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The effect of orally administered metoprolol on the frequency and severity of rocuronium injection pain

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ABSTRACT

Objectives: This study aimed to examine the effects of orally administered metoprolol on the frequency and severity of pain caused by rocuronium injection in patients who started to use and were currently using oral metoprolol for any reason such as ischemic heart disease, hypertension, and arrhythmias.

Methods: Patients were evaluated in four groups. Group M: patients currently using metoprolol and who did not receive lidocaine before the application of rocuronium. Group ML: patients currently using metoprolol and who received lidocaine before rocuronium application. Group L: patients currently not using metoprolol and received lidocaine before rocuronium application. Group C: patients currently not using metoprolol and who did not receive lidocaine before rocuronium application. Following the induction of general anesthesia with thiopental sodium, a researcher blind to the groups observed the pain during rocuronium injection based on the following scale: (1) no reaction, (2) movement only in the ankle, (3) movement or withdrawal only in the arm (shoulder and ankle), and (4) diffuse reaction (movement or withdrawal in more than one extremity, coughing and holding breath).

Results: Two hundred patients with 50 in each of four groups were included. The incidence of pain was statistically significantly lower in Group ML compared to Groups M and C ($p = 0.001$). The correlations between pain caused by rocuronium injection and duration of metoprolol usage and the time since the last dose were not statistically significant (for all, $p > 0.05$).

Conclusions: Oral metoprolol combined with lidocaine reduced pain and withdrawal reflex caused by rocuronium injection. No significant difference was observed between the last dose and the duration of metoprolol usage.

Keywords: Rocuronium, metoprolol, lidocaine, general anesthesia, pain, reflex

Rocuronium is a nondepolarizing neuromuscular blocker that produces muscle relaxation to help facilitate surgery and lung ventilation during elective and emergency procedures [1]. It is preferred for rapid onset of action and reversibility [2]. However, the injection of rocuronium is associated with severe burn-

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ing pain and spontaneous movement in the arm observed after induction of anesthesia, known as rocuronium withdrawal reflex [3]. Rocuronium administered in awake patients often leads to complaints of burning pain at the injection site [4]. If rocuronium is used following the loss of consciousness, some patients show withdrawal reflex and recall injection pain postoperatively. Rocuronium-induced withdrawal reflex has been reported between 50and 84% [5]. This reflex's exact mechanism has not been clearly understood, but it can cause severe complications such as aspiration pneumonia [6]. It has been proposed that this reflex occurs due to the release of local mediators or stimulation of C nociceptors [7].

Non-pharmacological and pharmacological methods have decreased the frequency of withdrawal reflex following rocuronium injection. Non-pharmacological techniques include cooling the reagent, topical warming, and decelerating the injection rate [8]. Numerous pharmacological agents such as opioids, ketamine, tramadol, magnesium sulfate, and lidocaine have been studied to decrease the severity and frequency of pain and reflexes following rocuronium injection [3]. Also, animal models using new rocuronium formulations not causing vascular pain in flexor reflex anesthetized rats are ongoing [9].

Metoprolol is a selective β1 receptor blocker. β blockers, as a class of drugs, are primarily used to treat cardiovascular diseases and other conditions. The possibilities for their use in treating different conditions continue to evolve. β adrenoreceptors are localized in the areas directly associated with pain pathways and have proinflammatory properties with the production of IL1β and IL6. Pain control of β adrenoreceptors depends on the type of nociceptive stimulus. Whereas both β1 and β2 are effective in physical stimuli, β1 adrenoceptors are more effective in chemical stimuli [10]. Some β blockers have been proven to show local anesthetic effects and cause activation of GTPase in vitro. Other studies have demonstrated that esmolol, a β1 blocker, was used to prevent rocuronium injection pain and effectively reduce this pain [119. Asik *et al.* [12] found that iv metoprolol was as effective as lidocaine in preventing propofol-induced pain, like rocuronium.

There are studies investigating of the effects of metoprolol administered intravenously. However, no study was found to investigate its effects via oral way. This study aimed to investigate the effect of metoprolol on the frequency and severity of pain after rocuronium injection in patients who were using oral metoprolol for any reason.

METHODS

The local ethics committee approved the study protocol of our hospital with the 07/05/2014 dated and 2014-4/94 numbered decision. The study was registered with the Clinical Registration Number: NCT05457751. All patients were informed about the study and gave informed written consent. The study was conducted per the ethical principles of the Declaration of Helsinki and was planned as a prospective, placebo-controlled cohort study.

