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The Effect of Nicotine Treatment on Propofol Injection Pain

Propofol İnjeksiyon Ağrısına Nikotin Tedavisinin Etkisi

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Objectives: Smokers had higher risk than nonsmokers for pain. The incidence of pain on injection of propofol has been reported to be 70%. We explored the relationship between smoking habits and propofol injection pain, whether nicotine replacement has an influence on intensity or incidence of pain associated with propofol in smokers.

Patients and Methods: Two hundred patients ASA (American Society of Anesthesiologists) physical status 1, undergoing elective surgical procedures were studied. Hundred (50-50) patients who used cigarette were included in smoker group and nicotine group. Hundred (50-50) patients who never used tobacco were included in nonsmoker (NS) group and NS+nicotine group. Prior to surgery, the anesthesiologist gave a nicotine gum to nicotine group which was randomized in smokers and nonsmokers. The severity of propofol injection pain was evaluated using four point scale (none, mild, moderate, and severe).

Results: Incidence of pain was higher in the smoker group compared with the nonsmoker, nicotine and NS+nicotine groups. The intensity of mild pain was higher in the smoker group compared with the nonsmoker group. The intensity of moderate+severe pain was lower in the NS+nicotine group compared with the nonsmoker and smoker and nicotine groups.

Conclusion: The incidence of propofol injection pain and intensity of mild pain increased in smokers deprived of nicotine. Nicotine replacement in these patients reduced the incidence of propofol injection pain similar to nonsmokers. When nonsmokers were given nicotine, intensity of moderate+severe pain decreased. These results suggest that smokers' awareness of pain increases and nicotine has an analgesic effect.

Key words: Propofol injection pain; smoker; nicotine.

Amaç: Sigara içenlerde içmeyenlere oranla ağrı riski daha fazladır. Propofol injeksiyon ağrısının insidansı %70'tir. Bu çalışmada, sigara içme alışkanlıkları ile propofol injeksiyon ağrısı arasındaki ilişkiyi, sigara içenlerde nikotin replasmanının propofol injeksiyon ağrısının yoğunluk ve insidansı üzerine etkisi olup olmadığını araştırdık.

Hastalar ve Yöntemler: Elektif cerrahi girişim geçirecek olan ASA (American Society of Anesthesiologists) fiziksel durumu I, iki yüz hasta, sigara kullananlar (50'si sigara içenler-50'si sigara içenler/nikotin replasmanı yapılanlar) ve sigara kullanmayanlar (50'si sigara içmeyenler, 50'si sigara içmeyenler/nikotin replasmanı yapılanlar) olarak rasgele gruplandırıldılar. Cerrahi öncesi anestezist, rasgele olarak sigara içenlerin 50'sine ve sigara içmeyenlerin 50'sine nikotin sakızı verdi. Propofol injeksiyon ağrısının şiddeti, dört nokta skalası (hiç, hafif, orta, şiddetli) kullanılarak değerlendirildi.

Bulgular: Ağrı sıklığı, sigara içenler grubunda sigara içmeyenler grubuna, sigara içen/nikotin grubuna, sigara içmeyen/nikotin grubuna oranla daha yüksekti. Hafif ağrının yoğunluğu, sigara içenler grubunda, sigara içmeyenler grubundan daha yüksekti. Orta şiddetli ağrının yoğunluğu, sigara içmeyen/nikotin grubunda; sigara içmeyenler, sigara içenler ve sigara içenler/nikotin grubuna oranla daha düşüktü.

Sonuç: Propofol injeksiyon ağrısının sıklığı ve hafif ağrının yoğunluğu, nikotinden mahrum edilen sigara içicilerinde artmıştır. Bu hastalardaki nikotin replasmanı, propofol injeksiyon ağrısının insidansını sigara içmeyenler düzeyine düşürmüştür. Sigara içmeyenlere nikotin verildiğinde, orta ve şiddetli ağrının yoğunluğu azalmıştır. Bu sonuçlar göstermektedir ki; sigara içenlerde ağrının farkındalığı daha fazladır ve nikotinin analjezik etkisi vardır.

Anahtar sözcükler: Propofol injeksiyon ağrısı; sigara içicileri; nikotin.

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It is generally accepted by anesthetists that smokers are more prone to peroperative complications such as coughing and desaturation. It is also established that smokers are more prone to postoperative complications such as atelectasis and respiratory infections.[1] A positive association has been found between smoking and pain at body sites, including the back, neck, shoulder and legs in epidemiological surveys that have examined the link.[2-5] A study has observed that smoking is associated with an increased use of narcotics by patients with chronic pain.[6] However, in controlled laboratory conditions, the acute effect of cigarette smoking has been demonstrated to either increase or decrease the tolerance for controlled painful stimulus.[7,8] Several explanations for the association have been proposed. Smoking might provoke disc herniation through coughing, or lead to pathological changes in the intervertebral disc through alterations in its nutrition, pH, or mineral content.[9-11] Another possibility is that smoking has a pharmacological effect on pain perception.

