Turkish Journal of Clinics and Laboratory

To cite this article: Sahap M, Gulec H, Ozayar E, Ozdemir O, Kacan M, Kurtay A, Horasanlı E, But A. Effects of COX 1-2 Inhibitors on Prevention of Rocuronium Injection Pain: Controlled, Randomised, Double Blind Study Turk J Clin Lab 2023; 1: 48-52

Original Article

Effects of COX 1-2 Inhibitors on Prevention of Rocuronium Injection Pain: Controlled, Randomised, Double Blind Study

COX 1-2 İnhibitörlerinin Roküronyum Enjeksiyon Ağrısının Önlenmesine Etkileri: Randomize, Kontrollü, Çift Kör Çalışma"

Mehmet Sahap*[1], Handan Gulec[1], Esra Ozayar[2], Ozlem Ozdemir[3], Merve Kacan [4], Aysun Kurtay[3], Eyup Horasanlı[1], Abdulkadir But[1]

[1]Ankara Yildirim Beyazit University Faculty of Medicine, Department of Anaesthesiology
[2]Ankara City Hospital, Department of Anaesthesiology
[3]Ankara Keçiören Training and Research Hospital of Department of Anaesthesiology
[4]İstanbul Beylikdüzü Hospital of Department of Anaesthesiology

ABSTRACT

Aim: Rocuronium bromide is a painful agent during induction of general anaesthesia. The aim of the study is to investigate the effects of Cyclooxygenase (COX) inhibitors as a resque agent against the rocuronium pain.

Material and Methods: Sixty patients of either sex scheduled for under general anesthesia were enrolled in this study. Patients were allocated into two groups (Group 1: Dexkethoprofen group, Group 2: Control group). Pain was evaluated by during rocuronium injection, patients were scored by a scale showed below. 0; No movement response to injection, 1; Mild movement response to injection, 2; Hand withdrawal response to injection, 3; Arm withdrawal response to injection. We also evaluated the pain with 2 questions when the patient was in the recovery room. Question 1. What was the last feeling before you fall into sleep? and question 2. Did you feel any pain on your hand during medication injection for anesthesia?

Results: There were differences between the groups in terms of total pain score for example in group 1 there were 16 (53%) patients who did not make any movement during rocuronium injection while there were 22 (73%) patients in group 2.There was significant difference in injection rocuronium bromide pain between group 1: dexkethoprofen group, Group 2: control group in terms of the answer to the second question. Patients felt less pain than the control group. In the second question, 16% in group 2 stated that they felt pain, while this rate was observed as 3% in group 1.

Conclusion: The effect of cox inhibitors on rocuronium pain was seen in our study but control group is also effective in reducing pain in vascular width.

Keywords: Rocuronium; injection, pain; cyclo-oxygenase inhibitors.

Corresponding Author*: Mehmet Sahap, Ankara Yildirim Beyazit University Faculty of Medicine, Department of Anaesthesiology Ankara/Turkey
E-mail: drsahap@gmail.com
Orcid : 0000-0003-3390-9336
Doi:10.18663/tjcl.1166599
Recevied: 25.08.2022 accepted: 22.11.2022

ÖZ

Amaç: Roküronyum bromür genel anestezi indüksiyonu sırasında ağrılı bir ajandır. Bu çalışmanın amacı Siklooksijenaz (COX) inhibitörlerinin roküronyum enjeksiyon ağrısına karşı etkilerini araştırmaktır.

Gereç ve Yöntemler: Çalışmaya genel anestezi ile opere olacak toplam 60 hasta dahil edildi. Hastalar iki gruba ayrıldı (Grup 1: Deksketoprofen grubu, Grup 2: Kontrol grubu). Roküronyum enjeksiyonu sırasında hastalar tarafından hissedilen ağrı aşağıda gösterilen bir skala ile puanlandı. 0; Enjeksiyona hareket yanıtı yok, 1; Hafif enjeksiyona hareket yanıtı, 2; Enjeksiyona el çekme yanıtı, 3; Enjeksiyona kol geri çekme yanıtı. Ayrıca hastalara uyanma odasında iken 2 soru ile ağrıyı değerlendirdi. Soru 1. Uyumadan önceki son hissettiğiniz duygu neydi, soru 2. Anestezi için ilaç enjeksiyonu sırasında elinizde herhangi bir ağrı hissettiniz mi?

