1   *Article*

2   # The Effects of Intravenous Lipid Emulsion Therapy in
3   # the Prevention of Depressive Effects of Propofol on
4   # Cardiovascular and Respiratory Systems: An
5   # Experimental Animal Study

6   **Fatih Doğanay [1,*]; Rohat Ak [2]; Halil Alışkan [3]; Serdar Abut [4]; Engin Sümer [5]; Ozge ONUR [6]**

7   [1]   Erciş State Hospital, Department of Emergency Medicine, Van, Turkey.
8   [2]   Şehit Prof. Dr. *İlhan Varank Sancaktepe* Education and Research Hospital, Department of Emergency
9   Medicine, Istanbul, Turkey
10   [3]   Şişli Hamidiye Etfal Education and Research Hospital, Department of Emergency Medicine, Istanbul,
11   Turkey
12   [4]   Institute of Science, Van Yüzüncü Yıl University
13   [5]   Department of Pharmaceutical Toxicology, Graduate School of Health Sciences, Yeditepe University
14   [6]   Marmara University Faculty of Medicine, Department of Emergency Medicine, Istanbul, Turkey
15   *   Correspondence: drdoganay@gmail.com; Tel.: +905356002600

16

17   **Abstract:** *Background and objective:* Propofol is an anesthetic agent that is frequently used in
18   anesthesia induction, maintenance and sedation. Propofol has severe side effects such as
19   hypotension, bradycardia and respiratory depression. Although propofol is commonly used, there
20   is no known antidote for its toxic effects. An approach to prevent toxic effects of propofol would be
21   beneficial. The aim of this study was to assess the effects of intravenous lipid emulsion (ILE) therapy
22   in the prevention of depressive effects of propofol on cardiovascular and respiratory systems.
23   *Materials and methods:* Twenty-eight Sprague-Dawley adult rats were randomly divided into 4
24   groups. The saline-administered group was determined as the Control group. The second group
25   was administered propofol (PP group); the third group was administered ILE (ILE group), and the
26   fourth was administered propofol with ILE therapy (ILE+PP group). Systolic blood pressure (SBP),
27   Diastolic blood pressure (DBP), Mean arterial blood pressure (MAP), Respiratory rate (RR), Heart
28   rate (HR) and mortality were recorded at 10 points during 60 minutes. A repeated measures linear
29   mixed-effect model with unstructured covariance was used to compare the groups. *Results:* In the
30   PP group, SBP, DBP, MAP, RR and HR levels were declining steadily; all rats in this group died
31   after 60 minutes. In the ILE+PP group, after a while, the decreased SBP, DBP, MAP, RR and HR
32   levels increased SBP, DBP, MAP, RR and HR levels of the Propofol group were found to be
33   significantly lower than those of the other groups (p<0.01). The mortality rate was 100% (surviving
34   period, 60 min) for the PP group, whereas 0% for the ILE, ILE+PP and Control groups. *Conclusion:*
35   Our results suggest that undesirable side effects that can be seen after propofol application such as
36   hypotension, bradycardia and respiratory depression might be prevented by using ILE therapy.

37   **Keywords:** Acute Toxicity; Cardiovascular Depression; Intravenous Lipid Emulsion; Propofol; Rat
38   Model; Respiratory Depression

39

40

41

1. Introduction

Propofol is the general anesthetic used for anesthesia induction and its continuation. It is also commonly used for sedation [1]. Propofol is generally safe but it does not have an antidote. It has severe side effects such as cardiovascular depression and hypotension. The most common cardiovascular effect of propofol is causing hypotension by lowering systemic vascular resistance, cardiac contractility and cardiac preload.

There are many studies examining the cardiac depressant effects of propofol in the literature. In one of those studies, the incidence of hypotension (SBP <90 mmHg) was found to be at 15.7% in patients receiving induction dose propofol, and 77% of the hypotension attacks were recorded within the first 10 minutes. In the same study, bradycardia was observed in 4.8% of the patients (HR<50 pulse/min), and 42% of the bradycardia attacks were recorded in the first 10 minutes [2]. Abdul Zahoor et al. reported decrease in blood pressure and pulse values in patients who had minor surgery after propofol application [3]. In the study by Ebert et al. on healthy volunteers, propofol and placebo were compared and a significant decrease was reported in respiratory rate, blood pressure and pulse rate in the propofol group [4].

Intravenous lipid emulsion (ILE) therapy was first used to prevent the toxic effects of local anesthetics [5]. Weinberg et al. reported ILE to be an efficient therapy method for hemodynamic recovery in resuscitated rats with bupivacaine overdose and again in dogs with bupivacaine overdose [5, 6]. In later studies, it was shown that it could be used as an effective antidote in poisonings caused by lipophilic drugs [7]. ILE therapy has been used successfully in toxicities due to many lipophilic drugs such as beta blocker [8], calcium channel blocker [9], and tricyclic antidepressants [10], apart from local anesthetics [11]. In the case report of Tsui et al., it was stated that vasopressor and fluid treatment resistant hypotension were recovered with ILE therapy after post-epidural anesthesia [12].

