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Title Page

Title: The effects of intravenous lipid emulsion treatment in the prevention of depressive effects of propofol on cardiovascular and respiratory system: an experimental animal study

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Abstract

Propofol is the general anesthetic used for the anesthesia induction and its continuation. Propofol is generally safe and it doesn't have an antidote. Propofol has severe side effects such as cardiovascular depression and hypotension. The aim of this study was observed the effects of intravenous lipid emulsion (ILE) treatment in the prevention of depressive effects of propofol on cardiovascular and respiratory system. Twenty-eight Sprague-Dawley adult rats randomly divided into 4 groups. The saline administered group was defined as the control group. The second group administered propofol, the third group administered ILE, and the fourth administered propofol with ILE therapy. Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Median arterial blood pressure (MAP), Respiratory rate (RR), Heart rate (HR) and mortality were recorded during 60 minutes of follow-up. In the propofol group, SBP, DBP, MAP, RR and HR scores were decline steadily, after 60 minutes all rats in this group died. In the ILE group with propofol, after a while, decreased SBP, DBP, MAP, RR and HR scores was increased, and these values were observed close to the control group. The mortality ratio of the propofol group was detected as 100%, and survival ratio was found 100% in ILE + propofol group. The side effects such as hypotension, bradycardia and respiratory depression which can be seen after propofol application in rats could be recovered with ILE treatment and mortality due to these side effects were prevented.

Key words: Acute Toxicity; Intravenous Lipid Emulsion; Propofol; Rat Model

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1. Introduction

Propofol is the general anesthetic used for the anesthesia induction and its continuation. It is also commonly used for sedation. Propofol is generally safe and it doesn't have an antidote. It has severe side effects such as cardiovascular depression and hypotension. Its most common cardiovascular effect is causing hypotension by lowering systemic vascular resistance, cardiac contractility and cardiac preload. These cardiac side effects are related to the channel blockage of molecular level voltage gated sodium (Na) and potassium (K) channel blockage [1, 2]. Propofol suppresses baroreceptor reflex and decreases sympathetic nerve activity. In previous studies, it was reported that propofol formed baroreceptor inhibition related bradycardia depending on dose [3, 4]. Propofol is also a strong dose-related respiratory depressant [5].

Intravenous lipid emulsion (ILE) treatment was first used to prevent the toxic effects of local anesthetics [6]. Later, ILE treatment was used successfully in toxicity due to many lipophilic drugs such as beta blocker, calcium channel blocker and tricyclic antidepressants apart from local anesthetics [7-10]. Although the effect mechanism is not completely explained, different theories are used to try to explain ILE treatment. The first theory presented on ILE effect mechanism is that it provides the separation of lipophilic drugs from the target tissue by forming lipid-rich compartment in the plasma (lipidsink) [11-12]. Providing energy resource to myocardium with a high dose of free fatty acid as another effect mechanism, it is considered that long chain fatty acids activate voltage -gated calcium channels in cardiac myocytes [13,14]. On the other hand, researches on ILE treatment continue anyway.

ILE binds lipid-soluble drugs [15]. Causing the inhibition of mitochondrial metabolism of lipids, ILE decreases tissue acidosis in myocardial ischemia and also decreases CO_2 production [14]. It was also observed that ILE improved myocyte functions by increasing intracellular calcium level [16]. It was also shown that similar to calcium channel opening agents, free fatty acids activate voltage-gated calcium channels in isolated cardiac muscle tissue [17]. Another effect is the hydrolization of circulating lipids on free fatty acids through lipoprotein lipase and its used as energy source by myocytes [18]. In addition to these characteristics, it is considered that ILE

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can be effective on reversing respiratory depression, vasodilatation and cardiac depressant effect of propofol with high lipophilic characteristic.

The aim of this study was observed the effects of ILE treatment in the prevention of depressive effects of propofol on cardiovascular and respiratory system.

