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Review Article

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Use of lipid emulsion as an antidote in the treatment of intoxication by local anesthetics and other lipophilic drugs

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ABSTRACT

Local anesthetics are commonly used in surgical procedures, they are able to promote a reversible blockade of nerve conduction, with loss of sensation in circumscribed area of the body without changing the individual's level of consciousness. The aim of this study was to review the literature that can compose the body of evidence on efficacy and safety of Lipid Emulsion (ELI) for use as an antidote in the treatment of intoxication by local anesthetics and other lipofílicos. Trata is a review drugs literature that we used the Fat Emulsions terms Intravenous AND Antidotes for the search in the following databases: Pubmed; Cochrane Library and Trip Database and were raised studies found in these bases until November 2015. The review conducted showed that the use of ELI as an antidote seems to be a possible alternative for the treatment of poisoning caused by local anesthetics and other lipophilic drugs. Recently the ELI have been used also as an antidote against cardiovascular collapse induced by bupivacaine and other local anesthetics lipophilic. Early studies reported more frequently the use of Intralipid®, intravenously, which is sold in formulations containing soybean oil at different concentrations (10, 20 or 30%) in admixture with other lipids and phospholipids. The effects produced by Intralipid® have also been attributed to other lipid emulsions of formulations composed of different extracts of oils. However, current evidence supporting this use are scarce and uncertain, pointing to the need for additional studies. With respect to this fact, recently the American Academy of Clinical Toxicology.

Key words: Fat Emulsions, Antidotes, Toxicology, Local anesthetics

INTRODUCTION

Local anesthetics are commonly used in surgical procedures, because they are able to promote a reversible blockade of nerve conduction, with sensation loss in circumscribed area of the body without changing the individual's level of consciousness. Thereby, the produced block is selective for the chosen part of the body. In general, the action of local anesthetics is restricted to the site of their application and they can be administered by various routes: topical, infiltration, field and nerve blockade, regional, spinal or epidural intravenous, according to the clinical circumstances [1].

With the advent of local anesthetics long-acting, loco regional anesthesia has gained great momentum, being increasingly used. Blocking new techniques have been described and this procedure is often associated with general anesthesia for the purpose of providing postoperative analgesia. The downside is the need to use large doses of anesthetic, with risk of injury by intravascular injection inadvertently [2].

The systemic toxicity exercised by local anesthetics is a serious iatrogenic occurrence estimated incidence of approximately 1 in 1000 procedures. The clinical presentation varies with manifestation of seizures and arrhythmias to cardiac arrest. The treatment comprises oxygenation, ventilation, atropine and the usual resuscitation this condition is not always effective. Other exposure conditions commonly reported as the cause of poisoning local anesthetics are repeated use of the therapeutic dose and the unintentional administration of a toxic dose [2,4].

Currently, among the local anesthetic, bupivacaine in stands out for being the most used in locoregional anesthesia due to the quality of the anesthesia and the duration of action [2]. On the other hand, it is the agent with potential for cardiotoxicity. Bupivacaine and other local long-acting lipophilic anesthetics, have been implicated in numerous cases of cardiac arrest resistant to conventional therapeutic approaches to resuscitation of the patient [1,5].

Despite the development of new local anesthetics with similar chemical characteristics, but less toxic than bupivacaine such as levobupivacaine (S isomer (-) - pure bupivacaine) and ropivacaine cardiotoxicity of these drugs was not abolished. Several cases of cardiac arrest induced by ropivacaine were reported [6].

Long ago, the lipid emulsions (EL) administered intravenously (i.v.) are used to supply calories in the form of free fatty acids, as a component of parenteral nutrition therapy [7]. Recently, they have been used also as an antidote against cardiovascular collapse induced by the bupivacaine and other local anesthetics lipophilic [8].

Early studies reported more frequently the use of Intralipid® (i.v.), which is sold in formulations containing soybean oil at different concentrations (10, 20 or 30%) in admixture with other lipids and phospholipids. The effects produced by Intralipid® (i.v.) have also been attributed to other property lipid formulations composed of different extracts of oils [8].

The prevailing theory for the IL mechanism of action (i.v.) is that they generate an intravascular expanded lipid phase and thus, a new equilibrium is established with the target tissues of agent displacing their toxicity lipid deposits (lipid sink) newly formed [1,3,5].

