A clinical comparison of etomidate-lipuro, propofol and admixture at induction

Fatma Saricaoglu,
Sennur Uzun,
Oguzhan Arun,
Funda Arun,
Ulku Aypar
Department of Anesthesiology and Reanimation, Ankara, Turkey

Address for correspondence:
Dr. Fatma Saricaoglu,
Hacettepe University, Department of Anesthesiology and Reanimation, 06100, Sıhhiye, Ankara, Turkey.
E-mail: fatmasaricao@yahoo.com

INTRODUCTION

Propofol (propofol 1% fresenius, Fresenius Kabi AB., Germany) is a nonopioid, nonbarbiturate, sedative-hypnotic agent with rapid onset and short duration of action. Adverse effects include hypotension and injection pain.1,2

Etomidate is a hypnotic agent causing minimal histamine release and very stable hemodynamic profile. However, pain on injection and myoclonus are the most common side effects of this drug.3 Pains on injection, venous irritation and hemolysis have been abolished by new fat emulsion of etomidate (Medium chain triglyceride and soya bean named Etomidate – Lipuro, B.Braun, Melsungen, Germany), but the new solvent has not reduced the incidence of myoclonus after etomidate injection. Myoclonus is a serious problem in patients either with open globe injury or emergency nonfasting conditions.4

Bispectral index (BIS) monitoring has emerged as convenient and versatile tool to titrate hypnotic agents and to reduce drug consumption. BIS is a dimensionless number scaled from 100 to 0, with 100 representing an awake electroencephalogram and 0 representing electrical silence.5

The aim of the present prospective randomized controlled single centre double-blind trial was to evaluate the effect of intravenous propofol/etomidate-lipuro combination (etofol) in the same syringe for induction in general anesthesia in reference to doses for same BIS values, hemodynamics, myoclonus, and injection pain.

METHODS

Following written patient consent, 89 patients listed...
for various types of surgery were scheduled to be included (ASA I–II). The study used a single centre prospective, randomized, double blind controlled design. Randomization was based on computer generated random numbers. The study was approved by University Ethics Committee and adhered to Good Clinical Practise (GCP) guidelines. Patients with vascular diseases, habituation to analgesics, sedatives or antianxiety drugs; allergic diseases or sensitivity to propofol or etomidate, lipid emulsions

The syringes containing the study drugs were prepared by the same anesthesia resident to assure a proper blinding procedure. The coded syringes contained either etomidate-lipuro 2 mg/ml or propofol 1% fresenius 20 mg/ml or etofol prepeared as 1:1 mixture of propofol 1% fresenius 20 mg/ml and etomidate-lipuro 2 mg/ml. The syringes were prefilled to contain 20 ml for blinding purposes (no visual difference could be detected between syringes).

Upon arrival in the operating room, patients were equipped with a Standard anesthesia monitoring (Datex-Ohmeda™/5™, Helsinki, Finland). The BIS was monitored using the XP device (version 4.0) and specific quatro sensor (Aspect Medical Systems, Newton, MA, USA and Leiden, The Netherlands). The BIS sensor was appropriately applied on the left side of the forehead. In all patients general anesthesia was induced using a perfuser at a constant rate 200ml h with all three agents. During induction, three agents were titrated until the target level of BIS 40 was obtained; the patients were ventilated by face mask with 100% O₂. As soon as BIS was decreased to index values of 40, the investigation was completed and additional propofol, opioid, and muscle relaxant were given and anesthesia was continued according to standard clinical practice.

Assessments
Systolic, diastolic and mean blood pressure, heart rates were recorded at every 30 s until the BIS 40 values.

Injection pain was measured using four-graded scale (0: no pain, 1: verbal complain of pain, 2: withdrawal of the arm, 3: both verbal complain and withdrawal of the arm) as described previous study. Pain was assessed by the same resident (OA) in all patients. In order to preserve blinding the score was noted immediately after the patient lost consciousness, thus before possible myoclonic activity would potentially occur.

Patients were observed visually for myoclonus, and when present, myoclonus severity was graded by a trained blind resident (OA). The degree of such muscular activity was scored as follows: 0 = no myoclonus; 1 = minor myoclonus; 2 = moderate myoclonus; 3 = severe myoclonus.

Statistical analysis
Data are presented as the mean (S.D.). Categorical data are described as number of patients (n). Physical characteristics, SBP, MBP, and BIS values all time intervals were compared using a one-way ANOVA after normal distribution had been ascertained by Kolmogorov– Simirnov test. All categorical data including the incidence of myoclonus were compared using the χ²-test. The post hoc Bonferroni correction was used to compare the two groups. All differences were considered significant at P < 0.05. Statistical analysis was performed using SPSS 13.0.

RESULTS

Demographic data were similar between three study groups [Table 1].

The incidence of injection pain was significantly lower in Etotol group. There were no injection pain in group PE as the incidence were (83.8%) in group P and in (63.2%) group E. The distribution of pain scores is shown in Figure 1.

A higher incidence of myoclonic activity was seen in etomidate-lipuro group (93.4%) compared with propofol fresenius and etofol groups (0% and 14.3%, respectively) (P < 0.000). The distribution of myoclonic movement scores is shown in Figure 2.

