THE ROLE OF LIPID EMULSION IN TREATMENT OF ACUTE TRAMADOL TOXICITY IN ADULT MALE ALBINO RATS

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ABSTRACT

Background: Tramadol is a synthetic centrally acting analgesic used for treatment of moderate to severe acute or chronic pain. In tramadol overdose, seizures and hypotension are present. Intravenous lipid emulsion (ILE) is considered as effective treatment for local anesthetic-induced cardiovascular collapse, and treating overdoses of parasiticides, and herbicides. Aim: the aim of this work was to evaluate the role of ILE in acute tramadol toxicity as regarding hemodynamic instability and seizures in adult male albino rats. Materials and Methods: Eighty adult male albino rats were divided into five groups: Group I (control group). Group II normal saline, Group III lipid emulsion group (subdivided into ILE10, ILE19 subgroups). Group IV (tramadol treated group). Group V: (tramadol and normal saline treated group). Group VI: divided into tramadol+ILE10 and tramadol+ILE19 subgroups. Measurement of blood pressure, monitoring of heart rate and observation for occurrence of seizures were recorded. Results: Different doses of ILE significantly normalized DBP and HR. After infusion of ILE 20%, MAP was significantly stabilized. The ILE10 group had higher MAP at 6 hours, whereas such effect was seen only in ILE19 after 24 hours. There was a decrease in seizures occurrence in ILE treated groups. Serum CPK levels were significantly raised after tramadol toxicity and reduced to normal ranges when ILE was administered in both doses. Tramadol causes Hemodynamic instability and appearance of seizures after once administration (150 mg/kg). ILE could significantly normalize Hemodynamic and seizures of tramadol toxicity. In conclusion: Single administration of tramadol in a dose of 150 mg/kg causes hemodynamic instability and appearance of seizures in adult male albino rats. ILE10 and ILE 19 could significantly normalize hemodynamic and ameliorated the occurrence of tramadol toxicity induced seizures. It is recommended: to do further in vivo studies needed to evaluate role of ILE in chronic tramadol using. Clinicians can consider administration of ILE in resuscitation protocols toxicities causing hemodynamic compromise but the potential risks of administering the quite high doses of ILE are uncertain and needs more researches.

Key words: Tramadol, acute toxicity, seizures, Intravenous lipid emulsion.

INTRODUCTION

Tramadol is a synthetic centrally acting analgesic used in treatment of moderate to severe acute or chronic pain **(Nossaman et al., 2010)**. Tramadol is structurally similar to morphine and codeine with effects similar to those of codeine and 10 times less than morphine. Its analgesic effects recognized as a weak μ-opioid receptor agonist with norepinephrine and serotonin reuptake inhibitor. Its opioid-like effect is the cause of tramadol misuse is a public health concern **(Marquardt et al., 2005; Vahabzadeh et al., 2013& Nazarzadeh et al., 2014).**

The mechanism of action of tramadol has not yet to be fully clarified, but it is supposed to work through of opioid and non-opioid mechanisms. Tramadol and its metabolite bind to the μ -opioid receptors in the brain, only 1/6000 of that of morphine although its selectivity for this sub-type of receptor is greater than that of morphine. Tramadol modulates the gamma-aminobutyric acid GABAergic, noradrenergic and serotonergic systems **(Mehrpour, 2005& Volpe et al., 2011),** as it inhibits reuptake of 5-hydroxytryptamine (5-HT) and noradrenaline. The late mechanism is important since the analgesic effects of tramadol are not fully antagonized by the μ -opioid receptor antagonist naloxone **(Gasse et al., 2000).**

Tramadol multi-formulation availability and its low serious side effect except at high doses and in prolonged use, increased its short and

long term use in communities and hospitals **(Shipton, 2000)**.

In tramadol overdose, the most serious and significant adverse effects are dizziness, headache, agitation, movement disorders, seizures and hypotension**.** Less common findings are central nervous system depression, tachycardia, nausea and vomiting **(Kathy et al., 2005& Shadnia et al., 2008).**

Intravenous lipid emulsion (ILE) is composed of triglycerides and a phospholipid emulsifier. It provides calories and essential fatty acids within total parenteral nutrition **(Bania et al., 2007).** ILE has been reported to reverse cardiovascular collapse in overdoses of local anaesthetic agents in addition to other medications **(Picard et al., 2009; Jamaty et al., 2010& Kosh et al., 2010).** In addition, ILE have successful use in case reports and animal studies of drug toxicity other than local anesthetics as in tricyclic antidepresent overdose (**Arslan et al., 2013& Perza et al., 2013).**

The aim of this work is to evaluate tramadol-induced hemodynamic instability (heart rate & blood pressure) and tramadol-induced seizures in adult male albino rats and to evaluate the role of ILE in acute tramadol toxicity in adult male albino rats.

MATRIALS AND METHOD

Chemicals:

1-Tramadol tablets: each one contains 225 mg tramadol hydrochloride obtained from October Pharma Company.

2- Intravenous lipid emulsion (ILE): SMOFlipid™ 20%, 500 mL of injectable emulsion that is a white homogeneous emulsion, obtained from Fresenius Kabi Company, Austria.It is composed of (6% soybean oil, 6% medium chain triglycerides, 5% olive oil and 3% fish oil).

Animals:

All animals received human care in compliance with the Animal Care Guidelines and Ethical Regulations in accordance with "The Guide for the Care and Use of Laboratory Animals" **(Institute of Laboratory Animal Resources, 1996).**

Experimental design:

The study was carried out on 80 adult male albino rats, their weights ranging from 180- 220 gm for each, they were obtained from the Animal House of the Faculty of Veterinary Medicine , Zagazig University. The study had been conducted in Animal House of the Faculty of Medicine, Zagazig University. Before commencing the experiment, all animals were subjected to 14 days period of passive preliminaries in order to adapt themselves to their new environment, to ascertain their physical well-being and to exclude any diseased animals. The animals were housed in plastic cages free from any source of chemical contamination under controlled conditions with an ambient temperature range of 22 ± 2 oC, relative humidity of 50 ±5% and a 12 hours light–cycle. Soft wood shavings were used for bedding and changed during the cleaning of cages on alternate days. The rats received balanced food rich in all stuffs necessary to maintain their health before and during drug administration. It consisted of bread, barley and milk. Water was offered in separate clean containers.

