The Effect of Lidocaine on Injection Pain of Different Propofol Concentrations in Patients Receiving Remifentanil

Lidokainin Remifentanil Alan Hastalarda Farklı Propofol Konsantrasyonlarına Bağlı Enjeksiyon Ağrısına Etkisi

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ABSTRACT Objective: The effectivity of remifentanil and lidocaine combination on the injection pain with 1% propofol was reported previously. However, this finding has not been investigated with different propofol concentrations. In this prospective, randomized, double-blind trial, we aimed to compare the effect of lidocaine on the injection pain of 1% or 2% propofol in patients receiving remifentanil. **Material and Methods:** One hundred patients undergoing ear-nose-throat surgery were randomly assigned into four groups (n= 25 each). Following 0.5 μg/kg/min remifentanil, patients in Group 1 and Group 2 received 1 mg.kg^{-1} 1% or 2% propofol the mixed with 2 mL of saline, respectively. Patients in Group 3 and Group 4 received 1 mg.kg^{-1} 1% or 2% propofol mixed with 2 mL of 2% lidocaine after 0.5 μg kg^{-1} min^{-1} remifentanil. Pain during the injection of propofol was assessed on a four-point scale (0= none, 1= mild, 2= moderate, 3= severe) **Results:** The incidence of none-mild pain on injection of 1% propofol was significantly lower in Group 1 (56%) compared to Group 3 (100%) (p= 0.00017). This finding was also seen between Group 2 (36%) and Group 4 (72%) (p= 0.010). However, the number of patients suffering from the injection pain was significantly greater in Group 4 compared to Group 3 (p= 0.004). **Conclusion:** Lidocaine 2% 2 mL mixed with propofol completely abolished moderate-severe pain induced by 1% propofol in patients who were given 0.5 μg/kg/min remifentanil. However, some patients still suffered from injection pain caused by 2% propofol in spite of the combined effect of lidocaine and remifentanil.

Key Words: Propofol; injections, intravenous; pain; remifentanil; lidocaine

ÖZET Amaç: Yüzde 1'lik propofole bağlı enjeksiyon ağrısı üzerinde remifentanil ve lidokain kombinasyonunun etkisi daha önce çalışılmıştır. Ancak bu bulgu farklı propofol konsantrasyonları ile araştırılmamıştır. Bu prospektif, randomize, çift-kör çalışmada remifentanil alan hastalarda lidokainin %1'lik veya %2'lik propofol konsantrasyonlarının enjeksiyon ağrısı üzerindeki etkisini karşılaştırmayı amaçladık. **Gereç ve Yöntemler:** Kulak-burun-boğaz cerrahisi yapılan yüz hasta randomize olarak dört gruba ayrıldı (n= 25, herbiri). Grup 1 ve 2'deki hastalara 0.5 μg/kg/dk remifentanili takiben ayrı ayrı 1 mg/kg %1'lik propofol veya %2'lik propofolün 2 mL serum fizyolojik ile karışımı uygulandı. Grup 3 ve Grup 4'teki hastalara 0.5 μg/kg/dk remifentanili takiben 1 mg/kg %1'lik propofol veya %2'lik propofolün 2 mL %2 lidokain ile karışımı uygulandı. Propofol enjeksiyonu sırasındaki ağrı dört-puanlık ölçek üzerinden değerlendirildi. (0= hiç, 1= hafif, 2= orta, 3= şiddetli) **Bulgular:** Propofolün 1% enjeksiyonunda olan hiç-hafif ağrı insidansı Grup 3 (%100) ile kıyaslanınca Grup 1'de (%56) anlamlı olarak daha düşüktü (p= 0.00017). Bu bulgu Grup 2 (36%) ve Grup 4 (72%) arasında da benzerdi (p= 0.010). Ancak enjeksiyon ağrısı çeken hastaların sayısı Grup 3 ile kıyaslayınca Grup 4'te anlamlı olarak daha fazlaydı. (p= 0.004). **Sonuç:** 0.5 μg/kg/dk remifentanil alan hastalarda propofole eklenen %2'lik 2 mL lidokain, %1'lik propofolün neden olduğu orta-şiddetli ağrıyı tamamen önledi. Ancak bazı hastalarda lidokain ve remifentanilin kombine etkisine karşın %2'lik propofolün neden olduğu enjeksiyon ağrısı önlenemedi.