The dosage for induction was significantly higher in propofol group than etomidate and etofol group in milliliter range (P < 0.000) [Table 1]. Induction (time to reach BIS to 40) was faster in etofol group (163.5(±20.6) s) than propofol (119.4(±40.9) s) (P < 0.000) and etomidate group (176(±31.6)s (P = 0.026) [Figure 3].

The mean and systolic blood pressures were significantly decreased in propofol group compared to etomidate and etofol group at 30 and 60 s and significantly lower than the basal levels at 210 and 240 [Figures 4 and 5].

DISCUSSION

The main finding of the present study was the use of etomidat-lipuro-propofol 1:1 admixture for induction

Table 1: Patient characteristic data in groups

|                        | Group P | Group E | Group etofol |
|------------------------|---------|---------|--------------|
| Age (year)             | 34 (28–41) | 36 (32–42) | 41 (35–47) |
| Weight (kg)            | 68 (62–74) | 71 (66–75) | 76 (72–80) |
| Height (cm)            | 169 (158–178) | 171 (156–180) | 165 (155–178) |
| Gender (M/F)           | 13/16 | 14/16 | 17/15 |
| Dosage (mL)            | 11.4 (±1.9) | 9.8 (±1.8) | 9.5 (±1.5) |
| Dosage (mg) (mean ±SD) | 114 (±19) | 19.6 (±3.6) | 47.5 ±8.50E |

P<0.000, Results of statistical analysis are also provided as (mean [min-max])
of anesthesia associated with no injection pain, a very low rate of myoclonus and significantly faster induction time compared to propofol and etomidate lipuro with hemodynamic stability.

In this study, we want to examine the of etomidate-lipuro-propofol 1:1 admixture for induction of anesthesia and compare the problems that can be occurred when we use these agents separately like injection pain and myoclonus.

A serious problem with the use of propofol is the high incidence of pain on injection. The currently most common practice to reduce this problem is by adding lidocaine to the propofol solution but despite this the incidence of pain on injection remains unacceptably high (20%–39%).[7,8]

Etomidate is a well-known substituted imidazole induction agent that is associated with very high degree of hemodynamic stability.[4] A problem with etomidate was that the solvent used also caused pain on injection. The side effects of etomidate dissolved in PG can be eliminated while retaining the profile of actions when etomidate is dissolved in lipofundin (medium chain triglycerides).[6] This drug preparation has now been approved and is available in numerous European and non-European countries (etomidate lipuro, B. Braun Melsungen, Melsungen, Germany). Etomidate dissolved in lipofundin has an almost physiological osmolality and is devoid of pain upon injection, postoperative thrombophlebitis or hemolytic effects.[6,9]

These two drugs were studied at Hacettepe University, Faculty of Pharmacy (Department of Pharmaceutical Technology) for availability for admixture. They reported that these dugs can be mixed and physically available for
an admixture; we named this admixture etofol.

The use of etofol was found to significantly reduce the incidence of pain on injection, compared with propofol and etomidate-lipuro. It is already reported that etomidate-lipuro is associated with significantly less pain on injection than propofol added lidocain in children. In our study no incidence of pain on injection was observed in etofol group but the incidence was significantly high in propofol group than etomidate lipuro group.

The decrease in pain when using LCT/MCT in etomidate lipuro is considered to be attributed to the lipid solvent that decreases the propofol concentration in the Etofol group. Thus, it is possible that a reduction in either bradikinin generation or the propofol concentration decreases the pain on injection with propofol.

The other disturbing side effect is myoclonus especially with etomidate. Fifty to eighty percent of unpremedicated patients may develop myoclonic movements after etomidate administration. Myoclonus is especially problematic in nonfasting patients, patients with open eye injuries, or those who have limited cardiovascular reserves. A myoclonus from pain response on injection of etomidate was distinguished by timing of the assessments. We assessed injection pain while we were infusing the etomidate, but myoclonus was assessed after etomidate in order to differentiate among different effects of the pretreatment drugs on pain and on myoclonus.

In agreement with previous literature the use of etomidate was found to be associated with higher incidence of myoclonic activity than propofol. There were only two patients at stage 2 in etofol group where as no patient with myoclonus in propofol group. There was not any statically significance among myoclonus between propofol and etofol group (P > 0.05). Previous studies in adults have also shown that the incidence of myoclonic movements can be reduced either by premedication with fentanyl or by preinduction priming with subanesthetic dose etomidate. The propofol in the mixture can be act as preinduction priming in our study.

The induction time (Time to reach BIS to 40) is faster in Etofol group than propofol and etomidate group (etofol > propofol > etomidate). The rapid induction without any side effect is a valuable characteristic that wanted from an ideal induction agent. Both etomidate and propofol are known to have short duration of action that will allow rapid induction.

Hemodynamic stability is the other part of the ideal induction agent. Although propofol decreased the blood pressure Etofol is associated with hemodynamic stability as etomidate in our study.

