Comparison of Effects of Ketamine, Esmolol and Lidocaine on Propofol Injection Pain

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Abstract

Objective: Propofol is the most frequently used agent for intravenous anesthesia administration. However, during propofol injection, pain may develop in the hand and forearm region and cause unwanted situations. Different applications have been used to prevent propofol injection pain. Although lidocaine is often used for propofol injection pain, anesthetic agent ketamine, which has an analgesic feature, is also preferred. In recent years, the analgesic feature of esmolol, a short-acting beta blocker, has been emphasized.

Our aim was to evaluate the effects of three different agents, ketamine, esmolol or lidocaine, on the severity of pain developing by propofol injection. Also, hemodynamic effects were investigated.

Methods: Sixty cases in ASA groups I and II, aged from 18 to 80 years old undergoing elective operations included in the study. To reduce the pain due to propofol injection, patients were given either 0.5 mg/kg ketamine, 0.5 mg/kg esmolol HCl or 0.5 mg/kg lidocaine.

For induction 1% propofol injection was administered, presence and severity of pain in the arm was questioned and recorded. To evaluate the severity of pain developing due to propofol injection, a 4-point numerical scale was used (no pain: 1, mild pain: 2, moderate pain: 3 and severe pain: 4). Arm pull motion was also recorded.

Results: There were no significant differences between the groups according to the severity of pain and pulling arm rates. There was no significant difference between hemodynamic parameters in the groups preoperatively, first, 5th, 10th, 15th, 20th and 30th minute.

Conclusion: Ketamine, esmolol, and lidocaine can safely control the severity of pain developing by propofol injection. Esmolol, ketamine and lidocaine provided effective analgesia at the doses used in our study without affecting the hemodynamic findings of the patients.

Keywords: Propofol injection pain, analgesic effect, esmolol, ketamine, lidocaine

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Ketamin, Esmolol ve Lidokainin Propofol Enjeksiyon Ağrısı Üzerine Etkilerinin Karşılaştırılması

Öz

Giriş: Propofol, intravenöz anestezi uygulamasında en sık kullanılan ajandır. Ancak propofol enjeksiyonu sırasında el ve ön kol bölgelerinde ağrı meydana gelmekte ve istenmeyen durumlara sebep olmaktadır. Propofol enjeksiyon ağrısını önlemek için farklı uygulamalar kullanılmaktadır. Propofol enjeksiyon ağrısı için lidokain sıklıkla kullanılmakla birlikte, analjezik özelliği de olan, anestezik ajan ketamin de tercih edilmektedir. Son yıllarda kısa etkili beta bloker olan esmololün analjezik özelliği üzerinde durulmaktadır.
Çalışmamızın amacı, ketamin, esmolol veya lidokainin propofol enjeksiyonuyla gelişen ağrının şiddeti üzerindeki etkilerini değerlendirmek ve hemodinamik etkilerini araştırmaktır.

Yöntemler: Yaşları 18-80 aralığında olan, ASA I, II grubunda elektif operasyon uygulanan, 60 olgu çalışmaya dahil edildi.

Propofol enjeksiyonu öncesinde ağrı şiddetini azaltmak için hastalara 0,5 mg/kg lidokain, 0,5 mg/kg ketamin, 0,5 mg/kg esmolol HCl verildi. İndüksiyonda %1 propofol ile enjeksiyon yapılan kolda ağrı varlığı ve şiddeti sorularak kaydedildi. Propofol enjeksiyonuna bağlı olarak gelişen ağrı şiddetinin değerlendirilmesi 4’lü sayısal skala (ağrısız:1, hafif ağrı:2, orta şiddette ağrı:3, şiddetli ağrı:4) kullanılarak yapıldı, kol çekme hareketi kaydedildi.

Bulgular: Ağrı şiddeti ve kol çekme oranları açısından gruplar arasında anlamlı fark bulunmadı. Ameliyat öncesi, 1, 5, 10, 15, 20, 30. dakikalarda hemodinamik parametreler arasında anlamlı fark yoktu.

Sonuç: Ketamin, esmolol ve lidokain ile propofol enjeksiyonuyla bağlı olarak gelişen ağrı şiddetini hemodinamik etkilere yol açmadan güvenle kontrol edilmiştir. Esmolol, ketamin ve lidokain çalışmamızda kullanılan dozlarda, hastaların hemodinamik bulgularını etkilemeden etkin analjezi sağlamıştır.

