Deksmedetomidin And Fentanyl Attenuate The Propofol Injection Pain

Deksmedetomidin ve Fentanil Propofol Enjeksiyon Ağrısını Gideriyor

Yrd.Doç.Dr. Ayşe MIZRAK
Yrd.Doç.Dr.Senem KORUK
Yrd.Doç.Dr. Rauf GÜL
Doç.Dr. Süleyman GANİDAĞLI
Arş.Gör.Dr. Şemsettin BOZGEYİK
Prof.Dr. Ünsal ÖNER

Gaziantep University Faculty of Medicine, Department of Anesthesiology And Reanimation

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Özet

Bu çalışmayı, venöz yol ile verilen deksmedetomidin ve fentanilin propofol enjeksiyon ağrısı üzerine olan etkisini karşılaştırmak üzere gerçekleştirdik. Genel anestezi altında elektif cerrahi geçirecek olan, premedikasyon yapılmamış (18-65 yaş), yetişkin hasta ile bir prospektif, randomize ve çift kör çalışma planladık. Hastalar gelişigüzel 3 gruba ayrıldı (n=40): Fentanil (F), deksmedetomidin (D) ve Kontrol (C). 10 mililitrelik çalışma solüsyonu sabit 10 saniye içinde enjekte edildi. Fentanil (1 µg/ kg) ya da deksmedetomidin (0.15 µg/ kg) ya da plasebo verildikten 60 saniye sonra propofol 2,5 mg/kg 20 ml/ dakika hızla infüze edildi. Enjeksiyon ağrısı four-point sözel skalası kullanılarak değerlendirildi. Propofol ilişkili enjeksiyon ağrısının oranları grup C için: %65 (26), F grubu için: %27 (16) ve grup D için %25 (10) idi. Ağrı oranı fentanil ve özellikle de deksmedetomidin grubunda kontrol grubuna göre daha azdı ($p< 0.05$). Gruplardaki şiddetli ağrı, D<F<C şeklinde idi ($p< 0.05$). F ve D gruplarının kalp atım hızları ve ortalama arteriyal kan basınçları başlangıç, 0, 5, 10, 15, 30. dakikalarda kontrol grubuna göre daha düşüktü ($p< 0.05$). D grubunun kalp atım hızları başlangıç döneminde F grubununkinden daha düşüktü ($p< 0.05$). Ayrıca, D grubunun MAP değerleri 10, 15, 30. dakikalarda F grubununkinden daha düşüktü ($p< 0.05$). Subklinik dozda deksmedetomidin ve fentanil ile premedikasyon, propofole bağlı ağrıyı ve şiddetini etkili bir şekilde azaltmıştır.

Anahtar kelimeler: Intravenöz anestezik, Propofol, Deksmedetomidin, Komplikasyonlar, Ağrı, Premedikasyon, Ağrı kesiciler, Hemodinamik değişiklikler.

Abstract

We performed this study to compare the effects of intravenous dexmedetomidine and fentanyl on propofol injection pain. We conducted a prospective, randomized and double blind study of 120 adult unpremedicated patients (18-65 years of age) scheduled to undergo elective surgery under general anesthesia. The patients were allocated randomly into three groups (n= 40): fentanyl (F), dexmedetomidine (D), and Control (C). Ten ml of the study solution was injected over 10 seconds. One minute after the administration of fentanyl (1 µg/ kg) or dexmedetomidine (0,15 µg/ kg) or placebo, propofol 2,5 mg/ kg was infused at a rate of 20 ml/ min. Injection pain was assessed using a four – point verbal rating scale. The incidence of propofol-associated injection pain were 65% (26) for group C, 27% (16) for group F, and 25% (10) for group D. The incidence of pain were less in the fentanyl, and especially in the dexmedetomidine groups than control group ($p< 0.05$). Severe pain in groups were D<F<C ($p< 0.05$). Heart rate and the mean arterial blood pressure of the groups F and D were lower than control groups at baseline, 0, 5, 10, 15, 30 minutes ($p< 0.05$). HR of the group D was lower than that group F at baseline period ($p< 0.05$). In addition, MAP of the group D was lower than that group F at 10, 15, 30 min ($p< 0.05$). Premedication of subclinical doses of dexmedetomidine and fentanyl effectively reduced propofol-induced pain and its intensity.

