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Original Article / Orijinal Araştırma

Placebo-controlled comparison of using lidocaine or ketamine to reduce the pain during injection of propofol containing a mixture of medium-chain triglyceride/long-chain triglyceride

Orta ve uzun zincirli trigliserit karışımı içeren propofol enjeksiyonu sırasındaki ağrının azaltılmasında lidokain veya ketamin kullanımının plasebo kontrollü karşılaştırılması

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Abstract

Aim. The objective of this study was to compare the efficacy of ketamine or lidocaine on relieving the pain during the injection of a new formulation of propofol containing a mixture of medium-chain triglyceride/long-chain triglyceride (MCT/LCT). **Methods.** This study including patients, ASA I and II, was conducted as double-blinded and placebo-controlled randomized trial on 75 subjects aged 18-65 years scheduled for elective surgical operation under general anesthesia. Propofol MCT/LCT 1% (2.5 mg/kg) plus 40 mg lidocaine, 10 mg ketamine, and normal saline were administered in groups I, II, and III, respectively. Scores of pain intensity and arm withdrawal were assessed during the propofol injection. **Results.** There was no significant difference among the study groups with regard to the ratios of no and mild pain ($p>0.05$); however, the ratios of moderate pain of the lidocaine and ketamine groups were significantly lower than that of the normal saline group (2% vs. 28%; $p<0.05$). The study groups were found comparable with regard to the arm withdrawal score ($p>0.05$). **Conclusion.** Propofol MCT/LCT as the new formation of propofol generally cause less pain during injection and for reducing its pain, ketamine 10 mg has similar effects with lidocaine40 mg.

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Keywords: Propofol medium-chain triglyceride/long-chain triglyceride, lidocaine, ketamine, pain

Özet

Amaç. Orta zincirli trigliserit/uzun zincirli trigliserit (MCT/LCT) karışımı içeren yeni formülasyon propofolün enjeksiyon ağrısının giderilmesinde ketamin ve lidokainin etkinliğinin karşılaştırılması amaçlandı. **Yöntem.** Çalısma ASA I-II, 18-65 yaş arasında genel anestezi altında elektif cerrahi operasyon uygulanan 75 olgu üç gruba ayrılarak randomize, çift kör ve plasebo kontrollü olarak planlandı. Grup 1'e (n=25) 40 mg lidokain ile, grup 2'ye (n=25) 10 mg ketamin ile, ve grup 3'e (n=25) serum fizyolojik ile birlikte 2,5 mg/kg dozunda %1'lik propofol MCT/LCT verildi. Propofol enjeksiyonu sırasında ağrı yoğunluğu ve kol çekme skorlaması yapıldı. **Bulgular.** Ağrı görülmeme ve az ağrı görülme oranları gruplara göre anlamlı farklılık göstermezken (p>0,05); lidokain ve ketamin ile orta düzeyde ağrı oranları serum fizyolojik grubuna göre anlamlı olarak daha düşük bulundu (%28'e karşın %2; p<0,05). Gruplara göre kol çekme yanıtları arasında istatistiksel olarak anlamlı farklılık bulunmadı (p>0,05). **Sonuç.** Propofolun yeni formu olan propofol MCT/LCT genel olarak çok fazla enjeksiyon ağrısına neden olmazken, oluşabilecek ağrıyı önlemede 10 mg ketamin 40 mg lidokaine benzer etkinlik sağlayabilir.

Anahtar sözcükler: Propofol orta zincirli trigliserit/uzun zincirli trigliserit, lidokain, ketamin, ağrı

Introduction

The synthesis of propofol (diisopropyl phenol) has performed in 1989. And nowadays it is most commonly used agent thanks to its specifications such as having short-term effect and providing early recovery. But the most frequently encountered disadvantages are the pain of injection and hypotension which occurred during induction [1]. The sense of pain and discomfort during propofol injection was reported as 28-90% [2].

The most notably mechanisms related to the pain of propofol injection are lipid transmitter and free propofol concentration of emulsion on the aqueous phase. Free concentrations of propofol release brandikinin by activating the kinin-kallikrein system with a direct irritation to vessel endothelium (particularly tunica media and intima), thus venous dilatation generates a hyper permeability and this causes pain by providing more contact from propofol to nerve endings [3-7].

For reducing the pain arising from propofol, a wide range of pharmacologic and non-pharmacologic approaches have been attempted. Adding lidocaine to propofol, adjusting pH of propofol, giving alfentanyl, remifentanyl, ketamine, metoclopramide, nafamostat, granisetron, oral clonidyn, cold saline solution, ketorolac, thiopental, magnesium sulphate, ephedrine prior to injection; applying nitroglycerin to skin, applying EMLA or 60% lidocaine tape; applying propofol in different temperatures; applying venous occlusion; adjusting rate of infusion; diluting; using different concentration, diluting with transmitter liquids, adding long and medium chained lipid; and using wide antecubital veins can be counted among those pharmacologic approaches (8-9).