2. Materials and Methods

Ethical approval for this study was provided by the Ethichal Committee of Yeditepe University Medical Faculty Experimental Animals Research Laboratory **(**Atasehir, Istanbul, Turkey 34755**)** on 05 April 2016 by 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 performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

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

2.1. Subject Selection

This research was carried out in May 2016. 28 Spraque-Dawley adult rats of 200-300 g weight were used for the study. All experimental animals were kept at dark and light 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 hair in the lower parts of the body of the rats was shaved to make the applications easier. They were kept in supine position with their extremities stabilized during the study.

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Inhaler isofluran (Izofluran, Isofludem 100 ml) was used in all rats and anesthesia was provided with animal anesthesia machine. After providing satisfactory anesthetic depth, femoral artery cannulation was made with 26-G catheter in both groups (i.v. NEO ALPHA, La-med Healthcare, Haryana, India). Using disposable pressure transducer set (OKUMAN Medikal Sistemler Ltd. Şti., Ankara, Turkey), momentary blood pressure follow-up was provided during the study with a standard cardiac monitor (NIHON KOHDEN Kardiyolife Monitörü TEC-7721 K, NihonKohden Corporation, Tokyo, JAPAN). Four rats died due to intervention complication during application of femoral artery cannulation. The study continued with six rats in each group.

Electrocardiography electrodes were placed on both the forefoot and right hind leg. Respiratory and pulse rates were followed with the same monitor (NIHON KOHDEN Kardiolife Monitor TEC-7721 K, NihonKohden Corporation, Tokyo, JAPAN).

Tail vein cannulation was made with 26 G branule (i.v. NEO ALPHA, La-medHealthcare, Hayrana, India) in both groups to apply the drugs used in the study. The propofol used in the study was given with ILE and 0.9% infusion pump (SwissMade, ArcomedAgVolumed VP7000, Switzerland). ILE (ClinOleic %20 lipid 500 ml, ECZACIBAŞI Baxter/Belgium), Propofol (PROPOFOL-LİPURO %1, 10 mg/ml, I.V. Infüzyonluk 20 Ml Ampul İlaçsan®/Turkey) and 0.9%NaCl were used. Dosages and drug application methods were determined according to previous studies and the mentioned resources [8,9].

Rats were randomly separated into four equal groups.

Group 1 (n=6) : It was applied in the form of infusion in four minutes with a dose of 0.9% NaCl 16 mL/kg in the control group.

Group 2 (n=6) : In PP group, 0.9% NaCI was applied in the form of infusion in four minutes with a dose of 16 mL/kg and propofol was applied i.v. bolus with a dose of 42 mg/kg in the second minute.

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

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Group 4 (n=6) : In ILE+Propofol (ILE+PP) group, ILE was applied in the form of infusion in four minutes with a dose of 16 mL/kg and propofol was applied i.v. bolus with a dose of 42 mg/kg in the second minute.

At 10 different points in the first 60 minutes (0, 1, 3, 5, 6, 8, 10, 20, 30 and 60th minutes), 5 different measurements of each rat (Systolic blood pressure (SBP), Diastolic blood pressure (DBP), median arterial blood pressure (MAP), Respiratory rate (RR) and Heart rate (HR)) were taken. Additionally, cardiac or respiratory arrest occurrence up to the 60th minute was observed. Mortality time was registered for the rats which died after drug application. Decapitation was provided in all rats with guillotine under anesthesia on the 60th minute.

2.3. Statistical Examinations

Trend analysis approach examines the relation between the treatment order and response size. Trend analyses in clinical studies focus on causal treatment effects rather than simple comparisons [19]. Thus we aimed to use Repeated Measures (RM) ANOVA in the comparisons of the groups due to the structure of our study.

In RM ANOVA method, participants with one or more missing value are excluded from the analysis. This condition limits RM ANOVA usage [20]. In our study, there is missing data as the rats in propofol group died. As all rats in propofol (PP) group died in different time points of the first 60 minutes (Figure 1F), Independent Samples t test was used for 5 measurement types in the comparisons between PP group and Control group and ILE+PP group in order. In the comparison of the groups other than PP, as measurements could be taken in different time ranges from the same rat and as there is no missing data (contrary to PP group), RM ANOVA was used as the suitable analysis method for this situation. Sphericity hypothesis among the hypotheses of this analysis was tested with Mauchly's test for sphericity.