Propofol is most commonly used intravenous anesthetic. However, pain on injection is a major disadvantage with reported incidence of approximately 70% when a standard formulation of propofol administered with no intervention to reduce pain.[12] The cause of this injection site pain is obscure and there are several proposed mechanisms. Propofol may activate the kallikrein-kinin system and release bradykinin, thereby producing venous dilatation and hyperpermeability, which increases the contact between the aqueous phase of propofol and free nerve endings resulting in pain on injection.[13,14]

The purpose of this study was to explore the relationship between smoking habits and pain on injection of propofol. We also investigated whether nicotine replacement has an influence on intensity or incidence of pain associated with propofol in smokers.

PATIENTS AND METHODS

According to the Principles of Helsinki Declaration, after obtaining the approval of the Local Ethics Committee and written informed consent from the patients, 200 patients ASA (American Society of Anesthesiologists) physical status 1, undergoing elective surgical procedures were studied.

Hundred (50-50) patients who used more than five cigarettes a day and who are used to smoking more than five years were included in smoker group and nicotine group. Hundred (50-50) patients who has never used tobacco in their life time were included in nonsmoker (NS) group and NS+nicotine group. The exclusion criteria were patients having diffuculty in communication, obesity (body mass index >30 kg/m^2), diffuculty in venous access.

One hour prior to surgery, the anesthesiologist gave a nicotine chewing gum (Nicotinell 2 mg, Novartis, Nyon, Swiss) to the group of smokers and nonsmokers randomized to recieve nicotine.

On arrival in the operating room, a 20 gauge intravenous canula was inserted in the dorsum of the nondominant hand after placing the routine monitors. Patients did not receive any sedatives or analgesics before entering operating room.

The induction of propofol (propofol 1% Fresenius Kabi, Hamburg-Germany) was 2.5 mg/kg. 10 mL propofol (at room temperature) was injected over 30 seconds. Other investigators, who were unaware of the patients smoking status, assessed the level of pain. Intravenous propofol induction of anaesthesia was completed with the remaining dose of propofol and tracheal intubation was facilitated with vecuronium. Anesthesia was maintained with 40% O_2 in N_2O, sevoflurane and fentanyl.

The severity of propofol injection pain was evaluated using the four point scale.[15] Expression of pain by strong vocal response or response accompained by facial grimacing, or withdrawal of arm, or tears was scored as 3 = severe pain. If these signs and symptoms were absent then patients were questioned every 10 s during induction regarding the presence of pain or discomfort. Negative response to questioning was scored as 0 = none. Pain reported in response to questioning only, without any behavioral signs was scored as 1 = mild pain. Pain reported in response to questioning and accompanied by a behavioral sign, or pain reported spontaneously without questioning was scored as 2 = moderate pain.

Data are expressed mean±SD or number (%). Statistical analysis was performed using the GraphPad InStant (GraphPad Software V2.O2). Statistical significance was determined by Student's t-test, analysis of variance and X^2. All tests were considered significant at $p<0.05$.

RESULTS

Groups were comparable with respect to age, weight and height of patients (Table 1).

Incidence of propofol injection pain scores in each group is shown in Table 2. There was a significant difference in the incidence of injection induced pain. The incidence of pain was more frequent in the smoker group compared with the nonsmoker group (78% versus 54%, respectively; p=0.02) and the NS+nicotine group (78% versus 46%, respectively; p=0.002) and the nicotine group (78% versus 56%, respectively; p = 0.033).

The intensity of mild pain was higher in the smoker group compared with the nonsmoker group (38% versus 18%, respectively; p=0.045). The intensity of severe pain was higher in the smoker group compared with the the NS+nicotine group (22% versus 6% respectively; p=0.044). The incidence and intensity of pain were similar in the nonsmoker group and the NS+nicotine group and the nicotine group (p>0.05).

Table 1. Patients characteristics

Characteristic	Nonsmoker group (n=50)	NS+Nicotine group (n=50)	Smoker group (n=50)	Nicotine group (n=50)
Age (y)	31.6±6.6	32.6±6.1	33.9±7.2	33.8±6.7
Weight (kg)	68.3±8.7	70.7±10.4	70.1±13.3	69.8±11.1
Height (cm)	168.8±7.8	167.6±6.7	169.3±8.9	168.5±7.2
Sex (M/F)	27/23	30/20	28/22	28/22
Duration of smoking (y)	–	–	15.7±6.1	13.8±5.4
Amount of smoking (cigarettes/day)	–	–	13.1±5.8	12.8±5.4

Values are presented as mean±SD.

The intensity of moderate+severe pain was 36% (n=18) in the nonsmoker group and 14% (n=7) in the NS+nicotine group and 40% (n=20) in the smoker group and 36% (n=18) in the nicotine group.The intensity of moderate+severe pain was lower in the NS+nicotine group compared with the nonsmoker group (14% versus 36%, respectively; p=0.02) and the smoker group (14% versus 40%,respectively; p=0.007) and the nicotine group (14% versus 36%, respectively; p = 0.002).