The rats were divided into five groups as the following: **Group I (Control group):** It consisted of 10 adult male albino rats. Each rat of this group received only regular diet and tap water for 48 hours. **Group II normal saline group:** It consisted of 10 adult male albino rats. Each rat of this group received normal saline 0.9% NaCl I.V. infusion with infusion rate of 1.5 mL/min for 30 minutes once **(Jamaty et al., 2010)**.

Group III Intravenous lipid emulsion group (ILE): It consisted of 20 adult male albino rats. Rats in this group further equally subdivided into 2 subgroups: **Subgroup IIIA:** It consisted of 10 adult male albino rats. Each rat of this group received 10 mL/kg of ILE **(Carreiro et al., 2013)** by I.V. infusion once. **Subgroup IIIB:** It consisted of 10 adult male albino rats. Each rat of this group received 19 mL/kg of ILE **(Carreiro et al., 2013)** by I.V. infusion once .**Group IV (Tramadol group):** It consisted of 10 adult male albino rats. Each rat of this group received a toxic dose of 150 mg/kg of tramadol (1/2 of LD50) by oral gavage once **(Matthiessen et al., 1998). Group V (Tramadol + Saline group):** It

consisted of 10 adult male albino rats. Each rat of this group received 150 mg/kg of tramadol (1/2 of LD50) by oral gavage once **(Matthiessen et al., 1998)**. Thirty minutes later **(Vahabzadeh et al., 2013),** each rat received normal saline 0.9% NaCL I.V. infusion with infusion rate of 1.5 mL/min for 30 minutes **(Jamaty et al., 2010). Group VI (Tramadol + ILE group):** It consisted of 20 adult male albino rats. Rats in this group subdivided equally into **2 subgroups: Subgroup VIA:** It consisted of 10 adult male albino rats. Each rat of this group received 150 mg/kg of tramadol (1/2 of LD50) by oral gavage once. Thirty minutes later, each rat received 10 mL/kg of ILE **(Carreiro et al., 2013)** by I.V. infusion once. **Subgroup VIB:** It consisted of 10 adult male albino rats. Each rat of this group received 150 mg/kg of tramadol (1/2 of LD50) by oral gavage once. Then 30 minutes later, each rat received 19 mL/kg of ILE **(Carreiro et al., 2013)** by I.V. infusion once .

Throughout the experiment, **rats from each group were subjected to:**

I-Measurement of blood pressure and heart rate recording.

II-Assessment of seizures:

All of the control and treated rats were observed for 48 hours for occurrence of seizures using camera and digital video recorder.

Racine's scale, originally developed for the amygdala-kindling model, is also frequently used as an intensity measurement in other experimental seizure or epilepsy models **(Lüttjohann et al., 2009) .**

According to **Racine (1972),** Classical stages of seizures are :

-Mouth and facial movement .
-Head nodding .
-Forelimb clonus .
-Rearing with forelimb clonus .
- Rearing and falling with forelimb clonus .

III-Creatine phosphokinase:

After that rats were anesthetized by ether anesthesia and blood samples were collected from the retro-orbital plexuses for estimation of creatinine phosphokinase by spectrophotometry according to **Graeber et al. (1981).**

IV-Assessment of body weight and mortality.

Statistical analysis

Data were analyzed by Statistical Package of Social Science (SPSS), software version 22.0 **(SPSS Inc., 2013).**

RESULTS

Regarding Hemodynamic Parameters: There were non-significant differences determined between time points (baseline, after 30 minutes, 6 hours, 24 hours and 48 hours) in Control, Normal saline, ILE10 & ILE19) ($P>0.05$) as regard hemodynamic parameters within the same group. In addition, there was no statistical significance ($p>0.05$) in the hemodynamic parameters among Control, Normal saline, ILE10 & ILE19 (tables 1A, 1B, 1C and 1D). So, the control group was used as a control group for comparison with other treated groups.

Single injection of tramadol (150mg/Kg), taramadol + saline, Tramadol + ILE10 or Tramadol + ILE19 couldn't induce any significant differences in SBP At different time points (after 30 minutes, 6 hours, 24 hours and 48 hours of treatment administration) (table 2A & Figure 1).

The results of this study showed that At different time points (after 30 minutes, 6 hours, 24 hours and 48 hours of treatment administration), single injection of tramadol (150mg/Kg) significantly decreased both DBP and MAP ($P < 0.001$), and increased HR ($P< 0.001$) (but did not have any obvious effect on SBP ($p>0.05$) (table 2A, 2B, 2C and 2D. figure 2, 3 &4).

The changes in DBP, MAP and HR in tramadol + normal saline group which significantly different from 0 hour did not return to normal level even after 48 hours ($P>0.05$). Both of ILE 10 and ILE19 administration at different time points (after 30 minutes, 6 hours, 24 hours and 48 hours after treatment) could significantly antagonized tramadol effect on DBP ($P< 0.001$), MAP ($P < 0.05, <0.001, <0.05$& 0.05 respectively) and HR ($P <0.001$) when compared with tramadol group. Moreover, the effects of ILE10 were more powerful than ILE19 especially at 6 hours after administration ($P< 0.05$). The ILE10 group

had higher MAP at 6 hours (P< 0.05), whereas such effect was seen only in ILE19 after 24 hours. Although there was a slight decrease in MAP by different doses of ILE within 24 hours of poisoning, this increase was not considered significant compared with tramadol + normal saline. (Table 2B,2C and 2D).

Regarding occurrence of seizures, No observed seizures were detected in control groups (Control, Normal saline, ILE10 or ILE19). There were statistical significant differences in incidence of seizures among treated groups (Tramadol, Tramadol+Normal saline, Tramadol+ILE10 and Tramadol+ILE19) (P < 0.05). The incidence of seizures in tramadol was 80%, reduced to 50% in tramadol with normal saline group. It became 10% in tramadol + ILE10 group and 30% in tramadol + ILE19 group (Table 3).