In addition to these characteristics, it is considered that ILE can be effective on reversing the respiratory depression, vasodilatation and cardiac depressant effects of propofol due to its high lipophilicity.

The aim of this study was to assess the effects of ILE therapy in the prevention of depressive effects of propofol on cardiovascular and respiratory systems.

2. Materials and Methods

The ethical approval for this study was provided by the Ethical Committee of Yeditepe University, Medical Faculty, Experimental Animals Research Laboratory **(Atasehir, Istanbul, Turkey 34755)** on 05 April 2016 with the protocol number 529. Authors declare here that all applicable international, national and/or institutional guidelines for the care and use of animals were followed. All procedures and practices performed in the study involving animals were in accordance with the ethical standards of the institution at which the studies were conducted.

Consent for this study was taken from the ethical board of experimental animals, and the ethics committee allowed an upper limit of 28 rats.

2.1. Subject Selection

This research was carried out in May 2016. 28 Sprague-Dawley adult rats of 200-300 g weights were used for the study. All experimental animals were kept in a day and night cycle for 12 hours each at 24±4°C for seven days until the start of the experiment, and their adaptation to the environment was provided. Standard diet and water were given to the rats.

2.2. Experiment Protocol and Groups

The hairs in the lower parts of the bodies of the rats were shaved to make the applications easier. They were kept in supine position with their extremities stabilized during the study.

Inhaler isoflurane (Isoflurane, Isofludem 100 ml) was used in all rats, and anesthesia was provided with an animal anesthesia machine. After providing satisfactory anesthetic depth, femoral

90   artery cannulation was made with 26-G catheter in all groups (i.v. NEO ALPHA, La-med Healthcare,
91   Haryana, India).   Using a disposable pressure transducer set (OKUMAN Medikal Sistemler Ltd. Şti.,
92   Ankara, Turkey), momentary blood pressure follow-up was provided with a standard cardiac
93   monitor (NIHON KOHDEN Cardiolife Monitor TEC-7721 K, NihonKohden Corporation, Tokyo,
94   JAPAN). Four rats died due to intervention complications during the application of femoral artery
95   cannulation. The study was continued with six rats in each group.

96   Electrocardiography electrodes were placed on both the forefeet and right hind legs. Respiratory
97   and pulse rates were followed with the same monitor (NIHON KOHDEN Cardiolife Monitor TEC-
98   7721 K, NihonKohden Corporation, Tokyo, JAPAN).

99   Tail vein cannulation was made with 26 G branule (i.v. NEO ALPHA, La-medHealthcare,
100   Hayrana, India) in all groups to apply the drugs used in the study.   The propofol used in the study
101   was given with ILE and 0.9% NaCl infusion pump (SwissMade, ArcomedAgVolumed VP7000,
102   Switzerland). ILE (ClinOleic %20 lipid 500 ml, ECZACIBAŞI Baxter/Belgium), Propofol (PROPOFOL-
103   LİPURO %1, 10 mg/ml, I.V. 20 Ml Ampul for Infusion, İlaçsan®/Turkey) and 0.9% NaCl were used.
104   Dosages, drug application methods and experimental protocols were determined according to the
105   previous studies and the mentioned sources [8, 13, 14].

106   Rats were randomly separated into four equal groups.

107   **Group 1 (n=6):** In the Control group, 0.9% NaCl was applied in the form of infusion in four

108   minutes with a dose of 16 mL/kg as a pro-drug,

109   **Group 2 (n=6):** In the PP group, 0.9% NaCI was applied in the form of infusion in four minutes
110   with a dose of 16 mL/kg as a pro-drug. After pretreatment with 0.9% NaCI, propofol was applied i.v.
111   bolus with a dose of 42 mg/kg at the fifth minute.

112   **Group 3 (n=6):** In the ILE group, ILE was applied in the form of infusion in four minutes with a
113   dose of 16 mL/kg as a pro-drug.

114   **Group 4 (n=6):** In the ILE+PP group, ILE was applied in the form of infusion in four minutes
115   with a dose of 16 mL/kg as a pro-drug. After pretreatment with ILE, propofol was applied i.v. bolus
116   with a dose of 42 mg/kg at the fifth minute.

117   At 10 different points in the first 60 minutes (0, 1, 3, 5, 6, 8, 10, 20, 30 and 60th minutes), 5 different
118   measurements of each rat (Systolic blood pressure (SBP), Diastolic blood pressure (DBP), mean
119   arterial blood pressure (MAP), Respiratory rate (RR) and Heart rate (HR)) were taken. Additionally,
120   cardiac or respiratory arrest occurrences up to the 60th minute was observed. The mortality times
121   were registered for the rats which died after the drug application. Decapitation was provided in all
122   rats with guillotine under anesthesia at the 60th minute.