A probability vaule ($p \leq 0.01$) was set as a less significant value of data analysis. IBM SPSS Statistics 22 for Mac was used for data analysis.

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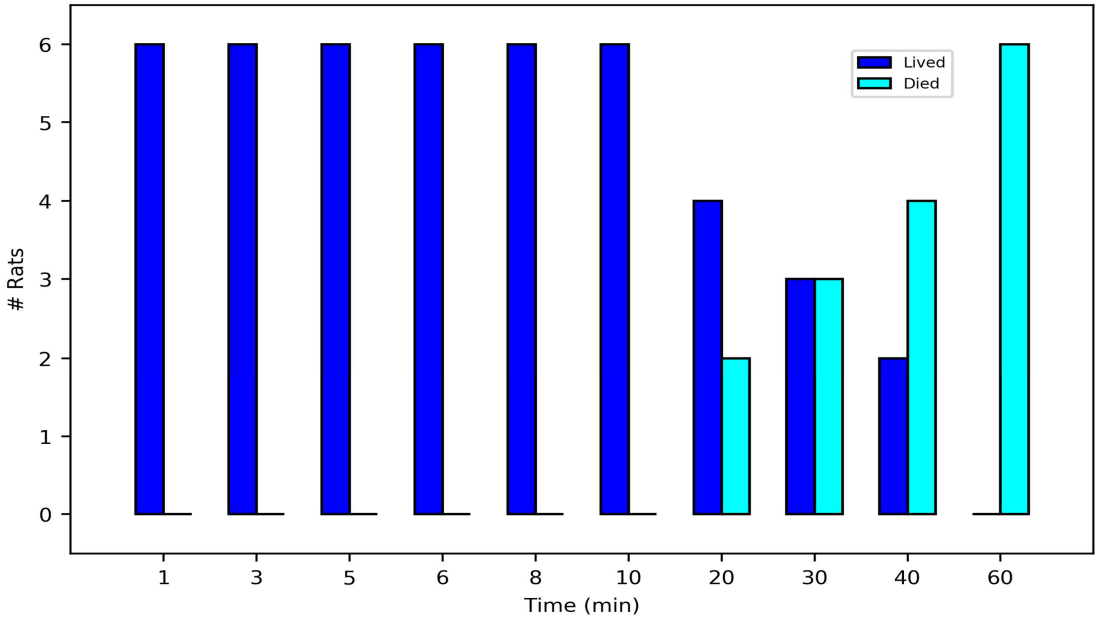
3. Results

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

Figure 1) Number of lived or died rats in propofol group versus time**.**



Five independent sample t-tests were conducted to compare Systolic Blood Pressure (SBP), Diastolic blood pressure (DBP), Median Arterial Blood Pressure (MAP), Respiratory Rate (RR) and Heart Rate (HR) between control and propofol (PP) groups. In PP group, SBP score (M=85.02 SD=26.20), DBP score (M=61.15, SD=25.60), MAP score (M=69.11, SD=25.58), RR score (M=22.64, SD=10.63) and HR score (M=234.77, SD=84.24) were found lower than SBP score (M=121.35, SD=5.59), DBP score (M=84.80, SD=8.32), MAP score (M=96.98, SD=7.24), RR score (M=37.61, SD=2.39) and HR scores (M=367.26, SD=23.62) of the control group respectively ($p<0.01$) **(Table 1, Figure 2, 3, 4, 5, 6).**

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Table 1: Independent samples t-tests and repeated measures of ANOVA results related to Systolic Blood Pressure, Diastolic Blood Pressure, Median Arterial Blood Pressure, Respiratory Rate and Heart Rate subfactors of the rats in the Control, Propofol, Intralipid and Intralipid+Propofol groups

