Effect of Saline Dilution on Propofol Injection Pain: Comparison with Lidocaine

Propofolün İzotonik Sodyum Klorür ile Dilüsyonun Propofole Bağlı Enjeksiyon Ağrısına Etkisi: Lidokain ile Karşılaştırılması

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ABSTRACT Objective: Recent attempts aim to decrease propofol-induced pain either with pharmacologic or nonpharmacologic methods. The aim of this study was to find out whether saline dilution had a favorable effect on propofol injection pain and to compare the effect of saline dilution with that of lidocaine. **Material and Methods:** 200 patients were randomized into four groups. In group 1, only propofol solution with a concentration of 10 mg/mL was used; in group 2, the solution comprised 10 mg/mL propofol and 2 mg/mL lidocaine; in group 3, only propofol solution 5 mg/mL and in group 4, propofol solution 2.5 mg/mL were used. Pain during induction with propofol was scored using a 4-point verbal rating scale. **Results:** Verbal rating scale scores (VRSs) of the groups were significantly different ($p< 0.001$). When groups were compared in pairs, group 2 had better analgesia than groups 1, 3 and 4 for all VRS values (all p values < 0.001); group 3 and group 4 were similar (all p values > 0.05) and each had better analgesia than group 1 (all p values < 0.001). **Conclusions:** We suggest that saline dilution can be used to alleviate propofol-induced pain. Although lidocaine seems to be more effective, accompanying factors that would make the use of pharmacological adjuncts contraindicated may outweigh. Therefore, in such cases, saline can be used safely.

Key Words: Propofol; pain; lidocaine

ÖZET Amaç: Propofole bağlı enjeksiyon ağrısını azaltmaya yönelik son çalışmalar farmakolojik veya farmakolojik olmayan yöntemlerle yapılmaktadır. Bu çalışmanın amacı, izotonik sodyum klorür ile propofol dilüsyonunun, propofole bağlı olarak oluşan enjeksiyon ağrısı üzerindeki etkisini araştırmak ve bunu lidokain ile karşılaştırmaktır. **Gereç ve Yöntemler:** 200 hasta randomize çift-kör yöntemle dört gruba ayrıldı. Birinci grupta, standart olarak kullanılan 10 mg/mL konsantrasyonda propofol çözeltisi kullanıldı; ikinci grupta, 10 mg/mL konsantrasyonda propofol ve 2 mg/mL lidokain içeren çözelti karışımı kullanıldı; üçüncü grupta, 5 mg/mL propofol konsantrasyonu olacak şekilde sodyum klorür ile dilüsyonu yapılan çözelti kullanıldı; dördüncü grupta ise 2.5 mg/mL propofol konsantrasyonu olacak şekilde izotonik sodyum klorür ile dilüsyonu yapılan çözelti kullanıldı. Propofol ile yapılan indüksiyon esnasında oluşan ağrı dört nokta sözel değerlendirme skalası kullanılarak yapıldı. **Bulgular:** Dört nokta sözel değerlendirme skalasına göre, dört grubun değerleri birbirinden farklıydı ($p< 0.001$). Gruplar ikişer ikişer karşılaştırıldığında, sözel değerlendirme skalasına göre grup 2, grup 1, 3 ve 4'e göre daha iyi analjezi sağladı (tüm p değerleri <0.001); grup 3 ve grup 4'ün bulguları benzer bulundu (tüm p değerleri > 0.05) ve her ikisi de grup 1 ile kıyaslandığında daha iyi analjezi sağladı (tüm p değerleri < 0.001). **Sonuç:** Propofolün izotonik sodyum klorür ile dilüsyonu, propofol enjeksiyon ağrısını azaltmaktadır. Bununla birlikte propofole lidokain ilavesi, propofolün izotonik sodyum klorür ile dilüsyonuna göre propofol enjeksiyon ağrısını azaltmada daha etkindir. Lidokain gibi farmakolojik ajanların kullanılamadığı durumlarda, propofolün izotonik sodyum klorür ile dilüsyonu, propofole bağlı enjeksiyon ağrısını azaltmak için güvenle kullanılabilir.