Anahtar kelimeler: Propofol enjeksiyon ağrıısı, analjezik etki, esmolol, ketamin, lidokain.

INTRODUCTION

Propofol is the most frequently used agent for intravenous anesthesia administration. However, during propofol injection, pain develops in the hand and forearm region and may cause unwanted situations.

It is reported that the incidence of propofol injection pain ranges from 28% to 90% in adults and 28% to 85% in children in the absence of other pretreatments.

During the induction, pain felt by the patient may increase anxiety and cause sympathetic stimulation.

Painful stimulation causing the arm-pull reflex in unconscious patients may cause dangerous situations like pulling the intravenous catheter out of the vein.

Different applications have been used to prevent propofol injection pain in clinical anesthesia practice. Various factors, including propofol temperature, and the concomitant use of various drugs appear to influence this pain.

Additionally to prevent propofol pain various agents such as dexmedetomidine, remifentanil, nitroglycerine, fentanyl, and magnesium have been used and found to reduce propofol injection pain.

In our study, the aim was to evaluate the effects of three different agents, ketamine, esmolol or lidocaine, on the severity of pain developing by propofol injection. Hemodynamic effects on systolic arterial pressure (SAP), diastolic arterial pressure (DAP) and heart rate (HR) were investigated.

METHODS

Sixty cases in ASA groups I and II, undergoing elective operations at Okmeydanı Training and Research Hospital in the Anesthesia Clinic aged from 18 to 80 years old were included in the study after receiving ethics committee...
Patients who underwent elective surgery with ASA 1, 2 were included in the study. Patients with chronic pain syndrome, thrombophlebitis, physical disorders, neurological diseases, pregnancy, hypertension, hypotension, ischemic heart disease, allergy and those using analgesics were excluded from the study.

A 22 gauge cannula was inserted into a vein on the back of the hand and 0.9% isotonic infusion was initiated. No premedication was applied to the patients who participated in the study.

A tourniquet was applied on the upper arm and injections of pretreatment drugs such as ketamine, esmolol or lidocaine were started. The pretreatment drugs were injected over a period of 10 seconds. The tourniquet was kept during the injection (10 sec) and thirty second after the injection. Thirty second after the injecting pre-treatment drugs, the tourniquet was removed and then propofol was injected through angiocatheter over a period of 20 second (10 mg/sec).

Before propofol injection, to reduce the severity of pain, 0.5 mg/kg ketamine, 0.5 mg/kg esmolol HCl or 0.5 mg/kg lidocaine were administered to the arm with a tourniquet. During induction with 1% propofol injection, the presence and severity of pain in the arm was questioned and recorded. To evaluate the severity of pain due to propofol injection, a 4-point numerical scale was used (no pain: 1, mild pain: 2, moderate pain: 3 and severe pain: 4). Arm pull motion was recorded.

For anesthesia induction, 2.5 mg/kg propofol and 0.6 mg/kg rocuronium were used. The patients were observed by dividing into three groups as those using ketamine (Group K), lidocaine (Group L), or esmolol (Group E) for propofol pain. There were 20 patients in each group. Fentanyl was administered after intubation and repeated every 30 minutes. While anesthesia maintenance was provided by 2% sevoflurane, 50% O2 and 50% air.

After induction and at the first, 5th, 10th, 15th, 20th and 30th minute, SAP, DAP, and HR values were recorded. The hemodynamic response to intubation and side effects (nausea, vomiting, nystagmus, laryngospasm, excessive secretions, agitation, vision disorders, headache, allergic reactions) were also noted.

**Statistical Analysis**

In the pre-study evaluation, Standard Impact Size was determined as 0.92 with 5% Error margin, and 80% Power. For each group, it was found to be sufficient to taken=19 as a model.

Data are presented using descriptive statistics as mean, standard deviation, median, minimum, maximum, frequency, and percentage. The distribution of variables was assessed with the Kolmogorov-Smirnov test. Quantitative data analysis used the ANOVA Kruskal-Wallis test. Analysis of qualitative data used the chi-square test, while the Fisher test was used if chi-square test conditions were not valid. Analyses were completed with the SPSS 22.0 program. The present study protocol was reviewed and approved by the ethics committee of Okmeydani Teaching and Research Hospital (approval date: 05.11.2013, numbered: 143).