	I (Control)	II (Propofol)	III (Intralipid)	IV (Intralipid + Propofol)	Independent t tests		Repeated Measures ANOVA	
					I – II	IV – II	III– I	I – IV
Variable	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**P**	**P**	**P**	**P**
Systolic blood pressure	121.35 (5.59)	85.02 (26.20)	120.97 (2.97)	113.55 (11.01)	0.00*	0.00*	0.45	0.00*
Diastolic blood pressure	84.80 (8.32)	61.15 (25.60)	83.63 (5.55)	88.58 (10.98)	0.00*	0.00*	0.32	0.00*
Median arterial blood pressure	96.98 (7.24)	69.11 (25.58)	96.08 (4.54)	96.91 (10.69)	0.00*	0.00*	0.33	0.00*
Respiratory rate	37.61 (2.39)	22.64 (10.63)	50.75 (8.48)	36.55 (6.48)	0.00*	0.00*	0.00*	0.00*
Heart rate	367.26 (23.62)	234.77 (84.24)	391.35 (11.19)	344.42 (31.07)	0.00*	0.00*	0.29	0.00*

* $p<0.01$, there is significant difference in the related variables between two groups.

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Figure 2. A) Mean Systolic blood pressure (SBP) scores of Control (C), Propofol (PP), Intralipid (ILE) and Intralipid+Propofol (ILE+PP) groups of rats versus time. **B)** Grand Means of SBP scores (n.s.: non significance, **: P<0.01, Error bars: 95% confidence interval)

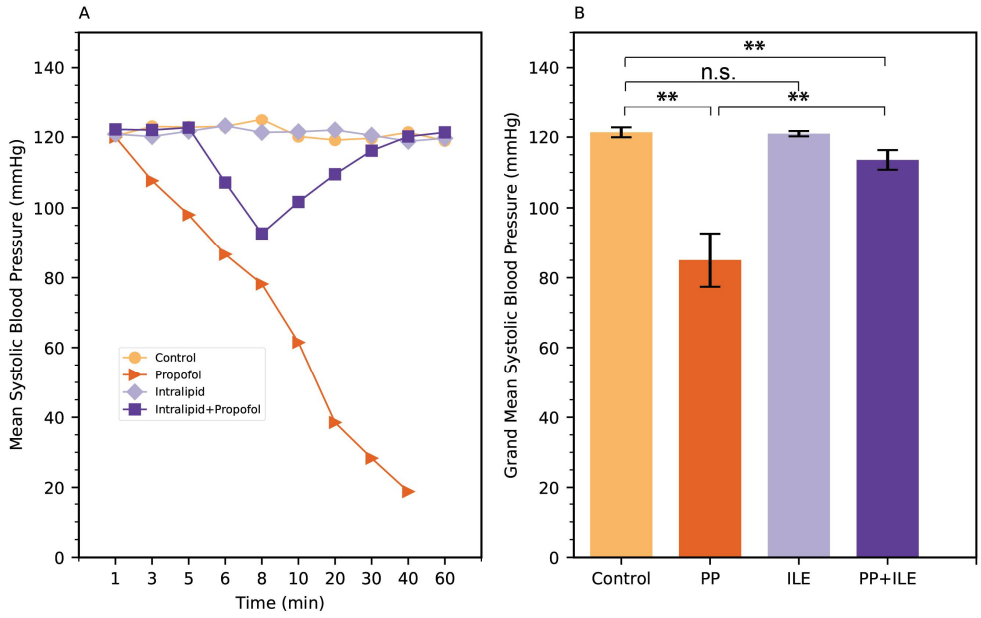

Figure 3. A) Diastolic blood pressure (DBP) scores of Control (C), Propofol (PP), Intralipid (ILE) and Intralipid+Propofol (ILE+PP) groups of rats versus time. **B)** Grand Means of DBP scores (n.s.:non significance, **:P<0.01, Error bars: 95% confidence interval)