Anahtar Kelimeler: Propofol; enjeksiyonlar, intravenöz; ağrı; remifentanil; lidokain

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Propofol (2.6-diisopropylphenol) is the most frequently used intravenous (IV) drug for the induction and maintenance of anesthesia. However, its IV injection is associated with pain in up to 70% of patients.[1,2] Many strategies have been used to reduce the injection pain of propofol including the injection speed and the carrier fluid,[3,4] its dilution,[5,6] pretreatment with alfentanil[7] or remifentanil[8] and the injection of lidocaine before propofol[9,10] or mixing the two drugs before injection.[11-13]

Recently, two studies have shown that combination of remifentanil and lidocaine completely abolishes moderate and severe pain during the injection of 1% propofol when compared to each drug used alone.[14,15] However, a more concentrated new preparation of propofol (propofol 2%) has been developed mainly for intensive care unit (ICU) use and marketed as an acceptable alternative to 1% propofol for the induction of anesthesia in adults.[16] It is suggested that 2% solution has a higher concentration of free propofol and is therefore more painful on injection.[5,17] Until today, the effect of the propofol concentration and the use of lidocaine is not clear in patients receiving remifentanil.

The aim of this prospective, randomized, double-blind trial was to compare the effect of lidocaine on the injection pain caused by 1% or 2% propofol in patients receiving remifentanil for the induction of anesthesia in ear-nose-throat surgery.

MATERIAL AND METHODS

Following approval of the local ethics committee and written informed consent of patients, 100 ASA I-II patients aged 18-60 years scheduled for elective ear-nose-throat surgery under total intravenous anesthesia (TIVA) were recruited in this prospective, randomized, double-blind study. Exclusion criteria included the presence of neurological or psychiatric disease, difficulty with communication, suspected or known difficult airway, hypersensitivity to the study drugs, use of sedatives or analgesics within 24 hours preceding surgery or request of, anxiolysis. None of the patients received premedication. Patients were randomly assigned to four groups of 25 each using sealed envelopes. On arrival at the operating room, standard monitoring was performed (noninvasive arterial blood pressure, electrocardiogram and pulse oximetry), a 18-gauge IV cannula (BD Venflon™ Pro, Beckton Dickinson, Helsingborg, Sweden) was inserted into a dorsal left hand vein and a three-way tap was connected directly to the catheter. During the induction of anesthesia, 5-7 mL kg^{-1} IV infusion of 0.9% sodium chloride was given as and 0.5 μg kg^{-1} remifentanil was administered within 60 seconds to all patients by means of an infusion pump. At the end of one minute, patients in Group 1 and in Group 2 received 1mg kg^{-1} 1% or 2% propofol (Propofol 1% or 2% Fresenius™, the Netherlands) mixed with 2 mL of saline, respectively. Patients in Group 3 and in Group 4 received 1mg kg^{-1} 1% or 2% propofol mixed with 2 mL of 2% lidocaine (Lidocaine HCl, B. Braun Melsungen AG), respectively.

For the preparation of the solutions, 200 mg of 1% or 2% propofol was mixed with 2 mL of either normal saline or 2% lidocaine in a 30-mL polyethylene syringe, kept at room temperature and used within 10-15 minutes of preparation. Study drugs were administered by a blinded investigator over five seconds. If there was no spontaneous complaint of pain, patients were asked if they experienced any pain in the arm 10 seconds after the beginning of the injection, pain scores were recorded using a four-point verbal rating scale: 0= no pain (negative response to questioning), 1= mild pain (pain reported in response to questioning only, without any behavioural signs), 2= moderate pain (pain reported in response to questioning and accompanied by a behavioural sign, or pain reported spontaneously without questioning), and 3= severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears).[18] None-mild pain was considered as clinically acceptable pain whereas moderate-severe pain was as considered clinically unacceptable pain. Once the assessment of injection pain completed, the induction of anesthesia continued with the remainder of the calculated propofol dose and remifentanil-propofol was infused to all patients according to the anesthetist's

routine practice. Based on the previous literature,[8,19] we expected a 40% incidence of propofol pain after remifentanil infusion and minimum 23 patients per group would be required to decrease this incidence to 5% by adding lidocaine (power 80%, α= 0.05).