Regarding creatinine phosphpkinase serum levels, CPK levels among Control, Normal saline, ILE10& ILE19 groups, were not statistically significant (p>0.05) (table 4 A). So, the control group was used as a control group for comparison with other treated groups**.** CPK levels showed a highly significant difference (p<0.001) among the different treated groups (Tramadol, Tramadol+ Normal Saline, Tramadol+ILE10& Tramadol+ILE19) in comparison to control group (table 4B).

There were highly significant elevations (P<0.001) in tramadol& tramadol+normal saline groups & a non-significant elevation (p>0.05) in tramadol+ILE10 group and a significant increase (p<0.05) in tramadol+ILE19 group when compared with the control group. Additionally, there was a significant decrease (p<0.05) in CPK serum levels in tramadol+normal saline group but highly significant reductions (p<0.001) in tramadol+ILE10& tramadol+ILE19 groups when compared with tramadol group. Also, there were significant reductions (P<0.05) in tramadol+ILE10& tramadol+ILE19 groups when compared with tramadol+normal saline group. There was a significant elevation (p<0.05) in tramadol+ILE19 group when compared with tramadol+ILE10 group.

Regarding Body Weight mean values**,** Paired t- test regarding showed non-significant differences (p>0.05) before and after treatment as regard all studied groups.

Mortality rate in this study was zero as no deaths were recorded in any group of the study.

Table 1A: Statistical comparison among Control, Normal saline, ILE10 and ILE19 groups as regard the systolic blood pressure measurements by One-way repeated measures ANOVA at the same duration among groups (horizontal) and within the same group in different durations (vertical) of adult male albino rats.

Groups / Duration after administration	Group (I) Control Mean±SD	Group (II) Normal saline Mean±SD	Group (IIIA) ILE10 Mean±SD	Group (IIIB) ILE19 Mean±SD	F	P
0 hour	136±4.08	135±6.498	135.4±6.398	135.2±5.350	0.06	>0.05
30 minutes	135.6±4.06	134.6±6.004	134.8±6.161	135.1±5.216	0.06	>0.05
6 hours	134.4±4.58	132.4±6.132	131.9±5.896	131.7±5.870	0.48	>0.05
24 hours	137.9±7.52	135.9±6.437	135±6.733	135.7±6.946	0.32	>0.05
48 hours	136.6±5.40	135.1±5.705	133.2±7.036	133±6.464	0.76	>0.05
F	0.86	0.55	0.63	1.16		
P	>0.05	>0.05	>0.05	>0.05		

Number of sacrificed rats for each group was 10 rats; ANOVA: Analysis of variance; SD: Standard Deviation; p>0.05: non-significant.

Table 1B: Statistical comparison among Control, Normal saline, ILE10 & ILE19 groups as regard the diastolic blood pressure measurements by One-way repeated measures ANOVA at the same duration among groups (horizontal) and within the same group in different durations (vertical) of adult male albino rats.

Groups / Duration after administration	Group (I) Control Mean±SD	Group (II) Normal saline Mean±SD	Group (IIIA) ILE10 Mean±SD	Group (IIIB) ILE19 Mean±SD	F	P
0 hour	115.2±6.14	112.4±6.75	112.5±6.36	114.1±6.44	0.44	>0.05
30 minutes	115±6.63	111.1±5.97	113.3±6.91	113.1±7.78	0.54	>0.05
6 hours	114.2±6.66	113.8±7.54	111.6±7.04	114.5±7.11	0.34	>0.05
24 hours	112.6±7.26	115.4±7.96	115.4±8.85	111±8.43	0.71	>0.05
48 hours	113.2±7.73	111.6±7.33	114.8±7.94	112.2±7.07	0.34	>0.05
F	0.74	0.84	0.74	0.57		
P	> 0.05	>0.05	>0.05	>0.05		

Number of sacrificed rats for each group was 10 rats; ANOVA: Analysis of variance; SD : Standard Deviation; p>0.05 : non-significant.

Table 1C: Statistical comparison among Control, Normal saline, ILE10 & ILE19 groups as regard mean arterial blood pressure measurements by One-way repeated measures ANOVA at the same duration among groups (horizontal) and within the same group in different durations (vertical) of adult male albino rats.

Groups / Duration after administration	Group (I) Control Mean±SD	Group (II) Normal saline Mean±SD	Group (IIIA) ILE10 Mean±SD	Group (IIIB) ILE19 Mean±SD	F	P
0 hour	106.3±3.02	106.8±5.633	104.6±4.624	107±3.162	0.66	>0.05
30 minutes	104.3±3.20	107±5.888	105.3±6.272	107.2±5.827	0.66	>0.05
6 hours	107±5.83	106.5±4.116	105.8±5.453	106.1±3.213	0.12	>0.05
24 hours	108.2±5.69	105.1±4.581	105.2±5.245	106.4±3.718	0.88	>0.05
48 hours	107.5±5.13	108.2±6.893	107.2±6.408	109.3±5.012	0.25	>0.05
F	1.19	1.38	1.39	1.26		
P	>0.05	>0.05	>0.05	>0.05		

Number of sacrificed rats for each group was 10 rats; ANOVA: Analysis of variance; SD : Standard Deviation; p>0.05 : non-significant.

Table 1D: Statistical comparison among Control, Normal saline, ILE10 & ILE19 groups as regard heart rate recording by One-way repeated measures ANOVA at the same duration among groups (horizontal) and within the same group in different durations (vertical) of adult male albino rats.

Groups / Duration after administration	Group (I) Control Mean±SD	Group (II) Normal saline Mean±SD	Group (IIIA) ILE10 Mean±SD	Group (IIIB) ILE19 Mean±SD	F	P
0 hour	166.9±10.49	167.6±9.57	166.1±12.07	168.1±12.26	0.06	>0.05
30 minutes	165.8±8.55	167.5±11.15	165.7±9.60	166.1±11.26	0.07	>0.05
6 hours	165.1±6.10	167.6±7.31	166.9±10.55	162.7±7.349	0.16	>0.05
24 hours	168.8±9.86	169.6±11.55	168.9±7.36	167.3±10.51	0.09	>0.05
48 hours	168.6±8.86	166.9±8.69	168±7.72	167.1±9.94	0.08	>0.05
F	0.63	0.26	0.38	0.07		
P	>0.05	>0.05	>0.05	>0.05		

Number of sacrificed rats for each group was 10 rats; ANOVA: Analysis of variance; SD : Standard Deviation; p>0.05 : non-significant.