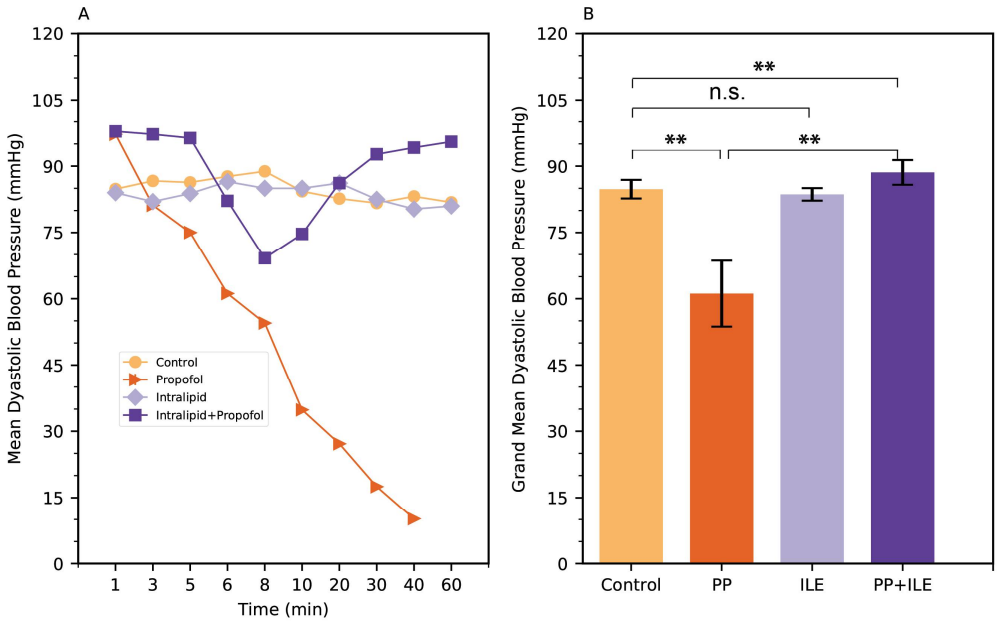

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Figure 4. A) Median arterial blood pressure (MAP) scores of Control (C), Propofol (PP), Intralipid (ILE) and Intralipid+Propofol (ILE+PP) groups of rats versus time. **B)** Grand Means of MAP scores (n.s.:non significance, **:P<0.01, Error bars: 95% confidence interval)

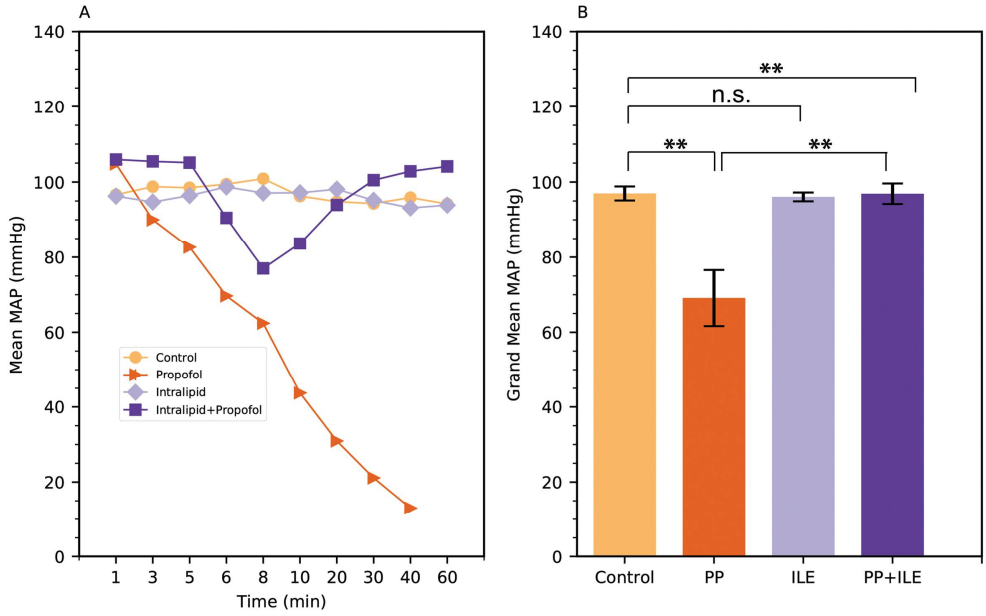

Figure 5. A) Respiratory rate (RR) scores of Control (C), Propofol (PP), Intralipid (ILE) and Intralipid+Propofol (ILE+PP) groups of rats versus time. **B)** Grand Means of RR scores (n.s.:non significance, **:P<0.01, Error bars: 95% confidence interval)

