

CLINICAL RESEARCH / KLİNİK ÇALIŞMA

PROPOFOL INJECTION PAIN: A RANDOMISED, CONTROLLED TRIAL COMPARING THE EFFECT OF LOCAL WARMING AND LOCAL COOLING OF INJECTION SITE

PROPOFOL ENJEKSİYON AĞRISI: LOKAL ISITMA VE LOKAL SOĞUTMANIN ETKİSİNİN RANDOMİZE, KONTROLLÜ ÇALIŞMAYLA KARŞILAŞTIRILMASI

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SUMMARY

Objective: Various drugs and techniques have been proposed in order to prevent propofol induced pain. Although warming of propofol and local warming have been reported to be effective in reducing the pain, local cooling has not been studied yet. In this study, we have aimed at studying the effect of local warming and cooling on the pain induced by propofol.

Method: 120 patients of ages between 18-65 undergoing elective surgery were included in this prospective, single-blinded study. Patients were randomized into 3 equal groups. In group I (Control), no intervention was applied, in Group II warming at + 40°C, in Group III cooling at +2- 4°C was applied for 2 minutes prior to propofol administration at the site of venous access. In each patient, propofol was injected over a period of 1 min at a dose of 2,5 mg/kg. Pain scores during propofol injection was recorded using the 5-point Verbal Rating Scale.

Results: Demographic data were comparable between groups. 21 of 40 patients in the local warming group, 9 in the local cooling group (Group III) and 7 in the control group (Group I) had no pain ($p=0,006$), ($p<0,05$). There was a significant difference in the number of patients with severe pain between local warming group and control group. In local warming group none of the patients experienced severe pain whereas in the control group, 6 patients experienced severe pain ($p<0,05$). The frequency of pain (with a pain score of 1, 2, 3 and 4) at propofol injection was lower in Group II (47.5%) compared to Group III (77.5%) and I (82.5%) ($p= 0.006$), ($p= <0,001$). There was no significant difference in pain between Group I and III.

Conclusion: Application of local warming prior to propofol administration has decreased the pain induced by propofol effectively whereas local cooling had no impact.

KEY WORDS: Propofol, Injection, Pain, Local warming, Local Cooling

ÖZET

Amaç: Propofolün enjeksiyon ağrısını önlemek amacıyla çeşitli ilaçlar ve teknikler önerilmiştir. Propofolün ısıtılmasının ya da lokal ısıtmanın, ağrıyı azaltmada etkin olduğu bildirilmiş olmasına rağmen henüz lokal soğutmanın etkisi çalışılmamıştır. Bu çalışmada propofole bağlı oluşan ağrıda lokal ısıtma ve lokal soğutmanın etkisini araştırmayı amaçladık.

Yöntem: Bu prospektif, tek kör çalışmaya, 18-65 yaş arası, elektif cerrahi geçirecek 120 hasta dahil edildi. Hastalar randomize olarak 3 eşit gruba ayrıldı. Grup I (Kontrol)'de; hastalara herhangi bir işlem uygulanmadı. Grup II'de; +40°C'lik ısı, Grup III'de ise +2-4°C'lik soğuk 2 dakika boyunca ilacın uygulanacağı intraketen takılı olduğu ven trasesine ilaç verilmeden önce uygulandı. Her bir hastaya propofol 2,5 mg/kg dozunda ve 1 dk'dan uzun sürede enjekte edildi. Propofol enjeksiyonu esnasındaki ağrı skoru 5 değerli VRS (Verbal Rating Scale) skoru kullanılarak kaydedildi.

Bulgular: Demografik veriler gruplar arasında benzerdi. Lokal ısıtma grubunda (Grup II) 40 hastadan 21'inde hiç ağrı yakınması olmazken, lokal soğutma grubunda (Grup III) 9, kontrol grubunda ise (Grup I) 7 hastanın ağrı yakınması olmadı ($p=0,006$), ($p<0,05$). Ciddi ağrı yakınması olan hasta sayısında da lokal ısıtma grubu ile kontrol grubu arasında anlamlı farklılık saptandı. Lokal ısıtma grubunda hiçbir hasta ciddi ağrı tariflemeyenken, kontrol grubunda 6 hastanın ciddi ağrı yakınması oldu ($p<0,05$). Propofol enjeksiyon ağrısının sıklığı (ağrı skoru 1, 2, 3, 4 olan hastalar); Grup II'de (%47,5), Grup III (%77,5) ve Grup I (%82,5)'le karşılaştırıldığında düşük bulundu ($p= 0.006$), ($p= <0,001$). Ağrı sıklığı açısından Grup I ve III arasında anlamlı farklılık bulunmadı.

