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Comparison of Acetaminophen (with or without Tourniquet) and Lidocaine in Propofol Injection Pain

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ÖZET:

Propofol enjeksiyon ağrısında asetaminofen (turnikeli veya turnikesiz) ve lidokainın karşılaştırılması

Amaç: Anestezi indüksiyonu sırasında propofol kaynaklı ağrının önlenmesinde IV asetaminofen kullanımının (turnikeli veya turnikesiz) lidokain ile karşılaştırıldığındaki etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Hastaların kolları 20 sn boyunca yukarıya kaldırıldıktan sonra turnike uygulandı. Grup 1'de 10 ml salin; grup 2'de 10 ml salin içinde 40 mg lidokain; grup 3'de 10 ml (100 mg) asetaminofen; grup 4'de turnike 100 mmHg'ya şişirildikten sonra 10 ml (100 mg) asetaminofen uygulandı ve 2 dk sonra turnike indirildi. Tüm gruplarda solüsyonların uygulanma hızı sabit tutuldu (10sn). Standart propofol solüsyonu (10 mg/ml), oda sıcaklığında hazırlandı ve çalışma gruplarını bilmeyen biri tarafından bir infüzyon pompası ile verildi. Tüm gruplar 3 dk içerisinde 2 mg/kg dozunda propofol alacak şekilde tasarlandı.

Propofol indüksiyonu sırasında oluşan ağrı 4 puanlık verbal ağrı skalası (VAS) ile değerlendirildi (ağrı yok: 0, hafif: 1, orta: 2 ve çok: 3). Solüsyonun ¼' ünün, ½' sinin ve eğer hipnoz oluşmadı ise ¾' ünün infüzyonunu takiben hastalardan enjeksiyon alanındaki ağrıyı değerlendirmeleri istendi.

Bulgular: VAS skorlarına göre gruplar birbirinden farklı bulundu ($p<0.001$). Çiftler halinde gruplar karşılaştırıldığında; tüm VAS değerlerinde grup 1'e göre grup 2,3,4'te daha iyi bir analjezi görüldü (tüm p değerleri <0.001); grup 2 ve 4 birbirine benzerdi (tüm p değerleri >0.05) ve tüm VAS değerlerinde grup 3'e göre diğer tüm gruplar daha iyi bir analjeziye sahipti (tüm p değerleri <0.001).

Sonuç: IV asetaminofenin turnike ile beraber uygulandığında propofol kaynaklı ağrı üzerinde lidokain kadar etkili olduğuna karar verdik. İlaveten, turnike ile asetaminofen uygulanması turnikesiz asetaminofen uygulanmasına göre daha üstündür.

Anahtar sözcükler: Propofol, ağrı, lidokain, asetaminofen, anestezi

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ABSTRACT:

Comparison of acetaminophen (with or without tourniquet) and lidocaine in propofol injection pain

Background: We aimed to evaluate the effectiveness of i.v. acetaminophen (with or without tourniquet application) in comparison with that of lidocaine for the prevention of propofol-induced pain during induction of anaesthesia.

Methods: The patients' arms were elevated for 20 s and a tourniquet was placed. In group 1, 10 ml saline; in group 2, 40 mg lidocaine in 10 ml saline; in group 3, 10 ml (100 mg) acetaminophen were administered; in group 4, the tourniquet was inflated to 100 mmHg, then 10 ml (100 mg) acetaminophen was given and after 2 min, the tourniquet was deflated. In all groups the duration of administration of the solutions were kept constant (10 s). Standard propofol solution (10 mg ml^{-1}) was prepared at room temperature and propofol was given using an infusion pump by a person blinded to the study groups. All treatments were designed to deliver a 2mg/kg dose of propofol in a duration of 3 min. Pain during induction with propofol was scored using a 4-point verbal rating scale (none; 0, mild; 1, moderate; 2, and severe; 3) (VRS). 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.

Results: The groups were found to be different with regard to VRS scores ($p<0.001$). When the groups were compared in pairs; groups 2,3,4 had better analgesia than group 1 for all VRS values (all p values <0.001); groups 2 and 4 were similar (all p values >0.05) and both had better analgesia than group 3 for all VRS values (all p values <0.001).

Conclusion: We concluded that i.v. acetaminophen when given using a tourniquet is as effective as lidocaine on propofol associated pain. Further, acetaminophen administration with tourniquet seems to be superior to acetaminophen without use of a tourniquet.