DISCUSSION

In this study, we demonstrated that incidence of propofol injection pain and intensity of mild pain were increased in smoker group. When the smokers were given nicotine before propofol injection, pain was reduced similar to nonsmokers. When the nonsmokers were given nicotine, incidence of propofol injection pain remained the same but intensity of moderate+severe pain decreased.

Propofol is only minimal soluble in water and is therefore formulated in a soybean oil-based fat emulsion. It belongs to the group of phenols, which can irritate the skin, mucous membrane, and venous intima.[15] There are many factors which are known to influence propofol-induced pain, such as vein size, speed of injection, diluting it with glucose or intralipid, temperature of propofol, pretreatment with IV injection of lidocaine, ketamine, opioid or thiopental and mixing lidocaine in propofol.[16,17] Our study showed that smoking status could also effect pain during IV injection of propofol.

Smoking habits were related to age, social class, reported of headaches, tiredness or stress. Current and ex-smokers had higher risks than life-time nonsmokers for pain. There is a positive association between smoking and report of regional pain.[18] This could arise from a pharmacological effect of tobacco smoke (for example, on neurological processing of sensory information or nutrition of peripheral tissues); another possibility is that these people have a low threshold for pain. Smokers deprived of nicotine required more opiates for postoperative pain control than did nonsmokers.[19,20] Patients who smoked had worse postoperative pain scores than nonsmokers.[21]

The mechanism of nicotine-mediated cholinergic analgesia appears to involve several pathways. Nicotine acts on nicotinic cholinergic receptors in both brain and spinal cord to activate spinal cord descending inhibitory pain pathways. Antinociceptive effect of nicotine was demonstrated in rodents and it was shown in some studies that smoking tobacco cigarettes decreased sensitivity to pain, at least in some tests.[22] Antinociception from neuronal nicotinic receptor activation has been demonstrated in several animal models and is thought to result from activation of native descending inhibitory pain pathways.[23,24] Inhibition of nicotinic receptors by nicotinic antagonists enhances pain sensitivity whereas treatment with the classical agonist nicotine prevents the pain enhancing action of isoflurane.[25] Studies in both smoking and nonsmoking human volunteers have

Table 2. Pain scores

Pain score	Nonsmoker group (n=50)	NS+Nicotine group (n=50)	Smoker group (n=50)	Nicotine group (n=50)
None	23 (46)*	27 (54)**	11 (22)	22 (44)†
Mild	9 (18)	16 (32)	19 (38)‡	10 (20)
Moderate	10 (20)	4 (8)	9 (18)	12 (24)
Severe	8 (16)	3 (6)§	11 (22)	6 (12)

*p=0.02 versus smoker group; †p=0.033 versus smoker group; ‡p=0.045 versus nonsmoker group; **p=0.002 versus smoker group; §p=0.044 versus smoker group; values are presented as n (%).

shown that nicotine has a mild to moderate analgesic effect in experimental paradigms including heat-induced pain, cold-induced pain and pain induced by electrical shock.[26-28]

Treatment with single dose of nicotine immediately before emergence from anesthesia was associated with lower pain scores during first day after surgery in nonsmokers.[29] In this study, in smokers deprived of cigarettes, the incidence of pain on propofol injection increased. The increased pain might be associated with discontinuation of nicotine in nicotine-dependent patients or low threshold for pain in smokers. However, nicotine replacement in these patients reduced the incidence of propofol injection pain to nonsmokers' and nicotine administration to nonsmokers reduced the intensity of moderate+severe pain. Hong et al.[30] also found similar results in their study with 40 nonsmokers undergoing pelvic or abdominal surgery, in which patients were given placebo, 5, 10, or 15 mg/16 h nicotine patches before surgery. They concluded that nicotine treatment resulted in lower pain scores and lower amounts of morphine consumption postoperatively. However, authors found no evidence of a nicotine dose–response relationship. Habib et al.[31] reported on 90 nonsmoking men undergoing retropubic prostastectomy who were treated with placebo or transdermal nicotine 7 mg/24 h 30-60 min before surgery. There was no significant difference in self-reported pain score, but patients who received nicotine used significantly less morphine via PCA at 6 and 24 h. Plasma nicotine concentrations measured at 6, 12, and 24 h after surgery were negatively correlated with morphine consumption. In contrast to our study, Turan et al.[32] who studied 97 women undergoing abdominal hysterectomy found that pretreatment with transdermal nicotine 21 mg/24 h patches, beginning 1 h before induction of anesthesia and continuing for two days after surgery, provided no benefit with respect to postoperative pain. There was no difference between nicotine and placebo patch-treated patients. In conclusion, the possible explanations for these results are that nicotine has an analgesic effect. This action also occurs in smokers who experience chronic changes in nicotinic receptor pharmacology and smoking status could also effect pain during IV injection of propofol.

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