Table 2A: Statistical comparison among control group and treated groups (Tramadol, Tramadol+Normal Saline, Tramadol+ILE10 and Tramadol+ILE19) tabulated as regard the systolic blood pressure measurements by One-way repeated measures ANOVA; at the same duration among groups (horizontal) and within the same group in different durations (vertical) of adult male albino rats.

Groups / Duration after administration	Group (I) Control Mean±SD	Group (IV) Tramadol Mean±SD	Group (V) Tramadol + saline Mean±SD	Group (VIA) Tramadol +ILE10 Mean±SD	Group (VIB) Tramadol +ILE19 Mean±SD	F	P
0 hour	136±4.082	137.9±4.606	135.2±4.894	138.2±6.426	136±6.0808	0.609	>0.05
30 minutes	135.6±4.061	136.3±4.620	136.6±5.796	137.7±5.926	137.1±6.082	0.220	>0.05
6 hours	134.4±4.575	134.9±5.130	132.4±5.254	134.4±5.562	134.5±6.078	0.339	>0.05
24 hours	137.9±7.519	134.7±7.040	137.4±5.232	136.6±7.545	136.9±6.118	0.328	>0.05
48 hours	136.6±5.399	133.7±6.019	134.5±5.276	134.7±6.717	133.9±7.355	0.343	>0.05
F	0.859	1.113	2.038	0.750	0.541		
P	>0.05	>0.05	>0.05	>0.05	>0.05		

Number of sacrificed rats for each group was 10 rats; ANOVA: Analysis of variance; SD : Standard Deviation; p>0.05 : non-significant.

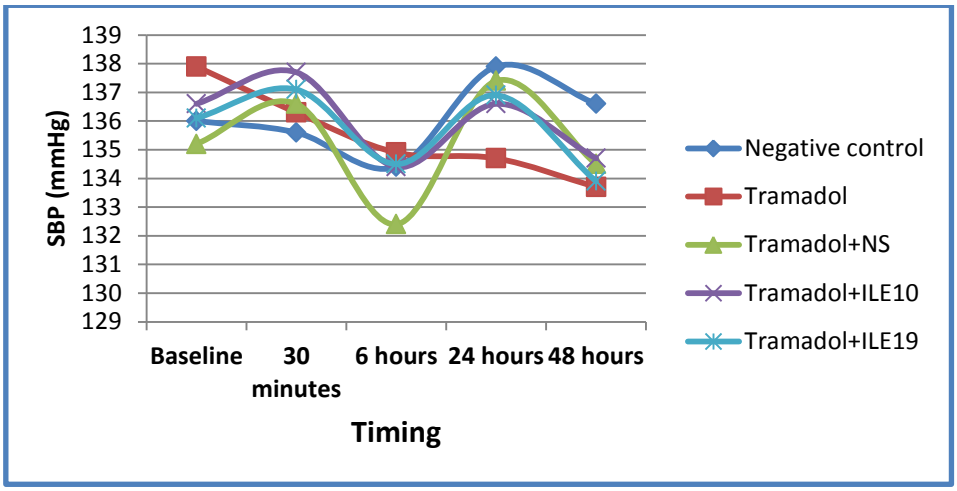

Figure 1: Line graph showing comparison between control group& other treated groups (Tramadol, Tramadol+Normal Saline "NS", Tramadol+ILE10& Tramadol+ILE19) as regard systolic blood pressure between time points (baseline"0hour", 30 minutes, 6 hours, 24 hours and 48 hours after treatment).

Table 2B: Statistical comparison among control group and treated groups (Tramadol, Tramadol+Normal Saline, Tramadol+ILE10& Tramadol+ILE19) tabulated as regard the diastolic blood pressure measurements by One-way repeated measures ANOVA at the same duration among groups (horizontal) and within the same group in different durations (vertical) and LSD tests of adult male albino rats.

Groups / Duration after administration	Group (I) Control Mean±SD	Group (IV) Tramadol Mean±SD	Group (V) Tramadol+ saline Mean±SD	Group (VIA) Tramadol +ILE10 Mean±SD	Group (VIB) Tramadol +ILE19 Mean±SD	F	P
0 hour	115.2±6.14	115.5±8.59	113.2±8.99	114.8±7.32	115.1±8.09	0.132	>0.05
30 minutes	115±6.63	49±4.91 [a]	79.7±9.48[a,b]	94.1±9.32[a,b,c]	93.8±9.40[a,b,c]	86.66	<0.001
6 hours	114.2±6.66	41.5±6.64[a]	61.4±8.88[a,b]	90.5±8.23[a,b,c]	79.1±11.04[a,b,c,d]	107.59	<0.001
24 hours	112.6±7.26	50.6±4.45[a]	80±9.82 [a,b]	93.2±6.56[a,b]	85.30±9.30[a,b,d]	85.23	<0.001
48 hours	113.2±7.73	60.6±6.74[a]	94.7±7.51[a,b]	106.7±6.60[b,c]	95.60±9.70[a,b,d]	68.87	<0.001
F	0.742	310.44	56.60	22.198	22.99		
P	>0.05	<0.001	<0.001	<0.001	<0.001		

Number of sacrificed rats for each group was 10 rats; ANOVA: Analysis of variance; SD : Standard Deviation; p>0.05 : non-significant; P>0.001:Highly significant; Significant of LSD a= significant VS Control. b= significant VS Tramadol. c= significant VS Tramadol+ saline d= significant VS Tramadol +ILE10.

