Turk J Anaesth Reanim 2013; 41: 34-7 DOI: 10.5152/TJAR.2013.09

Original Article / Özgün Araştırma

Influence of Temperature and pH Changes on Propofol Injection Pain

Propofol'ün Sıcaklık ve pH Değişiminin Enjeksiyon Ağrısı Üzerine Etkisi

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Abstract / Özet

Objective: Propofol has been widely used for anaesthesiology, although about 60%-70% of patients experience pain on injection. The aim of our study was to compare two storage patterns of propofol, namely room temperature versus refrigeration, in terms of their effect on incidence and severity of pain caused by its injection.

Methods: Two hundred patients referred to gastrointestinal or urologic surgery with general anaesthesiology were included in a prospective randomized, double-blind study. After routine monitoring, 5 mL of propofol at room temperature and 5 mL of propofol kept in the fridge was administered within 10 seconds to patients in Group 1 and Group 2, respectively. An investigator assessed pain intensity. Propofol temperature-pH were measured by another researcher.

Results: The overall incidence of pain on injection of propofol was 73.7% in Group 1, and 83.2% in Group 2. There was no significant difference between groups regarding the incidence of pain. There was a significant difference between groups in terms of pain severity based on a 6-point verbal rating scale. While the median VRS value for Group 1 was 2, it was 3 in Group 2.

Conclusion: Cold application has a local anesthetic effect of its own. In the present study it was observed that cold application of propofol caused pain more frequently, although it was statistically not significant; moreover, it was found that it statistically significantly increased the severity of pain. These findings indicate that propofol should be kept at room temperature instead of in the refrigerator in order to reduce injection pain.

Key Words: Propofol, injection, pain, pH

Amaç: Propofol, %60-70 oranında enjeksiyon ağrısına neden olmasına rağmen anestezide yaygın kullanılır. Bu çalışmada buzdolabında ve ameliyathane odasında saklanan propofol ampullerinin enjeksiyon ağrısı şiddeti ve sıklığı üzerine etkisini saptamayı amaçladık.

Yöntemler: Genel anestezi altında gastrointestinal ve ürolojik cerrahi geçirecek 200 hasta bu prospektif,randomize, çift kör çalışmaya dahil edildi. Rutin monitörizasyonun ardından oda ısısındaki 5 mL propofol (Grup 1) ve buzdolabındaki 5 mL propofol (Grup 2) 10 sn içinde enjekte edildi. Bir araştırmacı ağrıyı diğer bir araştırmacı ise propofolün sıcaklık ve pH'sını değerlendirdi.

Bulgular: Propofol enjeksiyon ağrısının genel insidansı Grup 1'de %73,7, Grup 2'de %83,2 idi ve istatistiksel olarak anlamlı bulunmadı.Verbal Rating Skala kullanılarak değerlendirilen ağrı şiddeti açısından ise gruplar arasında anlamlı fark saptandı. Ortalama VRS değeri Grup 1'de 2, Grup 2'de 3 bulundu.

Sonuç: Soğuk uygulama lokal anestetik etkiye sahiptir. Sunulan çalışmada istatistiksel olarak anlamlı olmasa da soğuk propofol'ün daha fazla hastada ağrıya neden olduğu; istatistiksel olarak anlamlı şekilde ise daha şiddetli ağrıya neden olduğu bulundu. Bu bulgular ışığında propofol'ün buzdolabı yerine oda ısısında saklanmasının enjeksiyon ağrısını azaltacağını düşünmekteyiz.

Anahtar Kelimeler: Propofol, enjeksiyon, ağrı, pH

Introduction

Being an intravenous short-acting anaesthetic agent, propofol has been widely used for sedation and anaesthesiology. It not only produces smooth and rapid induction and recovery, but has an antiemetic effect as well, making propofol preferable for day care anaesthesiology. However, despite these positive effects, about 60%-70% of patients experience pain on injection of propofol (1). To prevent propofol injection pain, several studies have been performed using pharmacologic and non-pharmacologic methods, such as selecting an antecubital vein or a hand vein, slower or faster injection rates, using different temperatures of propofol (2). Manufacturer notes that pH value of propofol is 6-8.5 and it can effectively be used between 4-37°C. The aim of this study was to compare the effect of storing propofol at room temperature or refrigerator on severity of injection pain.

