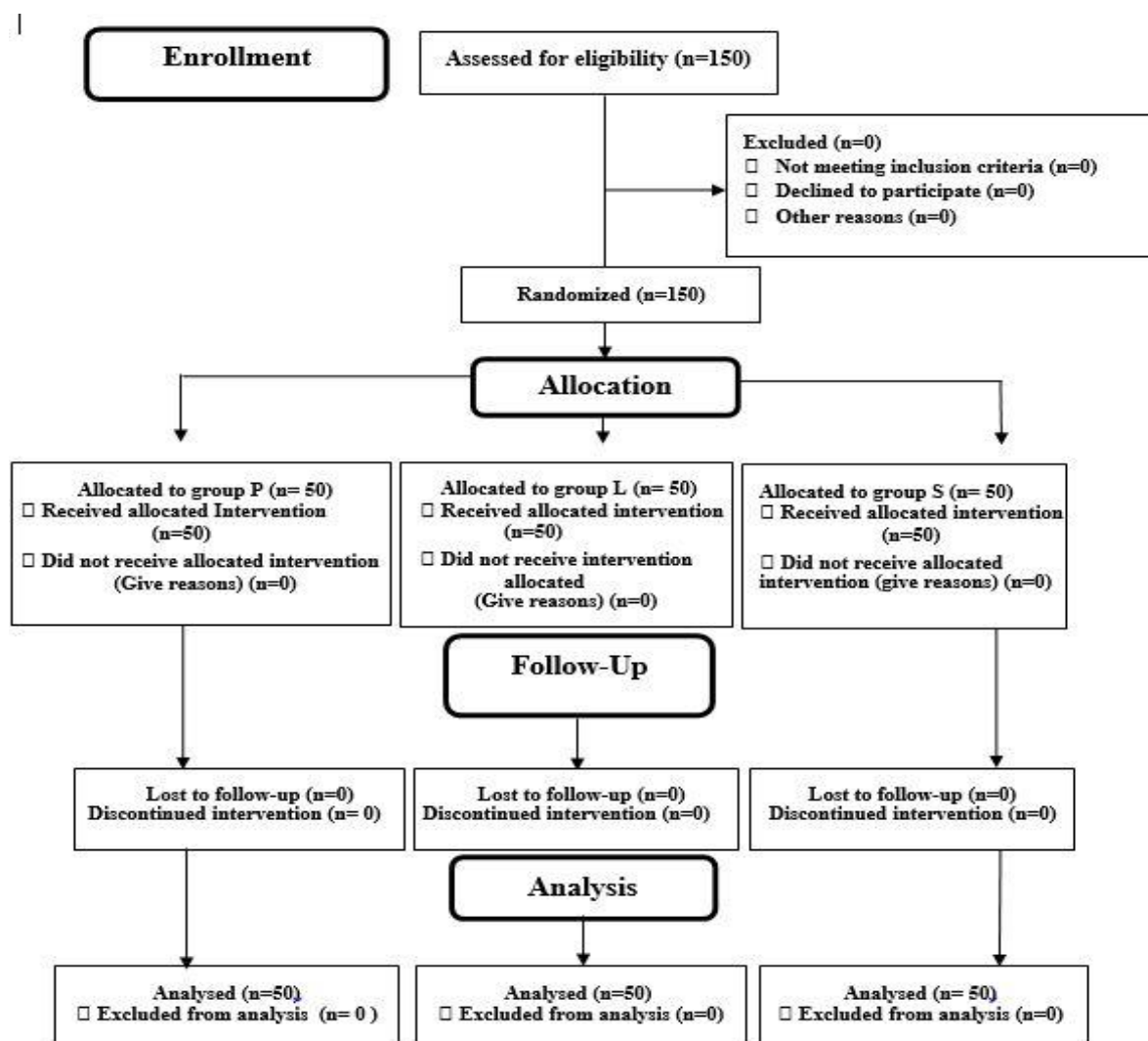


Fig. 1: Consort flow diagram

Demographic characteristics were comparable in three groups. (Table .1)

