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# Effect of Local Cooling with Ice Gel Pack to Prevent Propofol and Rocuronium Injection Pain: A Prospective, Randomized Controlled Study

## Propofol ve Roküronyum Enjeksiyon Ağrısını Önlemek İçin Buz Jel Paketi ile Lokal Soğutmanın Etkisi: Prospektif, Randomize Kontrollü Bir Çalışma

Kenan Kart[1], Erol Toy[2], Duygu Taskin[1], Kamil Toker[3]

[1]Karabük University, Department of Anesthesiology and Reanimation, Karabük, Türkiye
[2]Bilkent City Hospital, Intensive Care Unit, Ankara, Türkiye
[3]BHT Tema Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Türkiye

**ABSTRACT**

**Objective:** In the present study, the purpose was to investigate the effectiveness of cooling the vascular trace on pain caused by propofol and rocuronium injection.

**Methods:** This prospective, single-blind study included 60 patients, aged 18-65 and scheduled for elective laparoscopic cholecystectomy. After vascular access was established with a 20 G intravenous cannula over the hand, cold was applied to the intravenous catheter trace for 1 minute with the help of ice gel packs before propofol and rocuronium injection in Group S (n=30 patients). Propofol and rocuronium were administered without any intervention in Group C (n=30 patients). Propofol pain was evaluated with the McCririck and Hunter Scale, and rocuronium injection pain was evaluated with the 4-point scale.

**Results:** The demographic data and the propofol and rocuronium doses were similar between the groups. Propofol injection pain was statistically higher in the Cold Group than in the Control Group (p<0.05). Rocuronium injection pain did not differ at statistically significant levels between the groups.

**Conclusion:** It was concluded that regional cooling before propofol injection increases pain and results in hyperalgesia.

**Keywords:** Propofol pain, rocuronium pain, cold application, injection pain, regional cooling

**ÖZ**

**Amaç:** Bu çalışmada propofol ve rokuronyum enjeksiyonun neden olduğu ağrının önlenmesi için damar trasesinin soğutulmasının etkinliğinin araştırılması amaçlandı.

**Yöntem:** Bu prospektif, tek kör çalışmaya, 18-65 yaş arası, elektif laparoskopik kolesistektomi planlanan 60 hasta dahil edildi. El üstünden 20 G intravenöz kanül ile damar yolu açılmasını takiben Grup S'de (n=30 hasta) intravenöz kateter trasesi üzerine 1 dakikalık buz jelleri yardımı ile soğuk uygulanmasından sonra, Grup K'de (n=30 hasta) ise hiçbir işlem uygulanmadan propofol ve roküronyum enjeksiyonu yapılmıştır. Propofol ağrısı, McCrirrick ve Hunter skalası, roküronyum enjeksiyon ağrısı ise dört nokta skalası ile değerlendirilmiştir.

**Bulgular:** Demografik veriler, propofol ve roküronyum dozları gruplar arasında benzerdi. Propofol enjeksiyon ağrısı Soğuk Grupta Kontrol Grubu'na göre istatistiksel olarak daha yüksekti (p<0,05). Roküronyum enjeksiyon ağrısı gruplar arasında istatistiksel olarak anlamlı düzeyde farklılık göstermedi.

**Sonuç:** Propofol enjeksiyonu öncesi bölgesel soğutmanın ağrıyı artırdığı ve hiperaljeziye neden olduğu sonucuna varıldı.

**Anahtar sözcükler:** Propofol ağrısı, roküronyum ağrısı, soğuk uygulama, enjeksiyon ağrısı, bölgesel soğutma

## INTRODUCTION

Propofol and rocuronium are frequently used together in anesthesia practice (1). However, they both cause pain during injection. The incidence of pain varies between 28-90% in adults (2). After loss of consciousness, rocuronium injection may cause reflexive withdrawal of the hand or general movements of the body, which is probably because of the pain at the injection site (3).

Various medications and methods have been employed to mitigate the injection pain associated with propofol and ro-

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***Corresponding author:** Kenan Kart • kenankart@karabuk.edu.tr
Kenan Kart 0000-0001-7112-8878 / Erol Toy 0000-0001-6888-9924
Duygu Taskin 0000-0001-7082-0555 / Kamil Toker 0000-0002-3168-0489

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curonium. These include intravenous (iv) lidocaine administration with venous occlusion immediately prior to drug injection, mixing lidocaine with propofol, adjusting the pH of propofol, and administering agents such as opioids, dexmedetomidine, gabapentin, magnesium sulfate, ketamine, fentanyl, remifentanil, and non-steroidal anti-inflammatory drugs before injection. Additionally, non-pharmacological approaches such as the application of vibration have also been explored (1,4-6).