Inclusion criteria included patients aged between 18 - 75 years, ASA 1-III, patients undergoing elective surgery under generala anesthesia, patients using thiopental sodium for induction of general anesthesia, and patients who used oral metoprolol for any medical reason in the preoperative period.

Patients under 18 and above 75 years of age, with ASA IV class, those with known allergy to rocuronium and lidocaine, patients with chronic pain, pregnant women, those who had received analgesics or sedatives, and patients who were receiving calcium channel blocker that could affect pain were excluded from the study.

After being taken to the operating table, patients were routinely monitored with 3-channel ECG, non-invasive blood pressure, and oxygen saturation (SpO_2). We provided IV access, with a 22 G branule from the most prominent vein, the dorsum of the hand. Time since the last use of the metoprolol and metoprolol usage duration were recorded. Before the rocuronium injection, anesthetic agents administered for induction were recorded, and only patients who received thiopental sodium were included in the analysis to provide standardization.

Following the induction of general anesthesia with thiopental sodium, a researcher blind to the groups observed the pain during rocuronium injection based on the following scale: (1) no reaction, (2) movement only in the ankle, (3) movement or withdrawal only in

the arm (shoulder and ankle), and (4) diffuse reaction (movement or withdrawal in more than one extremity, coughing and holding breath).

Patients were evaluated in four groups. Group M: patients currently using metoprolol and who did not receive lidocaine before the application of rocuronium. Group ML: patients currently using metoprolol and who received lidocaine before rocuronium application. Group L: patients currently not using metoprolol and received lidocaine before rocuronium application. Group C: patients currently not using metoprolol and who did not receive lidocaine before rocuronium application.

Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and SpO_2 values were recorded before rocuronium administration, 1 and 3 minutes after rocuronium induction, and after intubation. Anesthesia maintenance was performed according to the discretion of the anesthetist. We checkedthe injection site regarding edema, rash, and thrombophlebitis after the first 24 hours of the operation.

Statistical Analysis

Considering withdrawal of 70% as described in the previous studies [13], the power analysis determined that each group should have 50 patients at 95% confidence interval ($\alpha = 0.05$) and 92% power. Sampling analysis was performed using PASS 13 statistical software. Data obtained in the study were statistically analyzedutilizing SPSS version 20.0 (SPSS, Statistical Package for Social Sciences, IBM Inc. Armonk, NU, USA) program. All data are presented as mean ± standard deviation or number (percentage) of patients. The normal distribution of variables was studied using the Kolmogorov-Smirnov test. One-way analysis of variance and χ^2 test were used in the analysis of the demographic data of the patients. χ^2 test was employed to evaluate the incidence of the pain caused by rocuronium bromide injection. In the variables showing normal distribution, such as HR, SBP, DBP, and MBP, statistically, significant differencesamong the groups wereanalyzed with the Repeated Measures ANOVA test. Bonferroni adjusted test was utilized to reveal the measurement times that led to the significant difference between values. $P < 0.05$ values were considered statistically significant.

RESULTS

A total of 200 patients, with 50 being in each group, were included in the study. The mean overall age was found as 55.95 ± 12.33 years. The mean age was statistically significantly higher in Groups M and ML compared to Groups L and C ($p < 0.001$). No statistically significant difference was found between the groups in terms of gender, height, weight, BMI, time

Table 1. Demographic data of the patients

	Group M (n = 50)	Group ML (n = 50)	Group L (n = 50)	Group C (n = 50)	*p* value
Gender (F/M)	22/28	17/33	15/35	10/40	0.079
Age	61.1 ± 11.6	63.4 ± 11.5	48.7 ± 11.5	50.6 ± 14.7	**0.001***
Height	164.4 ± 16.1	165.4 ± 8.0	165.2 ± 7.7	164.7 ± 5.0	0.956
Weight	78.2 ± 12.3	76.4 ± 15.2	77.5 ± 13.3	76.3 ± 12.3	0.880
BMI	30.9 ± 17.6	28.0 ± 5.6	28.5 ± 5.0	28.2 ± 4.6	0.419
Last time (hr)	6.3 ± 5.8	8.7 ± 11.5	--	--	0.183
Metoprolol usage time (day)	42.1 ± 53.8	35.6 ± 49.7	--	--	0.534

All values are presented as mean ± standard deviation or number of patients. BMI = body mass index, F = female, M = male, Group M = patients currently using metoprolol and who did not receive lidocaine before the application of rocuronium, Group ML = patients currently using metoprolol and who received lidocaine before rocuronium application, Group L = patients currently not using metoprolol and received lidocaine before rocuronium application, Group C = patients currently not using metoprolol and who did not receive lidocaine before rocuronium application. *Group M and ML compared with group L and group C.