123   *2.3. Statistical Examinations*

124   Trend analysis approach examines the relation between the treatment order and response size.
125   Trend analyses in clinical studies focus on causal treatment effects rather than simple comparisons
126   [19]. Of the 24 rats, only 18 of them had completed data. A total of 240 data points were available for
127   statistical analyses (24 rats × 10 time points). In our study, there were missing values due to the death
128   of the rats in the PP group. All rats in the PP group died at different points of the first 60 minutes. We
129   had 15 time points out of 240 (~%6) instead of 6 out of 24 rats (%25). The main aim of the statistical
130   analyses was to demonstrate the significant differences between the repeated measures in the four
131   experimental groups. Thus, due to the unbalanced data structure, we aimed to use the linear mixed-
132   effect model (LMM) to compare the groups. Changes in values in the groups were compared using
133   an unstructured covariance linear mixed model. P values <0.05 were considered statistically
134   significant. All mixed model statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary,
135   NC, USA).

136

137

3. Results

In the PP group, cardiac arrest developed in 1 rat at the 15th minute, 1 rat at the 20th minute, 1 rat at the 25th minute, 1 rat at the 40th minute, 1 rat at the 44th minute and 1 rat at the 55th minute, and no rats remained in the PP group after this period **(Figure 1)**. Unlike the PP group, mortality was not observed in the other three groups of rats within 60 minutes.

Figure 1. Survival rate of rats in PP group versus time**.**

Linear mixed model was conducted to compare Systolic Blood Pressure (SBP), Diastolic blood pressure (DBP), Mean Arterial Blood Pressure (MAP), Respiratory Rate (RR) and Heart Rate (HR) values between groups. SBP, DBP, MAP, RR and HR values in the PP group were found to be lower than those of the Control, ILE and ILE+PP groups (p<0.05). **(Table 1, Figure 2B, 3B, 4B, 5B, 6B).**

Table 1: Differences of least squares means (MD) and adjusted p (Adj p) value of all pairwise comparisons among groups (1: Control, 2: PP, 3:ILE, 4: ILE+PP).

Scores	1 – 2 MD	Adj P	1 - 3 MD	Adj P	1 - 4 MD	Adj P	2 - 3 MD	Adj P	2 - 4 MD	Adj P	3 - 4 MD	Adj P
SBP	**36.78**	*<.0001*	0.38	*1.000*	**7.80**	*0.009*	**-36.40**	*<.0001*	**-28.98**	*<.0001*	7.42	*0.013*
DBP	**24.63**	*<.0001*	1.17	*1.000*	-3.78	*1.000*	**-23.46**	*<.0001*	**-28.41**	*<.0001*	-4.95	*0.937*
MAP	**28.68**	*<.0001*	0.91	*1.000*	0.08	*1.000*	**-27.77**	*<.0001*	**-28.60**	*<.0001*	-0.83	*1.000*
RR	**14.11**	*<.0001*	**-13.13**	*<.0001*	1.07	*1.000*	**-27.25**	*<.0001*	**-13.05**	*<.0001*	**14.20**	*<.0001*
HR	**135.14**	*<.0001*	-24.08	*0.183*	22.85	*0.234*	**-159.23**	*<.0001*	**-112.29**	*<.0001*	**46.93**	*0.0012*

Bonferonni's correction was used for multiple comparisons.

Figure 2. A) Least squares means of Systolic blood pressure (SBP) values of Control, PP, ILE and ILE+PP groups of rats versus time. **B)** Least squares means of SBP values (Error bars: 95% confidence interval).