**RESULTS**

There was no significant difference (p>0.05) between patients in Group K, Group E and Group L in terms of demographic data like age and body weight.

There was no significant difference (p>0.05) between Group K, Group E and Group L patients in terms of pain severity and arm-pull rates (Table 1).
There was no significant difference (p>0.05) between SAP, DAP, and HR mean arterial pressure and HR values in Group K, Group E and Group L preoperatively, first, 5th, 10th, 15th, 20th and 30th minute (Table 2-5) (Figure 1-4).

### Table I: Propofol injection pain

| Pain scale | Esmolol | Ketamine | Lidocaine | p  |
|------------|---------|----------|-----------|----|
| Mild       | 20 100.0% | 19 95.0% | 18 90.0%  | >0.05 |
| Moderate   | 0 0.0%   | 1 5.0%   | 1 5.0%    |    |
| Severe     | 0 0.0%   | 0 0.0%   | 1 5.0%    |    |

### Table II: Systolic blood pressure

| Systolic blood pressure | Esmolol Mean ±SD | Median | Ketamine Mean ±SD | Median | Lidocaine Mean ±SD | Median | p   |
|-------------------------|------------------|-------|-------------------|-------|---------------------|-------|-----|
| At the start            | 133.2 ± 18.0     | 127.0 | 122.6 ± 20.5      | 128.0 | 136.7 ± 14.9        | 132.0 | 0.185 |
| 1st minute              | 123.3 ± 25.2     | 127.0 | 128.2 ± 25.6      | 123.5 | 114.9 ± 8.5         | 112.0 | 0.370 |
| 5th minute              | 123.5 ± 27.6     | 116.0 | 128.0 ± 19.8      | 130.5 | 117.9 ± 18.2        | 111.0 | 0.625 |
| 10th minute             | 133.6 ± 24.7     | 126.0 | 117.6 ± 16.7      | 117.0 | 119.8 ± 19.8        | 120.0 | 0.132 |
| 15th minute             | 125.3 ± 14.5     | 123.5 | 122.1 ± 17.3      | 113.0 | 123.0 ± 16.8        | 123.0 | 0.886 |
| 20th minute             | 125.5 ± 14.0     | 132.0 | 118.6 ± 14.6      | 121.0 | 122.1 ± 27.7        | 107.0 | 0.701 |
| 30th minute             | 127.6 ± 15.7     | 130.5 | 115.7 ± 15.1      | 112.5 | 135.9 ± 13.3        | 142.0 | 0.072 |

**ANOVA**

### Table III: Diastolic blood pressure

| Diastolic blood pressure | Esmolol Mean ±SD | Median | Ketamine Mean ±SD | Median | Lidocaine Mean ±SD | Median | p   |
|-------------------------|------------------|-------|-------------------|-------|---------------------|-------|-----|
| At the start            | 77.9 ± 11.6      | 79.0  | 80.0 ± 18.4       | 72.5  | 80.3 ± 9.6          | 81.0  | 0.880 |
| 1st minute              | 77.5 ± 14.5      | 82.0  | 81.5 ± 19.9       | 76.5  | 73.6 ± 11.2         | 72.0  | 0.508 |
| 5th minute              | 74.8 ± 21.1      | 72.0  | 87.4 ± 13.2       | 87.5  | 72.0 ± 10.1         | 70.5  | 0.094 |
| 10th minute             | 80.9 ± 20.7      | 78.0  | 76.4 ± 11.7       | 77.0  | 73.0 ± 11.5         | 72.0  | 0.468 |
| 15th minute             | 76.0 ± 13.7      | 80.5  | 78.9 ± 13.8       | 77.0  | 78.0 ± 12.4         | 73.0  | 0.869 |
| 20th minute             | 80.7 ± 15.5      | 80.0  | 78.9 ± 16.2       | 77.0  | 73.3 ± 11.4         | 69.0  | 0.553 |
| 30th minute             | 81.6 ± 12.5      | 84.5  | 72.0 ± 8.2        | 72.0  | 87.3 ± 8.9          | 81.0  | 0.056 |

