ORIGINAL RESEARCH

DOI: 10.4274/globecc.galenos.2022.99608
Glob Emerg Crit Care 2022;1(3):66-69

Use of Intravenous Lipid Emulsion Therapy to Prevent the Undesirable Effects of Midazolam

Halil Alışkan[1], Rohat Ak[2], Fatih Doğanay[3], Özge Onur[4], Tevfik Patan[5], Engin Sümer[6], Ertuğrul Altınbilek[1]

[1]University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[2]University of Health Sciences Turkey, İstanbul Kartal Dr. Lütfi Kırdar City Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[3]Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[4]Marmara University Pendik Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[5]Fatih Sultan Mehmet Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
[6]Yeditepe University Faculty of Veterinary, İstanbul, Turkey

Abstract

Objective: Midazolam is a lipophilic benzodiazepine used for moderate and deep interventional sedation and sedoanalgesia in emergency departments. It may cause undesirable outcomes such as bradycardia and hypotension when used. Intravenous lipid emulsion (ILE) therapy is performed to prevent the toxic effects of local anesthetics, β-blockers and lipophilic drugs. In this study, it was aimed to evaluate the effect of ILE infusion on undesirable outcomes such as bradycardia, hypotension and respiratory depression that may occur after midazolam infusion in rats.

Materials and Methods: For the study, 24 Sprague-Dawley rats with the same characteristics were randomly divided into four groups as follows: (1) 0.9% NaCl 16 mL/kg intravenously (IV), (2) midazolam 5 mg/kg IV bolus at an infusion rate of 5 mg/kg/h, (3) 16 mL ILE at an infusion rate of 16 mL/kg/min infusion, and (4) 16 mL ILE at an infusion rate of 16 mL/kg/min infusion for 4 min, then Midazolam 5 mg/kg IV bolus at an infusion rate of 5 mg/kg/h over 60 min. Vital parameters and mortality were monitored.

Results: Mean arterial pressure (MAP) and pulse rate was significantly lower in the midazolam-infused group compared to the other groups ($p<0.05$). In the group receiving midazolam + ILE treatment, MAP decreased at a later period and no significant difference was observed compared to the control group in the measurements after the 40th minute ($p>0.05$). The mortality rate of the midazolam group was 100%, and the survival rate of the other groups was 100%. A significant increase in respiratory rate was observed in the group receiving ILE treatment compared to the control group ($p<0.05$).

Conclusion: It has been shown that effects such as hypotension and respiratory depression that may occur after midazolam administration can be eliminated with ILE treatment and mortality can be reduced.

Keywords: Midazolam, intravenous lipid emulsion, rat

Introduction

Benzodiazepine (BdZ) group drugs are frequently used drugs due to their rapid onset of action, low toxicity potential, and sedative, anxiolytic and anticonvulsant effects [1-3].

Midazolam is a short-acting BdZ and a safe antidote agent used for moderate and deep interventional sedation analgesia in emergency departments. Due to the effect of midazolam on calcium (Ca^{2+}) and potassium (K^{+}) channels, it may have adverse effects such as bradycardia and hypotension. Its effects

Address for Correspondence: Assoc. Prof. Ertuğrul Altınbilek, University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital, Clinic of Emergency Medicine, İstanbul, Turkey
Phone: +90 505 904 68 33 **E-mail:** dr_ertugrul@yahoo.com **ORCID-ID:** orcid.org/0000-0003-4201-8850
Received: 20.07.2022 **Accepted:** 24.11.2022