Key Words: Intravenous anaesthetics, Propofol, Dexmedetomidine, Complications, Pain, Premedication, Analgesics, Haemodynamic changes

Introduction

Propofol is a popular, rapidly acting drug to induce anesthesia and it provides smooth induction and rapid recovery. But it causes evoke considerable pain on intravenous (iv) injection, the incidence of which is between 40% and 86% (1). There are many factors appear to affect the incidence of pain on propofol injection. These are the size of vein, the speed of injection (2), propofol concentration in the aqueous phase (3). Several methods have been used to reduce this pain: Diluting the propofol solution, injection of propofol into a large vein (2), adding lidocaine, pre-treatment with ephedrine, ketamine, metoclopramide, thiopental and ketorolac (4-9). All have been tried with many different results. However, despite various methods to reduce propofol injection pain, the most effective methods have not been identified.

The most common method used in routine clinical practice is giving lidocaine before propofol or adding 10-40 mg of lidocaine to the propofol's syringe immediately with or without the use of a tourniquet (10). However the pain on injection still occurs about 40% despite this treatment and lidocaine does not completely eliminate this type of pain (4,10). It was reported that the addition of lidocaine may destabilise the emulsion formulation of propofol with a potential risk of causing pulmonary fat embolism (11).

One approache to reduce pain during propofol injection is the use of opioids. The use of fentanyl was found to be an effective preventor of propofol injection pain. Pang et al. reported that fentanyl reduced the intensity of propofol injection pain ($p<0.05$)(12).

Dexmedetomidine (D) is a potent, highly specific and selective $\mathbf{a}_2$ -adrenoceptor agonist, with potent sedative, analgesic and sympatholytic effects (13). Turan et al. concluded that dexmedetomidine decreases propofol injection pain as effectively as lidocaine (14).

Yrd. Doç. Dr. Ayşe MIZRAK, Gaziantep Üniversitesi Tıp Fakültesi, Anesteziyoloji ve Reanimasyon AD.
Adres: : Gaziantep Üniversitesi Tıp Fakültesi, Şehitkamil / GAZİANTEP
Gsm: 0533 718 10 25 **Fax:** 0342 360 22 44 **E-mail:** aysemizrak@mynet.com

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To date there are no studies comparing effects of fentanyl and dexmedetomidine on propofol injection pain in adults. The aim of the present study was to compare the effects of premedication with subclinical doses of fentanyl and dexmedetomidine on pain on propofol injection regarding the incidence and severity of pain and hemodynamic variables in adults.

Materials And Methods

The work presented has been performed in accordance with the most recent version of the Helsinki Declaration. After approval by the Institutional Ethics Committee, we obtained a written informed patient consent prior to enrolment in the study. 120 adult patient of ASA physical status I-II aged 18-65 years who were scheduled for elective thyroidectomy or cholecystectomy under general anesthesia were included in the study.

Patients having problems in communication, pregnancy, taking regular analgesics, suffering from acute or chronic pain syndromes, under the influence of a sedative medication within 24 hr before surgery, patients with sensitivity to propofol or lidocaine or fentanyl, or who have heart blocks, heart failure, hepatic failure, neurologic disease, and psychiatric disease were excluded from the study.

No patient was premedicated. Patients were randomly assigned into three groups to receive iv. either dexmedetomidine (D) 0,15 µg/ kg, or fentanyl (F) 1 µg/ kg or placebo solution (NS: Normal saline). A randomization list was prepared by a random number function on a computer spread sheet. All solutions were prepared immediately prior to induction by an assistant who took no further active part in this trial and an independent anesthesiologist, who was unaware of group assignments, assessed the level of pain. All study drugs were made into 10 ml with NS. On arrival to the holding area of the operating room, a 20-G cannula was inserted into the vein on the dorsum of the left hand. In the operating room all the patients were monitored with an electrocardiogram (ECG), pulse oximeter and an automatic non-invasive blood pressure device.

The solution was infused over 10 seconds through the iv. line in a vein on the dorsum of the hand without venous occlusion. One minute after the administration of fentanyl (1µg/ kg) (Fentanyl-Janssen, 5 ampoules, 0.05 mg/ ml) or dexmedetomidine (0,15 µg/ kg) (Precedex, Abbott, 200 µg/ 2 ml) or placebo solution, propofol (2,5 mg/ kg) (Propofol 1% Fresenius, 10 mg/ml) was infused at a rate of 20ml/ min at room temperature. In the same time 150 ml/ hr NS was run through which the propofol was injected. During the first 25% of propofol dose had been given, patients were continuously observed and injection pain was evaluated by arm withdrawal movement and vocal response to our question regarding the presence of pain or discomfort using a four-point verbal rating scale that had been previously explained to the patients.