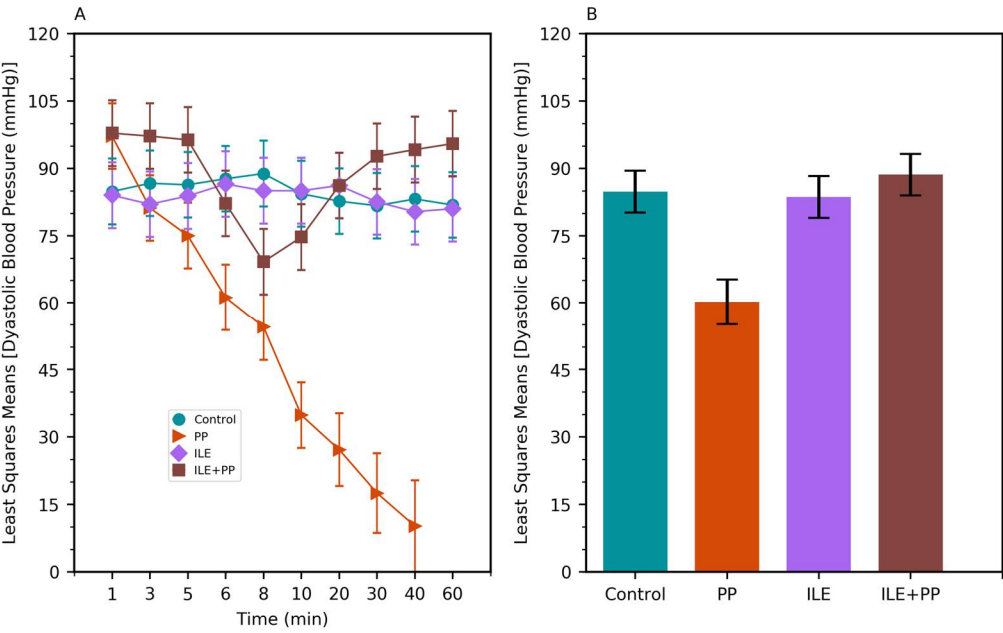
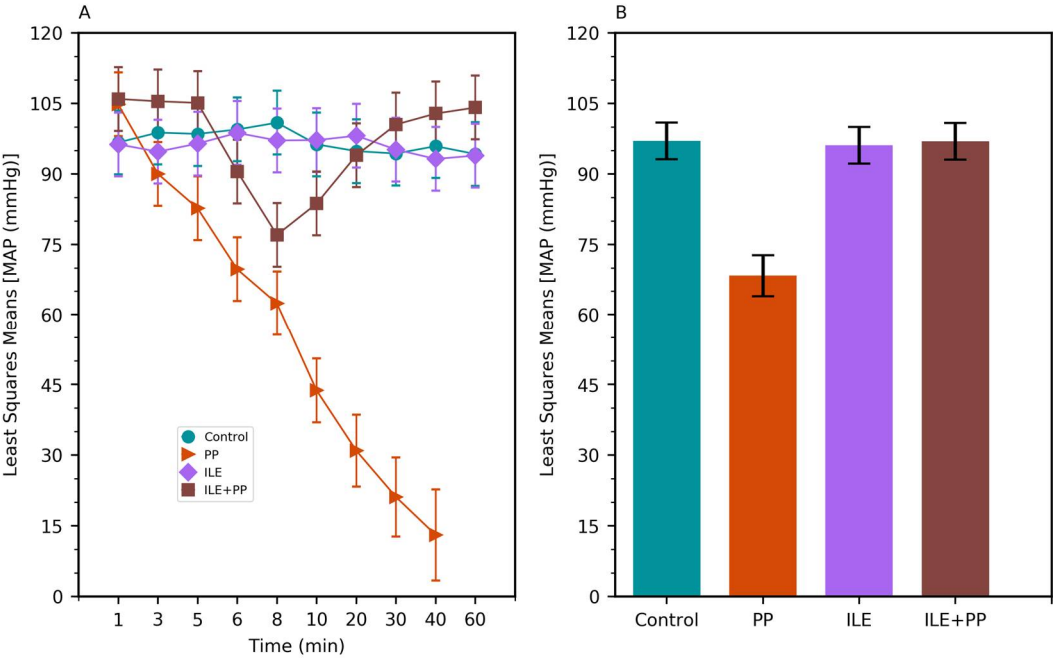
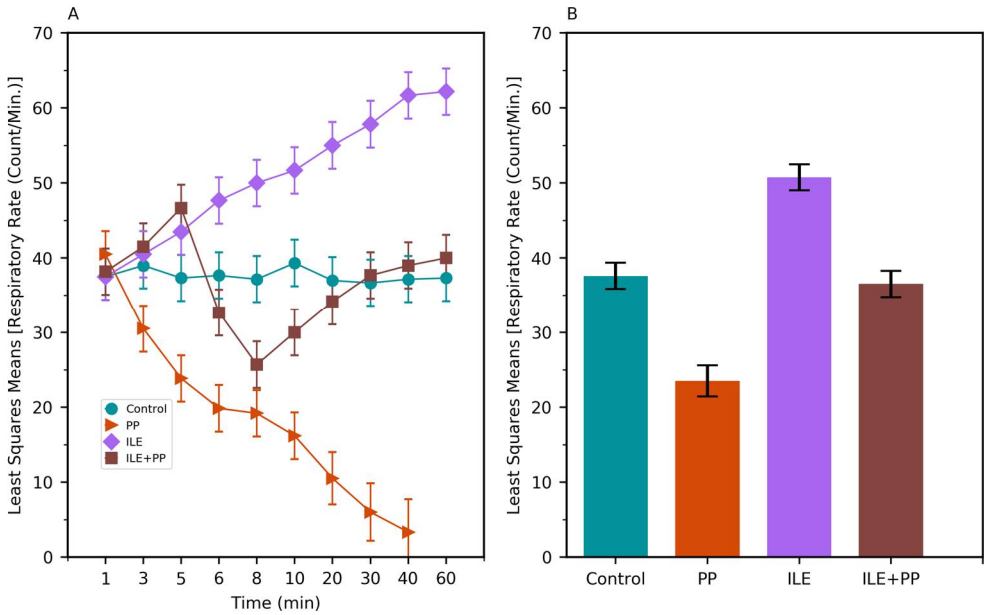



Figure 3. A) Least squares means of Diastolic blood pressure (DBP) values of Control, PP, ILE and ILE+PP groups of rats versus time. **B)** Least squares means of DBP values (Error bars: 95% confidence interval).