on these channels cannot be reversed by the antidote of midazolam, flumazenil. Various studies have been conducted to prevent and reverse these effects. The administration of intravenous lipid emulsion (ILE) is a attempt to these adverse effects. The first theory put forward regarding the mechanism of action of ILE is that it creates a lipid-rich compartment in the plasma (lipid sink), enabling the separation of lipophilic drugs from the target tissue [4]. As another mechanism of action, it is thought that long-chain fatty acids activate voltage-dependent calcium channels in cardiac myocytes by providing an energy source in the myocardium with high doses of free fatty acids [5]. ILE is an application that was first used to the toxic effects of local anesthetics and lipophilic drugs, and later studied in cardiac drug poisoning caused by several drugs such as beta-blockers due to its cardiac positive inotropic effect and is still under investigation. These emulsions consist of medium-chain triglyceride, long-chain triglyceride, or a combination of both. ILE in 20% formulation contains 20% soybean oil, 2.25% glycerin, 1.2% egg yolk phospholipid [6].

In our study, we investigated whether the undesirable effects that may occur on the cardiovascular and respiratory systems due to midazolam administration can be prevented by ILE administration.

Materials and Methods

This study was conducted in Yeditepe University Faculty of Medicine Experimental Animal Research Unit Laboratories, following the approval of the Ethics Committee dated 05.04.2016 and decision number 528. Rats with the same characteristics were randomly divided into four groups (n=6 in each group). Anesthesia was achieved by isoflurane administration. Treatment protocols were performed for 60 min.

Group 1: Control group, 0.9% NaCl [16 mL/kg intravenously (IV) for 60 min],

Group 2: Midazolam group (5 mg/kg midazolam IV bolus, 5 mg/kg/h IV for 60 min),

Group 3: ILE group (16 mL/kg/min IV, for 60 min),

Group 4: ILE + midazolam group (16 mL/kg/min IV for 4 min, then midazolam 5 mg/kg IV bolus, 5 mg/kg/h IV for 60 min).

Vital parameters were monitored via the pressure transducer set by cannulation of the femoral artery with a 26 G cannula.

Statistical Analysis

In the statistical analysis, IBM SPSS 22.0 (Armonk, New York) software was used. Mean, standard deviation, median, maximum, minimum, frequency, and ratio values were used in the descriptive statistics of the numeric data. The distribution of numeric variables was evaluated by the Kolmogorov-Smirnov test. Kruskal-Wallis, Mann-Whitney U tests was used to compare the independent quantitative data between the groups. For the analysis of independent qualitative data, the chi-square test was used. Fisher's exact test was used when chi-square test conditions were not met. In cases where the p value was less than 0.05 in a 95% confidence interval, the results of statistical analysis were considered as significant.

Results

The groups were evaluated in terms of mean arterial pressure (MAP), respiratory rate (RR) and pulse rate (bpm) during the implementation of selected treatment protocols. There was a statistically significant difference between the groups in terms of 0-3-minute MAP values ($p<0.05$). The MAP values at 5^{th}, 6^{th}, 8^{th}, 10^{th}, 20^{th}, and 30^{th} were found to be statistically significantly lower in group 2 compared to the other groups ($p<0.05$). In group 4, MAP values 6^{th}, 8^{th}, 10^{th}, 20^{th}, and 30^{th} were found to be statistically significantly lower compared to groups 1 and 3 ($p<0.05$). Groups 1 and 3 had similar MAP values on 5^{th}, 6^{th}, 8^{th}, 10^{th}, and 20^{th} minutes ($p>0.05$). In group 2, cardiopulmonary arrest developed in two rats on 8^{th} min, one rat on 10^{th} min, one rat on 33^{th} min, one rat on 36^{th} min, and on rat on 38^{th} min. On 40^{th} min, all rats died in group 2. Afterwards, there were no subjects left in group 2. No significant difference was found between groups 1.3 and 4 in terms of MAP values between the 40^{th} and 60^{th} minutes (Table 1).