Methods

After local Ethical Committee approval and informed consent obtained, 200 American Society of Anaesthesiologists physical status I-II patients scheduled for gastrointestinal or urological surgeries under general anaesthesiology were included in a prospective randomized,

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Geliş Tarihi / Received : 01.06.2012
Kabul Tarihi / Accepted : 01.10.2012

double blind study. All patients were educated on the 6-point verbal rating scale. Patients receiving analgesics or sedative drugs 24 hours prior to surgery and pre-anaesthetic medication, and patients with neurologic deficits, allergy to propofol, cardiovascular instability, lipid metabolism disorder, hepatic or renal problems, and psychiatric disorders were not included in the study. On arrival to the operating room, which is consistently kept at 22-24°C via central air-conditioning, a 20-gauge intravenous cannula was inserted into the largest dorsal vein of the patient's non-dominant hand. Isotonic NaCl solution at room temperature was connected to the cannula, but infusion was not initiated before propofol injection. After monitoring, baseline hemodynamic measurements (systolic and diastolic blood pressures, heart rate, saturation of oxygen with use of pulse oximetry) of patients were recorded. Five millilitre of 1% propofol at room temperature, and 5 mL of 1% propofol kept in the fridge (for at least 24 hours) were administered within 10 seconds to patients in Group 1 and Group 2, respectively. No other adjuvant drug was administered during this time. An independent anaesthesiologist and an investigator who did not know the type of the solutions prepared the injections. After injection of propofol, an investigator who was blinded to the group assignment asked the patient about pain at the injection site and assessed pain intensity using a 6-point verbal rating scale (VRS), with 1=no pain (negative response to questioning); 2=very mild pain (very mild pain reported only in response to questioning without any behavioural signs); 3=mild pain (mild pain reported only in response to questioning without any behavioural signs), 4=moderate pain (accompanied by a behavioural sign or a sign reported spontaneously without questioning); and 5=severe pain (vocal response or response accompanied by mild facial grimacing, arm withdrawal, or tears), and 6=very severe pain (strong vocal response or serious response accompanied by facial grimacing, arm withdrawal, or tears) (3). At the same time, remaining 15 mL of propofol were taken into a measuring cup, and temperature and pH values of propofol were measured via a AD12 waterproof pH tester (ADWA Instruments, Szeged, Hungary) by another researcher. Thereafter, anaesthesiology induction was completed with propofol (2 mg kg^{-1}). After the loss of consciousness, rocuronium bromide (0.6 mg/kg) was administered for muscle relaxation and to facilitate tracheal intubation. Two minutes after rocuronium bromide injection, the trachea was intubated and anaesthesiology was maintained with desflurane (4.0% to 8.0% inspired concentration) and nitrous oxide (50% in oxygen) with controlled ventilation. Baseline demographics, hemodynamic parameters (baseline, after 5 mL of injection, and after the induction dose of propofol injection), temperature and pH of propofol, and VRS scores were recorded. Patients were monitored for 12 hours postoperatively for adverse events (pain, oedema and inflammation) at the injection site.

Statistical analysis

Statistical analysis was performed using SPSS 11.5. Frequency (percentage) for categorical variables and mean±standard deviation [median (minimum-maximum)] for metric variables were used as descriptive statistics. For the comparison of two independent groups, Student's t test or Mann-Whitney U test was used. Chi-square test was performed to compare two independent groups in terms of categorical variables. Repeated measures analysis of variance (ANOVA) was used to compare more than two dependent groups in terms of metric variables. A p value <0.05 was considered as statistically significant.