159

160   **Figure 4. A)** Least squares means of Mean arterial blood pressure (MAP) values of Control,
161   PP, ILE and ILE+PP groups of rats versus time. **B)** Least squares means of MAP values
162   (Error bars: 95% confidence interval).

163

164   **Figure 5. A)** Least squares means of Respiratory rate (RR) values of Control, PP, ILE and
165   ILE+PP groups of rats versus time. **B)** Least squares means of RR values (Error bars: 95%
166   confidence interval).

167

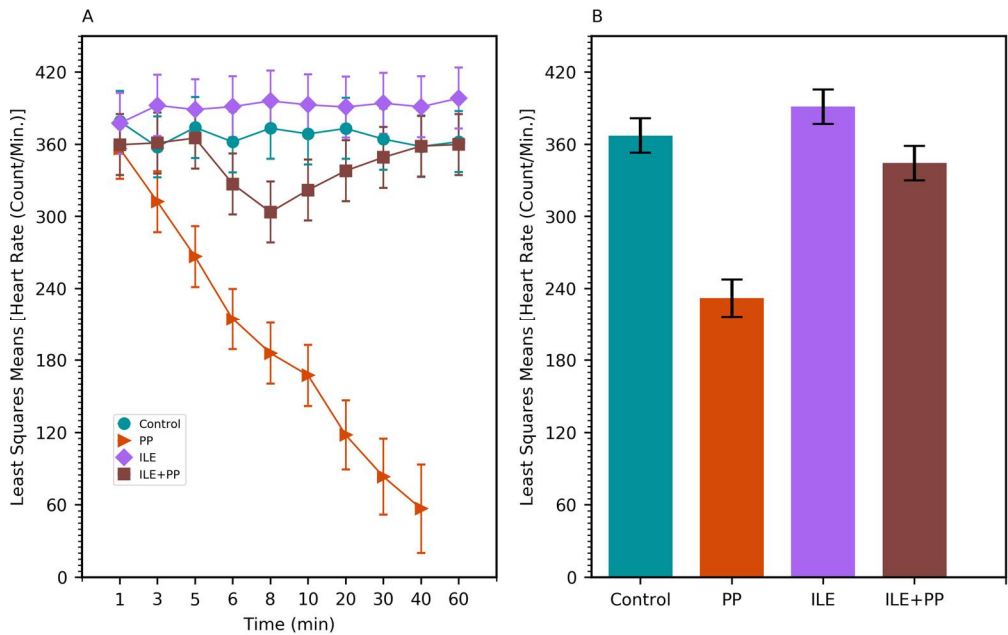



Figure 6. A) Least squares means of Heart rate (HR) values of Control, PP, ILE and ILE+PP
groups of rats versus time. **B)** Least squares means of HR values (Error bars: 95% confidence
interval).

As a result of the pairwise comparisons, we found that RR values of the ILE group were higher
than those of the Control group (mean difference=13.13 Count/Min., p<.0001). The difference between
SBP, DBP, MAP and HR values in the Control and ILE groups was not significant (p>.05) **(Table 1,
Figure 2B, 3B, 4B, 5B, 6B)**.

SBP values of the ILE+PP group were found to be significantly lower than the Control group
(mean difference=7.80 Count/Min., p=0.009). The difference between DBP, MAP, RR and HR values
in the ILE+PP and Control groups was not significant (p>.05) **(Table 1, Figure 2B, 3B, 4B, 5B, 6B)**.

SBP, RR and HR values of the ILE group was found to be higher than those of the ILE+PP group.
Mean differences were 7.42, 14.20, 46.93, respectively, and p values were p=0.013, p<.0001, p=0.0012,
respectively. The difference between other values (DBP and MAP) in the ILE and ILE+PP groups was
not significant (p>.05) **(Table 1, Figure 2B, 3B, 4B, 5B, 6B)**.

4. Discussion

Cardiac side effects of propofol are related to the channel blockage of molecular level voltage-
gated sodium (Na) and potassium (K) channel [15, 16]. Propofol stimulates the release of nitric oxide,
blocks the calcium channel and activates protein kinase C. [17, 18]. Therefore, administration of
propofol results in a decrease in cardiac output and arterial blood pressure. [2, 19]. Propofol
suppresses baroreceptor reflex and decreases sympathetic nerve activity. In previous studies, it was
reported that propofol formed baroreceptor inhibition-related bradycardia depending on the dose
[20]. The decrease in blood pressure can be explained by supression of sympathetic nerve activity,
vasodilatation and depression of myocardial contractility. Propofol is also a strong dose-related
respiratory depressant [21]. The mechanisms that explain the respiratory depressant effect of
propofol have not been fully clarified. Kashigawi et al. found that propofol reduced the activity of
inspiratory neurons located in the medulla and caused an inhibitory effect by activation of GABA$_A$
receptors [22].