Bulgular: Toplam ağrı skoru açısından gruplar arasında fark vardı. Roküronyum enjeksiyonu sırasında hareket etmeyen 1. grupta 16 (%53) tane hasta varken 2. Grupta 22 (%73) hasta vardı. Gruplar arasında ikinci soruya verilen yanıt açısından anlamlı fark vardı. Hastalar kontrol grubuna göre daha az ağrı hissettiler. İkinci soruda grup 2'de (%16) ağrı hissettiğini belirtirken bu oran grup 1'de (%3) olarak gözlendi. Brakiyel ven yolundan el dorsumuna göre daha az ağrı hissedildi.

Sonuç: Cox inhibitörleri, rokuronyum ağrısını azaltmada etkili olmakla birlikte damar çapının da ağrı hissedilmesinde etkili olduğu görülmüştür.

Anahtar Kelimeler: Roküronyum; enjeksiyon, ağrı; siklo-oksijenaz inhibitörleri.

Introduction

Due to its favorable pharmacological characteristics, rocuronium is frequently used during the induction and maintenance of general anesthesia [1]. Rocuronium is a painful agent which is mostly preferred muscle relaxant by anesthesiologists due to its rapid onset of action and low rate of adverse events. Even when rocuronium is used after loss of consciousness, some patients reportedly exhibit spontaneous movement of the upper limb and recall injection pain after the surgery [2]. The major disadvantage of rocuronium is injection pain causing withdrawal reaction of the arm and hand. This injection pain is an unconfortable experience for the patients undergoing general anesthesia. In the literature there many agents including lidocaine, ketamine, magnesium sulphate, tramadol, ondansetron and alfentanil were used in trials for alleviation of injection pain but their failure ratio were between 7%-35% [3-5]. The exact mechanism of rocuronium injection pain is stil not clear. Histamine and bradykinin release is a possible mechanism which is pointed out in some published trials [6].

The main mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs) is the inhibition of prostaglandin synthesis due to cyclo-oxygenase (COX) inhibition. Dexketoprofen trometamol is a non selective COX inhibitor which has a rapid onset of action. The aim of the study is to investigate the effects of Cyclooxygenase (COX) inhibitors as a resque agent against the rocuronium pain.

Material and Methods

This study conducted as a double blind controlled randomised study. Local ethical consent (No:2018/1634) was obtained from the scientific research ethics committee. Power analysis showed that a sample size of 30 for each group was necessary toill give a power of 0.80 at a level of significance level of =0.05. 60 patients undergoing general anesthesia were enrolled in this study (Figure 1). After obtaining ethical comittee approval patients randomly allocated into two groups. Patients non- allergic to dexketoprofen, 18-60 years old, ASA 1-2-3, 70-90 kg weigh were included to study while patients with pshychiatric and menthal problems were excluded from the study. Closed envelope randomisation method was used as a randomisation method. IV cannulation was performed on hand dorsum or brachial. Patients allocated in Group 1 were administered intravenous dexkethoprofen (50 mg/2ml) and 0.3 mg/kg midazolam 10 minutes prior to general anesthesia induction while patients in Group 2 were applied 2 ml of saline and 0.3 mg/kg midazolam in the premedication room. A third person resident unaware of the study applied this medication to both group 1 and 2. After the patient arrived to the operating theatre and the standart monitarisation performed with ECG, non-invasive blood

pressure and pulse oxymetry General anesthesia was induced with; %2 lidocaine (1mg/kg), 2 mg/kg propofol, and 0.6 mg/kg rocuronium respectively. During rocuronium injection, patients were scored by a scale showed below.

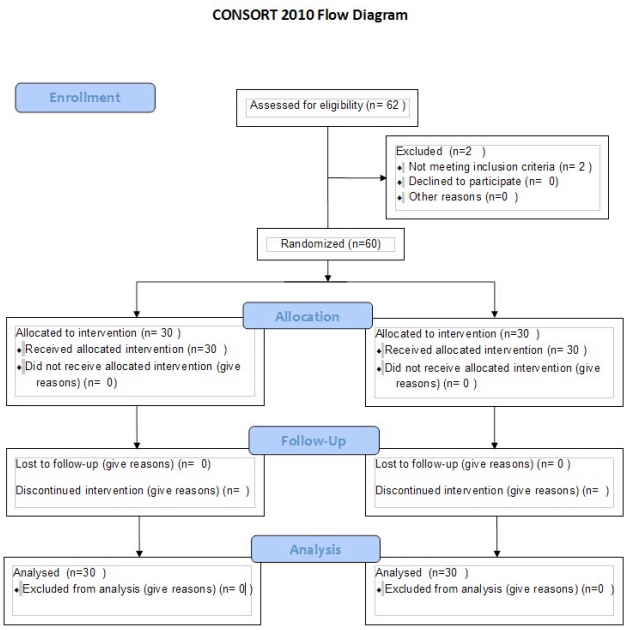

Figure 1. Flow diagram of patient data distribution

Response to rocuronium injection pain scale;

