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SCIENTIFIC ARTICLE

Lidocaine alleviates propofol related pain much better than metoprolol and nitroglycerin

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KEYWORDS

Propofol pain;
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Abstract

Background and objectives: Injection pain after propofol administration is common and may disturb patients' comfort. The aim of this study was to compare effectiveness of intravenous (iv) nitroglycerin, lidocaine and metoprolol applied through the veins on the dorsum of hand or antecubital vein on eliminating propofol injection pain.

Method: There were 147 patients and they were grouped according to the analgesic administered. Metoprolol ($n=31$, Group M), lidocaine ($n=32$, Group L) and nitroglycerin ($n=29$, Group N) were applied through iv catheter at dorsum hand vein or antecubital vein. Pain was evaluated by 4 point scale (0 – no pain, 1 – light pain, 2 – mild pain, 3 – severe pain) in 5, 10, 15 and 20th seconds. ASA, BMI, patient demographics, education level and the effect of pathways for injection and location of operations were analyzed for their effect on total pain score.

Results: There were no differences between the groups in terms of total pain score ($p=0.981$). There were no differences in terms of total pain score depending on ASA, education level, location of operation. However, lidocaine was more effective when compared with metoprolol ($p=0.015$) and nitroglycerin ($p=0.001$) among groups. Although neither lidocaine nor metoprolol had any difference on pain management when applied from antecubital or dorsal hand vein ($p>0.05$), nitroglycerin injection from antecubital vein had demonstrated statistically lower pain scores ($p=0.001$).

Conclusion: We found lidocaine to be the most effective analgesic in decreasing propofol related pain. We therefore suggest iv lidocaine for alleviating propofol related pain at operations.

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PALAVRAS-CHAVE

Dor no local da
injeção de propofol;
Lidocaína;
Nitroglicerina;
Metoprolol

Lidocaína é mais eficaz do que metoprolol e nitroglicerina para o alívio da dor relacionada à injeção de propofol

Resumo

Justificativa e objetivos: A dor no local da injeção após a administração de propofol é comum e pode causar desconforto nos pacientes. O objetivo deste estudo foi comparar a eficácia de nitroglicerina, lidocaína e metoprolol, aplicados intravenosamente através de veias do dorso das mãos ou antecubitais, para eliminar a dor causada pela injeção de propofol.

Métodos: Foram alocados em grupos 147 pacientes de acordo com o analgésico administrado: metoprolol (n = 31, Grupo M), lidocaína (n = 32, Grupo L) e nitroglicerina (n = 29, Grupo N). Os analgésicos foram aplicados via cateter intravenoso em veia do dorso da mão ou antecubital. A dor foi avaliada com uma escala de quatro pontos (0 = sem dor, 1 = dor leve, 2 = dor moderada, 3 = dor intensa) nos segundos cinco, 10, 15 e 20. Os dados demográficos dos pacientes, estado físico ASA, IMC, nível de escolaridade, efeito das vias de injeção e local das cirurgias foram analisados quanto a seus efeitos no escore total de dor.

Resultados: Não houve diferença entre os grupos em relação ao escore total de dor (p = 0,981). Não houve diferença no escore total de dor em relação ao estado físico ASA, escolaridade e local da cirurgia. No entanto, lidocaína foi mais eficaz em comparação com metoprolol (p = 0,015) e nitroglicerina (p = 0,001), na comparação entre os grupos. Embora lidocaína e metoprolol não tenham apresentado diferença no tratamento da dor quando aplicados em veia antecubital ou do dorso da mão (p > 0,05), a injeção de nitroglicerina em veia antecubital apresentou escores de dor estatisticamente menores (p = 0,001).

Conclusão: Lidocaína mostrou-se como analgésico mais eficaz para diminuir a dor relacionada à injeção de propofol. Sugerimos, portanto, lidocaína IV para aliviar a dor relacionada à injeção de propofol em operações.