Key words: Propofol, pain, lidocaine, acetaminophen, anesthesia

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INTRODUCTION

Propofol (2,6-diisopropylphenol) is one of the most commonly used intravenous anesthetics. It has been formulated in a concentration of 10 mg ml^{-1} and causes pain or discomfort on injection in 28-90% of the patients (1-3). Recent attempts have been made to decrease this propofol induced pain either with pharmacologic or

nonpharmacologic methods (4-8). The former comprise pretreatment with lidocaine (9), ketamine (10), thiopental (11), remifentanyl (12), nitric oxide (13), metoclopramide (14), flurbiprofen (15), efedrine (16) or acetaminophen (17). One of the effective methods is to inject lidocaine at 0.5 mg kg^{-1} i.v. before administering propofol. As an alternative to non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, whose action at a molecular level is still not known, is widely used for pain management. Although found to be no better than lidocaine, acetaminophen has been used to prevent propofol injection pain previously (17).

In this study, we aimed to evaluate the effectiveness of i.v. acetaminophen (with or without tourniquet application) in comparison with that of lidocaine for the prevention of propofol-induced pain during induction of anaesthesia.

METHODS

This was a prospective, randomized, double-blind study. All patients gave informed consent and the study was approved by the local ethics committee. One hundred sixty patients (ASA-I/II, aged between 20-60 years) undergoing general anesthesia for elective surgical interventions were randomized into four groups by means of a computer program. Patients with any of the followings were excluded: allergy to any of the study medications, psychiatric or neurologic disorder, liver/renal disease, ASA III-IV, age below 20 or above 60 and failure to place the 20-gauge catheter into the large dorsal vein of the hand at the first attempt.

None of the patients received premedication including 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 and a crystalloid solution was infused at 80 ml h^{-1}.

After 5 min, the crystalloid infusion was stopped. The patient's arms was elevated for 20 s and a tourniquet was put in placed. In group 1, 10 ml saline; in group 2, 40 mg lidocaine in 10 ml saline; in group 3, 10 ml (100 mg) acetaminophen (Perfalgan 10 mg ml^{-1}, Bristol-Myers Squibb, France) was administered; in group 4, the tourniquet was inflated to 100 mmHg, then 10 ml (100 mg) acetaminophen was given anf after 2 min, the tourniquet was deflated. In all groups the administration of the solutions were kept constant (10 s). Standard propofol (propofol 1% Fresenius) solution (10mg ml^{-1}) was prepared at room temperature and was given using an infusion pump by a personnel blinded to the study groups. All groups were designed so as to provide a 2mg kg^{-1} dose of propofol in a duration of 3 min.

Pain during induction with propofol was scored using a 4-point verbal rating scale (VRS) (none; 0, mild; 1, moderate; 2, and severe; 3) (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.

Within 24 h after the operation, the injection site was checked for pain, edema, or allergic reaction by an anaesthesiologist who was blinded to the group assignment.

Initial sample size estimation showed that approximately 37 patients were needed in each group to detect a clinically relevant reduction of the level of pain by 30% with a power of 0.80 and a level of significance of 5%. Statistical analysis was done with SPSS for Windows 11.5. Results are given as mean ± standard deviation and percentages. A one way ANOVA test was used to compare continuous variables. The Chi-square test and Kolmogorov-Smirnov Z were used for categorical variables. The Tukey test was used for posthoc comparison. Statistical significance was set at $p<0.05$.

RESULTS

Demographic features of the patients are summarized in Table 1. Mean values for age, height, weight, and distribution according to sex and ASA were similar between the groups (all p values >0.05).

The VRS scores of the patients are given in Tables 2-4. The groups were found to be different with regard to VRS scores ($p<0.001$). When groups were compared in pairs; groups 2,3,4 had better analgesia than group 1 for all VRS values (all p values <0.001); groups 2 and 4 were similar (all p values >0.05) and both groups 2 and 4 had better analgesia than group 3 for all VRS values (all p values <0.001).

We did not observe bradycardia or arrhythmia in any patient during the study and there were no complications such as pain, edema, flushing, rash, urticaria or allergic reaction at the injection site in the first 24 h after the operation.