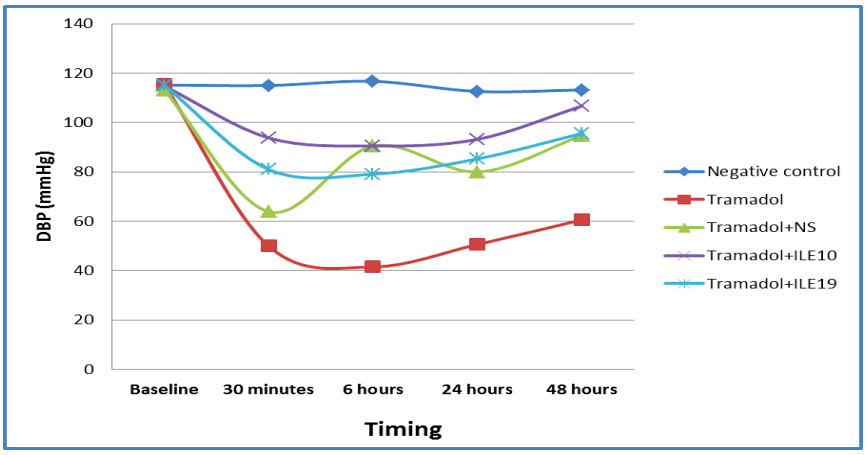

Figure 2: Line graph showing comparison between control group& other treated groups (Tramadol, Tramadol+Normal Saline, Tramadol+ILE10& Tramadol+ILE19) as regard diastolic blood pressure between time points (baseline"0hour", 30 minutes, 6 hours, 24 hours and 48 hours after treatment).

Table 2C: Statistical comparison among control group and treated groups (Tramadol, Tramadol+Normal Saline, Tramadol+ILE10& Tramadol+ILE19) tabulated as regard mean arterial blood pressure measurements by One-way repeated measures ANOVA at the same duration among groups (horizontal) and within the same group in different durations (vertical) and LSD tests of adult male albino rats.

Groups / Duration after administration	Group (I) Control Mean±SD	Group (IV) Tramadol Mean±SD	Group (V) Tramadol + NS Mean±SD	Group (VIA) Tramadol +ILE10 Mean±SD	Group (VIB) Tramadol +ILE19 Mean±SD	F	P
0 hour	106.3±3.02	104.8±3.85	107.1±3.38	106.2±4.94	107.9±5.15	0.77	>0.05
30 minutes	104.3±3.20	83.1±8.81 [a]	93.5±6.59 [a,b]	96.4±8.29 [a,b]	90.2±7.05 [a,b]	12.22	<0.001
6 hours	107±5.83	71.5±5.78 [a]	93.4±.36 [a,b]	94.2±6.75 [a,b]	92.2±6.41 [a,b]	41.88	<0.001
24 hours	108.2±5.69	86±7.29 [a]	87.8±9.74 [a]	96.9±2.81 [a,b,c]	94.4±6.92 [a,b,c]	16.44	<0.001
48 hours	107.5±5.13	84.3±6.60 [a]	86.3±0.07 [a]	95.5±3.66 [a,b,c]	91.4±7.31 [a,b]	17.84	<0.001
F	1.189	29.98	14.09	8.92	11.60		
P	>0.05	<0.001	<0.001	<0.001	<0.001		

Number of sacrificed rats for each group was 10 rats; ANOVA: Analysis of variance; SD : Standard Deviation; p>0.05 : non-significant; P>0.001:Highly significant; Significant of LSD: a= significant VS Control. b= significant VS Tramadol. c= significant VS Tramadol+ saline d= significant VS Tramadol +ILE10.

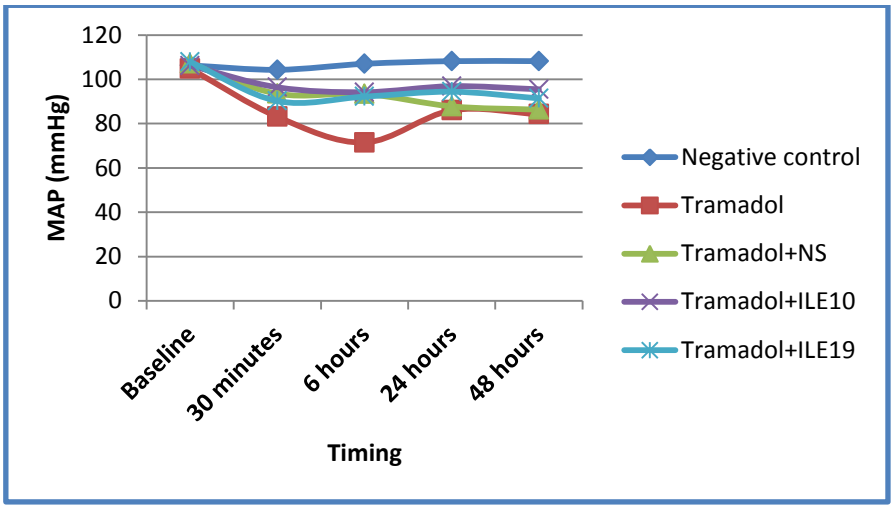

Figure 3: Line graph showing comparison between control group& other treated groups (Tramadol, Tramadol+Normal Saline, Tramadol+ILE10& Tramadol+ILE19) as regard mean arterial pressure between time points (baseline"0hour", 30 minutes, 6 hours, 24 hours and 48 hours after treatment).

Table 2D: Statistical comparison among control group and treated groups (Tramadol, Tramadol+Normal Saline, Tramadol+ILE10& Tramadol+ILE19) as regard the heart rate recording by One-way repeated measures ANOVA at the same duration among groups (horizontal) and within the same group in different durations (vertical) and LSD tests of adult male albino rats.

Groups / Duration after administration	Group (I) Control Mean ±SD	Group (IV) Tramadol Mean±SD	Group (V) Tramadol+ NS Mean±SD	Group (VIA) Tramadol +ILE10 Mean±SD	Group (VIB) Tramadol +ILE19 Mean±SD	F	P
0 hour	166.9 ±10.49	165±11.86	166.8±9.24	167.9±9.46	165.4±9.07	0.138	>0.05
30 minutes	165.8 ±8.55	265.7±24.79[a]	232.5±37.11[a,b]	186.5±16.09[a,b,c]	193.6±15.34[a,b,c]	31.145	<0.001
6 hours	165.1 ±6.10	347.1±23.55[a]	339.2±21.79[a]	190.5±12.19[a,b,c]	210.3±12.93[a,b,c,d]	268.665	<0.001
24 hours	168.8 ±9.86	264.5±13.41[a]	237.8±29.15[a,b]	178.8±12.77[b,c]	189.6±12.19[a,b,c]	59.145	<0.001
48 hours	168.6 ±8.86	244.7±37.51[a]	221±39.38[a,b]	171.6±13.50[b,c]	185.6±11.91[b,c]	16.477	<0.001
F	0.63	75.98	63.30	9.45	17.66		
P	>0.05	<0.001	<0.001	<0.05	<0.001		

Number of sacrificed rats for each group was 10 rats; ANOVA: Analysis of variance; SD : Standard Deviation; p>0.05 : non-significant; P>0.05: significant; P>0.001:Highly significant; Significant of LSD: a= significant VS Control. b= significant VS Tramadol. c= significant VS Tramadol+ saline d= significant VS Tramadol +ILE10.