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Introduction

Propofol is an intravenous agent which is often preferred for same day surgery and has short period effects. Injection pain is the most common pain and one of the adverse effects disturbing patients' comfort. Injection pain incidence rate is 28–90% for adults in the course of induction.^{1,2} Various methods and drugs are tested and suggested in order to eliminate injection pain caused by Propofol. For this purpose, some studies about injection speed of propofol, temperature of propofol and the vein immensity have been carried out for decreasing pain. Before propofol injection, some drugs such as alfentanil, tramadol, ketamine, fentanyl, morphine, meperidine, metoprolol and lidocaine have been used and the effectiveness of these drugs on eliminating injection pain has been tested.^{3–10}

Although there are many researches on analgesic effects of transdermal nitroglycerin, researches about effectiveness of nitroglycerin on eliminating propofol injection pain are limited.² The aim of this study was to compare effectiveness of intravenous (iv) nitroglycerin, lidocaine and metoprolol applied through the veins on the dorsum of hand on eliminating propofol injection pain and the main purpose of this study was to ensure satisfaction of patients.

Methods

After the approval of patients and hospital ethics committee, 92 patients at the ages between 19 and 70 years have been involved in the randomized double blind method for

the research planned in elective conditions at HM (Health Ministry) Ankara Training and Research Hospital in accordance with classification group I and II of American Society of Anesthesiologist. Hypertensive patients, diabetic patients or patients with another neuropathy, patients whose body mass index is 35 kg m^{-2} or above, patients with allergy to these drugs and with Parkinson's disease, with thrombophlebitis story have been excluded from this research.

Routine monitorization including ECG, pulse oximeter and non-invasive blood pressure have been applied to patients who have undergone intramuscular (im) premedication with 50 mg meperidine and 0.5 mg atropine after intravenous line (iv) has been opened at the dorsum hand vein with 20 G catheter. Drugs that had to be used in the research have been prepared as 2 ml in total and numbered by a researcher independent from applicator. After venous discharge, tourniquet were applied to arm manually for 45 s and 2 mg metoprolol to 31 patients in Group M, 20 mg lidocaine to 32 patients in Group L, 0.25 mg nitroglycerin to 29 patients in Group N were applied through iv catheter at dorsum hand vein. After tourniquet was loosened up, for anesthesia induction 2 mg/kg propofol was injected with a flow of 2 ml in 4 s. The administration pathways were used for comparison of different analgesics.

Pain during injection was evaluated in the 4 point scale (0 – no pain, 1 – light pain, 2 – mild pain, 3 – severe pain) at 5, 10, 15 and 20th seconds. Patients were grouped according to their education levels as: 1 – illiterate, 2 – primary school, 3 – secondary school, 4 – high school, 5 – university and comparison between education level and total pain

score was done. ASA classification and BMI were compared with total pain score using the abovementioned scale. In the pre-operative period, after propofol induction and shortly after intubation 5 min later, heart rate and blood pressure were recorded. The fifteenth second was determined as the main time because pain frequency was observed in this time at most. In that case, total pain score instead of pain score measured after injection is more effective in reflecting satisfaction of patients and total life quality score. Location of operation was recorded and it was compared with total pain score. The location was numbered as 0 – head-neck ($n=65$), 1 – thorax ($n=1$), 2 – upper abdomen ($n=23$), 3 – lower abdomen and pelvis ($n=57$), 4 – extremity and paraspinal area ($n=31$). The operation at thorax was not included into the evaluation because there was only one patient.

ANOVA variance analysis has been used for statistical analysis of the results and demographic data and χ^2 test has been used for comparison of groups in terms of pain. Because the distribution of groups was normal, pulse oximetry, arterial blood pressure and heart rate measurements among groups were evaluated according to the variance analysis and Bonferroni test. A $p < 0.05$ was considered significant.

Results

The mean age of the patients was 40 years (range, 19–70 years) and the mean BMI (body mass index) was $25.34 \pm 3.94 \text{ kg m}^{-2}$. There were 81 female and 66 male patients. No difference was found among the groups in terms of demographical data such as age, gender, and body mass index ($p > 0.05$). Also there were no differences in terms of total pain score depending on education level ($p > 0.05$). Number of patients with pain according to time intervals while administration of analgesic from antecubital area and dorsum of hand are shown in Tables 1 and 2. Also number of patients with pain when lidocaine ($n=60$), metoprolol

Table 1 Number of patients with pain according to time intervals while administration of analgesic from back of hand.