The groups were evaluated in terms of RR. There was no statistically significant difference in RR between the groups on 0^{th} min ($p>0.05$). On mins 3, 5, 6, 8, 10, 20, and 30, RR was found to be significantly lower than the other groups in group 2 ($p<0.05$). RR was found significantly higher in group 3 compared to RRs of the groups 1 and 4 at the 6^{th}, 8^{th}, 20^{th}, 30^{th}, and 60^{th} minutes ($p=0.004$ and $p<0.05$, respectively). On mins 8, 10, 20, 30, 60, RR in group 4 was found to be significantly lower than that in groups 1 and 3 ($p=0.004$ and $p<0.05$, respectively) (Table 2).

The groups were evaluated in terms of bpm. There was no statistically significant difference in terms of the bpm between the groups on min 0 ($p>0.05$). On mins 3, 5, 6, 8, 10, 20, and 30, bpm was found to be significantly lower than the other groups in group 2 ($p<0.05$). The bpm was found to be significantly lower in group 4 compared to the groups 2 and 3 at the 6^{th}, 8^{th}, 20^{th}, and 30^{th} minutes ($p<0.05$). At min 20, 30 and 40, bpm was found to be significantly lower in group 1 than in group 3 ($p<0.05$; Table 3)

Table 1. Evaluation of MAP at mins 0, 3, 5, 6, 8, 10, 20, 30, 40, and 60 within and between groups

Min	Group 1	Group 2	Group 3	Group 4	p
	Mean ± SD	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	
0	97.5±6.75 (95)	87.5±3.94 (107)	94.17±5.46 (97)	95.67±5.28 (94.5)	**0.298***
3	99.0±8.63 (96)	87.67±10.23 (89.5)‡	94.67±3.61 (95)	95.0±5.37 (97)	**0.314**
5	98.67±6.68 (96)‡	74.5±18.01 (79)‡	96.5±5.72 (96)	93.0±3.41 (92.5)	**0.003***
6	99.67±10.48 (101)	63.17±26.29 (64.5)‡	98.83±2.93 (99)	85.17±4.12 (86)‡	**0.002***
8	100.83±8.61 (99.5)	43.0±36.87 (53.5)‡	97.17±4.96 (97)	78.67±3.5 (80)‡	**0.001***
10	96.17±3.97 (95.5)	48.0±32.44 (61)	97.17±3.06 (96.5)	75.5±4.04 (77.5)‡	**0.001***
20	94.67±6.09 (95.5)	48.0±1.73 (47)	98±6.2 (97)	83.17±3.6 (83)‡	**0.001***
30	94.33±6.19 (93.5)	35.67±2.52 (36)	95.17±3.49 (95)	89.17±3.92 (89)‡	**0.012***
40	95.83±9.06 (94)	-	93.17±5.71 (92.5)	92.17±4.49 (93.5)	-
60	94.33±6.09 (94.5)	-	94.0±3.22 (94)	92.83±2.79 (93.5)	-

Kruskal Wallis test, ‡Wilcoxon Sign test, *p<0.05, SD: Standard deviation, MAP: Mean arterial pressure

Table 2. Evaluation of the respiratory rates of the groups on mins 0, 3, 5, 6, 8, 10, 20, 30, 40, and 60 within and between groups

Min	Group 1	Group 2	Group 3	Group 4	p
	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	
0	37.5±2.66 (37.5)	41.17±2.48 (41.5)	37.5±2.07 (37.5)	38.17±2.99 (37.5)	**0.064**
3	39.0±1.1 (39)	32.83±4.26 (34.5)‡	40.5±2.07 (40.5)‡	40.67±2.25 (40)‡	**0.002***
5	37.33±3.08 (36.5)	26.33±5.5 (27)‡	43.5±1.87 (43.5)‡	44.33±1.75 (43.5)‡	**0.001***
6	37.67±2.66 (37.5)	21.17±7.41 (22)‡	47.67±2.25 (48)‡	34.0±4.29 (33.5)‡	**0.001***
8	37.17±1.47 (37.5)	13.83±11.91 (16.5)‡	50.0±2.0 (49)‡	24.33±2.25 (23.5)‡	**0.001***
10	39.33±1.97 (39)	16.75±11.44 (21)	51.67±1.37 (51.5)‡	26.67±1.37 (26.5)‡	**0.001***
20	37.0±3.58 (36.5)	16.67±2.52 (17)	55.0±1.26 (54.5)‡	31.67±2.16 (31.5)‡	**0.001***
30	36.67±2.34 (37)	11.0±1.73 (12)	57.83±2.14 (58)‡	34.67±2.16 (34.5)‡	**0.001***
40	37.17±2.79 (37)	0±0 (0)	61.67±4.13 (61)‡	38.17±2.04 (38.5)‡	**0.001***
60	37.33±1.63 (37)	-	62.17±2.86 (62.5)‡	40.17±2.4 (39.5)‡	**0.001***