**ANOVA**
### Table IV: Mean arterial pressure

|                     | Esmolol        | Ketamine       | Lidocaine      |   |
|---------------------|----------------|----------------|----------------|---|
|                     | Mean ±SD       | Median         | Mean ±SD       | Median         | Mean ±SD       | Median | p   |
| Mean arterial       |                |                |                |                |                |        |
| pressure            |                |                |                |                |                |        |
| At the start        | 100.2 ± 11.6   | 101.0          | 98.1 ± 19.0    | 95.0           | 100.2 ± 11.4   | 99.0    | 0.927 |
| 1st minute          | 95.1 ± 16.2    | 99.0           | 100.4 ± 21.6   | 91.5           | 88.2 ± 10.3    | 84.0    | 0.247 |
| 5th minute          | 94.5 ± 23.2    | 92.0           | 105.9 ± 15.3   | 99.5           | 95.3 ± 13.1    | 99.0    | 0.286 |
| 10th minute         | 103.9 ± 21.5   | 99.0           | 92.3 ± 11.4    | 95.5           | 88.5 ± 12.7    | 85.5    | 0.070 |
| 15th minute         | 95.8 ± 16.4    | 96.5           | 97.4 ± 15.5    | 90.0           | 94.6 ± 16.2    | 100.0   | 0.929 |
| 20th minute         | 96.7 ± 15.9    | 103.0          | 95.4 ± 17.1    | 91.0           | 96.7 ± 14.9    | 95.0    | 0.984 |
| 30th minute         | 97.1 ± 14.3    | 99.5           | 90.5 ± 10.9    | 87.0           | 112.0 ± 3.0    | 112.0   | 0051  |

ANOVA

### Table V: Heart Rate

|                     | Esmolol        | Ketamine       | Lidocaine      |   |
|---------------------|----------------|----------------|----------------|---|
|                     | Mean ±SD       | Median         | Mean ±SD       | Median         | Mean ±SD       | Median | p   |
| Heart rate          |                |                |                |                |                |        |
| At the start        | 92.8 ± 11.0    | 87.0           | 84.3 ± 14.7    | 86.0           | 89.0 ± 13.0    | 92.0    | 0.283 |
| 1st minute          | 89.0 ± 9.9     | 87.0           | 83.1 ± 11.3    | 86.0           | 93.1 ± 16.7    | 98.0    | 0.210 |
| 5th minute          | 82.1 ± 7.5     | 82.0           | 79.9 ± 12.1    | 76.0           | 85.3 ± 14.8    | 88.5    | 0.566 |
| 10th minute         | 86.5 ± 5.7     | 86.0           | 83.3 ± 11.5    | 86.5           | 78.4 ± 11.0    | 74.5    | 0.112 |
| 15th minute         | 82.1 ± 9.6     | 79.0           | 79.3 ± 7.0     | 77.0           | 84.0 ± 18.9    | 74.0    | 0.722 |
| 20th minute         | 81.5 ± 15.0    | 80.0           | 83.0 ± 11.3    | 84.0           | 88.9 ± 9.0     | 94.0    | 0.481 |
| 30th minute         | 83.2 ± 11.0    | 82.0           | 75.4 ± 13.8    | 76.0           | 80.4 ± 10.4    | 75.0    | 0.441 |

ANOVA

### Figure 1. Systolic blood pressure

### Figure 2. Diastolic Blood pressure
There were no significant differences (p>0.05) between Group K, Group E and Group L patients in terms of nausea, vomiting, laryngospasm, nystagmus, excessive secretion, bronchospasm, headache, vision disorders, allergic reactions and erythema (Table 6).

**DISCUSSION**

Propofol, used as an intravenous anesthetic agent, is known to cause pain sensation during injection. However, the molecular mechanisms underlying this effect are not fully understood\(^{13}\).

A study by Nishimato et al.\(^{13}\) concluded that propofol may cause pain through multiple mechanisms involving TRPV1 (transient receptor potential vanilloid 1) and TRPA1 (transient receptor potential ankyrin 1) but also through activation of voltage-gated channels downstream of GABA A receptors.