We did not examine the cortisol levels of the groups. Although etomidate causes adrenocortical suppression, a single injection to induce anesthesia will only produce a transient and clinically insignificant interference with adrenocortical function. In a study by Schenarts and colleagues the use of etomidate for induction of anesthesia in emergency department, as compared with midazolam, was associated with reduced cosyntropin stimulation test response (30% of the control group response) at 3 h after administration. However, cosyntropin stimulation test response was back to normal at 12 h after the administration. Furthermore the reduce adrenal response to cosyntropin during the early phase after administration, the serum cortisol levels remained within the normal laboratory reference ranges during limited period of adrenal inhibition.

In conclusion, etofol (1:1 admixture of etomidate-lipuro and propofol) is associated with less pain on injection, myoclonus and with hemodynamic stability than etomidate lipuro and propofol and we think it is a valuable agent for induction.

REFERENCES

1. Schaub E, Kern C, Landau R. Pain on injection: a double-blind comparison of propofol with lidocaine pretreatment versus propofol formulated with long- and medium-chain triglycerides. Anesth Analg 2004;99:1699-702.
2. Canbay O, Celebi N, Arun O, Karagöz AH, Saricağlu F, Özgen S. Efficacy of intravenous acetaminophen and lidocaine on propofol injection pain. Br J Anaesth 2008;100:95-8.
3. Giese JL, Stockholm RJ, Stanley TH, Pace NL, Nelissen RH. Etomidate versus thiopental for induction of anesthesia. Anesth Analg 1985;64:871-6.
4. Mayer M, Doneicke A, Nebauer AE, Hepting L. Propofol and etomidate-Lipuro for induction of general anesthesia. Hemodynamics, vascular compatibility, subjective findings and postoperative nausea. Anaesthesist 1996;45:1082-4.
5. Bonhomme V, Deflandre E, Hans P. Correlation and agreement between bispectral index and state entropy of the electroencephalogram during propofol anaesthesia. Br J Anaesth 2006;93:340-6.
6. Nyman Y, Von Hofsten K, Palm C, Eksborg S, Lönnqvist PA. Etomidate-Lipuro is associated with considerably less injection pain in children compared with propofol with added lidocaine. Br J Anaesth 2006;97:536-9.
7. Nyman Y, von Hofsten K, Georgiadis A, Eksborg S, Lönnqvist PA. Propofol injection pain in children: a prospective randomized double-blind trial of a new propofol formulation versus propofol with added lidocaine. Br J Anaesth 2005;95:222-5.
8. Kam E, Abdul-Latif MS, McCluskey A. Comparison of Propofol-Lipuro with propofol mixed with lidocaine 10 mg on propofol injection pain. Anaesthesia 2004;59:1167-9.
9. Altmayer P, Grundmann U, Ziehmer M, Larsen R. Comparative effectiveness and tolerance study of a new galenic etomidate formula. Anaesthesiol Intensivmed Notfallmed Schmerzther
Saricaoglu, et al.: Etomidate-lipuro, propofol admixture (etofol) at induction

1993;28:415-9.

10. Adam S, van Bommel J, Pelka M, Dirckx M, Jonsson D, Klein J. Propofol-induced injection pain: comparison of a modified propofol emulsion to standard propofol with premixed lidocaine. Anesth Analg 2004;99:1076-9.

11. Krobbuaban B, Sirivan D, Kumkeaw S, Tanomsat M, Jamjamrat G, Thanetses K, et al. Does addition of lidocaine to medium- and long-chain triglyceride propofol emulsions significantly reduce pain on injection? J Med Assoc Thai 2008;91:383-7.

12. Doenicke AW, Roizen MF, Kugler J, Kroll H, Foss J, Ostwald P. Reducing myoclonus after etomidate. Anesthesiology 1999;90:113-9.

13. Guler A, Satilmis T, Akinci SB, Celebioglu B, Kanbak M. Magnesium sulfate pretreatment reduces myoclonus after etomidate. Anesth Analg 2005;101:705-9.

14. Wagner RL, White PF, Kan PB, Rosenthal MH, Feldman D. Inhibition of adrenal steroidogenesis by the anesthetic etomidate. N Engl J Med 1984;310:1415-21.

15. Schenarts CL, Burton JH, Riker RR. Adrenocortical dysfunction following etomidate induction in emergency department patients. Acad Emerg Med 2001;8:1-7.

Source of Support: Nil, Conflict of Interest: None declared.

---

Staying in touch with the journal

1) **Table of Contents (TOC) email alert**
   Receive an email alert containing the TOC when a new complete issue of the journal is made available online. To register for TOC alerts go to [www.saudija.org/signup.asp](http://www.saudija.org/signup.asp).

2) **RSS feeds**
   Really Simple Syndication (RSS) helps you to get alerts on new publication right on your desktop without going to the journal’s website. You need a software (e.g. RSSReader, Feed Demon, FeedReader, My Yahoo!, NewsGator and NewsCrawler) to get advantage of this tool. RSS feeds can also be read through FireFox or Microsoft Outlook 2007. Once any of these small (and mostly free) software is installed, add [www.saudija.org/rssfeed.asp](http://www.saudija.org/rssfeed.asp) as one of the feeds.