Table 2. The intensity and incidence of rocuronium-induced injection pain between the groups

Pain Score	Group M (n = 50)	Group ML (n = 50)	Group L (n = 50)	Group C (n = 50)	*p* value
1	31 (62%)	44 (88%)	36 (72%)	26 (52%)	
2	10 (20%)	3 (6%)	5 (10%)	4 (8%)	
3	9 (18%)	3 (6%)	8 (16%)	17 (34%)	
4	0 (0%)	0 (0%)	1 (2%)	3 (6%)	
Overall incidence (2+3+4)	19(38%)*	6(12%)†	14(28%)‡	24(48%)§	**0.001**

All values are presented as number of patients (percentages). Group M = patients currently using metoprolol and who did not receive lidocaine before the application of rocuronium, Group ML = patients currently using metoprolol and who received lidocaine before rocuronium application, Group L = patients currently not using metoprolol and received lidocaine before rocuronium application, Group C = patients currently not using metoprolol and who did not receive lidocaine before rocuronium application.

*p = 0.003, Group M compared with Group ML

†p = 0.001, Group ML compared with Group C

‡p = 0.047, Group L compared with Group ML

§p = 0.040, Group C compared Group L

since last use of the drug, and metoprolol usage duration (for all, $p > 0.05$) (Table 1).

The data relating toincidence and intensity of the pain during rocuronium injection were statistically different among all study groups ($p = 0.001$). In group ML, 88% of patients did not have rocuronium-related injection pain. The incidence of pain induced by rocuronium injection in metoprolol plus lidocaine group was 12%, compared with 28%, 38% and 48% in lidocaine, metoprolol, and control groups; respectively ($p = 0.001$) (Table 2). The incidence of the pain was statistically significantly lower in Group ML compared to Groups L, M, and C ($p = 0.047$, $p = 0.003$, and $p = 0.001$; respectively). On the other hand, the pain score was statistically significantly lower in Group L compared to Groups M and C ($p = 0.001$).There were no statistically significant differences between Group M and Group C ($p = 0.315$) and Groups M and L ($p = 0.290$) in terms of overall incidence.

The pain induced by rocuroniuminjection was significantly higher in Group C than in Groups L ML ($p = 0.02$ and $p = 0.001$). There were no statistically significant differences between Groups L M ($p = 0.416$)

Table 3. Comparison of heart rate values between the groups

Heart Rate	Group M (n = 50)	Group ML (n = 50)	Group L (n = 50)	Group C (n = 50)	*p* value	Difference
Pre-induction	77.9 ± 12.3	80.3 ± 13.5	83.1 ± 11.8	81.8 ±13.5	0.206	--
Post-induction	85.5 ± 13.0	84.8 ± 13.9	93.7 ± 11.7	89.7 ± 13.2	**0.002***	C and M-ML
Metoprolol 1st min	82.6 ± 14.5	85.7 ± 13.9	88.2 ± 11.0	88.3 ± 15.2	0.127	--
Metoprolol 3rd min	78.6 ± 13.7	80.0 ± 14.1	103.1 ± 117.1	85.0 ± 15.0	0.151	--
Post-intubation 1st min	85.9 ± 13.2	86.8 ± 14.5	97.7 ± 15.1	97.0 ± 15.6	**< 0.001**	M-ML and L-C
Post-intubation 5th min	77.7 ± 14.0	79.1 ± 13.3	87.6 ± 14.8	86.8 ± 14.2	**< 0.001**	M-ML and L-C

All values are presented as mean ± standard deviation. Group M = patients currently using metoprolol and who did not receive lidocaine before the application of rocuronium, Group ML = patients currently using metoprolol and who received lidocaine before rocuronium application, Group L = patients currently not using metoprolol and received lidocaine before rocuronium application, Group C = patients currently not using metoprolol and who did not receive lidocaine before rocuronium application. *Group M and ML compared with group L and group C.

Tablo 4. Correlation between pain and metoprolol usage duration- Last dose (hour)

Pain		Usage Duration	Last dose/hour
Group M	r	-0.80	0.153
	p value	0.579	0.289
Group ML	r	-0.172	-0.132
	p value	0.233	0.360
Overall	r	-0.091	-0.070
	p value	0.366	0.491

Group M = patients currently using metoprolol and who did not receive lidocaine before the application of rocuronium, Group ML = patients currently using metoprolol and who received lidocaine before rocuronium application

and Group M and C ($p = 0.08$).