Results

A total of 200 patients completed the study. The first group comprised 99 patients and the second group 101 patients. Two patients of the first group were excluded from the study because of unsuccessful response. Intravenous cannulation was successful at the first attempt in 99% of both groups. The age, weight, and sex were similar in both groups (Table 1). In Group 1 (propofol at room temperature), mean propofol temperature was 23.18±0.88°C and mean pH value was 7.29±0.05. In Group 2 (propofol from the fridge), mean propofol temperature was 17.55°C±1.47 and pH value was 7.45±0.03 (Table 2).

There was no difference between groups in terms of haemodynamic values. No difference was observed between groups in terms of SAP, DAP, HR, and SpO_2 values measured before and after drug administration; a decrease was observed in SAP and DAP; first an increase then a decrease in HR was observed, and an increase in SpO_2 was observed. These findings are in line with clinical expectations (Table 3).

The overall incidence of pain on injection of propofol was 73.7% (26/73) in Group 1, and 83.2% (17/84) in Group 2. There was no difference regarding the incidence of pain between the groups (p=0.10). There was a significant difference between groups in terms of pain severity based on the 6-point verbal rating scale (p=0.04). While the median VRS value for Group 1 was 2 (min 1-max 6), it was 3 (min 1-max 6) in Group 2 (Table 4).

Discussion

Our results showed that, although it was not statistically significant, the incidence of pain on injection of cold propofol was higher compared to room temperature propofol. However, the severity of pain measured by VRS was significantly higher in Group 2 compared to Group 1. Effects of pain on haemodynamics were not found remarkable.

Propofol vials used in most studies in the literature have been assumed and thereby reported to be at fridge temperature (2-8°C) even though in none of them their temperature and pH levels were measured (2). In the present study, the temperature and pH level of each vial were recorded and it was found that the mean temperature of propofol vials kept in the fridge for 24 h was 17.55°C and the pH value approached to alkaline as it gets colder.

Table 1. Demographic data of the patients in this study

	Grup 1 (n=99)	Grup 2 (n=101)	p
Age (yr)	54.2 (15.8)	52.3 (13.8)	0.359
Sex (M/F)	57/42	53/48	0.469
Weight (kg)	77.7 (12.9)	76.1 (16.9)	0.455

Values are shown as mean (SD) or number of patients. Group 1: Propofol at room temperature, Group 2: Propofol kept in fridge

Table 2. Temperature and pH values of propofol

	Grup 1 (n=99)	Grup 2 (n=101)
Temperature (°C)	23.19±0.89 [23.60 (21.40-24.70)]	17.56±1.47 [18.10 (13.30-19.60)]
pH Values	7.30±0.06 [7.29 (7.19-7.38)]	7.46±0.04 [7.46 (7.40-7.59)]

Values are shown as mean±SD [median (minimum-maximum). Group 1: Propofol at room temperature, Group 2: Propofol kept in fridge

Table 3. Hemodynamic data of the patients in this study

Basal	**SAP (mmHg)**	**DAP (mmHg)**	**KH (beat/min)**	**SpO_2**
Group 1	149.9±24.26	83.03±13.39	77.76±13.51	96.55±2.07
Group 2	151.02±26.20	85.14±13.10	82.35±14.86	96.62±1.84
After 5 mL propofol injection	**SAP (mmHg)**	**DAP (mmHg)**	**KH (beat/min)**	**SpO_2**
Group 1	138.27±21.94	79.53±13.99	79.39±14.72	98.06±1.50
Group 2	138.36±26.33	78.46±13.85	82.75±14.95	97.63±1.99
After induction	**SAP (mmHg)**	**DAP (mmHg)**	**KH (beat/min)**	**SpO_2**
Group 1	120.52±24.40	71.07±17.82	78.37±14.46	98.59±3.31
Group 2	115.97±22.89	69.13±15.89	81.07±14.39	99.22±1.95

Values are shown as mean±SD. Group 1: Propofol at room temperature, Group 2: Propofol kept in fridge