Two other IL mechanisms of action (i.v.) have been proposed and are described below. One of these is to increase the uptake and utilization of fatty acids by the myocardium with increased high energy phosphate production in the myocytes, which may help to improve the hemodynamic performance. The lipid bolus administration can, based solely on the mass action law or by a mechanism not yet known, serve to reverse possible impediments to mitochondrial oxidative phosphorylation due to bupivacaine, tricyclic or verapamil antidepressants [3,9].

Finally, EL (i.v.) can restore mitochondrial function by increasing the intracellular calcium concentration. It was shown that application of free fatty acids, unsaturated chain as much as saturated, can activate calcium channels regulated by voltage in isolated myocardium. The increase in cardiac performance by this mechanism can be of particular importance in poisoning calcium channel blockers [3,9].

All these assumptions allow conjecture convincing hypothesis that the beneficial effect of EL (i.v.) shown in the toxicity exerted by bupivacaine may extend to other lipophilic agents (in similar degree, that is, with oil partition coefficient/water similar to bupivacaine) and/or that inhibit the mitochondrial lipid metabolism [9].

Several examples of success in resuscitation of the use of EL (i.v.), after cardiovascular collapse caused by local anesthetics have been reported and currently beyond their use in the treatment of intoxication by local anesthetics, EL (i.v.) has been used in cases of poisoning other lipophilic agents such as tricyclic antidepressants, propranolol (β-blocker), verapamil and diltiazem (blockers of calcium channels), bupropion (selective inhibitor of dopamine reuptake and barbiturates [2,7].

Recently, in the United States of America, national consensus guidelines were issued, including a list of recommended antidotes for use in caring for toxicological emergencies in hospitals, which states the EL (Intralipid®) [7,10]. Despite such recommendations, any studs reported that the use of an antidote EL has not been approved by the Food and Drug Administration (FDA) [7].

In Brazil, it was observed that ALS is not among the antidotes recommended by the National List of Essential Medicines (RENAME) of 2014 or the Form National Therapeutic, 2010.

Given the need to update the antidotes list recommended by an Information Centre and Toxicological Assistance in Fortaleza, in Ceara State, a review study on the use of EL was made, with a view to its possible inclusion as a therapeutic option for treat poisoning.

The objective of this study was a literature that may compose the body of evidence of efficacy and safety of EL administered intravenously as an antidote for use in the treatment of intoxication by local anesthetics and other lipophilic drugs.

EXPERIMENTAL SECTION

For the development of this literature review we decided to do an adaptation of Mendes proposal; Silveira; Galvão (2008), according to the following steps: 1) identification of the research question, followed by the search of descriptors or keywords; 2) determination of the criteria for inclusion and exclusion of the research; 3) categorization of studies, summarizing and organizing relevant information; 4) presentation of the review and synthesis of knowledge of each reviewed article succinct and systematic way [11].

The strategy adopted for the elaboration of the question was the PICO method, in which are explained: the health problem which applies (P = population of interest = patients poisoned by local anesthetics or other lipophilic drugs, the technology being evaluated (I = action = fat emulsion used as an antidote), the alternatives compared technology (C = comparator = treatment) and the results or consequences on health concern (O = outcomes [results] = efficacy and safety [12]. Thus, it elaborated the following question: the lipid emulsion is an effective and safe antidote to treat poisoning caused by local anesthetics or other lipophilic drugs, compared to conventional treatment?

In this research were defined as inclusion criteria studies: Systematic Reviews, meta-analyzes and randomized controlled trials and were excluded from studies with lower methodological quality.

The terms used were: Fat Emulsions, Intravenous AND Antidotes for the search in the following databases: Pubmed; Cochrane Library and Trip Database and have raised the studies found in these bases until November 2015, with no time restriction. It is noteworthy that for the Pubmed and Cochrane databases Libray we used the MeSH terms.

LITERATURE REVIEW

The results of the search for studies reporting the safety and efficacy of the lipid emulsion, using as an antidote for treating poisoning local anesthetics or other lipophilic drugs, are presented in Table 1.