Table 1: Demographic features of the patients

	Group 1 (n= 40)	Group 2 (n= 40)	Group 3 (n= 40)	Group 4 (n= 40)
Age (year)	36.3±13.2	35.1±12.8	37.3±13.6	38.5±11.0
Weight (kg)	70.4±8.0	70.0±7.5	67.2±8.6	69.7±10.3
Height (cm)	168.5±5.1	166.4±8.0	166.2±7.5	167.3±6.6
ASA (I/II)	31/9	35/5	34/6	33/7
Sex(male/female)	12/28	17/23	11/29	12/28

Values are shown as number (n) of patients, mean ± SD
No significant differences were found between the two groups
ASA: American Society of Anesthesiologists

Table 2: Verbal rating scale scores of patients after infusion of ¼ of the solution

	Group 1 (n= 40)	Group 2 (n= 40)	Group 3 (n= 40)	Group 4 (n= 40)
0	0 (0%)	30 (75%)	0 (0%)	36 (90%)
1	3 (7.5%)	10 (25%)	10 (25%)	4 (10%)
2	26 (65%)	0 (0%)	30 (75%)	0 (0%)
3	11 (27,5%)	0 (0%)	0 (0%)	0 (0%)

Table 3: Verbal rating scale scores of patients after infusion of ½ of the solution

	Group 1 (n= 40)	Group 2 (n= 40)	Group 3 (n= 40)	Group 4 (n= 40)
0	0 (0%)	32 (80%)	0 (0%)	24 (60%)
1	3 (7,5%)	8 (20%)	6 (15%)	12 (30%)
2	14 (35%)	0 (0%)	32 (80%)	4 (10%)
3	23 (57,5%)	0 (0%)	2 (5%)	0 (0%)

Table 4: Verbal rating scale scores of patients after infusion of ¾ of the solution

	Group 1 (n= 40)	Group 2 (n= 40)	Group 3 (n= 40)	Group 4 (n= 40)
0	0 (0%)	32 (80%)	0 (0%)	24 (60%)
1	3 (7,5%)	8 (20%)	10 (25%)	12 (30%)
2	13 (32,5%)	0 (0%)	28 (70%)	2 (5%)
3	24 (60%)	0 (0%)	2 (5%)	2 (5%)

DISCUSSION

In this study, we aimed to evaluate the effectiveness of i.v. acetaminophen (with or without tourniquet) in comparison with lidocaine for the prevention of propofol-induced pain during induction of anaesthesia. In this study we found that acetaminophen (with or without tourniquet) and lidocaine were more effective than the control group, and the effect of acetaminophen with tourniquet was similar to that of lidocaine.

Propofol associated pain is affected by many factors like cannula 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 the pain is not well understood, propofol is known to irritate the skin, mucous membranes, and venous intima (18). 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 (19). Moreover, NSAIDs via decreasing prostaglandin synthesis and inhibit the kinin cascade, thus

reducing pain on injection of propofol.

As an alternative to NSAIDs, acetaminophen, whose action at a molecular level is still not known, has been used for management propofol related pain (20). Although it does not inhibit cyclooxygenase (COX) enzymes at therapeutic concentrations in vitro, Simmons et al (21) demonstrated a COX-2 variant, which was sensitive to acetaminophen in vivo. In a recent study, Lee and colleagues (22) showed that acetaminophen selectively suppressed peripheral prostaglandin (PG) E2 release and increased COX-2 gene expression in a clinical model of acute inflammation. Similarly, in another study, bradykinin and a bradykinin B2-receptor agonist have been shown to enhance both basal and lipopolysaccharide-induced PGE2 synthesis in rat neonatal glial cells in culture (23). Keeping in mind the fact that propofol characteristically causes vascular pain that occurs in response to prostanoids, particularly PGE2 (24), a relationship between PGE2 -selectively suppressed by acetaminophen- and bradykinin might be proposed to determine the intensity of propofol injection pain.

Previous studies have shown that the incidence of pain on injection of propofol is around 30% with lidocaine pretreatment and 60% in a saline group (17). Fujii et al (14) have comparatively studied the efficacy of lidocaine, metoclopramide, and flurbiprofen for reducing pain on injection of propofol. 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 (17), they have found that i.v. acetaminophen (50 mg) was effective, although not as much as lidocaine, in decreasing the incidence of pain during i.v. injection of propofol. In our study, we have found that i.v. acetaminophen (100 mg) with tourniquet was as effective as lidocaine, in decreasing the incidence of pain during i.v. injection of propofol. This could be due to the high dose of acetaminophen used in our study. Furthermore, we have also observed that acetaminophen with tourniquet was more effective than without in preventing pain on injection. To the best of our knowledge, this is the first time that the effect of tourniquet application during acetaminophen administration has been reported in the literature.

To summarize, according to our results, we may conclude that i.v. acetaminophen when given with tourniquet is as effective as lidocaine on propofol associated pain. Further, acetaminophen administration with tourniquet seems to be superior to acetaminophen without tourniquet. As such, although it may not be much convenient in our daily anesthesiology practice, we belive that tourniquet application facilitates propofol induced pain management.

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