Sonuç: Propofol enjeksiyonu öncesi lokal ısıtma uygulaması propofole bağlı ağrıyı etkin bir şekilde azaltırken lokal soğutmanın hiçbir etkisi olmamıştır.

ANAHTAR KELİMELELER: Propofol; Enjeksiyon; Ağrı; Lokal ısıtma; Lokal Soğutma

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INTRODUCTION

Even though propofol is frequently preferred in the induction and maintenance of anesthesia; pain during its injection is one of the most common side effects with an incidence of up to 70% (1).

The cause of the propofol related injection pain is not fully understood but the most probable mechanism is offering that, as a response to the irritant effect of aqueous phase propofol on the vessel endothelium, kinins are secreted and activation of kinin-kallikrein system causes the release of bradykinin. As a result of the impact of bradykinin on venous dilation and increased permeability, propofol contacts much more with free nerve endings, which may explain cause of the pain (2-4). In literature, many pharmacological and non-pharmacological methods have been applied to decrease the propofol related injection pain. These methods include alteration of propofol formulation (5), delivery rate (6), administration of various medications (7-13), use of different veins (3, 14, 15), dilution of the drug (16) and alterations made in the temperature of propofol (17-19).

The studies investigating the effect of injected temperature on propofol injection pain show that both cooling (4°C) and warming (37°C) of propofol are effective in reducing propofol injection pain (17, 18, 20). Mc Crirrick and Hunter (17) observed a significant reduction in pain, by cooling of propofol to 4 °C in their studies and they explained this effect with the lowered speed of kinin cascade as a response to cooling procedure. On the other hand, Fletcher et al. (20), who obtained similar result by heating propofol to 37 °C, suggested two different mechanisms. The first mechanism was the change in the release of mediators from the vessel wall and the second was the alternation of propofol concentration in aqueous phase as a result of heat. In the light of the mechanisms explained above, it has been hypothesized by these authors that externally cooling or warming of propofol injection site may cause temperature change in subcutaneous tissue and thus decrease the propofol injection pain.

To the best of our knowledge, local warming has been reported to be effective but local cooling has not been investigated on pain induced by propofol. Therefore we designed this study to investigate the effect of local cooling and local warming on propofol related injection pain by comparing them with no intervention group.

MATERIALS AND METHODS

Ethical approval for this study (Ethical Committee No: 0430) was provided by the Local Ethical Committee of Ankara Training and Research Hospital, Ministry of

Health, Ankara, Turkey (Chairperson Prof. Güler) on 24 August 2011. This prospective study was conducted in a single-blind, randomized fashion.

After obtaining patients' informed written consent, 120 patients were studied between age groups of 18 and 65 years old, of ASA groups I and III, and who were scheduled for elective surgery under general anesthesia. The exclusion criteria were having cardiac conduction failure, having lipid metabolism disorder, receiving antiarrhythmic or analgesic drugs, having liver or kidney failure, being allergic to propofol and having difficulty for intravenous (iv) cannulation.

Without any premedication, the patients were given 5 ml/kg/hour crystalloid solution, through a 20 G iv cannula which was attached on the dorsum of the hand. Patients in the operation room were monitored for standard electrocardiography (ECG), blood pressure non invasively and peripheral oxygen saturation (Drager; Infinity delta MS13466E539D,USA). The patients were allocated to one of the following 3 groups by simple randomisation by using a randomisation table created by computer software (i.e. computerised sequence generation).

1. No intervention group (Group I), (n=40) : Patients in this group were accepted as control group and were not subjected to any procedure.

2. Local warming group , (Group II), (n=40): Before anesthesia induction patients were subjected to 40 °C hot application for 2 minutes with a Bair Hugger® warming device blowing hot air, through the vein trace with the cannula attached to it.