Kruskal Wallis test, ‡Wilcoxon Sign test, *p<0.05, SD: Standard deviation

Table 3. Evaluation of the pulse rates of the groups on mins 0, 3, 5, 6, 8, 10, 20, 30, 40, and 60 within and between groups

Min	Group 1	Group 2	Group 3	Group 4	p
	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	
0	379±24.16 (379)	381±22.76 (388)	377.5±18.78 (373.5)	387±14.63 (387.5)	**0.754**
3	357.83±23.79 (355)‡	316.17±11.25 (318.5)‡	392.33±9.97 (395)	390±11.3 (391)	**0.001***
5	374±17.12 (373.5)	249.5±43.83 (261)‡	388.83±7.31 (385.5)	394.17±7.11 (396)	**0.001***
6	362±27.79 (361)	182.5±69.66 (200)‡	391.33±9.14 (393.5)	359.33±18.05 (362)‡	**0.001***
8	373.33±27.13 (368)	119±104.5 (139.5)‡	396±4.34 (396)	333±10.86 (337.5)‡	**0.001***
10	368.67±36.64 (377.5)	125.25±88.28 (147.5)	392.83±7.78 (394.5)	324.33±16.99 (325)‡	**0.002***
20	373.17±24.15 (383.5)	124±32.19 (114)	391±9.96 (394)	345.83±16.33 (348.5)‡	**0.001***
30	364.33±9.69 (365.5)	84.67±26.39 (72)	394.17±73.6 (393.5)	358.83±18.71 (361)‡	**0.001***
40	358.17±26.45 (359.5)‡	-	391.17±16.44 (397)‡	376.17±11.94 (378.5)	-
60	362.17±18.1 (363)	-	398.33±7.03 (397.5)	388.17±8.04 (389.5)	-

Kruskal Wallis test, ‡Wilcoxon Sign test, *p<0.05, SD: Standard deviation

Discussion

Our study is the first to investigate whether ILE treatment reduces the undesirable effects of midazolam on the cardiovascular and respiratory system. The study had remarkable results. On mins 8, 10, 20, 30, 60, RR in group 4 was found to be significantly lower than that in groups 1 and 3. The bpm was found to be significantly lower in group 4 compared to the groups 2 and 3 at the 6th, 8th, 20th, and 30th minutes ($p<0.05$). At min 20, 30, and 40, bpm was found to be significantly lower in group 1 than in group 3.

In a study examining the effect of midazolam on blood pressure in healthy people, 0.15 mg/kg midazolam decreased systolic blood pressure by 5% and diastolic blood pressure by 10%, and increased heart rate (HR) by 18% [7]. In a study by Jones et al. [8] examining the cardiovascular effects of midazolam and diazepam on dogs, midazolam was shown to decrease MAP and increase heart HR. Yao et al. [9] stated that the mechanism of the effect on MAP is through the inhibition of sarcolemmal L-type Ca2q channels. In that study, it was shown that flumazenil was not effective in the reversal of this type of channel inhibition.

