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Research Article

Comparison of Pain on Injection of Etomidate versus Etomidate-Lipuro in Patients Undergoing Elective Orthopedic Surgery: A Double-Blind Randomized Clinical Trial

Alireza Saliminia[1,*], Niloofar Esfahanian[2]

[1] Associate Professor, Department of Anesthesiology and Critical Care, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
[2] Research Development Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

[*]Corresponding author: Alireza Saliminia; Department of Anesthesiology and Critical Care, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran. Tel: +98-9121075078, Email: alirezasalimnia@yahoo.com

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Abstract

Background: Etomidate is an efficient general anesthetic associated with injection pain. Etomidate-Lipuro is its lipid emulsion, suggested to have less adverse effects. We aim to compare the injection pain of etomidate vs. etomidate-lipuro.
Methods: This double-blind randomized clinical trial investigated 46 hands (23 patients) undergoing elective orthopedic surgery referring to our hospital from May to September 2017. For each patient, intravenous (IV) access was put on both hands, on one of which 2 ml of etomidate (drug A) and on the other one, 2 ml of etomidate-lipuro (drug B) were infused simultaneously. Pain scores were compared between drug types by the Wilcoxon signed-rank test using the SPSS software.
Results: Among 23 patients included in the study, 8 (34.8%) were female. Mean ± standard deviation (SD) of the patients' age was 40.52 ± 13.07 years (range: 22-60 years). The type of drug injected to the right hand was drug A in 14 hands (60.9%) and drug B in 9 hands (39.1%). Mean ± SD of pain scores was 3.57 ± 3.30 for drug A ($P < 0.001$). The hand side (left/right) showed no significant effect on the pain scores ($P = 0.535$).
Conclusion: This randomized clinical trial used each person as his/her own control (left/right hands). Given the results, etomidate-lipuro showed significant superiority over etomidate regarding injection pain. In fact, most patients felt no pain, which suggests etomidate-Lipuro as an appropriate sedative.

Keywords: Anesthesia; Etomidate; Pain; Randomized Clinical Trial

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Background

General anesthesia is commonly induced before a variety of surgical and nonsurgical procedures and based on the type and duration of surgery, many drugs and techniques can be used to induce and maintain anesthesia (1-3).

Patients' comfort during induction of anesthesia is an important factor, which could help anesthesiologists induce general anesthesia smoothly with the least possible alterations in the hemodynamic profile.

Pain on injection of propofol and etomidate during induction of anesthesia has long been a cause for concern which has urged the use of additional drugs such as lidocaine or paracetamol to decrease the associated discomfort, yet, these drugs may cause additional adverse effects (4, 5).

Etomidate is a carboxylated imidazole derivative that acts through modulating or activating gamma-aminobutyric acid-type A (GABA-A) receptors (6). This drug has the advantage of maintaining hemodynamic stability and low respiratory depression, which are severe adverse effects of commonly used anesthetics (7, 8). It has also been proven that etomidate has lower incidence of body movement, with no nausea and vomiting, compared to propofol (9). Additionally, the injection pain of etomidate is less than that of propofol (9, 10).

However, it is still a major concern for anesthesiologists to reduce injection pain associated with the anesthetic used, thus, several combinations of analgesics, like granisetron and lidocaine, are suggested to reduce this adverse effect of etomidate (11).

The commonly used etomidate is formulated in propylene glycol solution and the other formulation of this drug is called Etomidate-lipuro, which is the lipid formulation of etomidate and is suggested to have lower hemolysis rate than that of etomidate (12).

Other advantages of etomidate-lipuro include less injection pain compared to the combination of lidocaine and propofol in children (13) and combination of etomidate-lipuro and propofol has the least injection pain than that of each of these drugs alone (14).

Injection pain is one of the important issues in orthopedic surgery and several anesthesia regimens have been suggested to reduce it (15).

Due to the proposed efficacy and safety of Etomidate-lipuro and less injection pain than other anesthetics, as well as the significance of this adverse effect in orthopedic surgeries, we aim to compare the injection pain of etomidate vs. etomidate-lipuro in patients undergoing elective orthopedic surgery, in order to help select the most appropriate drug for anesthesia in these patients.

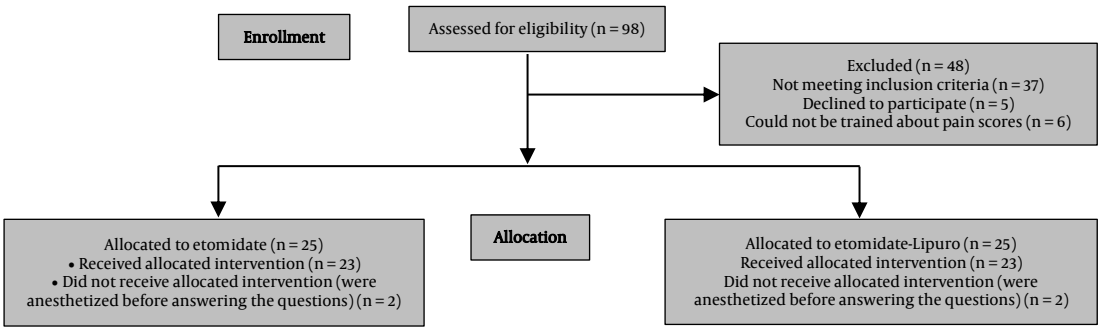

Figure 1. Flow diagram for study enrollment

Methods

The study protocol was approved by the Ethics Committee, Tehran University of Medical Sciences, Tehran, Iran (code: 2845). Before patient recruitment, the researchers explained the design, objectives, and stages of the study, as well as the pain scoring system to the subjects. They were ensured that their information would be kept confidential and analyzed with codes and without names. Those willing to participate in the study were asked to read and sign the written informed consent.

