Lipid emulsion improves Glasgow Coma Scale and decreases blood glucose level in the setting of acute non-local anesthetic drug poisoning – a randomized controlled trial

F. TAFTACHI, H. SANAEI-ZADEH, B. SEPEHRIAN, N. ZAMANI

Department of Forensic Medicine and Toxicology, Tehran University of Medical Sciences, Hazrat Rasoul Akram Hospital, Tehran (Iran)

Abstract. – Background: To date, no study has been performed to evaluate the antidotal effect of intravenous lipid emulsion on the poisoned patients’ level of consciousness and routine metabolic profile tests in non-local anesthetic drug overdose.

Objectives: 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.

Material and Methods: In this randomized controlled trial, a total of 30 patients with non-local anesthetic drug intoxication were enrolled and randomly assigned into case (n=15) and control (n=15) groups. In the case group, all patients received 10 cc/kg intralipid 10% infusion. The patients in the control group just received the supportive care. Patients’ demographic and clinical characteristics and results of their laboratory tests were evaluated at presentation 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 regarding age, gender, elapsed time between intubation and extubation, and 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, results of arterial blood gas analyses, serum sodium, potassium, urea, and creatinine on presentation and six hours later were not statistically significantly different between the two study 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.

Key Words: Intralipid, Non-local anesthetic overdose, Glasgow Coma Scale, Blood glucose, Antidote.

Introduction

Intravenous lipid emulsion is a new method for the treatment of local anesthetic systemic toxicity. Of course, this treatment is not limited to the local anesthetic toxicities. Because of recent published human case reports of successful resuscitation, there has been increasing interest in the potential benefits of this type of treatment in cardiac arrest, and hemodynamic instability attributable to lipophilic, non-local anesthetic drugs. Also, it has been suggested that intralipid emulsion therapy can be used as an antidote for resuscitation of lipophilic non-local anesthetic toxicity. To our best knowledge, no randomized controlled trial (RCT) has been performed to evaluate the antidotal 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), 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.
Material and Methods

This is a randomized controlled trial (RCT: 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%, \( \pi_1=0.1 \), and \( \pi_2=0.6 \) 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 transferred to the toxicological Emergency Department of Shohada Yaft Abad Hospital (Tehran, Iran) between October 2010 and March 2011. The patients were entered into the study if they had GCS \( \leq 9 \), had not received any type of 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 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, etc. All patients with documented head trauma were excluded. 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 mechanically been 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 characteristics. Samples were sent for ABG analysis and check of serum sodium, potassium, urea, creatinine, and blood glucose on presentation. In the case group, all patients received 10 cc/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 hospital presentation. The patients in the control group just received the supportive management. Secondary abovementioned vital signs, GCS, and laboratory tests were evaluated six hours after presentation in both groups. GCS difference (differences between GCS at hospital presentation and at 6-hour follow-up) was 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 into the study instead of those excluding from it.

Statistical Analysis

Statistical analysis was done using SPSS software version 17, (SPSS Inc., Chicago, IL, USA) and application of Kolmogorov-Smirnov, Mann-Whitney U-test, Pearson’s chi square or Fisher’s exact test, and 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 taken from all patients’ relatives entering into the study for administration of intralipid.

Results

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

There were no significant statistical differences between these two groups regarding age, gender, elapsed time between intubation and extubation, and 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 ABG analyses, serum sodium, potassium, urea, and creatinine on presentation and six hours later were not statistically significantly different between the two study groups. But, a significant difference was found between the two groups in terms of GCS difference \((p = 0.048, \text{ MWU test})\) and blood glucose six hours after presentation \((p = 0.04, \text{ MWU test})\).

**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. However, in the patients presenting 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 characteristic of the drug is, therefore, unknown, as well. However, in all patients referring with decreased level of consciousness, the culpable drug ingested has possibly high lipid solubility characteristics except if other confounding factors such as asphyxia have developed. Thus, if we are due to use intralipid as an antidote, we have to evaluate its effect on the cardiovascular and neurological parameters in a setting most similar to our study.

In the previously performed 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. 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) on presentation (Table II).