Ozturk et al. [10], in their study in which they applied midazolam to the rabbit heart and examined its effects on the cardiovascular system and they reported that flumazenil could not prevent the cardiac depressant effect of midazolam. In our study, MAP values were decreased by midazolam, which was consistent with the literature. We also observed that the ILE administration led the MAP value to occur later and normalize earlier. Bradycardia was observed in the rats receiving midazolam infusion, whereas no bradycardia was observed because of ILE administration before midazolam infusion. It was shown that ILE administration inhibited the bradycardia caused by midazolam.

Forster et al. [11], in their study conducted on healthy people, showed that there was a respiratory depression following the IV administration of 0.15 mg/kg midazolam. In our results, it was detected that the respiratory depression effect due to midazolam decreased in the group that was administered ILE before midazolam infusion. Only ILE infusion was observed to increase RR.

While 100% mortality was observed in the group that received only midazolam infusion, there was no mortality in the group that received ILE before midazolam infusion. It has been shown that mortality that may occur due to midazolam administration can be reduced by ILE administration.

Conclusion

It has been shown that undesirable side effects of midazolam, such as hypotension and respiratory depression, can be prevented by ILE administration.

Ethics

Ethics Committee Approval: Yeditepe University Faculty of Medicine Experimental Animal Research Unit Laboratories, following the approval of the Ethics Committee dated 05.04.2016 and decision number 528.

Informed Consent: Not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.A., Ö.O., T.P., F.D., R.A., Concept: H.A., Ö.O., T.P., F.D., Design: H.A., Ö.O., F.D., R.A., Data Collection or Processing: H.A., T.P., E.S., Analysis or Interpretation: Ö.O., R.A., Literature Search: H.A., T.P., R.A., E.A., Writing: H.A., Ö.O., F.D., E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Greenblatt DJ, Shader RI, Abernethy DR. Current status of benzodiazepines. N Engl J Med. 1983;309:410-6.
2. Schoch P, Richards JG, Häring P, Takacs B, Stähli C, Staehelin T, et al. Co-localization of GABA receptors and benzodiazepine receptors in the brain shown by monoclonal antibodies. Nature. 1985;314:168-71.
3. Enna S. Gaba receptor pharmacology functional considerations. Biochem Pharmacol. 1981;30:907-13.
4. Doğanay F, Ak R, Alışkan H, Abut S, Sümer E, Onur Ö. The effects of intravenous lipid emulsion therapy in the prevention of depressive effects of propofol on cardiovascular and respiratory systems: an experimental animal study. Medicina (Kaunas). 2018;55:1.
5. Fettiplace MR, Ripper R, Lis K, Lin B, Lang J, Zider B, et al. Rapid cardiotonic effects of lipid emulsion infusion*. Crit Care Med. 2013;41:e156-62.
6. Demirkol D. Kritik Hasta Çocuklarda Parenteral Beslenme. Klinik Gelişim. 2011;24:44-9.
7. Marty J, Nitenberg A, Blanchet F, Zouioueche S, Desmonts JM. Effects of midazolam on the coronary circulation in patients with coronary artery disease. Anesthesiology. 1986;64:206-10.
8. Jones DJ, Stehling LC, Zauder HL. Cardiovascular responses to diazepam and midazolam maleate in the dog. Anesthesiology. 1979;51:430-4.
9. Yao A, Su Z, Nonaka A, Zubair I, Spitzer KW, Bridge JH, et al. Abnormal myocyte Ca2+ homeostasis in rabbits with pacing-induced heart failure. Am J Physiol. 1998;275:H1441-8.
10. Ozturk T, Tuncok Y, Kalkan S, Guven H, Aran G. Midazolams cardiac depressant effects and their lack of reversal by flumazenil in isolated rabbit hearts. Pharmacological Res. 1999;39:283-7.
11. Forster A, Gardaz JP, Suter PM, Gemperle M. I.V. midazolam as an induction agent for anaesthesia: a study in volunteers. Br J Anaesth. 1980;52:907-11.