Statistical analysis was performed using SPSS 10.1 for Windows. Patient characteristics were compared with Kruskal-Wallis test. The incidence of clinically acceptable/unacceptable pain was analysed with Fisher's exact test and p< 0.05 was considered as statistically significant. Data were presented as either mean ± standart deviation (mean ± SD) or number of patients.

RESULTS

One hundred patients were enrolled in this study; there were 25 patients in each treatment group. There were no significant differences among four groups with regard to gender, age or weight (Table 1). The overall incidence and severity of pain during IV injection of 1% or 2% propofol in four groups are shown in Table 2. Although the incidence of moderate-severe pain was less in Group 1 (44%) compared to Group 2 (64%), the difference was not statistically significant (p= 0.156). There was no moderate-severe pain in Group 3 compared to 44% incidence in Group 1 with adding lidocaine (p= 0.00017). A significant decrease was also found in the incidence of moderate-severe pain on injection of 2% propofol in Group 4 (72%) compared to Group 2 (36%) with adding lidocaine (p= 0.010).

On analysis of the data of two groups given lidocaine, we found a 0% incidence of moderate-severe pain in patients given 1% propofol (Group 3) when compared to 28% in patients given 2% propofol (Group 4) (p= 0.004).

DISCUSSION

In the present study, 2 mL of 2% lidocaine mixed with 1% or 2% propofol was found to be significantly effective in reducing the incidence of moderate to severe pain following propofol injection in patients receiving remifentanil. However, reduction of the incidence of pain was greater in patients given 1% propofol compared to 2% propofol. In the current study, patients did not receive any anxiolytic or sedative premedication in order to avoid sedation that may affect the evaluation of propofol

TABLE 1: Demographic characteristics of patients (n= 100).

	Group 1 (n= 25)	Group 2 (n= 25)	Group 3 (n= 25)	Group 4 (n= 25)
Age (year)	39.6 ± 13.7	43.6 ± 14.7	44.6 ± 12.9	35.6 ± 11.8
Weight (kg)	73.3 ± 10.3	73.2 ± 12.4	68.2 ± 12.7	70.5 ± 14.5
Gender (F/M)	10/15	8/17	10/15	7/18

Data are presented as either number of patients or mean ± SD. F: Female, M: Male

TABLE 2: Distribution of incidence and severity of injection pain in the study groups.

Groups	Pain score			
	Clinically acceptable pain		Clinically unacceptable pain	
	No pain	Mild	Moderate	Severe
Group 1	7 (28%)	7 (28%)	9 (36%)	2 (8%)
Group 2	5 (20%)	4 (16%)	8 (32%)	8 (32%)
Group 3	19 (76%)	6 (24%)	0 (0%)	0 (0%)*
Group 4	15 (60%)	3 (12%)	5 (20%)	2 (8%)†§

Values are expressed as numbers (%).
Group 3 vs Group 1 *p< 0.001.
Group 3 vs Group 4 †p< 0.01.
Group 4 vs Group 2 §p< 0.05.

pain. As the incidence of injection pain of propofol varies between 67% and 85% in adults when used without any other treatment,[5,9] we decided not to take a placebo group.