Cold application eliminates or reduces pain by eliminating edema and muscle spasms. It is effective in relieving pain by slowing or blocking the conduction of peripheral nerves. In addition, it reduces pain by activating the gate-control mechanism, activating endogenous opioid release and stimulating touch receptors (7,8).

In the present study, the purpose was to investigate the effectiveness of regional cooling to relieve propofol and rocuronium injection pain during general anesthesia induction.

## MATERIALS and METHODS

The study was conducted in the prospective randomized controlled design between October 2022 and December 2023. The approval was received from the Karabük University Hospital's Research Ethics committee with Decision No. E-77192459-050.99-170160 and No. 2022/1051 for the study. Written informed consent was obtained from the participants included in this study. The patients between the ages of 18 and 65 who were scheduled for cholecystectomy under general anesthesia were included in the study. Pregnant patients, patients under 18 years of age, patients over 65 years of age, patients for whom propofol or rocuronium could not be used, and patients with ASA 3 and above were excluded from the study. The patients were not given premedication before the surgery.

The patients who were taken to the operating room underwent routine monitoring, including noninvasive blood pressure, electrocardiography, and peripheral oxygen saturation monitoring. A 20 G iv catheter was placed on over the left hand and a 0.9% sodium chloride infusion was initiated. Before the induction of the anesthesia, patients were preoxygenated with 100% $O_2$ at a flow of 6 L $min^{-1}$ for 3 minutes.

The patients were divided into 2 groups with a simple randomization method. At the beginning of the induction, cooling with ice gel packs was applied to the vascular trace to one of the groups where the injection would be made for 1 minute before the injection to prevent propofol and rocuronium injection pain. This group was named as Group S. The second group was planned as the Control Group and no cooling was made and was named as Group C.

In both groups, 1% propofol (Propofol 1%, Fresenius 20 mL vial, Germany) was administered at a dose of 2-2.5 mg $kg^{-1}$ in 15 seconds. Propofol, which was stored at +4°C, was left at room temperature for 1 hour before the injection and its temperature was measured before the administration after the temperature of all propofol vials was +22°C. After the propofol administration, the patients were observed for 20 seconds. Pain intensity during and after the propofol injection was evaluated by using McCririck and Hunter's 4-point Pain Response Scale.

Following the propofol administration, 0.6 mg $kg^{-1}$ rocuronium (Esmeron® 50 mg 5 $mL^{-1}$ NV Organon, Oss, Holland) was injected for 10 seconds. The same observer rated the movement reactions to rocuronium injection pain on the 4-point scale (FPS). The scale was designed as 0: No movement, 1: Wrist movement only, 2: Movement of the arm (elbow-shoulder) only, and 3: General response, more than one limb movement. The intubation was performed 3 minutes after the induction.

### Statistical Analysis

Mean, standard deviation, median, lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. In the study, power analysis was performed in the G Power program and was determined as 0.95. The distribution of the variables was measured with the Kolmogorov-Simirnov Test. Independent samples t-test and Mann-Whitney U test were used in the analysis of the quantitative independent data. The Chi-Square Test was used to analyze the qualitative independent data, and the SPSS 28.0 program was used in the analyses. In the study, significance was evaluated over 0.05.

## RESULTS

A total of 60 patients (30 in both groups) were included in the study. No patients were excluded from the study. The demographic structures and ASA scores of the groups were similar (Table I). The doses of propofol and rocuronium used for the induction were similar between the groups (Table I). The average propofol dose was 178.2 ± 26.2 mg in Group C and 172.8 ± 22.8 mg in Group S. The mean rocuronium dose was 46.8 ± 9.0 mg in Group C and 47.8 ± 6.8 mg in Group S. The pain score following the propofol injection in the Group S was significantly higher ($p<0.05$) than in Group C. According to McCririck and Hunter's 4-point Pain Response Scale, the rate of patients who experienced pain was 100% (30/30) in Group S and 63.3% (19/30) in Group C (Table II). The pain scores following the rocuronium injection did not differ significantly ($p>0.05$) between the groups. The rate of those who did not experience rocuronium pain was 10% (3/30) in Group S and 13.3% (4/30) in Group C (Table III).