Similarly in our study, a significant decrease was observed in SBP, DBP, MAP, HR and RR values
in the group that was only administered propofol, and all the rats in this group died at the end of the
60th minute. **(Figure 1)**.

198   The mechanism of action of ILE therapy is not completely explained and different hypotheses
199   are used to try to clarify this. The first hypothesis asserted on the mechanism of action of ILE is that
200   it provides the separation of lipophilic drugs from the target tissue by forming lipid-rich
201   compartments in the plasma (lipidsink) [23-24]. Scavenging Effect is not only a static sink effect; it is
202   considered a dynamic shuttle effect. The lipid compartment in the blood creates the shuttle effect by
203   transferring the lipophilic drugs from the organs. In this way, organs with high blood flow are
204   detoxified from the drug [25]. In one study, it has been shown that ILE therapy acutely decreased
205   drug concentrations in the heart and brain and increased concentrations in the liver. [23].

206   Other hypotheses assert ILE's cardiotonic and inotropic effects to explain the mechanism of
207   action. In one study, it has been indicated that ILE administration increased the left ventricular
208   contractility [26]. A study performed by Umpierrez et al. showed that ILE administration increased
209   blood pressure in African-American patients with type 2 diabetes [27]. nontheles, both the inotropic
210   and lusitropic effects of ILE have been shown in both in-vivo cardiac studies and isolated heart
211   studies, which were conducted in the absence of drug toxicity [28, 29].

212   Huang et al. demonstrated that, similar to calcium (Ca) channel opening agents, long-chain
213   fatty acids activated voltage-gated Ca channels in isolated cardiomyocytes [30]. In another study, it
214   was also observed that ILE showed an improvement of myocyte functions by increasing intracellular
215   Ca level [31]. Also, there are studies, the findings of which are opposite to those in the literature.
216   XIAO et al. conducted a study on Neonatal Rat Ventricular Myocytes to examine the role of
217   polyunsaturated fatty acids (PUFAs) on L-type Ca channel currents and sarcoplasmic reticulum Ca
218   release. They found that PUFAs reduced intracellular Ca level by both blocking the L-type Ca channel
219   currents and decreasing sarcoplasmic reticulum Calcium release [32]. In an another study, ILE and
220   verapamil were administered both together and separately. Both L-type Ca channel activity and
221   intracellular Ca level on ventricular cardiomyocytes were evaluated. They found that ILE had no
222   effect on intracellular Ca level and myocardial contractility in the absence of verapamil
223   administration [33]. The validity of the calcium hypothesis has not been clarified yet and needs
224   further studies.

225   In our study, it was observed that SBP, DBP, MAP and HR values in the group that was
226   administered Propofol with ILE (ILE+PP group) had a decreasing course from the 5th minute, when
227   propofol was started, until the 8th minute. After the 8th minute, an increase was observed in SBP,
228   DBP, MAP and HR values, and these values got closer to the Control group. A similar course was
229   detected in SBP, DBP, MAP and HR values in the Control group after the 30th minute. At this point,
230   it is considered that ILE treatment is advantageous for preventing the hypotension and bradycardia
231   side effects of propofol **(Figure 2, 3, 4, 6)**.

232   According to findings of this study, decreased values of SBP, DBP, MAP and HR due to propofol,
233   increased with ILE administration. The difference between SBP, DBP, MAP and HR values in the ILE
234   and Control groups was not significant (Table 1). Therefore, We did not observe any inotropic effects
235   in the group in which only ILE was administered. Our findings suggest that ILE has no direct
236   inotropic effect if it is administered alone. Again, parallel to other studies, it was observed that RR
237   values in the ILE+PP group had a decreasing course from the 5th minute, when propofol was started,
238   until the 8th minute. After the 8th minute, an increase was observed in RR values, and these values
239   got closer to the Control group. A similar course was detected in RR values in the Control group after
240   the 30th minute. We observed that ILE treatment is also advantageous in preventing the respiratory
241   depressant side effect of propofol **(Figure 5)**.

The mortality rate of the PP group was detected as 100% **(Figure 1)**; the survival rate was found to be 100% in the ILE+PP group. Our study is important as it shows that ILE therapy decreased propofol-related mortality. However, it is not possible to compare the results of our study with the literature, because ILE therapy was not tried to prevent propofol-induced mortality.

According to our findings, the RR level of the ILE group was found to be significantly higher than those of the other groups (Table 1). More detailed studies should be designed to explain the tachypneic effect of ILE therapy.

5. Conclusion

Due to the findings obtained during the research, it was concluded that side effects such as hypotension, bradycardia and respiratory depression, which can be seen after propofol application in rats, could be recovered with ILE therapy, and mortality due to these side effects were prevented. More extensive studies are required.