Table 1: Demographic data of the patients

Patient characteristics	Group L Lignocaine	Group S Saline	Group P Palonosetron	p value
Age (yrs)	34.34±10.50	30.34±7.34	33.16±8.96	0.079
Weight (kg)	56.88±6.97	55.56±6.13	54.9±6.93	0.324
Height (cm)	160.26±4.009	160.00±4.005	159.54±3.554	0.641
Gender (F/M)	37/13	44/6	50/0	0.001

Data are presented as mean  $\pm$  SD or number of patients,  $p$  value  $< 0.05$  was considered as significant.

The grades and incidence of rocuronium. Induced withdrawal response after injection of study drug in three groups are presented in (Table 2)

**Table 2: Grades and incidence of rocuronium induced withdrawal movements**

Withdrawal Response	Group L n=50	Group P n=50	Group S n=50
0	25(50%)	47(94%)	8(16%)
1	0(0%)	3(6%)	0(0%)
2	25(50%)	0(0%)	6(12%)
3	0(0%)	0(0%)	36(72%)
Overall incidence (1+2+3)	25(50%)**	3(6%)*†	42(84%)

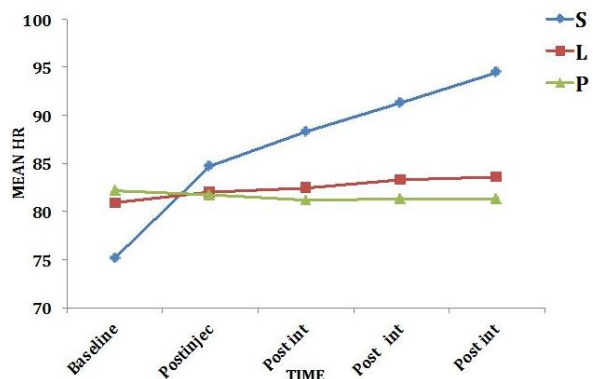
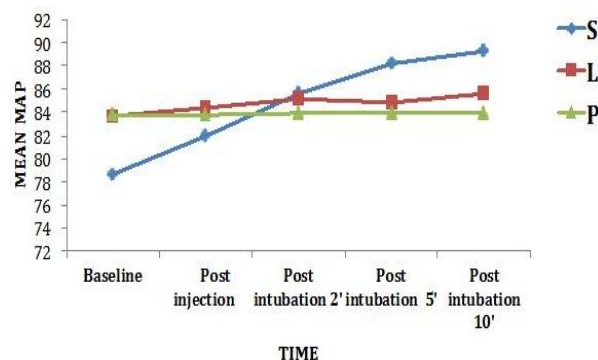
Data are presented as number of patients (percentages), p value <0.05 was considered as significant.

\*p=0.001 compared with group L

†p=0.001 compared to group S

\*\*P =0.001 compared to group S

The overall incidence of rocuronium induced withdrawal movements was significantly more in-group S (84%) than other study groups ( $p < 0.001$ ). Overall incidence of rocuronium induced withdrawal movement was significantly less in group P (6%) than in group L (50%) and group S (84%);  $p$  value <0.001 and <0.001 respectively. Additionally the overall incidence of rocuronium induced withdrawal movement was significantly less in-group L than in-group S ( $p < 0.001$ ). The frequencies of withdrawal grade in each group are also depicted in (Fig. 2). Statistically significant higher HR ( $p$  value <0.001) and MAP (0.001) values were observed in-group S. They were comparable in-group L and group P. Corresponding graphical plots are depicted in (Fig. 2) and (Fig. 3).

**Fig. 2: Profile Plot of HR****Fig. 3: Profile plot of MAP**

There were no complications such as erythema, rashes, pruritus, swelling following injection of the study drugs during intraoperative period and 24hrs post operatively in any of the three groups.