**Table I.** Demographic Data and Propofol and Rocuronium Dosages

| | | Group C | | Group S | | P |
|---|---|---|---|---|---|---|
| | | Mean ± SD n (%) | Median | Mean ± SD n (%) | Median | |
| Age (year) | | 47.8 ± 9.8 | 47.5 | 50.5 ± 9.2 | 52.5 | 0.290[t] |
| Gender | Female | 13 (43.3) | | 14 (46.7) | | 0.795[x²] |
| | Male | 17 (56.7) | | 16 (53.3) | | |
| Weight (kg) | | 79.2 ± 12.9 | 77.5 | 78.8 ± 10.5 | 78.0 | 0.904[t] |
| Height (cm) | | 170.3 ± 9.8 | 169.5 | 170.8 ± 8.5 | 168.5 | 0.855[t] |
| BMI | | 27.2 ± 3.7 | 27.0 | 26.9 ± 2.8 | 27.0 | 0.734[t] |
| ASA Score | I | 13 (43.3) | | 14 (46.7) | | 0.795[x²] |
| | II | 17 (56.7) | | 16 (53.3) | | |
| Propofol Dosage (mg) | | 178.2 ± 26.2 | 172.5 | 172.8 ± 22.8 | 172.5 | 0.404[t] |
| Rocuronium Dosage (mg) | | 46.8 ± 9.0 | 45.0 | 47.8 ± 6.8 | 49.0 | 0.368[m] |

[t] Independent sample ***t***-test / [m] Mann-Whitney U test / [x²] Chi-Square Test (Fischer's Test), **BMI:** Body mass index, **ASA:** American Society of Anesthesiologists.

**Table II.** The Distribution of the Propofol Injection Pain Scores of the Patients According to McCririck and Hunter's 4-Point Pain Response Scale

| Pain Score | 0 | 1 | 2 | 3 | Total |
|---|---|---|---|---|---|
| Group C, n (%) | 11 (36.7) | 6 (20.0) | 10 (33.3) | 3 (10.0) | 30 (100) |
| Group S, n (%) | 0 (0.0) | 7 (23.3) | 11 (36.7) | 12 (40.0) | 30 (100) |

**Chi-square:** 0.000; p<0.05

**Table III.** The Distribution of the Patients According to Movement Reaction to Rocuronium Injection Pain with the Four-Point Scale

| Pain Score | 0 | 1 | 2 | 3 | Total |
|---|---|---|---|---|---|
| Group C, n (%) | 4 (13.3) | 8 (26.7) | 13 (43.3) | 5 (16.7) | 30 (100) |
| Group S, n (%) | 3 (10.0) | 8 (26.7) | 11 (36.7) | 8 (26.7) | 30 (100) |

**Chi-square:** 0.499; p<0.05

In terms of hemodynamic data, no significant differences were detected between the groups in measurement times. No patient experienced bradycardia or hypotension. Peripheral oxygen saturation was ≥ 96% in the groups throughout the study. No complications such as allergic reactions, edema, or permanent redness were observed in any of the patients.

## DISCUSSION

In this present study, which was conducted with the hypothesis that cold application would reduce the pain caused by propofol and rocuronium injection, it was found that cold application especially increased the pain of propofol injection. Although all the patients in the cold-applied group felt pain, albeit at different degrees, the rate of patients who experienced pain was found to be 63.3% in the Control Group.

The pH of the solution, chemo-nociceptor activation, indirect activation of bradykinin, histamine, and other substances that mediate inflammation are attributed as the mechanisms of iv injection pain (9,10).

Propofol injection pain may occur right after the injection or within 15-20 seconds as a delayed pain. Although immediate pain is probably associated with direct irritant effects, pain that begins a short time later may stem from an indirect effect of the quinine Cascade. As well as irritating the skin, venous intima, and mucous membranes, propofol also has the potential to activate the kallikrein-quinine system. These systems can cause venous dilatation and hyperpermeability, which increases contact between free propofol in the blood and peripheral nerve endings, which then cause pain upon injection (11).