3. Local cooling group (Group III), (n=40) : Before anesthesia induction patients were subjected to +2-4 °C cooling application through the vein trace for 2 minutes with cold water bags kept in refrigerator.

Propofol prepared at room temperature (10 mg/ml ampoule, Fresenius) was administered as a bolus dose of 2,5 mg/kg to all groups within one minute. On the 15th second from the start of injection, the patients were asked whether they suffered any pain. The verbal responses to the question and behavioral reactions of the patient were recorded according to the 5-point scale by an anaesthesiologist who was blinded to group allocation (Table I). After propofol injection, opioid and muscle relaxant (only to the patients who would be intubated) were given. Then the operation progressed with an intubation or a laryngeal mask.

Statistical Analysis

The primary aim of this study was to compare the incidence of differences in no pain or mild pain feeling among groups. A total sample size of 114 cases (38 per

Table I. Pain Scoring

Pain Score	Pain Severity	Patient response
0	None	No pain or discomfort reported when questioned
1	Mild	Pain or discomfort reported by the patient to be mild when questioned
2	Moderate	Pain or discomfort reported by the patient to be moderate when questioned
3	Severe	Pain or discomfort reported spontaneously by the patient stated to be severe
4	Very severe	Pain or discomfort associated with a strong vocal response, hand or arm withdrawal, facial grimacing or crying, and reported to be very severe

group) was required to detect at least a 35% incidence difference between any of the two groups with a power of 85% at the 5% significance level. The difference of 35% was taken from both pilot study and clinical experience. Sample size estimation was performed by NCSS and PASS 2000 software.

Data analysis was performed by using Statistical Package for Social Sciences (SPSS) version 11.5 software (SPSS Inc., Chicago, IL, United States). Shapiro-Wilk test was used to test the normality of distribution for continuous variables. While, the data was expressed as mean \pm standard deviation, number of cases and percentages were used for the other statistical details.

The mean differences among groups were compared by One-Way ANOVA. Categorical data was analyzed by Pearson Chi-square or Fisher's exact test, where applicable. Repeated Measures of ANOVA was applied for evaluation of pulse rate, systolic, diastolic and mean blood pressures.

A p value less than 0.05 was considered statistically significant, and, the Bonferroni Correction was applied for all possible multiple comparisons controlling Type I error.

RESULTS

Among the 127 subjects screened, 4 were excluded from the study due to difficult venous cannulation and 3 were excluded due to analgesic medication prior to surgery. A total of 120 patients completed the study. The study was performed between September 1-December 5, 2011.

Table II. Demographic Data of the Patients (number, mean \pm SD)

Variable	Group I (n=40)	Group II (n=40)	Group III (n=40)	P value
Age (years)	46,1 \pm 13,0	40,0 \pm 13,7	41,2 \pm 13,4	0,098
Sex (M/F)	16/24	20/20	19/21	0,646
Weight (kg)	74,7 \pm 14,2	71,9 \pm 13,5	70,3 \pm 13,6	0,368

Table III. Frequency of no pain and pain among groups [Number of patients with no pain a pain score of 1, 2, 3, 4 (frequency %)].

Group	Group I (n=40)	Group II (n=40)	Group III (n=40)	P value
No Pain During Injection	7 (%17,5) †	21 (%52,5) *,†	9 (%22,5) *	<0,001
Pain During Injection	33 (%82,5)†	19 (47,5%)*,†	31 (77,5%)*	<0,001

†P = <0,001; Group I vs Group II, *P = 0.006; Group II vs Group III,

There was no statistically significant difference between groups for age, weight or gender distribution ($p>0,05$) (Table II).

The number of patients who reported no pain and any degree of pain (pain score of 1, 2, 3 and 4) during propofol injection is summarized in Table III. In local warming group (Group II) 21 of 40 patients had no pain. 9 patients in the local cooling group (Group III) and 7 patients in the no intervention group (Group I) had no pain ($p=0,006$), ($p<0,05$) as well. The frequency of pain at propofol injection was lower in Group II (47.5%) compared to Group III (77.5%) and I (82.5%) ($p= 0.006$), ($p= <0,001$). The frequency of pain did not differ statistically between Group I and III. In Figure 1, the degree of pain intensity which was experienced among three groups is shown. Although the number of patients