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In this study, we aimed to compare the efficacy of ketamine or lidocaine for relieving the pain during the injection of a new formulation of propofol MCT/LCT including less free propofol in a placebo-controlled, double blinded study.

Materials And Methods

The study has been performed in operating room of Haydarpaşa Numune Hospital after the Human Ethics Comittee approval and the informed consents of patients were taken. This study is planned as double-blinded and placebo-controlled randomized on 75 subjects, ASA I-II, between 18 and 65 years old, administered general anesthesia for an elective surgical operation. Providing that we took delta as 40% and minimum expected rate 8% for the VAS scores with β:0.20 and α:0.05, sample size was 24 for each group.

Exclusion criteria were defined as pregnancy and breastfeeding, presence of neurological problem, ischemic heart disease, and lipid metabolism disorders, antiaritmic or analgesic use, and presence of allergy to propofol and its components (soy oil, MCT, glycerol, egg lecithin, sodium oleate, and injection water). Subjects were randomized into three groups. Propofol MCT/LCT 1% (2.5 mg/kg) (Propofol-®Lipuro 10 mg/ml (1%), B. Braun Medikal Dış Ticaret A.Ş, İstanbul) plus 40 mg lidocaine, 10 mg ketamine, and normal saline were administered in groups I, II, and III, respectively.

Premedication of 0.15 mg/kg diazepam (IM) plus 0.01 mg/kg atropine (IM) were administered to all patients. All solutions were prepared in room temperature. The temperature of propofol alters the injection pain. Lidocaine, ketamine and 0.9% saline has been used as a solution of 2 mL. At least 30 min before being in the operation room, vascular access from non-dominant arm with 20 gauge IV cannula were established. Study drug prepared by another anesthetist was given to the patients as 2-mL solution. 30 sec after that ¼ of 2.5 mg/kg dosed propofol MCT/LCT %1 is given to the patients at a rate of 1 mL/sec. Following the injection, patient was questioned about pain if there is no symptom or complaining by him/herself. Rest of the dose has been injected again at the rate of 1 mL/sec. During the injection, pain was assessed according to pain intensity and arm withdrawal scorings as presented in Tables 1 and 2, respectively.

Table 1. Pain intensity scoring.

Pain score	Pain intensity	Respond
0	None	Negative responds to questions
1	Mild	No behavioral symptom, to say only when be asked
2	Moderate	Says when asked about pain and showing behavioral symptom/ indicating pain without be asked
3	Severe	Strong, voice response, grimacing, tear response

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Table 2. Arm withdrawal scoring.

Score	Arm withdrawal	Respond
0	None	None
1	Mild	Mild withdrawal of arm
2	Moderate	Moderate withdrawal of arm
3	Severe	Severe withdrawal of arm

Data were presented as mean±SD and percentage as appropriate. NCSS 2007 & PASS 2008 Statistical Software Program (NCCS, Kaysville, UT, USA) was used for for the statistical analyses. ANOVA test with post hoc Tukey test were used during the analyses of numeric data. Chi-square test was used for the comparison of nominal data. Significancy was estimated on level of $p<0.05$.

Results

Table 3 presents the age, height, weight, gender, and ASA of the groups 1, 2, and 3. The study groups were found similar with regard to these parameters.

Table 3. Selected characteristics of study groups.

	Group 1 (n=25)	Group 2 (n=25)	Group 3 (n=25)	Significance
Age (y)	41.3±16.2	32.8±9.8	38.9±13.4	0.075
Height (cm)	166.3±7.6	169.0±8.6	166.8±7.8	0.458
Weight (kg)	67.5±11.8	73.1±14.9	75.8±13.6	0.093
Gender Female Male	 11 (44%) 14 (56%)	 11 (44%) 14 (56%)	 9 (36%) 16 (64%)	0.803
ASA I II	 8 (32%) 17 (68%)	 8 (32%) 17 (68%)	 6 (24%) 19 (76%)	0.773

Table 4 shows the pain intensity score of the groups 1, 2, and 3. There was no significant difference among the study groups with regard to the ratios of no and mild pain ($p>0.05$); however, the ratios of moderate pain of the lidocaine and ketamine groups were significantly lower than that of the normal saline group (2% vs. 28%; $p<0.05$).

Table 4. Pain intensity scores of study population.