## Discussion

Pain accompanied with administration of rocuronium is frequent and troublesome for patients and has curtailed the rocuronium usage.<sup>3-4</sup> Pathophysiologic mechanism for its occurrence remains elusive. Possible etiologies mentioned in the studies include direct activation of C-nociceptors,<sup>12</sup> osmolality or pH of the solution<sup>13</sup> and local release of inflammatory mediators such as histamine, kinin.<sup>4</sup> Low pH of solution may be considered a plausible explanation but injection of acidic solutions are often not only associated with pain but also with perivenous edema and thrombophlebitis that are typically not seen after rocuronium injection. Few studies have mentioned the role of inflammatory mediators like histamine as the likely mechanism considering the rapid offset character of pain. Absence of associated erythema however, points against the role of these mediators. Borgate et al<sup>4</sup> implicated the involvement of kininogen cascade that is similar to the pain afflicted by propofol injection.

Reported pain after rocuronium injection may occur even after induction of anesthesia that results in withdrawal movements. These withdrawal movements may adversely affect the patient outcomes. Lui et al reported a child who had pulmonary aspiration due to gastric regurgitation induced by spontaneous movements after rocuronium injection.<sup>11</sup> Factors like pain, emotional stress and stimulation during induction of anesthesia may augment sympathetic activity and resultant cardiovascular effects. Also, these withdrawal movements may cause the removal of the venous catheter or cause injury during induction.<sup>7</sup>

Numerous pharmacological and non-pharmacological techniques with variable success rates have been discussed in meta-analysis of 41 studies in the Korean population by Choi et al. These modalities include the use of medications such as various combinations of lidocaine with rocuronium,<sup>7,14</sup> short acting opioids (fentanyl,<sup>15</sup> alfentanil,<sup>16</sup>

remifentanyl,<sup>10</sup> and tramadol),<sup>30</sup> sodium bicarbonate,<sup>16,17</sup> ketamine<sup>18,19</sup> and ondansetron<sup>29,30</sup> however this meta-analysis comprises of only one trial with pretreatment with palonosetron.<sup>28</sup> So, our study was designed since very few studies have compared effects of lignocaine and palonosetron for rocuronium induced withdrawal movements in Indian population. 5 HT3 receptor blockers (first generation) like ondansetron have been studied in the past for ameliorating the rocuronium induced withdrawal movements. Reddy et al.<sup>29</sup> had compared effectiveness of ondansetron and lignocaine in reducing rocuronium induced withdrawal movements. They demonstrated that both ondansetron and lignocaine were effective in reducing the incidence of rocuronium induced withdrawal movements, however lignocaine was found to be more effective. Overall reported incidence of rocuronium induced withdrawal movements was 84% in our study, which is similar to the incidence reported in previous trials. The overall incidence of rocuronium induced withdrawal movement was significantly less with palonosetron (6%) than with lignocaine (25%) and saline (84%); ( $p < 0.001$  and  $< 0.001$ ) respectively. Similarly, Park et al demonstrated statistically significant reduction of rocuronium-induced withdrawal movements with palonosetron as compared to lidocaine that substantiates the finding reported in our study. Better results with palonosetron in our study could be attributed to its higher potency of it in blocking 5HT3 receptors as compared to ondansetron.

Our study also assessed the stability following injection of study drug. Statistically significant higher heart rates and mean arterial pressure values following injection of study drug were observed in the placebo group that points to the sympathetic stimulation secondary rocuronium administration ( $p < 0.001$ ). There was no change in the hemodynamic variables in lignocaine and palonosetron group compared to baseline. In a study done by Kim et al which was done in children comparing HR and MAP during anesthesia induction with remifentanyl and saline for rocuronium induced withdrawal movements, showed that MAP and HR were significantly high in saline group which was comparable with our study.<sup>10</sup> So this study proved that both palonosetron and lignocaine negates the hemodynamic fluctuations during induction with rocuronium of the total 150 patients included in our study, 131 were female patients and 19 were males. So it was not possible to analyze the gender based difference in withdrawal movements. But there are studies showing that women reported more withdrawal movements than men due to rocuronium.<sup>32</sup> There were no complications such as erythema, rashes, pruritus, and swelling following injection of the study drugs in the intraoperative period or in the post-operative period in any of the group.