ASA classes were statistically significantly lower in Group L and Group C compared to Groups M and ML ($p < 0.001$).

When the groups were compared in terms of comorbidities, Groups M and ML were found to have more comorbidities compared to Groups L and C ($p < 0.001$).

No statistically significant differences were detected between the groups in HR measured pre-induction and 1st and 3rd minutes of metoprolol administration (for all $p > 0.05$). At the same time, statistically significant differences were observed between the groups regarding the HR measured post-induction and 1st and 5th minutes of intubation. Accordingly, HR was significantly higher post-induction in Group L patients than in Groups M and ML. In addition, HR was significantly higher in Groups L and C than in M and ML at the 1st and 5th minutes of the intubation (Table 3).

SBP, DBP, and MBP values were compared between the groups at pre- and post-induction, 1st and 3rd minutes after metoprolol administration, and 1st and 5th minutes of the intubation. The mean SBP value was significantly higher in Group C compared to Groups M and L at the 1st minute of metoprolol administration. We found no statistically significant difference between the groups in DBP values at all times (for all, $p > 0.05$).

Similarly, we found no statistically significant difference between the groups in MBP values at all times (for all, $p > 0.05$).

We examined the correlations between pain and duration of metoprolol usage and the time since the last dose, and no statistically significant difference was found (for all, $p > 0.05$). In addition, the pain was not correlated with other demographic and clinical features of the patients (for all, $p > 0.05$) (Table 4).

A comparison of pain scores according to the demographics was given in Table 5.No statistically sig-

Tablo 5. Comparison of demographics according to pain scores

	Pain 1 (n = 137)	Pain 2 (n = 22)	Pain 3 (n = 37)	Pain 4 (n = 4)	*p* value*	Difference
Age	58.3 ± 12.9	57.6 ± 13.8	48.1 ± 13.3	38.0 ± 17.3	**< 0.001**	4 and 1-2
Height	165.1 ± 11.5	164.5 ± 4.7	164.6 ± 6.2	164.0 ± 7.9	0.987	--
Weight	77.7 ± 13.5	77.6 ± 13.1	76.0 ± 11.9	62.3 ± 13.8	0.131	--
BMI	29.3 ± 11.4	28.7 ± 5.1	28.2 ± 4.9	23.2 ± 5.2	0.632	--
Last hour	7.9 ± 9.9	5.2 ± 5.9	7.6 ± 6.2	--	0.620	--
Usage duration	41.4 ± 54.5	35.1 ± 36.1	27.5 ± 48.8	--	0.666	--

All data were presented as mean ± standard deviation. BMI = body mass index. *One Way Anova

nificant difference was found among the pain scores in terms of height, weight, BMI, the time elapsed after the last use of metoprolol, and duration of metoprolol usage ($p > 0.05$). A statistically significant difference was found in age values ($p < 0.05$). A multiple comparison test (post-hoc) wasused to determine which group/groups caused the difference. There was a statistically significant difference between the patients with a pain score of 4 and those with a score of 1-2. The patients with a pain score of 4 were younger.There was a moderate negative correlation between pain score and age (r= -0.321, $p = 0.001$).

DISCUSSION

Rocuronium bromide is a nondepolarizing neuromuscular blocking agent characterized by a rapid onset and intermediate time of action. Rocuronium is often used to induce and maintain general anesthesia with its superior properties. However, during induction of anesthesia, the amino steroid neuromuscular blocking drug rocuronium usually causes pain and withdrawal reactions in the arm [14]. It is generally accepted that short duration burning severe pain is the cause of these spontaneous movements. In a similar study, Jimbo *et al*. [9] claimed that the primary cause of pain associated with rocuronium is not the active ingredient, but a high acetate buffer used as a solvent. So, the authors developed a new formulation of rocuronium using a low-acid concentration in a rat model, which caused no pain [9].

Although this is considered well-tolerated during injection, recent reports indicate severe pain and withdrawal reflexes after iv injection of rocuronium. Pain has been attributed to the effect of the acidic pH of rocuronium because it is supplied as an isotonic solution with a pH of 4. Blunk *et al*. postulated that the allogenic effect of amino steroid neuromuscular blocking drugs could be attributed to the direct activation of C-nociceptors, which causes pain [14].