The administration of propofol at different temperatures has been studied so far to reduce propofol-related pain. One study reported that refrigerated propofol caused less pain than propofol administered at room temperature (12). In an-

other study, it was reported that applying cold (+4°C) saline before propofol injection and the combination of cold (+4°C) saline and 0.05% lignocaine yielded almost similar results (13). These studies suggested that the possible mechanism may be decreased quinine release from the vascular wall because of the effect of cold.

Unlike these, some other studies have not supported the beneficial effects of cold propofol. In one study, the researchers concluded that cold propofol caused pain at a higher incidence and severity compared to propofol at room temperature and propofol supplemented with lidocaine at different concentrations (14). In another study, it was reported that cold propofol caused more pain when injected slowly, but hot propofol caused more pain when injected quickly (15). In another study, cold (+4°C) propofol was compared with propofol heated to 37°C. It was reported that neither cooled propofol nor heated propofol reduced the incidence of injection pain (16).

Although there are many studies investigating the effects of propofol on injection pain by changing its temperature, there are very few studies that suggest changing the temperature of the area where propofol is injected. In one study, the injection site was heated and the effect of propofol on injection pain was investigated. It was found that the incidence of pain was significantly lower in the heated group (17). In another study conducted by reducing the temperature of the injection area with ice gels, no superiority of cold application over lidocaine pre-application was detected (18). In a previous study, Köseoğlu et al. compared local heating of the injection site with local cooling. In this study, which is similar to our study, they found that cold application did not change the pain of propofol injection. However, unlike their study, we found that cold application increased the pain of injection. They did not measure the temperature of the applied propofol in their study and ignored this. They applied it at room temperature. However, we believe that the temperature of the applied propofol is an important factor and therefore we measured the temperature of the propofol vials and ensured that it was fixed at 22°C. Another difference of our study is the surgical operation distribution of the patient group. Only patients who would undergo cholecystectomy were included in the study, thus preventing changes in anxiety levels that could arise from differences in the type of operation from disrupting the homogeneity of the study. In addition, not only propofol but also rocuronium was used in our study and the results of both drugs were recorded (19).

Also, like propofol, the mechanism of injection pain caused by rocuronium is not known. However, some mechanisms have been suggested in this respect, some of which include the activation of C-Nociceptors because of the low pH of the solution (pH = 4), as well as released mediators such as bradykinin and histamine (20).

In a previous study based on similar hypotheses, local heating was applied to prevent rocuronium injection pain, and it was concluded that local heating effectively reduced rocuronium injection pain (21).

In this study, we aimed to alleviate propofol injection pain with local cold application. Cold application causes a delay in some reactions such as kinin release in peripheral endothelial tissue. Thus, we hoped that cold application would reduce the sensation of pain. However, unlike the literature data, the incidence and severity of pain were significantly higher in the local cold application group than in the Control Group. There might be several reasons for this. We associated this with the fact that propofol remains in interaction with the vascular wall for a longer period as a result of cold application, which causes vasoconstriction and slows down the blood flow in the vascular wall. Another reason might be that the mediators that cause injection pain cannot move away from the vein because of vasoconstriction. We think that another reason might be that the vascular wall cannot be cooled at sufficient levels and the release of mediators such as quinine cannot be delayed because the cold pack is applied for only 1 minute.

No studies were found in the literature investigating the effects of cold application on rocuronium injection pain. No superiority of cold application to rocuronium injection pain was detected over the Control Group in the present study and similar results were obtained with the literature.

There are some limitations of the present study. The temperature of the skin and subcutaneous tissues was not be measured. Temperature measurements could have been made separately before propofol administration and before rocuronium administration. The socioeconomic status of the patients was ignored. Propofol and rocuronium injections were made manually; however, their rate could be fixed by the infusion pump.

In conclusion, local cooling of the injection site before propofol administration increases propofol injection pain. For this reason, we believe that local cold application must not be used. We also believe that more studies must be conducted on local cold application to prevent propofol injection pain. Another result of our study is that cooling of the injection site has no significant effect on rocuronium injection pain. There are very few studies on this subject. We believe that more publications are needed investigating the effect of local cold application on rocuronium injection pain.

## AUTHOR CONTRIBUTIONS

**Conception or design of the work:** KK
**Data collection:** KK, DT
**Data analysis and interpretation:** KK, ET
**Drafting the article:** KK
**Critical revision of the article:** KT
The author (KK, ET, DT, KT) reviewed the results and approved the final version of the manuscript.

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