As shown in Table 1, the total of 69 studies found, systematic reviews were in number 07, controlled and randomized clinical trials 04 and no meta-analysis.

Table 1: Studies on efficacy and safety in the use of the lipid emulsion as an antidote for treating poisoning local anesthetics or other lipophilic drugs

Data base	Descriptors	Results	Study Type	Selected Studies
Medline (via Pubmed)	("Fat Emulsions, Intravenous"[Mesh]) AND "Antidotes"[Mesh]	3	Systematic review: 05 Meta-analysis: 0 RCTs: 04	Systematic review: 03 Meta-analysis: 0 RCTs: 02
The Cochrane Library (via Bireme)	("Fat Emulsions, Intravenous"[Mesh]) AND "Antidotes"[Mesh]		Systematic review: 0 Meta-analysis: 0 RCTs: 0	Systematic review: 0 Meta-analysis: 0 RCTs: 0
Trip Data Base	Fat Emulsions, Intravenous AND "Antidotes	6	Systematic review: 2 Meta-analysis: 0 RCTs: 0	Systematic review: 0 Meta-analysis: 0 RCTs: 0

After analysis, we selected 03 systematic reviews and 02 randomized controlled clinical trials because it was not possible to access in order to use the proxy of the Federal University of Ceará of 02 systematic reviews located on Trip Database. The other studies were not selected for our investigation, differed from the question asked, the subject of this research. The results of the selected articles were synthesized as follows:

Randomized Clinical Trials:

According Taftachi et al. (2012), previous studies have shown that hemodynamically unstable patients poisoned by many lipophilic drugs, in addition to local anesthetics, the said Intralipid® administration. Thus, these authors conducted a randomized controlled trial with 30 patients with documented diagnosis of poisoning lipophilic drugs not local anesthetics, attended by Toxicological Emergency Department of a hospital in Tehran in Iran between October 2010 and March 2011 [13].

The aim of this study was to evaluate the effect of EL administered intravenously as an antidote, on the level of awareness and routine tests of metabolic profile in poisoning lipophilic drugs not local anesthetics. Patients were assessed using the Glasgow Coma Scale, hemodynamic parameters, arterial blood gas analysis of the sodium, potassium, urea and creatinine in the serum and blood glucose.

The authors note that the use of Intralipid® applies those with high lipid solubility, bupivacaine in a similar degree, that is, partition coefficients oil/water similar to that local anesthetic. Thus, it was necessary to identify the drug to meet its lipid solubility.

Patients were randomly divided into two groups, case (n = 15) and control (n = 15), and to be included in the study all had a Glasgow Coma Scale ≤ 9. The case group patients received infusion 10 cc/kg of Intralipid® 10%, while the controls received supportive care only. The clinical features and the results of laboratory tests were evaluated in the admission of patients and 6 hours later.

Lipophilic drugs ingested by patients, both in the case group and the control were benzodiazepines, tricyclic antidepressants, antihistamines, muscle relaxants, selective serotonin reuptake inhibitors, antipsychotics, acetaminophen, nonsteroidal anti-inflammatory drugs, salicylates and opioids. In all cases the toxicity was due to suicide attempt.

It was noted that there was no statistically significant difference between the two groups with respect to age, gender, time between intubation and extubation and the need for intubation and/or mechanical ventilation. Between the two groups, too, there was no statistically significant difference in the results both in admission and six hours later, with respect to the hemodynamic parameters evaluated, the gas analysis of arterial blood and measurement of sodium, potassium, urea and creatinine in serum. Statistically significant difference was observed between the two groups in terms of difference in the Glasgow Coma Scale and glucose in the blood six hours after admission.

The authors report that the effect of Intralipid® increase the level of awareness, had been previously described in the literature. However, the reduction of the glucose level in the blood observed in this study contradicts the results of earlier studies showing that infusion of lipid is accompanied by a sharp increase in endogenous glucose production and plasma glucose levels.

The clinical trial conducted by Gil et al. (2013), investigated the use of EL (i.v.) as an antidote in poisonings by glyphosate (N- [phosphonomethyl] glycine), which is a commonly used herbicides in the world. Despite being very low toxicity to animals and be categorized by the World Health Organization as "unlikely to present acute hazard in normal use", the bulk intake results in severe toxicity manifestations in humans because of the surfactants present in the formulations of this herbicide [14].