Verbal Rating scale: 0 = none (negative response to questioning); 1 = mild pain (pain reported only in conresponse to questioning without any behavioral signs); 2 = moderate pain (pain reported in response to questioning and accompanied by behavioral signs or pain reported spontaneously without questioning); and 3 = severe pain (strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears) (15). At this time point patients were not still sedatized.

After patients fell asleep, they were given 0.1 mg/ kg vecuronium, 6 L/ min oxygen with N_2O and 1-3% sevoflurane during ventilation via a face mask. Three minutes after vecuronium injection, the trachea was intubated. Non invasive mean arterial blood pressure (MAP) and heart rate (HR) were recorded at 5 and 15-minute intervals from just before the injection of study drugs (baseline value) to 30 minutes after the drug administration. Hypotension was defined as a reduction of the systolic arterial blood pressure below 90 mmHg. Bradycardia was defined as a reduction of the heart rate below 50 beats/ min. Within 24 hr after the operation, the injection site was checked for pain, edema and wheal and flare response by a researcher blinded to group assignment.

Statistical analysis was carried out using SPSS version 15.0. The demographic characteristics of each group were compared using analysis of variance. For between-group analyses, one-way analysis of variance was used to compare the parametric (the arterial blood pressure and heart rate) data and the incidences and the intensities of propofol-induced pain on injection among groups were compared using Kruskal-Wallis test. All data are expressed as mean ± standart deviation (SD) or number (%). $P< 0.05$ was considered significant. All reported P-values are two sided.

Results

Demographic data were similar in all groups (Table 1). The incidence of patient who experienced no pain were 35% (14) for group C, 62.5% (25) for group F, and 75% (30) for group D. The patients in group D and F had significantly smaller pain scores compared with group C ($p< 0.05$). The total incidence of propofol-associated injection pain were 65% (26) for group C, 27% (16) for group F, and 25% (10) for group D. With respect to pain severity of the infusion, only 1 (2.5%) patient in group D, 7 patients in group F (17.5%) and 17 patients in group C (42.5%) experienced high- grade pain (score 3). The intensity and incidence of pain in groups F and D were lower than in group C ($p< 0.05$). In addition severe pain scores in group D was significantly lower than that in group F ($p< 0.05$, Table 2).

HR of group F and D were lower than that group C at 0, 5, 10, 15, and 30 minutes after induction of anesthesia. In addition, HR of the group D was lower than that group F at baseline period ($p< 0.05$, Figure 1, Table 2).

Table 1. Demographic Data of The Groups.

	Group C	Group F	Group D
Age(yr)	40±11	39±13	42±13
Sex(M/F)	19/21	17/23	11/29
	(47.5%/52.5%)	(42.5%/57.5%)	(27.5%/72.5%/)
ASA Class	18/22	20/20	17/23
(I/II)	(45%/55%)	(40%/50%)	(42.5%/57.5%)
Weight(kg)	65±8	66±9	66±14

p> 0.05 Data are presented as either number of patients or mean ± SD.

n= 40 in all groups.

MAP was significantly decreased in groups D and F compared with in group C at baseline, 5, 10, 15, 30 minutes after induction of the anesthesia. In addition, MAP of the group D was lower than that group F at 10, 15, 30 min (p< 0.05, Figure 2, Table 2). Three patients in group D developed hypotension that required ephedrine (10 mg, iv), and 2 patients group F developed bradycardia that required atropin (0.015 mg/ kg, iv) treatment.

There was no other adverse event such as dysrhythmias, allergic reactions, or cardiovascular collapse during induction and pain, edema, wheal and flare response at the injection site within the first 24 hr after the operation.

Discussion

In our study we observed that pretreatment with small doses of dexmedetomidine (0.15 µg/ kg) or fentanyl (1µg/ kg) was effective to attenuate the incidence and intensity of propofol injection pain without serious side effects.