1. No movement response to injection
2. Mild movement response to injection
3. Hand withdrawal response to injection
4. Arm withdrawal response to injection

During intraoperative period; heart rate, mean arterial pressure and SpO2 were recorded in intervals. Patients whose Aldrete score were nine point, asked to answer two questions below in the recovery room.

Question 1.What was the last feeling before you fall into sleep?

a. Nothing

b. Mild

c. Moderate

d. Severe

e. Do not remember

Question 2. Did you feel any pain on your hand during medication injection for anesthesia?

a. Yes b. No c. Do not remember

Statistical Analysis

Version 22.0 of SPSS (Statistical Package for the Social Sciences, Chicago, IL, USA) program was used for statistical analysis of the data. Kolmogorov-Smirnov normality test was performed for continuous variables. In comparison of groups, Student-T test was used for continuous variables, while ordered or non-normal variables were evaluated with Man Whitney U test. Chi-square and Fisher's exact tests were used in the analysis of categorical variables. A $p<0.05$ value was accepted for the statistical significance limit.

Results

There was no statistically significant difference in patient characteristics between groups (Table 1). Heart rates during intraoperative period were comparable between groups. (P=0.8) Oxygen saturation and mean arterial blood pressures were also similar.(P=0.30, P=0.65 respectively) In group 1 there were 16 (53%) patients who did not make any movement during rocuronium injection while there were 22 (73%) patients in group 2 (Table 2). The table contains the number of reactions in the Groups. For example, there are 16 people in Group1 who say response, no movement, and they constitute 53.3% of the group. The same number in Group2 is 22 (73.3%) and therefore higher than Group1. Other responses were lower in Group2 than in Group1. It was seen that the reactions in the groups were different. The answers to question 1 are the same in both groups. P = 0.83 Fisher exact test result as p value (Table 3). The answers to Question 2 are different (you read the numbers and percentages from the table) (Table 4). Even those who say I don't remember will be different. P = 0.0290 Fisher exact test result. The veins are not different. P=0.41 Chi-square test Table5).

Table 1. Patient characteristics.

	Group 1	Group 2	P value
Age	43±12	40±13	0.29
BMI	26±3	27±4	0.55
Gender (F/M)	19/11	15/15	0.3

Data were presented as ratios and percentages. A $p<0.05$ value was accepted for statistical significance.

Table 2. Hand and arm movement during rocuronium injection.

	Group 1(n)	Group 2 (n)	Total(n)	P value
No movement	16	22	38	0.047
Mild hand movement	6	0	6	0.015
Hand withdrawal	2	4	6	0.37
Arm withdrawal	6	4	10	0.38
Total	30	30	60	

Data were presented as ratios and percentages. A $p<0.05$ value was accepted for statistical significance.

Table 3. Last feeling before falling into sleep.(Question 1).

	Group 1	Group 2	Total	P value
Nothing	18	18	36	-
Mild pain	2	1	3	0.67
Moderate	1	0	1	1
Severe	0	0	0	-
Do not remember	9	11	20	0.83

The answers to question 1 do not seem different(p=0.83 Fisher exact as p value)

Table 4. Did you feel any pain on your hand during medication injection for anesthesia? (Question2)

	Group 1	Group 2	Total	P value
Yes	1	5	6	0.021
No	21	11	32	0.024
Do not remember	8	14	22	0.68

p<0.05 value was accepted for statistical significance.

Table 5. Intravenous cannulation location.

	Group 1	Group 2	Total	P value
Hand Dorsum	11	8	19	0.41
Brachial	19	22	41	0.40

p<0.05 value was accepted for statistical significance.

Discussion

Nociceptive stimulation can activate the sympathetic nervous system and increase blood pressure or heart rate. Original rocuronium was found to be the independent factor associated with a higher heart rate. However, there were no increases in mean blood pressure 3 minutes after the injection of rocuronium.In our study, we did not find the hemodynamic effect of rocuronium.