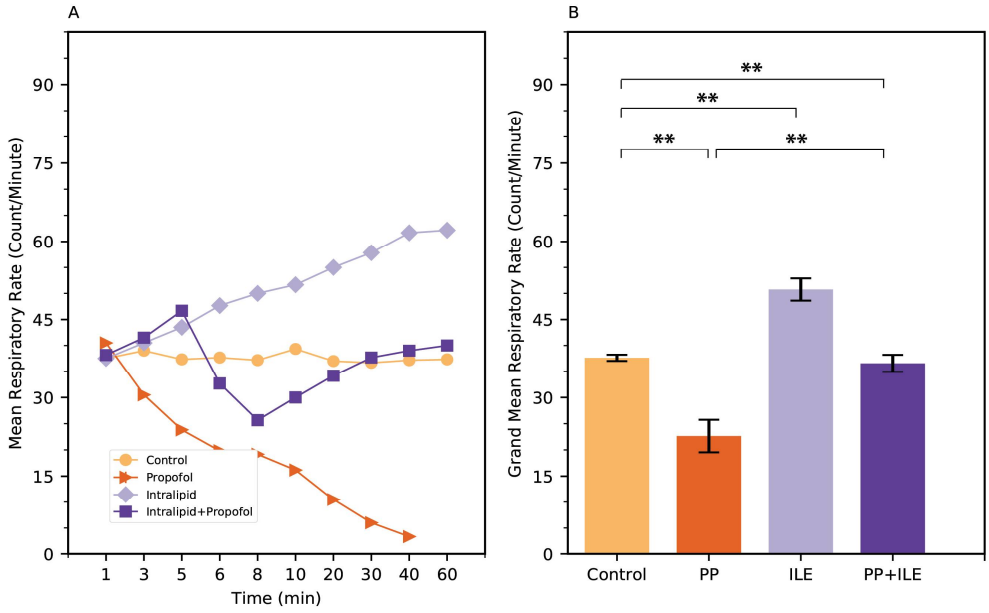

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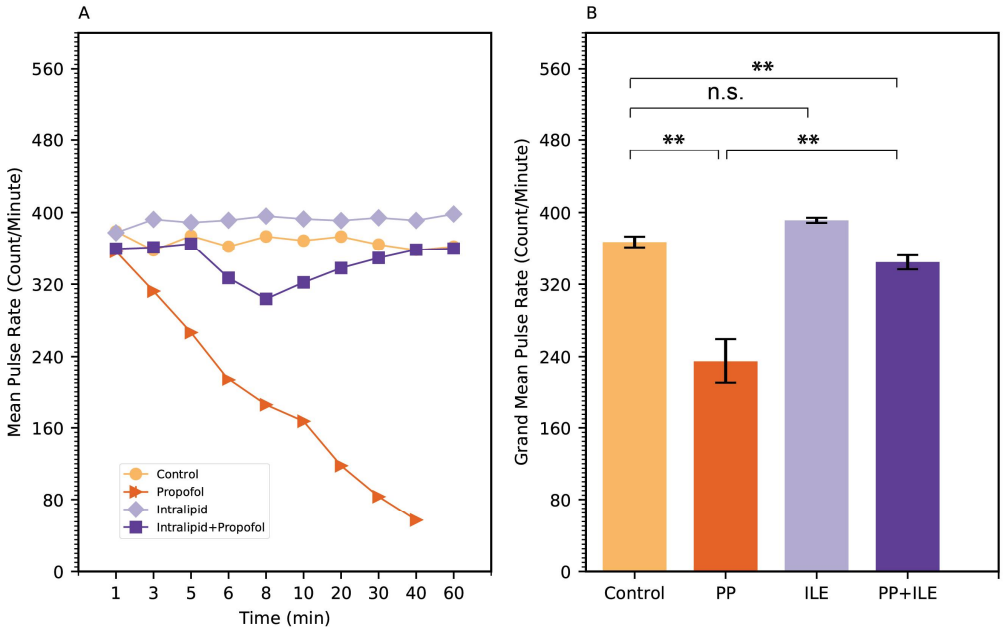
Figure 6. A) Heart rate (HR) scores of Control (C), Propofol (PP), Intralipid (ILE) and Intralipid+Propofol (ILE+PP) groups of rats versus time. **B)** Grand Means of HR scores (n.s.:non significance, **:P<0.01, Error bars: 95% confidence interval)