Author Contributions: Conceptualization, Fatih Doğanay; Data curation, Fatih Doğanay and Serdar Abut; Formal analysis, Fatih Doğanay; Funding acquisition, Fatih Doğanay; Investigation, Fatih Doğanay, Halil Alışkan and Engin Sümer; Methodology, Fatih Doğanay; Project administration, Fatih Doğanay; Resources, Fatih Doğanay, Rohat Ak and Serdar Abut; Software, Serdar Abut; Supervision, Fatih Doğanay, Rohat Ak and Özge Onur; Validation, Fatih Doğanay, Serdar Abut and Özge Onur; Visualization, Fatih Doğanay and Serdar Abut; Writing – original draft, Fatih Doğanay; Writing – review & editing, Fatih Doğanay, Serdar Abut and Rohat Ak

Funding: This work was supported by the University of Health Science, Istanbul, Turkey (Grant number 189).

Conflict of Interest: The authors declare that they have no conflict of interest.

References

1. Shafer, A., Doze, V. A., Shafer, S. L., & White, P. F. (1988). Pharmacokinetics and pharmacodynamics of propofol infusions during general anesthesia. *Anesthesiology*, *69*(3), 348-356.

2. Hug, J. C., McLeskey, C. H., Nahrwold, M. L., Roizen, M. F., Stanley, T. H., Thisted, R. A., ... & Grasela, T. H. (1993). Hemodynamic effects of propofol: data from over 25,000 patients. Anesthesia and analgesia, 77(4 Suppl), S21-9.

3. Zahoor, A. B. D. U. L., & Ahmed, N. A. U. M. A. N. (2010). The effects of duration of Propofol injection on hemodynamics. Middle East Journal of Anesthesiology, 20(6), 845-50.

4. Ebert, T. J. (2005). Sympathetic and hemodynamic effects of moderate and deep sedation with propofol in humans. *Anesthesiology: The Journal of the American Society of Anesthesiologists*, *103*(1), 20-24.

5. Weinberg, G.,Ripper, R., Feinstein, D.L. and Hoffman, W., Lipid emulsion in fusion rescues dogs from bupivacaine-induced cardiactoxicity. Regional anesthesia and pain medicine, 2003, 28(3), pp.198-202.

6. Guy L. Weinberg, Timothy VadeBoncouer, Gopal A. Ramaraju, Marcelo F. Garcia-Amaro, Michael J. Cwik; *Pretreatment or Resuscitation with a Lipid Infusion Shifts the Dose-Response to Bupivacaine-induced Asystole in Rats* . *Anesthesiology* 1998;88(4):1071-1075.

7. Cevik, S. E., Tasyurek, T., & Guneysel, O. (2014). Intralipid emulsion treatment as an antidote in lipophilic drug intoxications. The American Journal of Emergency Medicine, 32(9), 1103-1108.

8. Cave, G.,Harvey, M.G. and Castle, C.D., The role of fat emulsion therapy in a rodent model of propranolol toxicity: a preliminary study. Journal of medical toxicology, 2006, 2(1), pp.4-7.

9. Kang, C., Kim, D.H., Kim, S.C., Lee, S.H., Jeong, J.H., Kang, T.S., Shin, I.W., Kim, R.B. and Lee, D.H., The effects of intravenous lipid emulsion on prolongation of survival in a rat model of calcium channel blocker toxicity. Clinical Toxicology, 2015, 53(6), pp.540-544.

10. Tsujikawa, S., Matsuura, T., Hori, K., Mori, T., Kuno, M., & Nishikawa, K. (2018). Superior efficacy of lipid emulsion infusion over serum alkalinization in reversing amitriptyline-induced cardiotoxicity in Guinea Pig. Anesthesia & Analgesia, 126(4), 1159-1169.

11. Rothschild, L., Bern, S., Oswald, S., & Weinberg, G. (2010). Intravenous lipid emulsion in clinical toxicology. Scandinavian journal of trauma, resuscitation and emergency medicine, 18(1), 51.

12. Tsui, B. C., Cheung, S. S., Ziwenga, O., & Gragasin, F. S. (2015). Use of Intralipid® in managing refractory hypotension following epidural blockade. Canadian Journal of Anesthesia/Journal canadien d'anesthésie, 62(5), 548-549.

13. Harkness, J.E.,Turner, P.V., VandeWoude, S. andWheler, C.L., Harkness and Wagner's biology and medicine of rabbits and rodents, 5th ed. 2013. John Wiley&Sons.

14. Turan, C. A., Ozturk, T. C., Akoglu, E. U., Ak, R., Aygun, K., Sahiner, A., ... & Onur, O. E. (2018). The role of intralipid emulsion in the rat model of digoxin intoxication. *Cardiovascular toxicology*, *18*(4), 329-336.

15. Stoetzer, C., Reuter, S., Doll, T., Foadi, N., Wegner, F., & Leffler, A. (2016). Inhibition of the cardiac Na+ channel α-subunit Nav1. 5 by propofol and dexmedetomidine. Naunyn-Schmiedeberg's archives of pharmacology, 389(3), 315-325.