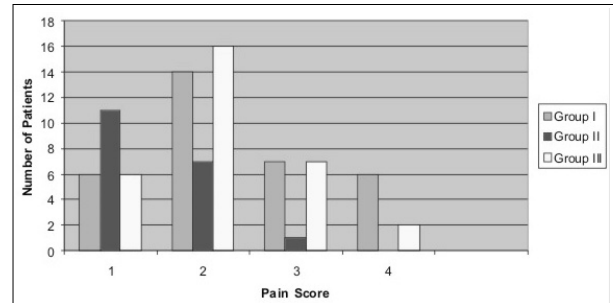


Figure 1. Distribution of pain score of 1, 2, 3 and 4 in the three groups.

†P = <0,05; Group I vs Group II

*P = 0.006; Group II vs Group III,

with a pain score of "1" was higher in Group II compared to Group I and III, in Group II none of the patients experienced severe pain (pain score of 4) whereas in the no intervention group 6 patients experienced severe pain ($p < 0.05$).

DISCUSSION

Local warming of the venous access site before propofol injection was effective in decreasing the frequency and intensity of pain during propofol injection. On the contrary, we failed to show any alleviation in propofol injection pain with local cooling when compared to local warming and no intervention group. In this study, the frequency of pain during propofol injection in the no-intervention group was 82.5% followed as 47.5% in the local warming group and 77.5% in the local cooling group.

The pain and discomfort seen during propofol injection is still reported in literature in 28-90% frequency (1, 2) and it is still an important problem causing patient discomfort. The cause of propofol injection pain is not fully explained but the most accentuated mechanism is the activation of kinin-kallikrein system and release of bradykinin from the vessel wall (2, 4, 21, 22). Many pharmacological and non-pharmacological methods were used for prevention or reduction of pain related with propofol injection. Even though lots of drugs were investigated for this purpose, the most commonly used pharmacological method is adding lidocaine to propofol or iv lidocaine injection just before propofol injection (23). On the other hand, non-pharmacological methods are, injection of propofol to a larger vein, rapid injection of propofol, administration of cold saline before propofol injection, administration of propofol after cooling or warming, administration of propofol after dilution, administration of different propofol formulations or some combined methods (23).

Administration of propofol in different temperatures for prevention of propofol related pain is one of the non-pharmacological methods suggested by various researchers until today. Mc Crirrick and Hunter (17) investigated the effect of propofol in room and cold temperature. They reported 46% pain incidence in room temperature and 23% pain incidence with cold temperature for propofol. Similarly Barker et al. (18) reported that administration of cold (4 °C) NaCl before propofol injection for the purpose of decreasing propofol injection pain almost revealed the same effect with cold (4 °C) propofol and propofol combined with 0.05% lidocaine. In another study covering children age group, Pickford et al. (24) reported a lower pain incidence with cold propofol

when compared to propofol in room temperature (29% vs 14%), which was not statistically significant. These studies, which show the effect of cold on decreasing propofol injection pain, the probable mechanism is suggested to be the delay of biochemical reactions like kinin release from the vessel wall with the effect of low temperature.

On the contrary, some studies do not support the beneficial effects of cold propofol. Parmar and Koray (25), concluded that cold propofol causes pain in higher incidence and intensity when compared to propofol at room temperature and propofol added lidocaine in different concentrations. Also, Shimizu et al. (26) reported that, cold propofol causes more pain when injected slowly and warm propofol causes more pain when injected rapidly. In their study Oztürk et al. (27) administered propofol coldly (4 °C), in room temperature and warmed to 37 °C). They showed that neither cold nor warmed propofol caused any decrease in injection pain. In another study investigating the effect of warming of propofol on injection pain, Fletcher et al. (20) reported a significant decrease in pain incidence from 59% to 22% with warmed propofol to 37 °C, differently from the results of the study of Oztürk et al. (27).

Although there are lots of studies investigating the effect of injected temperature on propofol injection pain in literature, there is only one study conducted by changing the temperature of the injection region. In this study Park et al. (28) investigated the effect of warming of injection area and forearm locally before propofol injection. They reported statistically significant decrease in pain incidence in warm applied group, compared to control group (36.7% vs 66.7%).