Table 4. Incidence and intensity of propofol injection pain

	Grup 1 (n=99)	**Grup 2 (n=101)**	**p**
Incidence of pain*	73 (73.7)	84 (83.2)	0.105
Pain score**	2.80±1.58 [2 (1-6)]	3.24±1.54 [3 (1-6)]	0.037
Pain intensity score*			
1 (No pain)	26 (26.3)	18 (17.8)	
2 (Very mild pain)	24 (24.2)	21(20.8)	
3 (Mild pain)	18 (18.2)	13 (12.9)	
4 (Moderate pain)	14 (14.1)	19 (18.8)	
5 (Severe pain)	9 (9.1)	28 (27.7)	
6 (Very severe pain)	8 (8.1)	2 (2.0)	

*Values are shown as the number of patients (%)
**Values are shown as mean±SD [median (minimum-maximum)
Group 1: Propofol at room temperature, Group 2: Propofol kept in fridge

Several factors, such as location of injection, vein diameter, injection speed, aqueous propofol concentration, buffering effect of blood, speed of intravenous infusion fluids, temperature of propofol, and the use of local anaesthetics/opioid, may affect the incidence of propofol injection pain (4-7).

In meta-analyses on propofol injection pain, use of antecubital veins instead of dorsal hand veins was reported as the only non-pharmacological method that has a clear positive effect (2). However, intravenous line through the antecubital vein may get occluded due to the flexion of the olecranon. Furthermore, extravasation may easily be detected on the back of the hand. In our practice, back of the hand is the most frequently used area for intravenous access during both operation and sedation. Therefore, in order to increase the quality of our daily practice, we used the back of the hand in the present study. In the literature, lidocaine was reported to be the most effective pharmacological method in preventing injection pain (2). In our daily practice we routinely administer 20-40 mg lidocaine before propofol injection.

While propofol is used at different parts of our hospital, we observed that they are kept in different conditions in each unit, and therefore we aimed to determine the effect of storage conditions of propofol on injection pain. Based on one of our findings, that is propofol kept at room temperature and co-administered with lidocaine may cause less pain, propofol vials kept in fridges were transferred to medicine cabinet at room temperature.

Klement et al. (8) reported that injection pain caused by some anaesthetic agents are because their pH or osmolality are not physiological. Based on this, high viscosity, osmolar concentration and pH of the propofol solution cause pain when superficial hand veins contact with the drug. Our findings showed that application of cold propofol increased the pain. The reason for aggravated pain may be that the viscosity of more alkaline propofol solutions containing high levels of lipid increases as it gets colder and therefore its contact time with vascular endothelium increases.

Propofol injection pain may occur immediately or might be delayed. The immediate pain may be due to the direct irritant effect of propofol; however, the delayed pain may be due to the indirect effect of kinin cascade (9, 10). Because the injection pain in the present study was immediately after injection, we focused on acute local irritant effect as the cause of pain.

Cold application has a local anaesthetic effect of its own; it was even reported that cold saline injection as well as tourniquet application just before propofol administration reduced pain (11). However, changing the temperature of administered propofol still produced conflicting results. Some studies have demonstrated a reduction in pain using cold propofol, and it has been suggested that this mechanism of pain reduction may be due to the stabilization of local pain mediators at lower temperatures (11-13). Conversely, some studies have failed to demonstrate a reduction in pain using cold propofol (12, 14). One other study has demonstrated a lower incidence of pain when propofol was warmed to 37°C compared to room temperature; the authors suggested that warmed injectate might reduce pain either by changes in nociceptor stimulation or changes in propofol partition between the aqueous and lipid phases. However, we found that cold application of propofol has no positive effect for decrease of pain.

Effects of injection speed on propofol pain have been studied before. Some studies included an injection speed of 20 mL in 5 sec and some others included a speed of 10 mL in 30 seconds (5). "Slow" and "fast" injections have not been clearly defined in the literature. In the present study, we administered 5 mL solution in 10 sec for all patients, and observed only the effect of the temperature of the solution.