Anahtar Kelimeler: Propofol; ağrı; lidokain

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Propofol (2,6-diisopropylphenol) is one of the most commonly used intravenous anesthetics. It was formulated in a concentration of 10 mg/mL and causes pain or discomfort on injection in 28-90% of pati-

ents.[1-3] Recent attempts aimed to decrease the propofol-induced pain either with pharmacologic or nonpharmacologic methods.[4-8] The former comprised pretreatment with lidocaine, ketamine, thiopental, remifentanyl, nitric oxide, metoclopramide, flurbiprofen, ephedrin or acetaminophen.[9-17] On the other hand, nonpharmacologic approaches included cooling or warming propofol, diluting and injecting it into a large vein. The concentration of free propofol in the aqueous phase is thought to be particularly associated with injection pain.[18] Propofol usually is available in a concentration of 1.0% propofol in a lipid emulsion containing 10% triglycerides. Dilution with a considerably higher quantity of lipid emulsion or with dextrose[19,20] were attempted; however, to our best notice, dilution of propofol with saline was not reported in the relevant literature. Therefore, the two goals of this current study was to find out whether saline dilution had a favorable effect on propofol injection associated pain and to compare the effects of saline dilution with saline and lidocaine combination on propofol induced pain.

MATERIAL AND METHODS

The study had a prospective, randomized, double-blind design. All patients gave informed consent and the study was approved by the local ethics committee. 200 patients (ASA-I/II, aged between 20-60 years) who were undergoing general anesthesia for elective surgical interventions were randomized into four groups. Patients with any of the following were excluded: allergy to propofol, psychiatric or neurologic disorder, liver/renal disease, ASA III-IV, age below 20 or above 60.

None of the patients received premedication including any analgesic or sedative drugs before surgery. All subjects were monitorized in the operation room in a standard way (electrocardiography, non-invasive arterial blood pressure and pulse oximeter). A 20-gauge catheter was placed into the large dorsal vein of the hand. Standard propofol (propofol 1% Fresenius) solution (10 mg/mL) was diluted with 0.9% NaCl. The syringes were prepared in room temperature and propofol was given with an infusion pump by a personnel blinded to the study groups. All groups were designed to administer propofol 2 mg/kg within 3 min. In group 1, only propofol solution 10 mg/mL was used; in group 2, the solution comprised 10mg/mL propofol and 2 mg/mL lidocaine; in group 3, only propofol 5 mg/mL and in group 4, propofol solution 2.5 mg/mL were used.

Pain during induction with propofol was scored using a 4-point VRS (Table 1).[6] Patients were asked to rate their pain at the injection site after infusion of ¼ of the solution, after ½ of the solution and, if hypnosis has not ensued, after ¾ of the solution.

Statistical Analysis

Statistical analysis was done with SPSS for Windows 11.5. Results were given as mean ± standard deviation and percentages. One-way ANOVA test was used to compare continuous variables. Chi-square test and Kolmogorov-Smirnov Z were used for categorical variables.

Tukey test was used for posthoc comparison. Statistical significance was set at $p< 0.05$.

RESULTS

Demographic features of the patients were summarized in Table 2. Mean values for age, height and weight and distribution of the patients according to sex and ASA were similar between the groups (all p values > 0.05). Verbal rating scale scores of the patients

TABLE 1: 4-point verbal rating scale.

0	No pain	Negative response to questioning
1	Mild pain	Pain reported only in response to questioning without any behavioral signs (ie, no spontaneous expression of pain)
2	Moderate pain	Pain reported only in response to questioning and accompanied by a behavioral sign or symptom (ie, expression of pain) reported spontaneously without questioning
3	Severe pain	Strong verbal response or response accompanied by facial grimacing, arm withdrawal

TABLE 2: Demographic features of the patients (mean ± SD).

	Group 1 (n= 50)	Group 2 (n= 50)	Group 3 (n= 50)	Group 4 (n= 50)	p
Age (year)	33.50 ± 12.93	33.44 ± 12.94	37.10 ± 13.99	37.78 ± 14.02	**0.393***
Weight (kg)	73.10 ± 8.03	70.68 ± 7.07	71.72 ± 9.73	71.22 ± 9.13	**0.532***
Height (cm)	170.02 ± 5.84	167.86 ± 7.40	169.38 ± 6.70	168.86 ± 7.51	**0.463***
ASA (I/II)	50/0	46/4	45/5	44/6	**0.864*****
Sex (male/female)	28/22	26/24	24/26	26/24	**0.887****

*ANOVA test,
** chi-square test,
*** Kolmogorov-Smirnov Z test ASA: American Society of Anesthesiologists.

were given in Tables 3, 4, and 5. Groups showed difference with regard to VRS scores ($p < 0.001$). When groups were compared in pairs, group 2 had better analgesia than groups 1, 3 and 4 for all VRS values (all p values < 0.001); group 3 and group 4 were similar (all p values > 0.05) and each had better analgesia than group 1 (all p values < 0.001).

