The Effects of Lipid Emulsion on the Improvement of Glasgow Coma Scale and Reduction of Blood Glucose Level in the Setting of Acute Non-Local Drug Poisoning: A Randomized Controlled Trial

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ABSTRACT

Background: Our aim was to evaluate the effect of intravenous intralipid administration as an antidote on the poisoned patients' Glasgow Coma Scale (GCS), hemodynamic parameters, arterial blood gas analysis, and routine metabolic profile tests (i.e. urea, glucose, sodium, and potassium) in the setting of non-local anesthetic drug overdose.

Methods: In this randomized controlled trial, a total of 30 patients with non-local anesthetic drug intoxication were enrolled and randomly assigned to case (n=15) and control (n=15) groups. In the case group, all patients received 10cc/kg intralipid 10% infusion. The patients in the control group just received supportive care. The patients' demographic and clinical characteristics and the results of their laboratory tests were evaluated upon admission and 6 hours after that.

Results: Mean age was 23±5 and 28±11 years in cases and controls, respectively. There were no significant statistical differences between these two groups in terms of age, gender, elapsed time between intubation and extubation, and prevalence of need for intubation and/or mechanical ventilation (P=0.70 and P= 1.00, respectively). Also, systolic blood pressure, pulse rate, mean rate- pressure product, respiratory rate, and results of acid-base gas, serum sodium, potassium, urea, and creatinine tests upon admission and six hours later were not significantly different between the two groups. However, a significant difference was found between the two groups in terms of GCS difference (P= 0.048) and blood glucose six hours after presentation (P= 0.04).

Conclusions: In the setting of non-local anesthetic drug overdose, intravenous intralipid infusion can increase GCS and interestingly, decrease the blood glucose.

Keywords: Antidote**,** Blood Glucose**,** Glascow Coma Scale, Intralipid, Non-Local Anesthetic Overdose.

INTRODUCTION

Intravenous lipid emulsion is a new method for the treatment of local anesthetic (LA) systemic toxicity (1, 2). Of course, this treatment is not limited to LA toxicities, though. Because of recent published human case reports of successful resuscitation (3-6), there has been an increasing interest in the potential benefits of this type of treatment in cardiac arrests (5,6), hemodynamic instability (7-10), refractory hypotension (11), ventricular fibrillation, and pulseless electrical activity (3) attributable to lipophilic, non-LA drugs. Also, it has been suggested that intralipid emulsion therapy can be used as an antidote for resuscitation of lipophilic non-local anesthetic toxicity (3,12, 13). To the best of our knowledge, no randomized controlled trials (RCT) have been carried out to evaluate this likely anti-dotal effect on the poisoned patients' level of consciousness and routine metabolic profile tests in non-local anesthetic overdoses. Therefore, our aim was to evaluate the effect of intravenous intralipid administration as an antidote on the poisoned patients' Glasgow Coma Scale (GCS),

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hemodynamic parameters, arterial blood gas (ABG) analysis, and routine metabolic profile tests (i.e. urea, glucose, sodium, and potassium) in the setting of non-local anesthetic drug overdose.

MATERIALS AND METHODS

In this RCT study (superiority trial with parallel design), the minimum required sample size per group was calculated according to the related formula for RCT studies with alpha of 0.05, power of 80%, π_1=0.1, and π_2=0.6 at two-sided 5% (14). Therefore, cases and controls with documented diagnosis of intoxication with non-local anesthetic drugs were enrolled from all patients with suspicion of poisoning who were transferred to the toxicological emergency department of Shohada Yaft Abad Hospital (Tehran, Iran) between October 2010 and March 2011. The patients were included in the study if they had GCS $\leq$ 9, had not received antidote, had not responded to the antidote therapy (e.g. naloxone), or had some kind of contraindication for receiving an antidote (e.g. flumazenil). Documentation of poisoning was based on a positive history of non-local anesthetic drug ingestion and a positive urine or serum drug screen test. The positive history of ingestion was defined as giving the name of the consumed medication by the patient him/herself before the incidence of a decrease in the level of consciousness (to his/her relatives or the ***personnel of*** emergency medical service) or after complete recovery from coma and identifying and retaining any evidence of medications (such as its bottle or packet) in the bedroom or household, workplace, and so forth. All patients with documented head trauma were excluded from the study. Information including age, gender, medication ingested (documented by urine and/or serum drug screen test, pill ID, or patient's history), manner of poisoning, need for intubation and mechanical ventilation, and the time elapsed between intubation and extubation were recorded in the standardized abstraction forms. Intubation had been performed due to hypoventilation, loss of protective airway reflexes, seizures, and hemodynamically significant dysrhythmia. Those with inadequate oxygenation and ventilation despite supplemental oxygen had been mechanically ventilated.