Conclusion

It was observed in the present study that cold application of propofol caused more frequent pain, although it was not statistically significant; moreover, it was found that it significantly increased the severity of

pain. These findings indicate that propofol should be kept at room temperature instead of refrigerator in order to reduce injection pain.

***Conflict of Interest* / Çıkar Çatışması**
No conflict of interest was declared by the authors.
Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir.

***Author Contributions* / Yazar Katkıları**
Concept / *Fikir* - A.D., A.Dö.; Design / *Tasarım* - A.D., B.A.; Supervision / *Denetleme* - A.D., Ö.E.; Funding / *Kaynaklar* - A.D.; Materials / *Malzemeler* - A.D.; Data Collection and/or Processing / *Veri toplanması ve/veya işlemesi* - A.D., B.A., B.T., P.U., E.İ.; Analysis and/or Interpretation / *Analiz ve/veya yorum* - D.Ö.; Literature Review / *Literatür taraması* - A.D., B.A., B.T.; Writer / *Yazı yazan* - A.D.; Critical Review / *Eleştirel İnceleme* - A.D., ÖE.

References

1. Picard P, Tramér MR. Prevention of pain on injection with propofol: A quantitative systemic review. Anesth Analg 2000; 90: 963-9. [CrossRef]
2. Jalota L, Kalira V, George E, Shi YY, Hornuss C, Radke O, et al. Prevention of pain on injection of propofol: systematic review and meta-analysis. BMJ 2011; 342: 1110. [CrossRef]
3. Brunelli C, Zecca E, Martini C, Campa T, Fagnoni E, Bagnasco M, et al. Comparison of numerical and verbal rating scales to measure pain exacerbations in patients with chronic cancer pain. Health Qual Life Outcomes 2010; 8: 42. [CrossRef]
4. Rushman GB. Intravenous anaesthesiology. Lee's Synopsis of Anaesthesiology. Butterworth Heinemann 1999; 174.
5. Tan CH, Onsiong MK. Pain on injection of propofol. Anaesthesiology 1998; 53: 468-76.
6. Morgan GE Jr. Nonvolatil anesthetics. Clinical Anaesthesiology. Mc Graw Hill Companies 2002; 151.
7. Miller RD. Nonbarbiturate intravenous anesthetics. Anesthesia. Churchill Livingtone 1994; 269.
8. Klement W, Arndt J. Pain on injection of propofol: effects of concentration and diluent. Br J Anaesth 1991; 67: 281-4. [CrossRef]
9. Sim JY, Lee SH, Park DY, Jung JA, Ki KH, Lee DH, et al. Pain on injection with microemulsion propofol. Br J Clin Pharmacol 2009; 67: 316-25. [CrossRef]
10. Scott R, Saunders D, Norman J. Propofol: clinical strategies for preventing pain on injection of propofol. Anaesthesiology 1988; 43: 492-4.
11. 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. Anaesthesiology 1991; 46: 1069-70.
12. Parmar AK, Koay CK. Pain on injection of propofol. A comparison of cold propofol with propofol premixed with lignocaine.anaesthesiology. Anaesthesiology 1998; 53: 79-88.
13. McCrirrick A, Hunter S. Pain on injection of propofol: the effect of injectate temperature. Anaesthesiology 1990; 45: 443-4.
14. Fletcher G, Gillespie J, Davidson J. The effect of temperature upon pain during injection of propofol. Anaesthesiology 1996; 51: 498-9.