Whereas surfactants have properties similar to lipids, they formulated the hypothesis that lipid emulsion circulation can attenuate the toxicity of such compounds in cases of acute poisoning glyphosate.

The study was prospective, unblinded and involved 44 patients poisoned by glyphosate due to suicide attempts, which were divided into two groups, the treated (n = 22), with EL (i.v.) and control (n = 22) which received only symptomatic treatment, conservative.

Before treatment with EL (i.v.) compared the two groups, patients did not differ with respect to clinical characteristics, age, gender, amount of ingested glyphosate and time after ingestion.

In the treated group, the 20% lipid emulsion was administered intravenously at a rate of 20 ml/hr in patients consumed less than 100 ml of glyphosate. Patients who have ingested 100mL of ≥ received a loading dose of 500 mL EL (i.v.) administered 2 to 3 h, depending on the patient's condition, followed by a maintenance dose of 1000 ml in 24 hours.

After treatment, the clinical parameters evaluated were: clinical outcome, duration of hospitalization, respiratory failure development, cardiovascular deterioration (arrhythmia), renal failure, altered mental status and seizures.

None of the patients treated with EL (i.v.) expressed hypotension, whereas approximately 41% of control group patients had this complication. In addition, there was the manifestation of arrhythmia among the patients in the control group, but not among those treated with EL (i.v.). Otherwise, the incidence of mental changes, respiratory failure and acute renal failure was similar in both groups.

Based on these results, the authors concluded that the EL administration (i.v.) appears to be an effective treatment in glyphosate intake cases in sufficient quantity to the severe toxicity of manifestation.

Systematic reviews:
The study Cave and Harvey (2009) reports involves poisoning cases in animals or humans because of lipophilic drugs from different classes: tricyclic antidepressants, calcium channel blockers and β-blockers, not including local anesthetics. In all these cases, the EL (i.v.) was used as an antidote for treating intoxication [9].

The search was conducted in the following databases: PubMed, OVID (1966 - February 2009) and EMBASE (1947 - February 2009) using the terms: " intravenous " AND [" emulsion fat " OR " lipid emulsion " OR " Intralipid '] AND [' toxicity " OR " resuscitation " OR " rescue " OR " arrest " OR " antidote "]. In addition, it made a manual search conference in Clinical Toxicology Congress publications in North America and Poisons Centres and the European Association of Clinical Toxicology meetings between the years 2005-2008.

In the literature were identified 149 potentially relevant citations. However, the studies included in this review were 14 experiments conducted on animals, a single human trial and four case reports of human intoxication. According to the authors, the only trial involving humans was conducted in a very small population and therefore the results can not be generalized to the clinical setting of acute poisoning by tricyclic antidepressants. As for case reports of human poisoning, although they are quite suggestive, could not categorically define the EL (i.v.) as the only responsible for the recovery of affected patients.

The authors concluded that the EL (i.v.) is a possibly beneficial antidote to cardiovascular collapse or cardiac arrest secondary to overdose lipophilic cardiotoxic drugs, as well as indication already currently accepted for intoxication by local anesthetics.

Cave et al. (2011) conducted a systematic review aimed to summarize the studies reporting the use of EL (i.v.) in humans, as an antidote to treat poisoning caused by both local anesthetics, as for other lipophilic drugs. The search was conducted in the following databases: PubMed, OVID (1966 - June 2010) and EMBASE (1947 - June 2010) using the terms' intravenous' AND ['lipid emulsion' OR 'emulsion fat' OR ' Intralipid '] AND [' toxicity 'OR' arrest 'OR' rescue 'OR' resuscitation 'OR' antidote ']. In addition, it made a manual search conference in Clinical Toxicology Congress publications in North America and Poisons Centres and the European Association of Clinical Toxicology meetings between the years 2005-2010 [15].

The search identified a total of 42 reported cases. Of these, only 19 cases poisonings were caused by local anesthetics. In the remaining 23 cases, other classes of drugs, such as sedatives/hypnotics, calcium channel blockers, β-blockers, tricyclic antidepressants, were responsible for the poisoning.