In this randomized, double-blind, clinical trial, 23 patients (46 hands) with American Society of Anesthesiologists (ASA) physical status class I aged between 25-60 years, who were candidates for elective orthopedic surgery requiring more than one intravenous (IV) access line were enrolled (Figure 1).

Patients with a history of any neurological diseases, chronic pain syndrome, thrombophlebitis or vascular diseases, advanced systemic disorders such as diabetes mellitus (DM) and any contraindications of the study protocol drugs, and addicted patients were not enrolled in the study. The exclusion criteria consisted of patients who became deeply sedated before giving a score for the injection pain and patients whose veins were punctured more than once to gain vascular access.

In the preoperative visit on the night before surgery, the numeric rating scale (NRS) for pain (with 0-10 indicating no pain and most severe pain, respectively) was thoroughly explained to all patients. No premeditations were administered.

On arrival to the operating room, all patients were monitored with an electrocardiogram (ECG), noninvasive blood pressure, and pulse oximetry.

Two 20-gauge cannulas were inserted into the veins on the dorsum of both hands and 100 ml of normal saline was administered during a 10-minute period through each cannula.

For each patient, a bolus dose of 2 ml of Etomidate (drug A) (Janssen, UKAG, Melsungen, Germany) on one hand and 2 ml of Etomidate-lipuro (drug B) (B Braun) on the other hand, were administered simultaneously with the same speed. The patients were asked to give a score from 0 to 10 to the pain sensed in each hand. The NRS scores were categorized as mild (1-3), moderate (4-6), or severe (7-10) (9).

The drugs were prepared by an assistant, in opaque syringes at the same volumes (marked by A and B) and the anesthesiologist who injected the drugs and scored the pain was unaware of the drug type.

The type of drug for each hand was randomly determined by block randomization (block size = 2) and the first drug according to the block was injected to the left hand and the second to the right hand. So, each patient was considered the control for him or herself, therefore, no matching was required.

The induction technique of anesthesia was left for the patient's anesthesiologist.

The sample size for this study was calculated to be 21 for each drug according to a similar study (16), and based on α = 0.05 and study power of 80%, with standard deviation (SD) of 2.5, based on the following formula:

Considering 10% lost cases, 23 patients were selected.

Any patient who was anesthetized before completing the questions was excluded from the study. Any case of complication of injection and the place were recorded and considered as the secondary outcome. The researcher recorded the demographic information of patients, such as age and weight from the medical records on the checklist designed for the study. Finally, the pain scores were compared according to the type of drug and hand side.

Statistical Analysis: Descriptive results were presented by percentage and mean ± SD (for categorical and numerical variables, respectively). Kolmogorov-Smirnov test was used to assess the normal distribution of data, which showed a statistically significant P value. As the data of pain scores did not have a normal distribution, interquartile range (IQR) was used for descriptive analysis and Wilcoxon signed-rank test for comparison of the pain scores between drug A and B. For statistical analysis, SPSS software (version 22, IBM Corporation, Armonk, NY, USA) was used. P values of 0.05 or less were considered statistically significant.

Results

Among the 23 patients included in the study, 8 (34.8%) were women and 15 (65.2%) were men. (Mean age ± SD of was 40.52 ± 13.07 years (range: 22-60 years). Mean weight ± SD was 73.57 ± 12.84 kg (range: 54-98 kg).

The type of drug injected to the right hand was drug A in 14 (60.9%) hands and drug B in 9 (39.1%) hands.

Mean ± SD of pain scores was 3.57 ± 3.30 for drug A (IQR = 5) and 0.13 ± 0.40 for drug B (IQR = 0) (P < 0.001). For drug A, the highest rates of scores 0 and 5 were 34.8% and 26.1%, respectively, while the most common score for drug B was score 0 in 91.3% (Table 1).

Analyzing the between-subject effect showed no significant effect for the hand side (left/right) on pain scores (P = 0.535), while the type of drug had a significant effect (P < 0.001).

There were no cases of injection site complications.