16. Friederich P, Benzenberg D, Urban BW. Ketamine and Propofol Differently Inhibit Human Neuronal K+ Channels. Eur J Anaesth. 2002; 18: 177-183.

17. Cook, D. J., & Housmans, P. R. (1994). Mechanism of the negative inotropic effect of propofol in isolated ferret ventricular myocardium. Anesthesiology, 80(4), 859-871.

18. Riou, B., Besse, S., Lecarpentier, Y., & Viars, P. (1992). In vitro effects of propofol on rat myocardium. Anesthesiology, 76(4), 609-616.

19. Claeys, M., Gepts, E., & Camu, F. (1988). Haemodynamic changes during anaesthesia induced and maintained with propofol. BJA: British Journal of Anaesthesia, 60(1), 3-9.

20. Ebert TJ, Muzi M, Berens R et al.,Sympathetic responses to induction of anesthesia in humans with propofol or etomidate. Anesthesiology, 1992; 76, 725–733.

21. Goodman, N. W., Black, A. M. S., & Carter, J. A. (1987). Some ventilatory effects of propofol as sole anaesthetic agent. BJA: British Journal of Anaesthesia, 59(12), 1497-1503.

22. Kashiwagi, Masanori, et al. "Optical imaging of propofol-induced central respiratory depression in medulla–spinal cord preparations from new born rats." Clinical and Experimental Pharmacology and Physiology, 2011; 38.3, 186-191.

23. Shi, K., Xia, Y., Wang, Q., Wu, Y., Dong, X., Chen, C., ... & Papadimos, T. J. (2013). The effect of lipid emulsion on pharmacokinetics and tissue distribution of bupivacaine in rats. Anesthesia & Analgesia, 116(4), 804-809.

24. Litonius, E., Tarkkila, P., Neuvonen, P. J., & Rosenberg, P. H. (2012). Effect of intravenous lipid emulsion on bupivacaine plasma concentration in humans. Anaesthesia, 67(6), 600-605.

25. Fettiplace, M. R., & Weinberg, G. (2018). The mechanisms underlying lipid resuscitation therapy. Regional anesthesia and pain medicine, 43(2), 138-149.

323 26. Holland, D. J., Erne, D., Kostner, K., Leano, R., Haluska, B. A., Marwick, T. H., & Sharman, J. E. (2011).
324   Acute elevation of triglycerides increases left ventricular contractility and alters ventricular-vascular
325   interaction. *American Journal of Physiology-Heart and Circulatory Physiology, 301*(1), H123-H128.
326 27. Umpierrez, G. E., Smiley, D., Robalino, G., Peng, L., Kitabchi, A. E., Khan, B., ... & Phillips, L. S. (2009).
327   Intravenous intralipid-induced blood pressure elevation and endothelial dysfunction in obese African-
328   Americans with type 2 diabetes. *The Journal of Clinical Endocrinology & Metabolism*, *94*(2), 609-614.
329 28. Shin, I. W., Hah, Y. S., Kim, C., Park, J., Shin, H., Park, K. E., ... & Lim, D. H. (2014). Systemic blockage
330   of nitric oxide synthase by L-NAME increases left ventricular systolic pressure, which is not augmented
331   further by Intralipid®. International journal of biological sciences, 10(4), 367.
332 29. Fettiplace, M. R., Ripper, R., Lis, K., Lin, B., Lang, J., Zider, B., ... & Weinberg, G. (2013). Rapid
333   cardiotonic effects of lipid emulsion infusion. Critical care medicine, 41(8), e156-e162.
334 30. Huang, J. M., Xian, H., & Bacaner, M. (1992). Long-chain fatty acids activate calcium channels in
335   ventricular myocytes. Proceedings of the National Academy of Sciences, 89(14), 6452-6456.
336 31. Park, J., Kim, Y. A., Han, J. Y., Jin, S., Ok, S. H., Sohn, J. T., ... & Shin, I. W. (2016). Lipofundin® MCT/LCT
337   20% increase left ventricular systolic pressure in an ex vivo rat heart model via increase of intracellular
338   calcium level. Korean journal of anesthesiology, 69(1), 57-62.
339 32. Xiao, Y. F., Gomez, A. M., Morgan, J. P., Lederer, W. J., & Leaf, A. (1997). Suppression of voltage-gated
340   L-type Ca2+ currents by polyunsaturated fatty acids in adult and neonatal rat ventricular
341   myocytes. *Proceedings of the National Academy of Sciences*, *94*(8), 4182-4187.
342 33. Kryshtal, D. O., Dawling, S., Seger, D., & Knollmann, B. C. (2016). In vitro studies indicate intravenous
343   lipid emulsion acts as lipid sink in verapamil poisoning. *Journal of Medical Toxicology*, *12*(2), 165-171.