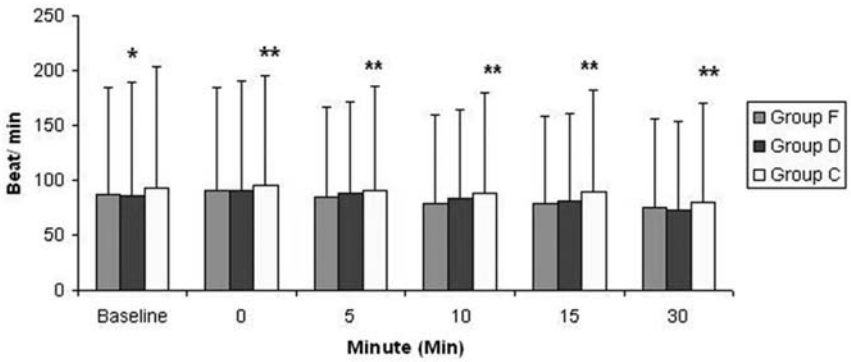
Propofol is a hindered phenol that is chemically dissimilar to any other compounds used in anesthesia. Propofol has a high incidence of pain on injection when compared to other intravenous anaesthetic agents. Pain on injection with propofol is a common problem can be very distressing to the patient.

The incidence of pain varies between 80% to 90% of patients. Propofol, by an indirect action on the endothelium, activates the kallikrein-kinin system and releases bradykinin, thereby producing venous dilation and hyperpermeability, which increases the contact between the aqueous phase of propofol and free nerve endings, resulting in pain on injection. Many different factors have been associated with this phenomenon, including temperature of the solution, size of the vein and speed of injection. There is no gender difference in the incidence of propofol. In addition, various methods have been used for attenuating pain during IV injection of propofol such as prior injection of lidocaine, thiopental, alfentanyl, fentanyl.

Table 2. Total pain score of the groups.

	Group C Median (IQR)	Group F Median (IQR)	Group D Median (IQR)	Kruskal-Wallis χ^2	p
Total Pain Score	0.6(0.07)	0.4(0.07)*	0.2(0.06)®	0.0000	0.001

n= 40, *® p< 0.05 when compared with group C.



n=40

*p< 0.05 When compared with group F.

**p< 0.05 When compared with group F and D.

Figure 1. HR of group F and D were lower than that group C at 0, 5, 10, 15, and 30 minutes after induction of anesthesia (p< 0.05). HR of the group D was lower than that group F at baseline period (p< 0.05).

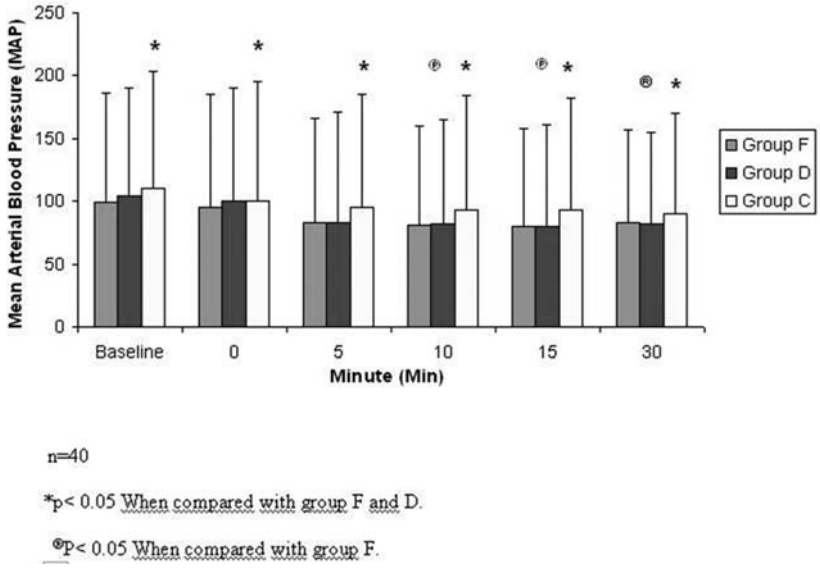


Figure 2. MAP was significantly decreased in groups D and F compared with in group C at baseline, 5, 10, 15, 30 minutes (p< 0.05). MAP of the group D was lower than that group F at 10, 15, 30 min (p< 0.05).

Despite the good results of studies which ephedrine (70µg/kg), ketamine (0.5mg/kg) lidocaine/metoclopramide combination and ketorolac were used nevertheless, propofol injection pain still occurs at a significant rate. After those reports, we tested fentanyl (1 µg/ kg) versus dexmedetomidine (0.15 µg/ kg) given 1 min before injection of propofol. We found that the pretreatment with low doses of dexmedetomidine and fentanyl significantly reduced the incidence of pain and its intensity during injection of propofol.

Dexmedetomidine, an imidazole compound, is the most recently developed and released agent for use in the ICU. It has an 8 times greater affinity for the $\mathbf{a}_{2}$-receptor and shorter acting than clonidine.