Patients with pain at	Group L ($n=32$)	Group M ($n=31$)	Group N ($n=29$)	p
5th sec	1	5	9	0.052
10th sec	6	9	18	0.023
15th sec	6	11	22	0.001
20th sec	3	14	22	0.001

L, Lidocaine; M, Metoprolol; N, Nitroglycerin.

Table 2 Number of patients with pain according to time intervals while administration of analgesic from antecubital area.

Patients with pain at	Group L ($n=29$)	Group M ($n=27$)	Group N ($n=29$)	p
5th sec	0	3	3	0.095
10th sec	0	5	4	0.261
15th sec	2	6	6	0.589
20th sec	0	4	10	0.011

L, Lidocaine; M, Metoprolol; N, Nitroglycerin.

Table 3 Number of patients with pain when Lidocaine ($n=60$) was injected from different pathways.

Patients with pain at	Group E ($n=31$)	Group A ($n=29$)	p
5th sec	1	1	1.0
10th sec	6	6	0.101
15th sec	6	2	0.317
20th sec	3	3	0.228

A, antecubital area; E, back of hand.

Table 4 Number of patients with pain when Metoprolol ($n=59$) was injected from different pathways.

Patients with pain at	Group E ($n=32$)	Group A ($n=27$)	p
5th sec	5	1	0.108
10th sec	3	2	0.463
15th sec	11	6	0.712
20th sec	14	4	0.071

A, antecubital area; E, back of hand.

($n=59$) and nitroglycerin ($n=58$) were injected from different pathways are shown in Tables 3–5. Although neither lidocaine nor metoprolol had any difference on pain management when applied from antecubital or dorsal hand vein ($p > 0.05$), nitroglycerin injection from antecubital vein had demonstrated statistically lower pain scores ($p = 0.001$).

Total pain score in women was 1.63 ± 2.89 and total pain score in men was 1.62 ± 2.44 . There were no differences between the groups in terms of total pain score ($p = 0.981$). When ASA I and II differences are taken into consideration, there were no significant differences that existed among the groups in terms of total pain score (ASA I = 134, ASA II = 42) ($p = 0.661$). The mean pain scores at ASA-I and ASA-II patients were 1.63 ± 2.58 and 1.42 ± 2.82 , respectively.

The total pain score in patients who have undergone extremity and spinal operations has been measured has the lowest rate when compared with other locations. There were no differences among other areas in terms of pain score. Lidocaine was more effective when compared with metoprolol ($p = 0.015$) and nitroglycerin ($p = 0.001$). Furthermore, metoprolol was least effective when compared with nitroglycerin in terms of total pain score ($p = 0.002$). In total pain score evaluation, injections in antecubital areas were determined to be more advantageous ($p = 0.001$). Total pain score for the group including patients with BMI lower than 30, with normal BMI and high BMI was $1.40 \pm 2.48 \text{ kg m}^{-2}$. For

Table 5 Number of patients with pain when Nitroglycerin ($n=58$) was injected from different pathways.

Patients with pain at	Group E ($n=29$)	Group A ($n=29$)	p
5th sec	9	3	0.132
10th sec	18	4	0.001
15th sec	22	6	0.001
20th sec	22	10	0.014

A, antecubital area; E, back of hand.

the obese group ($n = 30$), the score was $2.70 \pm 3.38 \text{ kg m}^{-2}$. The total pain score for obese patients was statistically higher ($p = 0.016$).

Discussion

Because propofol injection causes negative experiences about anesthesia and restricts comfort of patients, some studies have been carried out to find various methods and tools. The propofol, which is a phenol, causes irritation at skin, mucous membranes and intima of the veins.¹¹ Direct endothelial irritation of nerve endings caused by propofol causes secretion of bradykinin by stimulating kallikrein-kinin cascade system. This state brings out injection pain by causing increase in contact of free nerve endings and liquid phase of propofol as well as venous dilatation and increase of permeability. Every drug given before propofol injection alleviates pain by diluting liquid phase of propofol which has an endothelium irritant effect. It is thought that pain is related to concentration of liquid phase although there is no certain information about its mechanism.¹²