Rocuronium is widely used to provide neuromuscular blockade during anesthetic care. Intense pain induced by its intravenous injection is common in the clinical setting [7].

it is a muscle relaxant used in our clinic.

The mechanism of rocuronium-induced pain is unclear. Administration rocuronium following high dose bolus of remifentanil (1 mcg/kg) or fentanyl (1.5 mcg/kg) was also examined. However, high dose bolus of these agents could induce the adverse events such as cough, breath holding, and chest rigidity [8]. Although various techniques have been studied to alleviate rocuronium injection pain, there has been no widely accepted method to date.

Acidic or alkaline solution with high osmolality is known to cause injection pain [9]. Rocuronium is an isotonic solution with a pH value of 4. While normal saline is also buffered to pH 4, it does not cause injection pain. It has also been assumed that pain on rocuronium injection occurs as a result of the release of local mediators, such as kinins, stimulating the venous nociceptors [10.] Histamine and bradykinin release is a possible mechanism which is pointed out in some published trials therefore based on this theory, we aimed to prevent rocuronium pain with these cox inhibitors agents.

According to the answer in second question in our study; COX inhibitors drugs have effect on injection pain in group 1 (Table 3).

We could not achieve a meaningful result in the first question, in which we evaluated rocurum injection pain. The reason why there is less pain in group 2 according to the first question because of the vascular access of 22 patients may be from the brachial vein (Table 5).

Since vascular diameter is reportedly associated with the occurrence of the withdrawal reflex after rocuronium injection [11]. Multivariate analysis was performed to exclude the effects of catheter size and location on vessel diameter at the access site.

In our study, pain was less in the group 2 where rocuronium was applied through the brachial vein. (Table 5)

Conclusion

The effect of cox inhibitors on rocuronium pain was seen in our study but check is also effective in reducing pain in vascular width. We think that there are more dominant etiological causes other than the cyclooxygenase pathway in the etiology of rocuronium pain. Nevertheless, there is a need for further studies with larger patient groups to confirm these results.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

References

1. Oda Y.Rocuronium bromide: clinical application of single-dose pharmacokinetic models to continuous infusion.J Anesth. 2018;32(1):1–2.
2. Mencke T, Beerhalter U, Fuchs-Buder T.Spontaneous movements, local reactions and pain on injection of rocuronium. A comparison between female and male patients.Acta Anaesthesiol Scand. 2001;45(8):1002–5.
3. Memis D, Turan A, Karamanlioglu B, Sut N, Pamukcu Z. The prevention of pain from injection of rocuronium by ondansetron, lidocaine, tramadol, and fentanyl. Anesth Analg 2002;94:1517 - 20.

4. Reddy MS, Chen FG, Ng HP. Effect of ondansetron pretreatment on pain after rocuronium and propofol injection: a randomised, doubleblind controlled comparison with lidocaine. Anaesthesia 2001;56: 902 – 5
5. Cheong KF, Wong WH. Pain on injection of rocuronium: influence of two doses of lidocaine pretreatment. Br J Anaesth 2000;84:106 – 7
6. Yonghong Zhang MD, Yong Xiang MD , Jin Liu MD. Prevention of pain on injection of rocuronium: a comparison of lidocaine with different doses of parecoxib. Journal of Clinical Anesthesia (2012) 24, 456–459
7. Borgeat A, Kwiatkowski D. Spontaneous movements associated with rocuronium: Is pain on injection the cause?Br J Anaesth.1997;79:382–3
8. Oh AY, Seo KS, Goo EK, Park YO, Kim SJ, Kim JH. Pretreatment of withdrawal movement associated with injection of rocuronium in children: Comparison of remifentanil, alfentanil and fentanyl. Acta Anaesthesiol Scand.2007;51:1190–3.
9. Klement W, Arndt JO. Pain on iv injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations.Br J Anaesth.1991;66:189–95.
10. Kindgen-Milles D, Klement W, Arndt JO. The nociceptive systems of skin, paravascular tissue and hand veins of humans and their sensitivity to bradykinin. Neurosci Lett. 1994;181:39–42
11. Yilmaz S, Hatiboglu Y.The evaluation of the effect of venous diameter measurement by ultrasonography on pain and withdrawal response.J Anesth. 2018;32(3):375–80