In the present study, the intensity and incidence of pain were decreased by fentanyl and dexmedetomidine when compared with placebo (SF). In addition severe pain scores in group D was significantly lower than that in group F. Similar to the present study, Turan et al reported that dexmedetomidine decreases propofol injection pain as effectively as lidocaine, and can be an alternative to other pretreatment drugs. However, Ayoglu et al concluded that pretreatment with dexmedetomidine is not effective in reducing injection pain of propofol. The different doses they have used and the diffrent application methods may have been the main reason of these various results. Turan et al. and Ayoglu et al. prefered to use 0.25 µg/kg of dexmedetomidine with the tourniquet technique. But we used 0.15 µg/kg of dexmedetomidine without tourniquet. Dexmedetomidine has potent sympatholytic, analgesic and sedative properties mediated through $\mathbf{a}_{2}$ –adrenoceptors in the central and peripheral nervous systems . We can explain our results of dexmedetomidine with these effects. Fentanyl is an opioid and decreases pain associated with surgery and is commonly used as a pre- induction adjunct because of its quick onset.

Different results have been reported with the use of fentanyl. In this study, fentanyl was as effective as dexmedetomidine to decrease the incidence of propofol pain but less effective in the severity of pain. Similar to our study there are many previous reports. In Kobayashi et al's. trial, none of patients receiving pretreatment with fentanyl plus, cold propofol mixed with lidocaine reported the pain.

Bahar et al. reported that fentanyl 0.1 mg 3-5 min before propofol injection decreased the severity of pain but not the overall incidence. However a significant reduction in the incidence of propofol injection pain from 40% to 16% with the use of fentanyl (0.5 µg/ml) was reported by Helmers et al. In contrast to Helmers et al. we used a higher dose of (1 µg/kg) of fentanyl. Basaranoglu et al. compared fentanyl with remifentanyl and reported that using lidocaine alone was much more effective than fentanyl. Pang et al. informed that fentanyl reduced the intensity of propofol injection pain (p< 0.05). The site of action of opioids in reducing pain may be either peripheral or central.

Opioid receptors are present at peripheral sensory nerve terminals in humans. In most of studies it was reported that fentanyl was effective in reducing the propofol injection pain. The differences may have been due to the different doses and techniques they have used. It is possible that the reduction in injection pain was the result of peripheral action on peripheral terminal afferent nerves.

While dexmedetomidine has been shown to promote peripheral antinociception, its mechanism of action has not yet been clearly understood. However there are studies suggesting a novel role for inwardly rectifying hyperpolarization-activated conductance in peripherally mediated antinociception.

There was no significant difference between the groups regarding respiratory and hemodynamic side effects as none of the patients experienced respiratory depression, hypoxemia and vomiting. In this study, we observed that only three patients in group D developed hypotension that required ephedrine (10mg, iv), and 2 patients in group F developed bradycardia that required atropin (0.015 mg/ kg, iv) treatment. In Turan et al's and Ayoglu et al.'s studies, the haemodynamics did not measured. Therefore we could not compare our results with them. Dexmedetomidine possesses a dose-dependent bradycardiyac effect and hypotension. Slow bolus loading or ommiting bolus loading prevents initial hypertension and reflex bradycardia. Similarly, high concentration of fentanyl can decrease the blood pressure and the heart rate and cause respirator depression when infused with a high rate. With this in mind, the low dose of dexmedetomidine was given in this study.

Minimazing propofol injection pain is an important clinical goal because it may influence the patient's perception of quality and acceptability of anesthesia. Lidocaine was studied by Newcombe, Nathanson and King et al. and it was showed that there was an inverse relationship between the amount of lidocaine used and the incidence of pain. Mixing lidocaine 10 mg or 40 mg or 20 mg respectively was shown to decrease the incidence of propofol injection pain from 86.9% to %48.9 in Newcombe's.study, from 67% to 13% in Nathanson's study, and from 73% to 32% in King's study. Though lidocaine is accepted as an active and standart drug to prevent propofol injection pain, it was reported that lidocaine pretreatment with a rubber tourniquet on the forearm was effective to decrease pain on injection.

However, the failure rate was about 40% despite lidocaine treatment . In this study, the failure rate was 27% in group F and 25% in group D. The incidence of severe pain was 17.5% in group F, 2.5% in group D and 42.5% in group C.

In conclusion, we compared the effect of dexmedetomidine and fentany on injection pain. Premedication of subclinical doses of dexmedetomidine or fentanyl was effective to reduce propofol-induced pain and its intensity without significant hemodynamic side effects.

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