TEŞEKKÜR

Spinal Stenoz ameliyatımı başarı ile gerçekleştiren, çok değerli ve sevgili can kardeşim, Ortopedist

Prof. Dr. Azmi HAMZAOĞLU 'na ve ekibine,

Ameliyatım sırasında ve Yoğun Bakımdaki dönemde yakın ilgisini gördüğüm değerli bilim adamı, meslektaşım Anestezi bölüm başkanı, Prof. Dr. Osman BAYINDIR'a ve çalışma arkadaşlarına,

Çok sevgili öğrencim yoğun bakımlar sorumlusu, Anestezi ve yoğun bakım uzmanı Doç. Dr. Simru TUĞRUL'a

Rehabilitasyonumu üstlenen Fizik Tedavi ve Rehabilitasyon uzmanı Prof. Dr. Füsun UYSAL'a

Florance Nightingale Hastanesi'nin sevgi ve şefkat dolu, kat hemşireleri ve personeline hastanede yattığım sürede ve ev bakımı döneminde tıbbi ihtiyaçlarımı sağlayan" DOKTORUM evde Bakım hizmetleri kuruluşunun sahibi

Anestezi Uzmanı Dr. Hakan KARADENİZ'e

Teşhisimin konulmasında yardımcı olan Nörolog Doç. Dr. Ülkü TÜRK'e ve ekibindeki Doktor ve hemşire arkadaşlarıma,

Özel bakımımı üstlenen sevgili Hemşirem Şennur KARADAY'a

Tıbbi standartları ve hizmet kalitesiyle ülkemizin önde gelen Sağlık kuruluşlarından Şişli Florance Nightingale Hastanesi'ni üstün başarı ile yöneten ve ameliyatım sırasında yoğun mesaisine rağmen özel ilgilerini gördüğüm başta Prof. Dr. Cemşit DEMİROĞLU olmak üzere hekimlik mesleğinde kendisinden çok şeyler öğrendiğimiz, günümüz hekimlik mesleğinin önde gelen duayenlerinden, saydığım ve sevdiğim değerli ağabeyim, Prof. Dr. Mücahit ATMANOĞLU'na

ve can dostlarım yakın ilgileri ile beni yaşama bağlayan arkadaşlarım, Beyin Cerrahı Prof. Dr. Cengiz Kuday ve eşi FTR uzmanı Prof. Dr. Tülay KUDAY'a, Ortopedist Prof Dr. Aziz ALTURFAN'a, Psikiyatrist Prof Dr. Engin EKER'e, 68 mezunu sınıf arkadaşlarıma, 2 yıl sonra ani gelişen beyin tümörüm nedeniyle Florance Nightingale Şişli Hastanesi'nde ileri tıp teknolojisinin katkıları ile Beyin tümörü teşhisimi koyarak, ameliyatımı başarı ile gerçekleştiren Üstün ve donanımlı insan, değerli bilim insanı, Beyin cerrahı Prof. Dr. Talat KIRIŞ ve değerli ekibine, tedavilerimi ciddiyetle yürüten değerli insan, Onkolog Prof. Dr. Ufuk ABACIOĞLU'na, Radyolojik tetkiklerimi yaparak teşhis ve tedavimi takip eden EMAR çalışanları ve sahibi can Ağabeyim Rad. Dr. Alptekin PEKER'e

Rehabilitasyonum için yatarak tedavimi yapan İzmit Romatem FTR Hastanesi Hekim ve çalışanlarına, yönetim kurulu üyelerine ve sahibi, Sn. Dr. Köksal HOLOĞLU'na

Romatem'in Koordinatörü sevgili arkadaşım FTR Uzmanı Dr. Erdal ATALAY'a ve

Ülkenin dört bir yanından bizzat gelerek, telefon ile arayarak ve mesaj göndererek geçmiş olsun dileklerini ileten can dostlarım ve arkadaşlarıma, hocaları olarak yakın ilgilerini gördüğüm İstanbul Tıp Fakültesi Anesteziyoloji ve Reanimasyon AD öğretim üyelerine ve Bilim Üniversitesi mesai arkadaşlarım ve Anestezi , Yoğun Bakım AD öğretim üyelerine ve asistanlarıma, tüm üniversitelerin Anestezi ve Yoğun Bakım bölümlerindeki değerli bilim insanları yakın dostlarıma, Meslektaşlarıma, her an yanı başımda gördüğüm canım aileme ve akrabalarıma YÜREKTEN TEŞEKKÜR EDERİM.

Prof. Dr. Kutay AKPİR