DISCUSSION

In this study, we aimed to find out whether dilution of propofol with saline decreased the pain associated with its injection and we compared the effect of saline dilution with saline and lidocaine combination on pain scores. Overall, saline had favorable effects irrespective of the amount of dilution. However, saline dilution was not superior to concomitant lidocaine use.

Fujii et al comparatively studied the efficacy of lidocaine, metoclopramide, and flurbiprofen for reducing pain on injection of propofol.[14] The median pain score was less in patients who had received lidocaine, metoclopramide or flurbiprofen than in those who received placebo. The incidence and severity of pain were not significantly different between the lidocaine-, metoclopramide-, and flurbiprofen-treated groups. In another study by Canbay et al, iv acetaminophen was effective, although not as much as lidocaine, in decreasing the incidence of pain during iv injection of propofol.[17] In our study, addition of lidocaine was superior to saline dilution.

Various nonpharmacological interventions were tested to eliminate propofol-induced pain. Decreasing the concentration in the aqueous phase of propofol emulsion by diluting with additional solvents or changing the lipid carrier were shown to re-

TABLE 3: Verbal rating scale scores of patients after infusion of ¼ of the solution.

VRS	Group 1 (n= 50)	Group 2 (n= 50)	Group 3 (n= 50)	Group 4 (n= 50)
0	0 (0%)	37 (74.0%)	24 (48.0%)	17 (34.0%)
1	3 (6.0%)	13 (26.0%)	14 (28.0%)	20 (40.0%)
2	35 (70.0%)	0 (0%)	12 (24.0%)	13 (26.0%)
3	12 (24.0%)	0 (0%)	0 (0%)	0 (0%)

TABLE 4: Verbal rating scale scores of patients after infusion of ½ of the solution.

VRS	Group 1 (n= 50)	Group 2 (n= 50)	Group 3 (n= 50)	Group 4 (n= 50)
0	0 (0%)	40 (80.0%)	24 (48.0%)	18 (36.0%)
1	3 (6.0%)	10 (20.0%)	14 (28.0%)	18 (36.0%)
2	17 (34.0%)	0 (0%)	9 (18.0%)	9 (18.0%)
3	30 (60.0%)	0 (0%)	3 (6.0%)	5 (10.0%)

TABLE 5: Verbal rating scale scores of patients after infusion of ¾ of the solution.

VRS	Group 1 (n= 50)	Group 2 (n= 50)	Group 3 (n= 50)	Group 4 (n= 50)
0	0 (0%)	40 (80.0%)	24 (48.0%)	18 (36.0%)
1	3 (6.0%)	10 (20.0%)	14 (28.0%)	18 (36.0%)
2	13 (26.0%)	0 (0%)	9 (18.0%)	8 (16.0%)
3	34 (68.0%)	0 (0%)	3 (6.0%)	6 (12.0%)

duce the pain on injection.[19] The higher content of lipids were suggested to be the main reason for reducing the incidence of pain either in children or in adults.[1,18,21] On the other hand, addition of 5% dextrose in Ringer's acetate was shown to be comparable to lidocaine in decreasing propofol-induced pain.[20] According to our results, either form of saline dilution was shown to decrease propofol induced pain.

The incidence and intensity of propofol-associated pain seems to be affected by many factors like catheter size and site of insertion, volume, temperature and speed of injection, and concentration of propofol in the aqueous phase of the preparation. Although the mechanism of pain is not well understood, propofol is known to irritate the skin, mucous membranes, and venous intima.[22] By an indirect action on the endothelium, it also activates the kallikrein-kinin system, thereby producing venous dilation and hyperpermeability, increasing the contact between propofol and the free nerve endings.[23] In our study, propofol administration was performed with standard 20-G catheters for a constant period from a large vein on the dorsum of the hand. Therefore, the effects of the aforementioned factors were not elucidated in our study; however, we believe that saline dilution might have affected via direct and indirect ways, decreasing the amount of propofol in contact with the venous intima and the kallikrein-kinin system.

To summarize, according to our results, we may conclude that saline dilution can be used to alleviate propofol induced pain. Although lidocaine seems to be more effective in this regard, accompanying factors that would make the use of pharmacological adjuncts contraindicated, may outweigh (e.g. patients allergic to lidocaine; oculogyric/extrapyramidal signs due to previous metoclopramide use; asthma, renal failure or gastric ulceration for nonsteroidal anti-inflammatory drugs). In such cases, saline can be used safely.

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