Clinical studies are ongoing on using various agents with rocuronium as a nerve blockade agent and different variations and formulations of rocuronium [15]). In this observational study, we aimed to examine the effects of oral metoprolol or oral metoprolol plus lidocaine on rocuronium pain and reflex. Our findings showed that, although metoprolol was effective in pain reduction, its effect significantly increased when combined with lidocaine. We used the following scores were included to evaluate pain severity: (1) No reaction, (2) Movement only in the ankle, (3) Movement or withdrawal only in the arm, and (4) Diffuse reactions.

In our study, 62% of patients in Group M had no pain, while this rate was 88% in Group M+L. It means that, when added to lidocaine, the effect of metoprolol on the pain increased. On the other hand, none of the patients in Groups M and ML exhibited diffuse reactions, while three patients in the control group and one in the lidocaine groupshowed diffuse responses. In addition, the duration of using metoprolol and the time since the last dose did not affect the impact of metoprolol on reducing rocuronium pain. Lee *et al*. showed that simply through fast injection, the withdrawal response of rocuronium could be significantly reduced without using lidocaine as pretreatment [16].

Yavascaoglu *et al*. aimed to determine the effect of esmolol on the frequency and severity of pain and withdrawal reflex after injection of rocuronium with lidocaine and placebo. The authors reported that esmolol, like lidocaine, reduces the frequency of pain and withdrawal reactions associated with rocuronium injection [11].

Various pharmacological alternative agents have been attempted to reduce withdrawal reflex and pain induced by rocuronium injection. A study by Jeon *et al*. aimed to reduce withdrawal movements associated with rocuronium injection by pretreatment with acetaminophen; the pain was significantly reduced and lidocaine [17].

Davidson *et al*. [18] studied esmolol formalin's antinociceptive and cardiovascular properties in rats and found that esmolol leads to analgesia and reduces cardiovascular responses to pain.

Cheong *et al*. [19] investigated the effect of two doses of pretreatment lidocaine on the incidence of pain caused by rocuronium injection. They found that prior administration of lidocaine 10 mg or 30 mg iv decreased the incidence and severity of pain.

Mahajan *et al*. [5] investigated the effect of ketamine on rocuronium pain. Ketamine acts on a multitude of receptors. It is a non-competitive N-methyl-D-aspartic acid receptor antagonist and opioid μ receptor agonist in the central nervous system and vascular endothelium. The authors concluded that

these actions of ketamine might have attenuated the pain caused by rocuronium [59.

Asik *et al*. [12] compared the effects of lidocaine and metoprolol on pain with propofol injection. The pain mechanism of propofol is still unclear, but several factors have been accused, such as the speed of injection. It was suggested in the same study that metoprolol has a vasodilator effect, decreasing the contact of propofol with the endothelium of the vein used for the injection. This study showed that pretreatment with metoprolol was as effective as lidocaine in reducing pain associated with propofol injection [12]. As mentioned above, several studies have shown the effects of different agents on rocuronium pain and reflex. Some studies have used new formulations of rocuronium to reduce pain and reflex. However, there is still no standard method for this purpose, and reflections on this topic are still underworking.

There were some statistically significant differences between the groups regarding the other study parameters such as age, ASA, comorbidities, and heart rate. We found that the pain related to rocuronium injection was higher in younger patients. The mean age of patients using metoprolol was higher. Pain-related rocuronium injection was less among these patients. In the metoprolol group, a lower incidence of pain may not be related to metoprolol. It may be associated with their older age.

Limitations

The main limitation of the present study was its observational nature. Furthermore, participants in the groups are not enough to draw a definitive conclusion from the study. However, there is no study in the literature investigating the direct effects of orally administered metoprolol on rocuronium pain and reflex. We believe that our findings will be guiding for future studies.

CONCLUSION

This study shows that oral metoprolol reduces pain and withdrawal reflex of the arm into which the drug is injected. On the other hand, this effect further increased when metoprolol plus lidocaine were combined. There was no significant difference in the time since the last dose and duration of metoprolol usage. Further comprehensive prospective and multicenter studies are needed to clarify these effects.

Authors' Contribution

Study Conception: ÖŞ, DK; Study Design: ÖŞ, DK, TK, MK, SY; Supervision: ÖŞ; Funding: N/A; Materials: ÖŞ, DK, TK, MK; Data Collection and/or Processing: ÖŞ, SY; Statistical Analysis and/or Data Interpretation: ÖŞ, MK, SY; Literature Review: ÖŞ, MK, ŞY; Manuscript Preparation: ÖŞ, TK and Critical Review: ÖŞ, TK, MK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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