This investigation shows that in poisoning setting, intravenous intralipid infusion can increase GCS (of the clinical characteristics) and decrease the blood glucose (of the laboratory characteristics evaluated). The effect of intralipid in increasing the level of consciousness has previously

| Table I. The results of poisoned patients’ arterial blood gas (ABG) analysis, and routine metabolic profile tests. |
|---|---|---|
| **Parameter** | **Case** | **Control** | \( p \) value (applied statistical test) |
| pH | 7.32 ± 0.09 | 7.24 ± 0.13 | NS* (MWU) |
| pCO₂ (mmHg) | 38.7 ± 6.5 | 42.6 ± 10.5 | NS (MWU) |
| HCO₃⁻ (mmol/l) | 20.7 ± 2.8 | 20.1 ± 5.3 | NS (MWU) |
| Blood glucose (mg/dL) | 115 ± 26 | 118 ± 40 | 0.04 (MWU) |
| Potassium (mEq/l) | 3.9 ± 0.3 | 3.9 ± 0.5 | NS (MWU) |
| Sodium (mEq/l) | 139 ± 3 | 140 ± 3 | NS (MWU) |
| Urea (mg/dL) | 29 ± 5 | 33 ± 9 | NS (MWU) |
| Creatinine (mg/dL) | 0.8 ± 0.2 | 1.0 ± 0.3 | NS (MWU) |

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).
Setting of acute non-local anesthetic drug poisoning – a randomized controlled trial

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

<table>
<thead>
<tr>
<th></th>
<th>Case</th>
<th>Control</th>
<th>p value (applied statistical test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>23 ± 5</td>
<td>28 ± 11</td>
<td>NS*(MWU)</td>
</tr>
<tr>
<td>Male/female ratio</td>
<td>9/6</td>
<td>9/6</td>
<td>NS (P Chi²)</td>
</tr>
<tr>
<td>GCS difference</td>
<td>3 ± 1</td>
<td>2 ± 2</td>
<td>0.048 (MWU)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>101 ± 16</td>
<td>110 ± 17</td>
<td>NS(MWU)</td>
</tr>
<tr>
<td></td>
<td>112 ± 9</td>
<td>117 ± 23</td>
<td></td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>91 ± 25</td>
<td>97 ± 23</td>
<td>NS (MWU)</td>
</tr>
<tr>
<td></td>
<td>91 ± 16</td>
<td>98 ± 15</td>
<td></td>
</tr>
<tr>
<td>Mean pressure product (RPP)</td>
<td>9189 ± 3184</td>
<td>10529 ± 2726</td>
<td>NS (MWU)</td>
</tr>
<tr>
<td></td>
<td>10236 ± 2384</td>
<td>11327 ± 2326</td>
<td></td>
</tr>
<tr>
<td>Respiratory rate (/min)</td>
<td>17 ± 5</td>
<td>19 ± 7</td>
<td>NS (MWU)</td>
</tr>
<tr>
<td></td>
<td>18 ± 2</td>
<td>16 ± 3</td>
<td></td>
</tr>
<tr>
<td>Elapsed time between intubation and extubation (hours)</td>
<td>28 ± 20</td>
<td>37 ± 20</td>
<td>NS (MWU)</td>
</tr>
</tbody>
</table>

Data are presented as mean value (± standard deviation; SD); *MWU: Mann-Whitney U test; *NS: Not significant; ¶P Chi²: 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).

been reported in the literature⁴,¹⁶. It has been shown that intravenous infusion of lipid (an acute increase in plasma free fatty acids – FFA) in normal volunteers causes no change in the plasma glucose concentration as well as the rates of endogenous glucose production (EGP). However, plasma C-peptide concentrations rise suggesting the stimulation of insulin secretion. Additionally, when somatostatin prevents the increase in insulin, the rise in plasma FFA is accompanied by an acute increase in EGP and plasma glucose²⁵. It has also been shown that under such experimental conditions, a rise in gluconeogenesis is seen with an acute increase in plasma FFA²⁶. In contrast to these investigations, our study shows that by administration of intralipid, the level of blood glucose decreases. This cannot be justified by the previously mentioned mechanisms of lipid effect on the blood glucose.

The probable mechanisms for the action of intralipid emulsion infusion in local anesthetic drug toxicity include lipid sink phenomenon¹⁷-¹⁹, increasing intracellular fatty acid content (overcoming the reduction in the ATP production) in cardiomyocytes²⁰-²², and increase in the intramyocyte calcium level (leading to a direct positive inotropic effect)²³. Presumably, intralipid emulsion exerts the same lipid sink effect on lipophilic, non-local anesthetic drug toxicity²⁴.

While protocols exist for administration of intravenous intralipid in the setting of local anesthetic systemic toxicity¹, no optimal regimen has been established to date for the treatment of acute non-local anesthetic poisonings¹⁵. 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 Anesthesia, intralipid 20% should have been administered¹. Maybe, if we acted according to the above mentioned recommendations, the patients’ GCS would increase more or the intubated patients would be extubated faster. Also, this is the probable cause of lack of a difference between the GCS increment in the case and control groups in our investigation. 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 al¹ who had administered intralipid 20% to their patient.

Conclusions

The present study shows that in the setting of non-local anesthetic drug overdose, intravenous intralipid infusion can increase GCS and interestingly, decrease the blood glucose.

References


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