In both groups, initial emergency department GCS, systolic blood pressure, pulse rate, mean rate pressure product (RPP, systolic pressure x heart rate), and respiratory rate were recorded in addition to the patients' demographic data. The samples went through ABG analysis and serum sodium, potassium, urea, creatinine, and blood glucose check upon admission. In the case group, all patients received 10cc/kg intralipid 10% infusion in addition to the routine supportive management (i.e. cardiac monitoring, intubation, mechanical ventilation, volume expansion, use of inotropic/or vasopressor drug support, administration of sodium bicarbonate, and etc., when indicated) within the first six hours of admission. The patients in the control group just received supportive care. The abovementioned secondary vital signs, GCS, and laboratory tests were evaluated six hours after admission in both groups. GCS differences (differences between GCS upon admission and during the 6-hour follow-up) were also recorded. During the study, the patients were excluded from both groups if we retrospectively found that their urine and/or serum drug screen had been reported to be negative and our history was wrong, even when the intralipid had previously been administered. Other patients with the same inclusion criteria were randomly included in the study instead of those excluded from it.

Statistical Analysis

Statistical analysis was done using SPSS software (version 17, Chicago, Ill, USA) and application of Kolmogorov-Smirnov, Mann-Whitney U-test, Pearson's chi square or Fisher's exact test, Student's t-test. P values less than 0.05 were considered to be statistically significant. Our study was approved by the Regional Ethics Committee. Written informed consents were given to all patients entering the study for administration of the intralipid emulsion.

RESULTS

A total of 15 cases (9 men and 6 women) and 15 controls (9 men and 6 women) met the inclusion criteria and entered the study. Mean age was 23±5 and 28±11 years in case and control groups, respectively. A combination of medications including benzodiazepines, tricyclic antidepressants (TCAs), anticonvulsants, anticholinergics, antihistamines, muscle relaxants, selective serotonine reuptake inhibitors, antipsychotics, acetaminophen, nonsteroidal anti inflammatory drugs, salycilates, and opioids were ingested in both case and control groups. Manner of poisoning was suicidal in all patients. Nine patients in the case group and six patients in the control group were intubated. In each group, four patients were ventilated. Information on the patients' initial emergency department GCS, systolic blood pressure, pulse rate, mean rate pressure product, and respiratory rate, results of acid-base gas, serum sodium, potassium, urea, creatinine, and blood glucose on presentation and six hours later is presented in Tables 1 and 2.

Table1. The results of the poisoned patients' arterial blood gas (ABG) analysis, and routine metabolic profile tests

	Case	**Control**	**P value**
pH	7.32±0.09	7.24±0.13	NS*(MWU)†
	7.38±0.03	7.33±0.06	
pCO_2 (mmHg)	38.7±6.5	42.6±10.5	NS (MWU)
	39.6±6.5	39.7±8.6	
Hco_3 (mmol/l)	20.7±2.8	20.1±5.3	NS (MWU)
	21.5±3.6	22.0±4.4	
Blood glucose (mg/dL)	115±26	118±40	0.04 (MWU)
	98±10	110±19	
Potassium (mEq/l)	3.9±0.3	3.9±0.5	NS (MWU)
	3.9±0.4	3.8±0.4	
Sodium (mEq/l)	139±3	140±3	NS (MWU)
	138±3	140±3	
Urea (mg/dL)	29±5	33±9	NS (MWU)
	26±4	34±7	
Creatinine (mg/dL)	0.8±0.2	1.0±0.3	NS (MWU)
	0.9±0.2	0.9±0.2	

Data are presented as mean value (± standard deviation; SD**)**; †MWU: Mann-Whitney U test; *NS: Not significant; Comparison of the mean± SD of the patients' data at presentation (first row for each parameter) and six hours after presentation (second row)

Table 2. The results of the poisoned patients' demographic characteristics, Glasgow Coma Scale (GCS), hemodynamic parameters, and elapsed time between intubation and extubation