In another study based on the same hypothesis, Mahajan et al. (29), investigated the effect of local warming on rocuronium (a neuromuscular blocker) injection pain. They concluded that application of heat over the vascular trace prior to rocuronium administration effectively reduced injection-related pain. They also explained analgesic action of heat by the gate-control theory of pain.

The incidence of pain in this study (69.1%) is compatible with that of other studies (17, 30, 31). Also, in our study, the number of patients with no pain in the local warm group was significantly more than the local cold and control groups (52.5% vs 22.5% and 17.5% respectively) and this finding was in accordance with the results of Park et al.'s study (28). In this study, the authors suggest that by local warming of the injection site, vasodilatation and increased blood flow of the area, which is the physiological response to heat application (32), was achieved and it helped to clean out the suspected

metabolites from vessel wall causing pain which was induced by propofol injection

There is no study in literature investigating the local cooling effect on propofol injection pain. In this study we intended to alleviate propofol injection pain by local cold application in the study group, depending on the fact that local cold application is known to increase the pain threshold and to decrease pain signal conduction speed. Nevertheless, in the local cold application group, the pain incidence and severity were similar to control group (77% vs 82%). This finding in our study suggests that, local cold application is not as effective as cooling of propofol in decreasing propofol injection pain. There may be several reasons for that such as, slow injection of propofol in 60 seconds, or failure to provide sufficient decrease in the temperature of deep tissues, especially vessel wall for the delay of biochemical reactions like kinin release. Another reason may be that, due to the vasoconstriction of the vessel wall and decreased blood flow, which is a physiological response to cold therapy (32), there may have been an interruption of elimination of the chemical mediators from the vessel wall causing propofol injection pain.

We must state that there are some limitations in this study. In order to observe the physiological response to heat therapy that are stated above, a 3-4 °C increase in surface temperature is required. Also for cold application it is reported that it decreases the temperature of the skin and underlying tissues to a depth of 2 to 4 cm (32). However skin temperature at the venous access site was not measured in this study.

In conclusion, local warming of the injection site prior to propofol administration was found to be effective in reducing propofol injection pain compared to no-intervention group, whereas local cooling had no effect. Local warming can be used as an alternative to non-pharmacological method in reducing propofol injection pain especially when there is contraindication of use of other pharmacological agents. The authors also believe that further studies are needed in order to clarify the effect of local cooling on this subject.

REFERENCES

1. Picard P, Tramér MR: Prevention of pain on injection with propofol: A quantitative systemic review. *Anesth Analg* 2000; 90: 963-969.
2. Tan CH, Onsiong MK: Pain on injection of propofol. *Anaesthesia* 1998; 53: 468-476.
3. Briggs LP, Clarke RSJ, Dundee JW, Moore J, Bahar M, Wright PJ: Use of di-isopropyl phenol as main agent for short procedures. *Br J Anaesth* 1981; 53: 1197-1201.
4. Scott RP, Saunders DA., Norman J: Propofol: clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; 43: 492-494.
5. Yamakage M, Iwasaki S, Satoh JI, Namiki A: Changes in concentrations of free propofol by modification of the solution. *Anesth Analg* 2005; 101: 385-388.
6. Grauers A, Liljeroth E, Åkeson J: Propofol infusion rate does not affect local pain on injection. *Acta Anaesthesiol Scand* 2002; 46: 361-363.
7. Iyılkcı L, Balkan BK, Gökel E et al: The effect of alfentanil or remifentanil pretreatment on propofol injection pain. *J Clin Anesth* 2004; 16: 499-502.
8. Barbi E, Marchetti F, Gerarduzzi T, Neri E, Gagliardo A, Sarti A, Ventura A et al: Pretreatment with intravenous ketamine reduces propofol injection pain. *Paediatr Anaesth* 2003; 13: 764-768.
9. Fujii Y, Nakayama MA: Lidocaine/metoclopramide combination decreases pain on injection of propofol. *Can J Anesth* 2005; 52: 474-476.
10. Iwama H, Nakane M, Ohmori S, Kaneko T, Kato M, Watanabe K, Okuaki A: Nafamostat mesilate, a kallikrein inhibitor, prevents pain on injection with propofol. *Br J Anaesth* 1998; 81: 963-964.
11. Dubey PK, Prasad SS: Pain on Injection of Propofol: The Effect of Granisetron Pretreatment. *Clin J Pain* 2003; 19: 121-124.
12. Agarwal A, Dhiraj S, Raza M, Pandey R, Pandey CK, Singh PK, Singh U, Gupta D: Vein pretreatment with magnesium sulfate to prevent pain on injection of propofol is not justified. *Can J Anesth* 2004; 51: 130-133.
13. Cheong MA, Kim KS, Choi WJ: Ephedrine reduces the pain from propofol injection. *Anaesth Analg* 2002; 95: 1293-1296.
14. Briggs LP, White M: The effects of premedication on anaesthesia with propofol ('Diprivan'). *Postgrad Med J* 1985; 61: 35-37.
15. Tariq MA, Kamran M: Incidence of pain on propofol injection and efficacy of addition of lignocaine or selecting big vein or both combined in reducing it: a randomized control trial. *J PostgradMed Inst* 2006; 20: 8-11.
16. Stokes D, Robson N, Hutton P: Effect of diluting propofol on the incidence of pain on injection and venous sequelae. *Br J Anaesth* 1989; 62: 202-203.
17. McCrirrick A, Hunter S: Pain on injection of propofol: the effect of injectate temperature. *Anaesthesia* 1990; 45: 443-444.
18. Barker P, Langton JA, Murphy P, Rowbotham DJ: Effect of prior administration of cold saline on pain during propofol injection: a comparison with cold propofol and propofol with lignocaine. *Anaesthesia* 1991; 46: 1069-1070.
19. Lee SK, Lee SJ, Kil HY, Yoon YJ: Pain on injection of propofol: The effect of injectate temperature. *Korean J Anesthesiol* 1996; 30: 456-460.