The main limitation of our study was that we did not assess rocuronium induced pain using validated

pain scores. However, stable haemodynamic parameters after rocuronium administration aptly indicated less pain with pretreatment of lidocaine and palonosetron.

To conclude, this study demonstrated that palonosetron pretreatment and venous occlusion decreased incidence of rocuronium induced withdrawal movements more effectively than lignocaine. It also proved that both palonosetron and lignocaine provided hemodynamic stability during induction with rocuronium.

## References

1. Mayer M, Doenicke A, Hofmann A, Peter K. Onset and recovery of rocuronium (Org 9426) and vecuronium under enflurane anaesthesia. *Br J Anaesth.* 1992; 69:511-12.
2. William K. Mallon, Samuel M. Keim, Jan M. Shoenberger. Rocuronium vs. Succinylcholine in the emergency department: A Critical Appraisal. *J Emerg Med.* 2009; 37:183-188.
3. Steegers MA, Robertson EN. Pain on injection of rocuronium bromide. *Anesth Analg.* 1996; 83:203.
4. Borgeat A, Kwiatkowski D. Spontaneous movement associated with rocuronium: is pain on injection the cause? *Br J Anaesth.* 1997 ;79 :382-83.
5. Moorthy SS, Dierdorf SF. Pain on injection of rocuronium bromide. *Anesth Analg.* 1995;80:1067.
6. Baek SH, Woo CM, Lee HJ, Yoon JY. Rocuronium-induced withdrawal movements associated with different Rocuronium injection method. *Paediatr Anaesth.* 2008;18:515-19.
7. Shevchenko Y, Jocson JC, McRae VA, Stayer SA. The use of lidocaine for preventing the withdrawal associated with the injection of rocuronium in children and adolescents *Anesth Analg.* 1999;88:746-48.
8. T.Mencke, S, Soltesz, M.Sauer, A.Menzebach. Are women more sensitive to a pre-curarization dose of rocuronium than men? *The Acta Anaesth Scand.* 2008; 52:1051-55
9. Lee JI, Lim SH, Lee SE, Kim YH, Lee JH, Lee KM. Priming technique can alleviate the withdrawal responses associated with intravenous administration of rocuronium. *Korean J Anaesthesiol.* 2009; 56:628-33.
10. Cheong KF, Wong WH. Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment. *Br J Anaesth* 2000; 84:106-7.
11. Lui JT, Huang SJ, Yang CY, Hsu JC, Lui PW. Rocuronium-induced generalised spontaneous movements cause pulmonary aspiration. *Chang Gung Med J* 2002;25:617-20.
12. Turan A, Memis D, Karamanlioglu B, Sut N. The prevention of pain from injection of rocuronium by magnesium sulphate, lignocaine, sodium bicarbonate and alfentanil. *Anaesth Intensive Care* 2003Z; 31:277-81.
13. Klement W, Arndt JO. Pain on intravenous injection of some anesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. *Br J Anaesth* 199;66 :189-95.
14. Lee JI, Lim SH, Lee SE, Kim YH, Lee JH, Lee KM. Priming technique can alleviate the withdrawal responses associated with intravenous administration of rocuronium. *Korean J Anaesthesiol.* 2009; 56 :628-33.
15. Borgeat A, Kwiatkowski D, Ruetsch YA. Spontaneous movements associated with rocuronium injection: the effects of prior administration of fentanyl. *J Clin Anesth* 1997 ; 9:650-2.