Pain intensity	Group 1 (n=25)	Group 2 (n=25)	Group 3 (n=25)
None	12 (48.0%)	12 (48.0%)	11 (44.0%)
Mild	11 (44.0%)	11 (44.0%)	7 (28.0%)
Moderate	2 (8.0%)	2 (8.0%)	7 (28.0%)*
Severe	0	0	0
*P<0.05 vs. groups 1 and 2. There was no other significant difference.			

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Table 5 displays the arm withdrawal score of the groups 1, 2, and 3. We found no significant difference among the arm withdrawal scores of the study groups (p>0.05).

Table 5. Arm withdrawal score of study groups.

Arm withdrawal	Group 1 (n=25)	Group 2 (n=25)	Group 3 (n=25)
None	18 (72%)	21 (84%)	18 (72%)
Mild	2 (8%)	3 (12%)	5 (20%)
Moderate	5 (20%)	1 (4%)	2 (8%)
Severe	0	0	0
There was no significant difference with regard to the none, mild, and moderate arm withdrawal.			

Discussion

According to findings of this study, the injection of propofol MCT/LCT caused less discomfort and addition of lidocaine 40 mg and ketamine 10 mg provided similar effect as a decrease in pain intensity. The effect of study drugs were found comparable with regard to the arm withdrawal score.

Pain during the injection of propofol MCT/LCT depends on injection site and size of vein. Stark et al. [2] found that the incidence of pain related to the injection of propofol to the veins of antecubital fossa and forearm is about 6%, while about 28% for the hand and ankle. The intensity of pain has increased when propofol injected slowly, especially with a rate of 1 mL/sec. Temperature of injection solution and non-steroidal anti-inflammatory drugs can also reduce injection pain [10-15]According to knowledge in the pertinent literature, we determined a standart setup during propofol MCT/LCT injection: dorsum of the hand as injection site, 20G venous catheter as vascular access, room temperatue as the temperatuer of injection solution, and 1 mL per second as injection rate.

Liljeroth et al. [16] compare the influence of two different emulsions of propofol on local pain following iv administration in 80 adult patients (ASA I-II). They found that the total incidence of local pain (VAS>0) on injection of propofol was 52% for propofol MCT/LCT and 71% for propofol whereas moderate to severe pain (VAS>4) was induced in 10% of propofol MCT/LCT injections compared with 36% for propofol. They demonstrated that The intensity of drug-induced local pain was found to be meaningfully lower after the injection of propofol MCT/LCT as median 1 vs. median 3 VAS units. They suggested that propofol MCT/LCT provides considerable lower intensity of local pain and it should be preferred to traditional types for induction of anesthesia. Larsen et al. [17] demonstrated that propofol MCT/LCT caused less pain in pediatric patients.

The most attempted method in studies aiming to reduce the injection pain is 10-40 mg lidocaine additional to propofol or given before propofol (13-18). Lidocaine, which is a local anesthetic on its amid structure, reduces incidence of pain indirectly by stabilizing kinin cascade (19). Notwithstanding, it is informed that the rates of pain observed on patients are still between 5% and %48. (4)

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For reduction the injection pain of propofol, the most studied drug was lidocaine administered before and during its injection [13-18]. It was stated in many studies that for reducing the injection pain, adding lidocaine to propofol was more effective than applying IV lidocaine before propofol [4, 5, 7, 10-20]. Kam et al. [8] concluded that there was no significant difference between the injection pain caused by propofol MCT/LCT without lidocaine and standard propofol with 10-mg lidocaine. Ho et al. [18] conducted a study with additon of 0.05%, %0.1, or %0.2 lidocaine to the propofol injection. They concluded that the optimal effective concentration of lidocaine, successful for reducing the incidence of pain caused by propofol injection, was 0.1% in their study population. Overall, use of propofol MCT/LCT was more successful for reducing injection pain and addition of lidocaine decreases pain intensity according to the pertinent literature.

Mahmood et al. [21] investigated the efficacy of lidocaine 40 mg, ketamine 10 mg, and dexamethasone 4 mg to reduce injection pain of placebo. They found no considerable difference among the study drugs for reducing injection pain. In this study, we administered ketamine 10 mg and lidocaine 40 mg within 2 ml solution 30 sec before propofol MCT/LCT injection and obtained succecful results with regard to prevent injection pain of propofol MCT/LCT.

In conclusion, propofol MCT/LCT as the new formation of propofol generally cause less pain during injection and for reducing its pain, ketamine 10 mg has similar effects with lidocaine40 mg.

Conflict of Interest

The authors declare that there is no scientific and/or financial conflicts of interest.

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