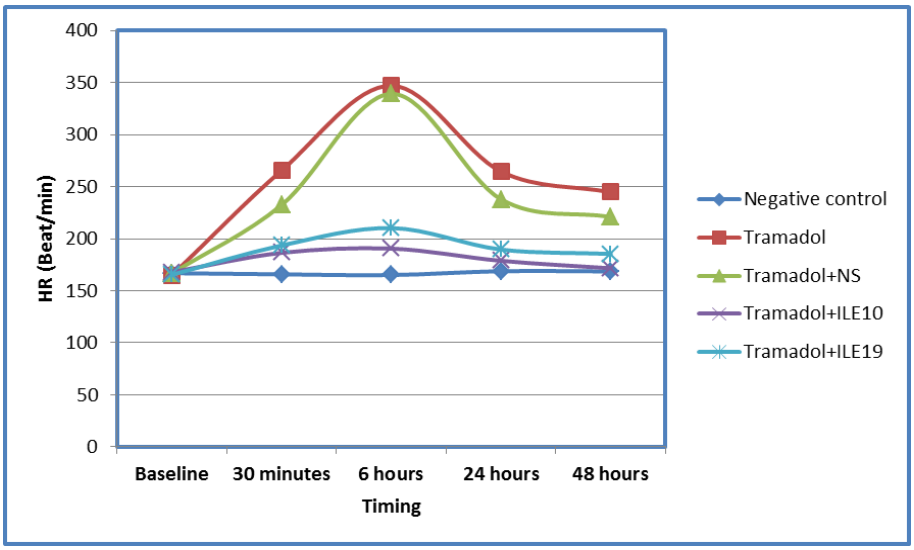

Figure 4: Line graph showing comparison between control group& other treated groups (Tramadol, Tramadol+Normal Saline, Tramadol+ILE10& Tramadol+ILE19) as regard heart rate between time points (baseline"0hour", 30 minutes, 6 hours, 24 hours and 48 hours after treatment).

Table 3: Statistical comparison regarding seizure attacks in treated groups along the period of the experiment.

Groups / Parameter	Group (IV) Tramadol TN=10		Group (V) Tramadol + NS TN=10		Group (VIA) Tramadol +ILE10 TN=10		Group (VIB) Tramadol +ILE19 TN=10		F	P
	N	%	N	%	N	%	N	%		
Seizure attacks	8	80%	5	50%	1	10%	3	30%	10.946	<0.05

Number of sacrificed rats for each group was 10 rats; TN: Total number of rats; N: Number of rats with seizures.

Table 4A: Statistical comparison among control groups (Control, Normal saline, ILE10& ILE19) as regard CPK levels by ordinary one-way ANOVA test in adult male albino rats at the end of the experiment.

Groups / Parameter	Group (I) Control Mean±SD	Group (II) Normal saline Mean±SD	Group (IIIA) ILE10 Mean±SD	Group (IIIB) ILE19 Mean±SD		
CPK (IU/L)	487.1±55.032	497±56.774	491±53.009	480.9±39.739	0.172	>0.05

Number of sacrificed rats for each group was 10 rats; SD : Standard Deviation; p>0.05 : non-significant.

Table 4B: Statistical comparison among treated groups (Tramadol, Tramadol+Normal saline, Tramadol+ILE10 and Tramadol+ILE19) and control group as regard CPK serum levels by ordinary one-way ANOVA test and LSD tests in adult male albino rats at the end of the experiment.

Groups / Parameter	Group (I) Control Mean±SD	Group (IV) Tramadol Mean±SD	Group (V) Tramadol + NS Mean±SD	Group (VIA) Tramadol +ILE10 Mean±SD	Group (VIB) Tramadol +ILE19 Mean±SD		
CPK (IU/L)	487.1±55.03	1434.4±160.96[a]	1239±1214.33[a,b]	540.5±100.95[b,c]	659.7±114.62[a,b,c,d]	117.928	<0.001

Number of sacrificed rats for each group was 10 rats; SD: Standard Deviation; P>0.001: Highly significant; Significant of LSD: a= significant VS Control. b= significant VS Tramadol. c= significant VS Tramadol+ saline d= significant VS Tramadol +ILE10

DISCUSSION

At different time points (after 30 minutes, 6 hours, 24 hours and 48 hours of treatment administration), While SBP measurements showed non-significant differences among the different treated group in comparison to control group, DPB showed highly significant differences among the different treated groups in comparison to control group. Injections of tramadol significantly decreased DBP. Different doses of ILE could significantly normalize DBP, whereas effects of ILE10 were more powerful on such phenomenon especially 6 hours after administration. However, the changes in DBP in tramadol + normal saline group did not return to normal level even after 48 hours.

The observations of the present work were in line with the results of **Ekemenet al., (2008)** study**,** which stated that tramadol did not affect systolic blood pressure when used for prevention of postoperative pain in children and with **Vahabzadeh et al., (2013),** who reported that, although ILE did not have major effect on systolic blood pressure, It normalized diastolic blood pressure and its maximum effect was achieved 6 hours post 12 mL/kg dose administration.

The mechanism by which tramadol reduced DBP may be partially through nitric oxide synthesis/release by endothelial cells as **Raimundo et al., (2006),** stated that the vaso-relaxant effect of tramadol was greater in arteries with an intact endothelium than in those without intact endothelium.