16. Turan A, Memis D, Karamanlioglu B, Sut N. The prevention of pain from injection of rocuronium by magnesium sulphate, lignocaine, sodium bicarbonate and alfentanil. *Anaesth Intensive Care*. 2003;31:277-81. 40.
17. Han DW, Koo BN, Choi SH, Lee JS, Shin YS, Sharma M, Kim KJ. Neutralized rocuronium (pH 7.4) before administration prevents injection pain in awake patients: a randomized prospective trial. *J Clin Anesth*. 2007;19:418-23
18. Akkaya T, Toygar P, Bedirli N, Yazicioglu D, Gumus H. Effects of pretreatment with lidocaine or ketamine on injection pain and withdrawal movements of rocuronium. *Turk J Med Sci*. 2008;38:577-82.
19. Mahajan R, Batra YK, Kumar S. Pain on injection of rocuronium: influence of ketamine pretreatment. *Can J Anaesth*. 2005 ;52 :111-2.
20. Younghoon Jeon, Jae Hyun Ha, Jeong-Eun Lee. Rocuronium-induced withdrawal movement: influence of ketorolac or a combination of lidocaine and ketorolac pretreatment. *Korean J Anesthesiol* 2013;64:25-28.
21. Gulnaz Ates, Emine Arzu Kose, Goksen OZ, Alpaslan Apan. Effect of Paracetamol pretreatment on rocuronium-induced injection pain. *J Clin Anal Med* 2013,10:4328-30
22. Mahajan C, Rath GP, Bithal PK, Prabhakar H. Local warming at injection site helps alleviate pain after rocuronium administration. *J Anesth*. 2010;24:845-48.
23. Milne RJ, Heel RC. Ondansetron. Therapeutic use as an antiemetic. *Drugs* 1991; 41: 574-95.
24. Ali Z, Wu G, Kozlov A, Barsai S. The role of 5HT3 in nociceptive processing in the rat spinal cord: results from behavioral and electrophysiological studies. *Neuro sci Lett*. 1996;208:203-7.
25. Ye JH, Mui WC, Ren J. Ondansetron exhibits the properties of a local anesthetic. *Anesth Analg* 1997; 85: 1116 -21.
26. Gregory RE, Ettinger. DS. 5-HT3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy. *Drugs* 1998;55:173-89.
27. Lily P.H. Yang, Lesley J. Scott. Palonosetron In the Prevention of Nausea and Vomiting. *Drugs* 2009 ; 69 : 2257-78.
28. Park SK, Cho EJ. A randomized, double-blind trial of palonosetron compared with ondansetron in preventing postoperative nausea and vomiting after gynaecological laparoscopic surgery. *J Int Med Res*. 2011; 39: 399-407.
29. Reddy MS, Chen FG, Ng HP. Effect of ondansetron pretreatment on pain after rocuronium and propofol injection: a randomized, double-blind controlled comparison with lidocaine. *Anaesthesia*. 2001;56:902-05.
30. Memiş D, Turan A, Karamanlioglu B, Süt N, Pamukçu Z. The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol, and fentanyl. *Anesth Analg*. 2002;94:1517-20.
31. Choi GJ, Lee S, Lee JH, Park SG, Kang H. Pharmacological and non-pharmacological intervention for rocuronium-induced withdrawal movement in the Korean population: a meta-analysis of 41 studies including 4,742 subjects. *Korean J Anesthesiol*. 2014 Jun; 66 (6): 419-32. doi: 10.4097/kjae.2014.66.6.419. Epub 2014 Jun 26.
32. Mencke T, Schreiber JU, Knoll H, Starcke C, Kleinschmidt S, Rensing H. Women report more pain on injection of a precurarization dose of rocuronium: a randomized, prospective, placebo-controlled trial. *Acta Anaesthesiol Scand*. 2004;48:1245-48.