Pain caused by propofol injection emerges at early and late periods. Pain at early period is related to direct effect of propofol and pain at late period is related to local secretion of kininogens. At the present day, the most common agent used for alleviating propofol injection pain is lidocaine.¹⁰ Scott et al. stated that lidocaine alleviates pain by stabilizing kinin cascade while Eriksson stated that this agent alleviates pain by decreasing pH and concentration.^{13,14}

Propofol, by an indirect action on the endothelium, activates the kallikrein-kinin system and releases bradykinin, thereby producing venous dilation and hyper permeability, which increases the contact between the aqueous phase of propofol and free nerve endings, resulting in pain on injection.¹⁵ Propofol, when drawn up in a disposable syringe, may lead to formation of irritants and propofol pain. It has been confirmed that propofol strips the silicone lubricant from the inside barrel of plastic syringes. A reduction in propofol pain by cooling it to 4°C and minimizing propofol injection pain is an important clinical goal because it may influence the patient's perception of quality and acceptability of anesthesia. In conclusion, pretreatment with lidocaine 40 mg, thiopental 0.25 mg/kg, and thiopentone 0.5 mg/kg after manual venous occlusion attenuates propofol pain. However, pretreatment with thiopental 0.5 mg/kg after manual venous occlusion was the most effective in attenuating propofol-induced pain. We therefore suggest routine pretreatment with thiopental 0.5 mg/kg along with manual venous occlusion for 1 min for prevention of pain associated with propofol injection.

Nitroglycerin is a commonly used agent in treatment of ischemic heart disease.¹⁶ Nitroglycerin, a strong vasodilator, is metabolized as nitric oxide (NO) in cells. NO causes intracellular concentration of cyclic guanosine monophosphate (cGMP) which leads to pain modulation in central and peripheral nervous system.¹⁷ NO, applied topically, shows anti-inflammatory and analgesic effect by blocking neurogenic component of inflammatory edema and hyper allergy and inhibits adhesion of neutrophils to endothelium surface. The fact that transdermal nitroglycerin is effective in pain treatment has been proven with various studies.¹⁸

Transdermal nitroglycerin shows vasodilation effect and analgesic effect by increasing diffusion of local anesthetics and arrival to nerve trunk.¹⁹ Nitroglycerin pomade shows analgesic effect and vasodilator effect in vein sizes.²⁰

Nitroglycerin is metabolized to nitric oxide (NO) in the cell.^{17,21} NO causes increase in the intracellular concentration of, which produces pain modulation in the central and peripheral nervous system. NO generators also induce anti-inflammatory effects and analgesia by blocking hyperalgesia and the neurogenic component of inflammatory edema by topical application.²² Another possible mechanism includes an analgesic effect through the direct stimulation of peripheral fibers mimicking the actions of locally applied acetylcholine.²³ Mechanisms mentioned above, or their combinations, might contribute to the analgesic effects of nitroglycerin added to lidocaine in intravenous regional anesthesia. The clinical efficacy of transdermal nitroglycerin for acute pain relief has been documented in several studies.²³ Nitroglycerin was found to be useful for the treatment of shoulder pain and thrombophlebitis and for enhancing the effect of spinal sufentanil or neostigmine.²² Lauretti et al. also showed that delivery of NO donors (transdermal nitroglycerin) together with.²⁴

Opioids may be of significant benefit in cancer pain management, delaying morphine tolerance and decreasing the frequency of adverse effects related to large doses of opioid. It has been concluded that 0.25 nitroglycerin is less effective in alleviating propofol injection pain compared to lidocaine and metoprolol. We have concluded that higher pain rates in obese patients stems from standard amount of premedication. In other words, amount of drugs per kilo is lower in obese patients

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In conclusion, we found Lidocaine to be the most effective analgesic in decreasing propofol related pain. We therefore suggest iv Lidocaine for alleviating propofol related pain at operations. However, nitroglycerin injection into antecubital veins has yielded lower levels of propofol related pain. Also we have confirmed that injection pain is not related to gender and education level. Furthermore, we found that injection pain is related to obesity and total pain score in obese patients was statistically higher. For evaluation of total pain score, antecubital area is more advantageous than the dorsum of the hand.

Conflict of interest

The authors declare no conflicts of interest

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