The intensity of pain was graded using a verbal rating scale similar to the previous studies.[14,15,18] It is known that this verbal scoring system is very simple to use by the patient, and suitable in all patients during the rapidly changing state of consciousness during anesthesia induction. The cause of pain on propofol injection is obscure and there are several proposed mechanisms. Immediate pain probably results from a direct irritation of afferent nerve endings within the vein, whereas delayed pain may be caused by triggering of kinin cascade and release of kininogens.[20] Sun et al.[17] found that the lower concentration of free propofol (Propofol-Lipuro1%-long and medium chain triglycerides-) in the aqueous phase was associated with reduced injection pain when compared to Diprivan®, which is formulated in an emulsion of long-chain triglycerides, similar to the studies of Liljeroth and Akeson.[21] These observations support the hypothesis that higher concentrations of free propofol in the aqueous phase of the emulsion correlate with the high incidence of pain on injection.[22-24] However, a study comparing injection pain following Propofol-Lipuro and Diprivan found no significant difference in the incidence of pain between the two formulations.[25]

The use of lidocaine to decrease propofol injection pain is based on its presumed local anesthetic effect on the vein, but it is not successful in 100% of cases.[7,19,20] Thus, the pain-reducing effect of lidocaine is not only based on its local anesthetic effect, but also to a decrease in the pH value of the propofol- lidocaine mixture. It was hypothesized that the lower pH value caused propofol to migrate into the lipid phase and progressively decreased the effective concentration of free propofol in the aqueous phase of the lipid emulsion.[26]

Remifentanil is a short-acting phenylpiperidine derivative with μ-opioid receptor agonist effects. Opiod receptors are found centrally in the dorsal root in the central terminals of primary afferent nerves and peripheral sensory nerve fibers and their terminals.[27] Pretreatment with remifentanil is effective in reducing propofol-induced pain[8,14,15] similar to findings with fentanyl and alfentanil.[7,28] Roehm et al.[19] reported that remifentanil given 0.25 μg kg^{-1} over 60 seconds before propofol injection provided effective pain relief comparable to lidocaine 40 mg as 70% and 67%, respectively. Başaranoğlu et al.[8] achieved better efficacy with remifentanil dose of 1μg kg^{-1} min^{-1} versus 0.25 μg kg^{-1} min^{-1}. However, our results obtained from patients given remifentanil pretreatment alone before propofol injection support previous reports[8,14,15,19] showing that the remifentanil does not completely eliminate the injection pain of propofol if it is used alone.

Recently, two studies from Kwak et al.[14] and Aouad et al.[15] have shown that the combination treatment including remifentanil and lidocaine completely abolished moderate and severe injection pain associated with 1% propofol when compared to each drug used alone. Kwak et al.[14] reported that the incidence of no-pain on injection of 1% propofol was similar (62%) in remifentanil group (0.35 μg.$kg^{-1}min^{-1}$) and in lidocaine group. However, they found that 38% of patients in both remifentanil and lidocaine groups suffered from injection pain of propofol. In contrast, there was a 0% incidence of moderate-severe pain and 8.7% incidence of mild pain in the combination group. Aouad et al.[15] also indicated similar incidences of mild (9.6%) and moderate-severe pain (0%) with the combination remifentanil 2μg kg^{-1} and lidocaine 40 mg. Although the dose of remifentanil in our study was greater than that of Kwak et al. and lower than that of Aouad et al. (0.5μg kg^{-1} versus 0.35μg kg^{-1} and 2μg kg^{-1}), our findings support that the incidence of moderate-severe pain induced by 1% propofol is 0% with the combination therapy, but this incidence is 28% in patients given 2% propofol despite combined effect of remifentanil and lidocaine in our study. This finding also supports the previous studies[22,23] in which higher concentrations of free propofol in the aqueous phase was associated with a higher incidence of pain on injection. Furt-

hermore, the efficacy of combined therapy in patients given 1% propofol showed that synergic interactions between remifentanil and lidocaine enhances the analgesic efficacy of these two drugs.

In conclusion, combined treatment including 0.5 μg kg^{-1} min^{-1} remifentanil pretreatment and lidocaine 40 mg mixed with propofol completely abolished moderate-severe pain in patients given 1% propofol whereas some patients still suffered from injection pain of 2% propofol. Further trials are necessary to completely abolish injection pain induced by 2% propofol.

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