20. Fletcher GC, Gillespie JA, Davidson JA: The effect of temperature upon pain during injection of propofol. *Anaesthesia* 1996; 51: 498-499.
21. Klement W, Arndt J: Pain on injection of propofol: effects of concentration and diluent. *Br J Anaesth* 1991; 67: 281-284.
22. Doenicke A, Roizen M, Rau J, Kellermann W, Babl J: Reducing pain during propofol injection: the role of the solvent. *Anesth Analg* 1996; 82: 472-474.
23. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, Pace NL, Apfel CC: Prevention of pain on injection of propofol: systematic review and meta-analysis. *BMJ* 2011; 342: d1110
24. Pickford A, Burden J, Lewis I: Propofol and pain on induction: the effect of injectate temperature in children. *Paediatr Anaesth*. 2000; 10: 129-132
25. Parmar A.K, Koay C.K: Pain on injection of propofol. A comparison of cold propofol with propofol premixed with lignocaine. *anaesthesia*. *Anaesthesia* 1998; 53: 79-88.
26. Shimizu T, Inomata S, Kihara S, Toyooka H, Brimacombe JR: Rapid injection reduces pain on injection with propofol. *Eur J Anaesthesiol* 2005; 22: 394-396.
27. Ozturk E, Izdes S, Babacan A, Kaya K: Temperature of propofol does not reduce the incidence of injection pain. *Anesthesiology* 1998; 89: 1041.
28. Park SE, Kang K, Park SH, Cho YW, Kim CH: Effect of Local Warming of the Injection Site and Forearm on Propofol-Induced Pain. *Korean J Anesthesiol* 2002; 43: 687-692.
29. Mahajan C, Rath GP, Bithal PK, Prabhakar H, Yadav R, Dube SK: Local warming at injection site helps alleviate pain after rocuronium administration. *J Anesth* 2010; 24: 845-848.
30. Uda R, Kadono N, Otsuka M, Sachiko S, Hidemaro MI: Strict temperature control has no effect on injection pain with propofol [letter]. *Anesthesiology* 1999; 91: 591
31. Kaya K, Ozkocak I, Akcabay M, Babacan A, Izdes S, Ocal E, et al: Effect of lidocaine addition to cold propofol and the propofol at room temperature on the propofol injection pain. *Br J Anaesth* 1995; 74: 140.
32. Nadler SF, Weingand K, Kruse RJ. The physiologic basis and clinical applications of cryotherapy and thermotherapy for the pain practitioner. *Pain Physician* 2004; 7: 395-399.