Table 1. Comparison of pain scores between drugs A and B in the study population

			Statistic	Standard error
Pain score for drug A	Mean		3.570	0.688
	95% confidence interval for mean	Lower Bound	2.140	
		Upper Bound	4.990	
	Median		4.000	
	SD		3.300	
	Minimum		0.000	
	Maximum		10.000	
	IQR		5.000	
	Skewness		0.496	0.481
	Kurtosis		-0.675	0.935
Pain score for drug B	Mean		0.130	0.095
	95% confidence interval for mean	Lower Bound	-0.070	
		Upper Bound	0.330	
	Median		0.000	
	SD		0.458	
	Minimum		0.000	
	Maximum		2.000	
	IQR range		0.000	
	Skewness		3.710	0.481
	Kurtosis		13.960	0.935
P value of comparison of pain scores (based on Wilcoxon test)			< 0.001	

SD: Standard deviation; IQR: Interquartile range

Discussion

The present study investigated the difference in pain on injection between the traditional formula of etomidate (the propylene glycol formulation), injected in one hand, and etomidate-lipuro (its lipid emulsion), injected in the other hand.

The results showed that the difference in the injection pain between the two drugs was statistically significant and the hand side (left/right) had no significant effect on the pain scores.

Previous studies with different study methods have compared the efficacy of etomidate-lipuro with other drugs such as propofol in adults (15) and children (14) and have declared that etomidate-lipuro has significantly less injection pain in comparison to propofol (15).

We have been working on pain on injection of various drugs for over ten years, as we believe that the importance of patient comfort and trust during the induction phase of general anesthesia is partially dependent on pain on injection of drugs; an issue which can be prevented and may have a great significance in helping to have a smooth induction of anesthesia.

What makes this study more prominent is the method used during the study which helps quantify the pain on injection more accurately as each patient was the case and control of him or herself. Another issue is that usually pain on injection is studied in children, whereas adult patients feel pain as much as children and this needs to be accounted for.

The results of the pain scores in the present study is similar to that of the combination of etomidate-lipuro and propofol in the study by Saricaoglu et al. (14). Moreover, in the study of Nyman et al. on children, etomidate-lipuro had less injection pain than propofol-lidocaine (13), which is consistent with the results of the present study regarding the superiority of etomidate-lipuro on injection pain. However, we found no injection pain in etomidate-lipuro group, while Nyman et al. showed 50% injection pain in the etomidate-lipuro group (13). In addition to the different choice of drug and type of surgery among these studies with the present study, the lower injection pain score in the present study could be due to the fact that the study design of the present randomized clinical trial enabled omission of the confounders, as each patient was considered as his/her own control and the differences in demographics or scoring would not affect these results. However, studies that have evaluated patients in two separate groups might be affected by the effect of confounders (14, 15).

The above-mentioned studies also indicated higher incidence of myoclonus in etomidate-lipuro group vs. propofol or propofol-lidocaine (14, 15), which has been suggested by several studies that can be controlled by addition of other drugs (16-21), but there were no cases of adverse effects in the present study. This difference could be due to the differences in the administration dose and the drug manufacturer.

Other researchers have compared induction and anesthetic characteristics between etomidate-lipuro and etomidate and have reported little local adverse effects, including pain, redness, swelling, and induration for etomidate-lipuro and have suggested alfentanil to reduce the injection pain of etomidate (22). But they have used radial artery and gauge 18 IV line, while we used gauge 22 IV line on patients' hand; in addition, the patients' pain scores at injection site were measured by visual analog scale (VAS), which could justify the differences among studies. By mechanism of action, it is suggested that intralipid administration of etomidate reduces the concentration of etomidate in aqueous phase in vitro (23). The injection pain of etomidate is suggested to be its solution in propylene glycol and the formulation of etomidate in medium chain-length lipids decreases, hence reducing the incidence of injection pain (13). The injection pain of etomidate has been suggested in previous research and several medications such as lidocaine which has been suggested to reduce the injection pain (24). This was confirmed in the present study, as about half the patients had moderate-to-severe injection pain, while etomidate-lipuro had no cases of injection pain that is a valuable finding of the present study. Because injection pain is one of the common adverse effects of most anesthetics. On the other hand, considering the comparable efficacy of etomidate, as well as lower adverse effects (such as hemodynamic instability) to efficient and commonly used anesthetics, such as propofol (25, 26), etomidate in lipid emulsion formulation with almost no injection pain is an appropriate choice for induction of general anesthesia. Other researchers have also determined that etomidate-lipuro is not associated with increased nausea and vomiting (27) and has less hemodynamic instability, compared to propofol (28).

The results of the above-mentioned studies, along with

the results of the present study confirm that etomidate-lipuro has minimal adverse effects and suggests it a good anesthetic choice.

As far as the authors are concerned, this study is the first to compare injection site of etomidate and etomidate-lipuro in patients undergoing cholecystectomy, but like any other study, it could have several limitations. One of the limitations of the present study was lack of follow-up, as we only measured injection pain after recovery and did not follow patients' injection pain afterwards.

Conclusion

This randomized clinical trial used each person as his/her own control (left/right hands). The results indicated that etomidate-lipuro has significant superiority over etomidate regarding injection pain. In fact, most patients felt no pain, which suggests etomidate-Lipuro as an appropriate sedative.

Conflict of Interest

The authors declare no conflict of interest in this study.

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