Five independent sample t-tests were conducted to compare SBP, DBP, MAP, RR and HR scores between in Intravenous lipid emulsion + Propofol (ILE+PP) and Propofol (PP) groups. In ILE+PP group, SBP score (M=113.55, SD=11.01), DBP score (M=88.58, SD=10.98), MAP score (M=96.91, SD=10.69), RR score (M=36.55, SD=6.48) and HR score (M=244.42, SD=84,24) were found higher than SBP score (M=85.02, SD=26.20), DBP score (M=61.15, SD=25.60), MAP score (M=69.11, SD=25.58), RR score (M=22.64, SD=10.63) and HR score (M=234.77, SD=84.24) of the PP group respectively ($p<0.01$) **(Table 1, Figure 2, 3, 4, 5, 6)**.

Oneway RM ANOVA was applied to compare SBP, DBP, MAP, RR and HR scores between Control and ILE groups in 10 time points. The differences between Control and ILE groups was not significant in terms of SBP, DBP, MAP and HR scores($p>0.05$). But RR score (M=50.75 SD=8.48) of ILE group was found higher than RR score of the control group (M=37.61 SD=2.39) and this difference was significant ($p<0.01$) **(Table 1, Figure 2, 3, 4, 5, 6)**.

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Oneway RM ANOVA was applied to compare SBP, DBP, MAP, RR and HR scores between Control and ILE+PP groups in 10 time points. Scores of SBP, DBP, MAP, RR and HR parameter of ILE+PP group were lower than the scores of Control group in the same parameter ($p<0.01$). As it can be seen in the graphics, this difference reached the maximum level at the 8th minute and gradually decreased between 8th and 30th minutes. No difference was observed after 30th minute **(Table 1, Figure 2, 3, 4, 5, 6)**.

4. Discussion

There are many studies examining the cardiac depressant effects of propofol in literature. In a study conducted, the incidence of hypotension (SBP <90 mmHg) was found to be 15.7% in patients receiving induction dose propofol and 77% of the hypotension attacks was recorded within the first 10 minutes. Again 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 [21]. Abdul Zahoor et al. reported decrease in blood pressure and pulse values in patients who had minor surgery after propofol application [22]. 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 [23].

In our study similarly, a dramatic decrease was observed in SBP, DBP, MAP, HR and RR scores in the group only administered propofol and all rats in this group died at the end of the 60th minute. **(Figure 1, 5)**.

ILE treatment was first used to prevent local anesthetic material related cardiovascular collapse and systemic toxicity. Weinberg et al. reported ILE to be an active treatment for hemodynamics recovery in rats with resuscitation for bupivacaine overdose and again in dogs with bupivacaine overdose [6, 24]. In latter studies, it was shown that it could be used as an effective antidote in poisonings caused by lipophilic drugs [25]. ILE treatment was used successfully in toxicity due to many lipophilic drugs such as beta blocker, calcium channel blocker and tricyclic antidepressants apart from local anesthetics [7,8,9,26]. In the case report of Ban C.H. et al., it was stated that vasopressor and fluid treatment resistant hypotension was recovered with ILE treatment after post-epidural anesthesia [27].

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

Again parallel to other studies, it was observed that RR values in the group ILE+PP had a decreasing course from the 2nd minute when propofol was started until the 8th minute. After the 8th minute, an increase was observed in RR values and these values got closer to the control group. A similar course was detected in RR values with the control group after the 30th minute. We observed that ILE treatment is also advantageous to prevent respiratory depressant side effect of propofol **(Figure 5)**.

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

5. Conclusions

Due to the findings acquired 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 treatment 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

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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 and Rohat Ak

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

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