	Case	Control	P value
Age (years)	23±5	28±11	NS*(MWU)†
Male/female ratio	9/6	9/6	NS (P Chi^2)¶
GCS difference	3±1	2±2	0.048(MWU)
Systolic Blood Pressure (mmHg)	101±16	110±17	NS(MWU)
	112±9	117±23	
Pulse Rate (bpm)	91±25	97±23	NS (MWU)
	91±16	98±15	
Mean Rate Pressure Product (RPP)	9189±3184	10529±2726	NS (MWU)
	10236±2384	11327±2326	
Respiratory Rate (/min)	17±5	19±7	NS (MWU)
	18±2	16±3	
Elapsed time between Intubation and Extubation (hours)	28±20	37±20	NS (MWU)

Data are presented as mean value (± standard deviation; SD); †MWU: Mann-Whitney U test; *NS: Not significant; ¶ P Chi ^{2}: Pearson's chi square test; Comparison of the mean± SD of the patients' clinical characteristics at presentation (first row for each parameter) and six hours after presentation (second row)

There were no significant statistical differences between these two groups in terms of age, gender, elapsed time between intubation and extubation, and prevalence of need for intubation and/or mechanical ventilation (P=0.70 and P= 1.00, respectively; Fisher's Exact Test). Also, systolic blood pressure, pulse rate, mean rate pressure product, respiratory rate, results of acid-base gas, serum sodium, potassium, urea, and creatinine on presentation and six hours later were not significantly different between the two groups. However, a significant difference was found between the two groups in terms of GCS difference (P= 0.048, MWU test) and blood glucose (P= 0.04, MWU test) six hours after presentation.

DISCUSSION

In toxicity due to local anesthetic drugs, intravenous intralipid infusion is a proven resuscitative method in the treatment of cases refractory to conventional modes of resuscitation (1,2). However, in patients referring to the emergency department with cardiac and neurologic compromise and without a clear history of toxicity, an unidentified drug overdose is possible. Even in those referring with a positive history of drug overdose, the drug ingested may be unknown. In these cases, the lipid solubility property of the drug is unknown, as well. However, in all patients referring with a decreased level of

consciousness, the culpable drug ingested has possibly high lipid solubility properties expect when other confounding factors such as asphyxia have developed. Thus, if we are to use intralipid emulsion as an antidote, we have to evaluate its effect on the cardiovascular and neurological parameters in a setting most similar to our study.

In previous studies, it has been shown that instable hemodynamic of the patients with overdose of non-local anesthetic drugs with lipophilic properties, such as beta blockers, calcium channel blockers, TCAs, and some psychotropic agents, respond to the administration of intralipid (15). Our study more or less covers the same drug groups. Of course, it should be mentioned that none of our patients needed advanced resuscitation (for cardiovascular collapse, refractory hypotension, or cardiac arrest) upon admission (Table 2).

The present study shows that in poisoning setting, intravenous intralipid infusion can only increase GCS (of the clinical characteristics) and interestingly, decrease the blood glucose (of the laboratory characteristics evaluated). The effect of intralipid on increasing the level of consciousness has been previously reported in the literature (4, 16).

The probable mechanisms for the action of intralipid emulsion infusion in LA drug toxicity include lipid sink phenomenon (17-19), increasing intracellular fatty acid content (overcoming the reduction in the ATP production) in cardyomyocites (20-22), and increase in the intramyocyte calcium level (leading to a direct positive inotropic effect) (23). Presumably, intralipid emulsion exerts the same lipid sink effect in lipophilic, non-local anesthetic drug toxicity (24). None of the suggested or proven mechanisms of intralipid effects can explain the cause of decrease in the level of blood sugar as seen in our cases. Further studies are warranted to determine the probable effects of intralipid on blood glucose.

While protocols exist for intravenous intralipid administration in the setting of LA systemic toxicity (1), no optimal regimen has be established to date for treatment of acute non-local anesthetic poisonings (15). We used a continuous infusion of the intralipid 10% for the treatment of our patients while according to the recommendations of American Society of Regional Anaesthesia, intralipid 20% should have been administered (1). Maybe, if we had acted according to the abovementioned recommendations, the patients' GCS would have increased more or the intubated patients would have been extubated faster. This is the probable cause of lack of a difference between the GCS increment in the case and control groups in our study. However, the mean time elapsed between intubation and extubation in our study (28.11±19.86 hours) is similar to the period mentioned in a case report (18 hours) by Weinberg et al who administered intralipid 20% to their patients (4).

CONCLUSION

The present study shows that in the context of non-local anesthetic drug overdose, intravenous intralipid infusion can increase GCS and interestingly, decrease the blood glucose. Further studies are warranted to determine the probable effects of intralipid on blood glucose.

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