Intravenous infusion of lipid emulsion in animal study have established as highly effective treatment of cardiac arrest caused by overdose of bupivacaine, which is a potent sodium channel blocking local anesthetic **(Weinberg, 2006).** Similar clinical efficacy of ILE in treating refractory cardiac arrest during regional anesthesia with bupivacaine/mepivacaine has been reported **(Rosenblatt et al., 2006).**

Young **et al., (2009)** the first reported patient stabiliztion rapidly after ILE administration in case of verapamil-induced refractory shock. In **2010**, the first report of human use of ILE to reverse tricyclic antidepressant-induced vasopressor-refractory shock has been documented **(Engels and Davidow, 2010)**, then in 2013 **Perza et al.,** established the use of ILE was as major line to overcome tricyclic antidepressant overdose**.** Moreover, **Macala and Tabrizchi (2014)** have mentioned ILE as an effective mode in resuscitating overdose of propranolol combined with clonidine**.** Also**, Repplinger et al. (2015)** has reported ILE as antidote for cocaine cardiac arrest toxicity.

The mechanism by which ILE elevated DBP is partially by enhance alpha 1 mediated vasoconstriction **(Haastrup et al., 1998)** and reduce endothelium-mediated vasodilation **(Steinberg et al., 1997).** Also due to central sympathetic activation may contribute to the beneficial hemodynamic effects of lipid emulsion **(Harchelroad and Palma, 2008).**

At different time points (after 30 minutes, 6 hours, 24 hours and 48 hours of treatment administration), MAP showed highly significant differences among the different treated groups in comparison to control group. The results of this study showed that after infusion of ILE 20%, MAP was significantly stabilized in groups receiving ILE. The ILE10 group had higher MAP at 6 hours, whereas

such effect was seen only in ILE19 after 24 hours. Although there was a slight decrease in MAP by different doses of ILE within 24 hours of poisoning, this increase was not considered significant compared with tramadol + normal saline.

The observations of the present work were consistent with the results of **Vahabzadeh et al., (2013),** who stated that ILE showed positive effects on normalizing mean arterial pressure.

According to **Carreiro et al., (2013),** ILE delayed and prolonged the MAP effect of administered epinephrine as ILE infusion caused reliable increase in MAP for an appropriate duration of time before return to baseline.

Regarding heart rate, injections of tramadol could significantly induce tachycardia; the two doses of ILE (10 and 19) were able to reduce the HR near normal levels. However, this effect of ILE was best shown in the dose of 10 mL/kg.

The observations of the present work were consistent with the results of **Vahabzadeh et al., (2013),** who stated that ILE showed positive effects on normalizing HR in rats previously received tramadol, especially 6 hours post administration.

According to **Maréchal et al., (2011)**, tachycardia in tramadol toxicity occurs as a part of serotonin syndrome. In tramadol overdose, mydriasis or tachycardia appears to indicate a higher risk for seizure **(Tashakori and Afshari, 2010).**

Tachycardia is reliable with sodium channel blockade effect of tramadol that has been demonstrated at high concentration **(Haeseler et al., 2006).** Though, the Potassium channel blockage effect of tramadol may also be suggested **(Roden, 2004).**

In the study of **Kang et al., (2015)**, pretreatment with ILE prolonged survival in a murine model of calcium channel blocker poisoning. Long-chain fatty acids may also directly activate calcium channels; attenuating toxicity **(Gueret et al., 2007).**

The results of this study are consistent with that of **Jovic-Stosicet al., (2011)** who reported the effective ILE treatment of severe propranolol and ethanol overdose induced complex tachycardia and the sinus rhythm was re-established during ILE infusion. They attributed their results to the possibility increasing of the fatty acid content and calcium level may recover cardiac contractility.

Beta-oxidation of free fatty acids, a process that accounts for 50-70 % of myocardial ATP production driven myocardial contraction may be another explanation of possible ILE action as it is composed primarily of long chain fatty acids **(Lopaschuk et al., 2010, Ciechanowicz and Patil, 2012).**

Fast infusion of ILE has been reported as a treatment for patients with cardiotoxicity induced by a lipophilic drug that does not react to conventional therapies **(Jovic-Stosicet al., 2011).**

Occurrence of seizures:

The results of present study showed that seizures occurrence was observed in 50% of the group treated with tramadol alone, while there was a considerable decrease in convulsions occurrence in groups that were treated with ILE. However, this effect of ILE was best revealed in the dose of 10 mL/kg.

The observations of the present study were agreed with the results of **Vahabzadeh et al., (2013),** who showed that ILE prevented tramadol-related seizures in doses of 6 and 12 mL/kg.

It has been shown that the appearance of seizures with tramadol is not dose dependent **(Talaie et al., 2009).**Seizures due to tramadol use may occur in both overdose and within therapeutic dose range **(Jick et al., 1998).**

Fewer than 1% of consumers have a presumed incident seizure right after their first tramadol prescription. Risk of seizure claim increases two- to six-fold between users adjusted for selected comorbidities and concomitant drugs. Risk of seizure is highest among those aged 25-54 years, those with more than four tramadol prescriptions, and those with a history of alcohol abuse, stroke, or head injury **(Gardner, 2000).**

Seizures caused by tramadol are most often tonic-clonic seizures, more commonly known as grand-mal seizures. Also when taken with selective serotonin reuptake inhibitor (SSRIs),

there is an increased risk of serotonin toxicity, which can be fatal **(Gillman, 2005).**

The GABA receptor inhibition caused by tramadol can be attributed to its opioid receptor agonist effect **(Rehni et al., 2008)**, and continuing this agonist activity on opioid receptor has been proven to cause seizure due to GABA inhibition **(Miura et al., 2007).**

The most severe complications of tramadol overdose include refractory seizures, rhabdomyolysis and renal failure **(Taghaddosinejad et al., 2011).**

Tramadol may increase the seizure risk in patients receiving other medications such as tricyclic antidepressants, phenothiazines, and selective serotonin reuptake inhibitors **(Kroenke et al., 2009).**

Tramadol-related seizures can be controlled by diazepam and not responsive to naloxone. Also tramadol-induced seizures can be precipitated by naloxone administration **(Raffa and Stone, 2008).**

Corman and Skledar, (2007) reported that no further convulsions were observed after ILE infusion in Local Anesthetic-induced CNS toxicity.

Levine et al., (2012) stated that ILE infusion seizures and dysrhythmias experienced in patient with TCA toxicity were terminated within 2 minutes of the second ILE bolus, however, they weren't rapidly to traditional treatment represented by benzodiazepines and sodium bicarbonate.