Propofol activates the plasma kinin-kallikrein system freeing bradykinin and which causes local vein changes like venous dilatation and hyperpermeability. This situation allows propofol to contact more with free nerve endings causing pain. Nakane et al.\(^{14}\) found that the lipid solvent for propofol activates the plasma kallikrein-kinin system and produces bradykinin which modifies the injected local vein. This modification of the peripheral vein

|                         | Esmolol       | Ketamine     | Lidocaine   | p           |
|-------------------------|---------------|--------------|-------------|-------------|
| Nausea                  | 0  0.0%       | 0  0.0%      | 0  0.0%     | p > 0.05    |
| Vomiting                | 0  0.0%       | 0  0.0%      | 0  0.0%     | p > 0.05    |
| Nystagmus               | 0  0.0%       | 1  5.0%      | 0  0.0%     | p > 0.05    |
| Excessive secretion     | 0  0.0%       | 0  0.0%      | 0  0.0%     | p > 0.05    |
| Laryngospasm            | 0  0.0%       | 0  0.0%      | 0  0.0%     | p > 0.05    |
| Bronchospasm            | 0  0.0%       | 1  5.0%      | 0  0.0%     | p > 0.05    |
| Headache                | 0  0.0%       | 0  0.0%      | 0  0.0%     | p > 0.05    |
| Vision disorders        | 0  0.0%       | 0  0.0%      | 0  0.0%     | p > 0.05    |
| Allergic reaction       | 1  5.0%       | 0  0.0%      | 0  0.0%     | p > 0.05    |
| Erythema at injection site | 2  10.0%    | 0  0.0%      | 0  0.0%     | p > 0.05    |

ANOVA / Kruskal-wallis / Ki-kare test (Fischer test)

**Figure 3.** Mean arterial pressure

**Figure 4.** Heart Rate
may increase contact between the aqueous phase propofol and the free nerve endings of the vessel, resulting in aggravation of propofol-induced pain.

Zahedi et al.\textsuperscript{15} compared different ketamine doses with lidocaine and found that 0.1 mg/kg ketamine administration before propofol injection was an effective and safe method in eliminating propofol pain.

Wang et al.\textsuperscript{16} observed that 0.3 mg/kg dose of ketamine was effective at resolving propofol pain in a study planned to determine an effective dose of ketamine to eliminate pain during propofol injection.

Zhao et al.\textsuperscript{17} in a pediatric study showed that 0.3 mg/kg ketamine administration reduced the severity of propofol injection pain without causing serious side effects.

In another study, with 0.5 mg/kg ketamine, propofol injection pain was reduced while it was totally eliminated with 1.0 mg/kg ketamine. Ketamine completely eliminated pain without affecting hemodynamics\textsuperscript{18}.

In our study, we found that 0.5 mg/kg ketamine provides effective analgesia without affecting hemodynamics.

Beside cardiac inhibitor effects, short-acting beta1-adrenergic receptor antagonists like esmolol are reported to exert anti-nociceptive and anesthetic sparing effects in animal and human subjects\textsuperscript{19}. However, the direct mechanism underlying anti nociceptive effects of short-acting beta1-adrenergic receptor antagonists has not been fully established.

The pain and arm pull reaction was shown to decrease with pretreatment with esmolol\textsuperscript{19-21}. Masaki\textsuperscript{19} considered that in the future, short-acting beta-adrenergic receptor antagonists would be used for anti-nociception.

It has been found that pretreatment with intravenous esmolol reduces propofol injection pain\textsuperscript{22}.

In our study, we found that esmolol reduced propofol injection pain. When compared with ketamine and lidocaine, esmolol had similar effects on injection pain.

Lidocaine is known to effectively reduce propofol pain\textsuperscript{6,7,23-25}. Ayatollahi et al.\textsuperscript{26} identified a similar efficacy of with ketamine and lidocaine in a study.

In our study, we identified effective treatment in all three groups.

When we examine them in term of side effects and hemodynamic effects, in our study doses of 0.5 mg/kg ketamine, esmolol or lidocaine used did not produce a significant difference in hemodynamic response and we reliably provided effective pain treatment.

**Limitation**

Our study was conducted with 60 patients. Multicenter studies with more patients are needed. In our study, doses used in the literature were used to prevent propofol injection pain, and in our study, effective analgesia was provided without any side effects. However, studies on more patients are needed to investigate whether the same effect can be achieved with lower doses.

As a conclusion, there was no difference in pain scales between the three groups in preventing profopol injection pain, and its analgesic properties were found to be similar. In addition, when the hemodynamic effects of all three agents were compared, it was observed that there was no difference between them. We consider that ketamine, esmolol, and lidocaine safely controlled the severity of pain developed by to propofol injection without causing hemodynamic effects. There is a need for studies on this topic.

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Ethics Committee Approval: The present study protocol was reviewed and approved by the ethics committee of Okmeydanı Teaching and Research Hospital (approval date: 05.11.2013, numbered: 143).

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