In poisoning by local anesthetics, the primary objective of the use of EL (i.v.) was reverse, cardiovascular collapse/cardiac arrest in 13 cases, and depression of the central nervous system (CNS) in six cases. With respect to other lipophilic drugs of this class, the main purpose of using EL (i.v.) was reverse cardiovascular collapse/heart failure in 18 cases, and CNS depression in five cases.

According to the authors, the data of the reports evaluated case, suggest a possible benefit of EL (i.v.) cardiotoxidade due to bupivacaine, mepivacaine, ropivacaine, haloperidol, tricyclic antidepressants, lipophilic β-blockers and calcium blockers channels, when this can lead the individual to death. Furthermore, in these cases, the adverse effects reported with the use of EL (i.v.) were minimal.

The authors concluded that, despite the increasing number of cases reporting the use of EL (i.v.) as an antidote in the treatment of poisoning by lipophilic drugs, described in the literature, an indication of EL (i.v.) for this use is not unconditional. Thus, in cases of intoxication by toxic lipophilic agents using EL (i.v.) may be considered in severe cardiovascular instability, especially when it does not respond to conventional treatment. In addition, the use of EL (i.v.) is not recommended when the CNS depression manifested by depressed level of consciousness, is the only reason.

Waring (2012) undertook a systematic review of studies in order to further characterize the clinical results of EL administration (i.v.) as a possible antidote capable of reversing the neurotoxicity and cardiotoxicity some local anesthetics and various other lipophilic agents different pharmacological groups [8].

The search was conducted in the following databases: PubMed, OVID (1966 - June 2011) and EMBASE (1947 - June 2011) using the terms: ['Intralipid' OR 'lipid emulsion' OR 'lipid terapy' OR ' lipid administration 'OR' fat

emulsion 'OR' fat terapy 'OR' fat administration] AND ['Parenteral' OR 'intravenuos' OR' administration 'OR' administer 'OR' antidote 'OR' rescue 'OR' treatment 'OR' terapy ']. In addition, it made a manual search conference in Clinical Toxicology Congress publications in North America and Poisons Centres and the European Association of Clinical Toxicology meetings between the years 2002-2011.

The search identified 399 articles, of which 140 were of direct relevance to human clinical toxicology. Of these, 76 clinical cases in which EL (i.v.) was administered to patients, were included in the study. Such cases (n = 76) reported that cardiotoxicity caused by various pharmacological groups agents. Local anesthetics accounted for 21 cases (27,6%), cardiovascular agents for 20 cases (26,3%), psychotropic agents by 19 cases (25,0%), antiepileptic agents for 8 cases (10,5%), and other agents for 8 cases (10,5%).

Significant clinical improvement was reported in 51 patients (67,1%), for which conventional resuscitation measures were deemed ineffective. It was reported clinical improvement of 100% of patients (n = 21) expressed by local anesthetic toxicity and 54,5% (n = 30) of 50 patients with cardiotoxicity due to other drugs.

According to Waring (2012), despite the recent interest in the possible role of EL (i.v.) as a new antidote for cardiotoxicity induced by drugs, the available data are insufficient to provide certainty with respect to their mechanisms of action, its effectiveness and profile of its adverse effects. The greatest strength of evidence comes from preclinical and clinical data that support the role of EL (i.v.) patients with cardiotoxicity associated with local anesthetics, which explains the inclusion of EL (i.v.) as a potential treatment for resuscitation protocols, current. The role of EL (i.v.) in cardiotoxicity due to other drugs is less clear and very few data are available to allow any conclusions to be drawn [8].

CONCLUSION

The review conducted showed that the use of EL (i.v.) as antidote seems to be a possible alternative for the treatment of intoxications caused by local anesthetic and other lipophilic drugs. However, current evidence supporting this use are scarce and uncertain pointing the need for additional studies.

Regarding this fact, recently the American Academy of Clinical Toxicology (AACT) created an international working group with the objective to summarize the available evidence on (1) the clinical efficacy of EL (i.v.) in the poisonings caused by local anesthetics (2) the clinical efficacy of EL (i.v.) in the poison not local anesthetics and (3) adverse effects of EL (i.v.) divided in clinical and analytical interference effects [3].

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