The clinical effect of ILE infusion on reversal of CNS and cardiac toxicity with serial LA plasma concentrations or other lipophilic drugs is mainly attributed to its mechanism of action by re-establishing equilibrium within an expanded plasma lipid phase (sink) with subsequent reduction in free drug levels **(Cave and Harvey, 2009)**, also by extracting lipophilic drugs from tissues or by counteracting local anesthetic inhibition of myocardial fatty acid oxygenation **(Corman and Skledar, 2007).**

Regarding effect of ILE on tramadol-induced seizures can be also attributed to the lipid sink theory as ILE removes tramadol from the tissues preventing it from coupling to its receptors **(Vahabzadeh et al., 2013).**

In this study, Serum CPK levels were dramatically raised after tramadol toxicity, whereas ILE could powerfully reduce it to normal ranges when administered in both doses (10 and 19 mL/kg), but the decrease was more significant with dose of 10 mL/kg.

The previous result agreed with **Afshari and Ghooshkhanehee, (2009)** and **Tashakori and Afshari, (2010),** who reported dramatic rise of CPK in cases with tramadol overdose because of frequent seizures.

While **Vahabzadeh et al., (2013)** stated that ILE could powerfully reduce it to normal ranges when administered in higher doses (12 and 18 mL/kg).

The serum level of skeletal muscle enzymes is considered as a marker of muscle tissue function and varies in both pathological and physiological conditions. Increased level of these enzymes indicates acute or chronic cellular necrosis and tissue damage **(Brancaccio et al., 2007).**

In tissues and cells that consume ATP rapidly, as skeletal muscle, CPK acts as an energy reservoir for the rapid ATP buffering and regeneration **(Wallimann and Hemmer 1994).**

Total CPK levels depend on age, gender, race, physical activity, muscle mass, and climatic condition **(Stomme et al., 2004).** Young adult males have high serum levels of CPK, which decline to some extent with age during the geriatric period **(Borges and Essen-Gustavsson, 1989 , Tietz et al., 1992).**

The serum CPK level can be elevated from the damage of the muscle tissue because of intense prolonged training. This may be a consequence of both metabolic and mechanical causes. Certainly, metabolically exhausted muscle fibers exhibit a decrease in the membrane resistance following an increase in the internal free calcium ions, which promotes the activation of the potassium channel **(Fink et al., 1983).**

Another mechanism could be the local tissue damage with sarcomeric degeneration from Z-disk fragmentation. CPK is an indicator of muscle necrosis, increasing with its extent **(Nakada et al., 1984, Martinez-Amat et al., 2008).**

Creatine phosphokinase acts as an enzyme in the conversion of creatine to phosphocreatine, producing adenosine diphosphate and consuming ATP in between. Such enzyme reaction is reversible; therefore, ATP can be produced from phosphocreatine and adenosine diphosphate **(Goldblatt et al., 1969, Vahabzadeh et al., 2013).**

In normal cellular conditions, fatty acids are the preferred substrate for oxidative phosphorylation, providing up to 90% of ATP particularly for myocytes. One alternative mechanism of action suggested for ILE is that it can provide cells with ATP **(Rothschild et al., 2010).**

In conclusion, Single administration of tramadol in a dose of 150 mg/kg causes hemodynamic instability and appearance of seizures in adult male albino rats. ILE10 and ILE 19 could significantly normalize hemodynamic and ameliorated the occurrence of tramadol toxicity induced seizures.

It is recommended, to do further in vivo studies needed to evaluate role of ILE in chronic tramadol using. Clinicians can consider administration of ILE in resuscitation protocols toxicities causing hemodynamic compromise but the potential risks of administering the quite high doses of ILE are uncertain and needs more researches.

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تقييم دور مستحلب الدهون في علاج التسمم الحاد بالترامادول في ذكور الجرذان البيضاء البالغة

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المقدمة:الترامادول هو وصفة طبية شائعة الاستخدام كمسكن للآلام المتوسطة والشديدة. عادة يترافق تعاطي جرعة زائدة من الترامادول مع حدوث تشنجات وانخفاض ضغط ، الدم. وقد تم استخدام مستحلب الدهون الوريدي لعلاج التوقف الفجائي للقلب الناتج عن تعاطي جرعات زائدة من العقاقير المستخدمة كمخدر موضعي بالإضافة إلى المبيدات .**الهدف من البحث:** هو تقييم دور مستحلب الدهون في علاج التسمم الحاد بالترامادول
في تحسين الخلل في مؤشرات الدورة الدمويةو تقليل معدل حدوث التشنجات التي يسببها الترامادول في ذكور الجرذان البيضاء البالغة.**خطة البحث:** تم اجراء البحث على ٨٠جرذ من الذكور البيضاء البالغة مقسمة إلى خمس مجموعات كالاتي:المجموعة الأولي (المجموعة الضابطة السالبة) العادية وذلك لقياس المعايير الأساسية.
المجموعة الثانية مجموعة محلول الملح . المجموعة الثالثة مجموعة مستحلب الدهون .المجموعة الرابعة (مجموعة الترامادول) .المجموعة الخامسة (مجموعة الترامادول والمحلول الملح).المجموعة السادسة (مجموعة الترامادول ومستحلب الدهون).في كافة مراحل التجربة، تم إخضاع الجرذان من كل مجموعة إلى قياس ضغط الدم، ورصد معدل ضربات القلب والمراقبة عن حدوث التشنجات. **أظهرت نتائج**:أن الترامادول يسبب عدم الاستقرار في مؤشرات الدورة الدموية وتشنجات وان هذة التغيرات تستجيب للعلاج بالمستحلب الدهنى. **نستنتج:** أن المستحلب الدهنى له فاعلية فى علاج حالات التسمم الحاد بالترامادول. **ونوصى:** بإجراء دراسات أخرى لتقييم ما إذا هناك دور لمستحلب الدهون الوريدي في علاج تسمم الترامادول المزمن. و عمل دراسات أخرى لتقييم دور مستحلب الدهون الوريدي في علاج التسمم بالادوية التى تؤدى الى اختلال ملحوظ بمؤشرات الدورة الدموية مع تحديد جرعة دقيقة من مستحلب الدهون الوريدي من أجل تقليل مخاطر استخدام جرعات أعلى.