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Review Article **Pediatrics**

Lipid Emulsion Treatment for Drug Toxicity in Pediatric Patients

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Abstract

Medication mistakes continue to be one of the most serious issues in hospitals. Such mistakes can occur during the prescription, distribution, or administration of medications. Lipid emulsions are commonly utilized in whole or partial parenteral feeding initially, Following convincing results from animal models and effective case reports in humans, the use of intravenous lipid emulsions (ILEs) as an antidote in local anesthetic systemic toxicity has acquired considerable acceptance. Although intravenous lipid emulsion (ILE) was initially employed to treat life-threatening local anesthetic (LA) toxicity, its application has broadened to cover non-LA poisoning and less severe symptoms of toxicity. However, in recent years, the function of lipid emulsions in the treatment of lipophilic chemical toxicity and overdose has been established. In addition to typical poisoning treatment, lipid emulsion therapy was employed. The observed sequence of events provides substantial support for the importance of ILE treatment in the effective management of both instances. However, further study is needed in this area to provide definite guidelines for the use of intravenous lipid emulsions in pediatric lipophilic agent poisoning. The body of data supporting the use of ILEs in acute drug intoxication is growing. The current data supports the use of ILEs only when there is an imminent threat to life from local anesthetic systemic toxicity or lipophilic cardio-toxin poisoning. Lipid emulsion therapy is a potential and less expensive alternative in cases of acute lipophilic poisoning where a specific antidote is unavailable.

Keywords: Lipid Emulsion, Intravenous Lipid Emulsion, Pediatrics, Drug Toxicity, Overdose, Local Anesthesia, Non-Local Anesthesia.

INTRODUCTION

Drug toxicity continues to be a serious concern in hospitals, and such errors might be connected to medicine prescription, dispensation, or administration. The majority of these errors are caused by human factors, but other elements, such as infusion pump programming errors, should always be taken into account. Medication mistakes have been found to afflict 2-3% of patients worldwide, depending on the institution. The consequences of pharmaceutical mistakes vary depending on the kind of medicine involved; the dosage supplied, the patient's age, the timing of error discovery, and the availability of antidotes and reversal solutions. Children and neonates are more vulnerable to negative outcomes, including drug-related fatalities [1]. As one of the primary causes of safety accidents in neonatal intensive care units (NICUs) is medication mistake or drug toxicity. An estimated 1-8% of these iatrogenic occurrences are fatal, most of which are caused by mistakes in prescribing or configuring the flow rates of electric infusion pumps tenfold or more. Patients with the lowest gestational age and birth weight, the most severe disease on admission, and a protracted duration of stay are the most at risk among neonates hospitalized in NICUs [2]. The usage of lipid emulsion infusion as part of total parenteral nutrition among hospitalized pediatric patients in Jordan and other surrounding Middle Eastern nations has expanded in recent years [1].

Lipid emulsions were originally utilized as part of complete or partial parenteral feeding in pediatric patients or patients who were unable to consume orally. It is frequently utilized as a vehicle for lipid-soluble medicines such as propofol. However, lipid emulsions have been used to treat poisoning in both animal models and people during the past years [3]. Weinberg *et al.*, [4] discovered that pretreatment of

rats with bupivacaine-induced cardiac arrest with a lipid infusion prolonged the time to cardiac arrest and the time to recovery was earlier. Lipid emulsion has thus gained recognition as both a parenteral feeding alternative and a therapy for local anesthetic systemic toxicity (LAST); as a result of the publishing of several experimental results, it is currently the first-line treatment of LAST. However, its method of action remains unknown. The first case report demonstrating the relevance of intravenous lipid emulsion therapy as a therapeutic option for acute drug intoxication was reported in 2006 [5]. Following that, several further instances and subjective accounts support the function of intravenous lipid emulsions in the treatment of toxicity induced by various medications and pesticides [6]. Besides the main indication of nutritional support, it is used to treat lipophilic drug toxicity where it redistributes these medications away from tissues and helps in their excretion, and it is shown to be effective in intoxications with calcium channel blockers (CCBs), beta-blockers, neuroleptics, antidepressants, and anticonvulsants [7].

Many alternative terms have been used to describe lipid emulsions, including intravenous lipid emulsion, lipid emulsion treatment, lipid resuscitation therapy, lipid rescue, intravenous fat emulsion(ILE), and Intra-lipid (Fresenius Kabi, Uppsala, Sweden), a brand name that has come to be used interchangeably with ILE since it is the most common lipid emulsion used in the US. ILE is most commonly utilized at a 20% isotonic concentration [8].

ILE is a revolutionary approach for treating LAST, as well as a promising antidote for other lipophilic drug poisonings [9]. The most dangerous consequence of local anesthetic (LA) absorption or intravascular injection during regional anesthesia is cardiovascular collapse. Lipid treatment has also been used in individuals who have been poisoned for reasons other than LA toxicity. Recent studies have focused on the effectiveness of lipid emulsions in resuscitating individuals who have overdosed on lipophilic, non-LA drugs [10]. Several clinical case reports shown that prompt ILE delivery to patients with local anesthetic systemic toxicity improved electrocardiographic and blood pressure abnormalities when traditional resuscitation techniques failed [11, 12]. ILE treatment is now included in worldwide resuscitation recommendations for patients with local anesthetic systemic toxicity. The American Heart Association and the European Resuscitation Council, for example, presently recommend bolus intravenous injection followed by repeated bolus administration and, depending on response, a maintenance intravenous infusion [13, 14].

ILE were created as a source of necessary fatty acids to meet nutritional requirements when enteral food was not tolerated or was insufficient. Fats, in addition to providing a rich source of cellular energy, influence several cellular activities such as cell membrane creation, participation in signal cascades as second messengers, control of inflammation and platelet function, and cholesterol and endogenous hormones biosynthesis [15].

The utility of ILE has been extended to therapeutics, allowing for the delivery of drugs that are poorly soluble in water and are poorly absorbed from the gastrointestinal tract, as well as nutraceuticals, which incorporate improved nutritional and physical properties due to modifications of new fatty acids [16, 17]. Several explanations for ILE's antidote qualities have been hypothesized, including preferential distribution of lipid-soluble medicines into a circulating lipid phase, decreasing tissue drug concentrations [18]. Improved fatty acid oxidative metabolism may also have a direct inotropic impact and restore cardiac contractility [19, 20].

The transmission of these and additional clinical examples of ILE has seen it go from bench-top modeling to clinically used antidote without the data basis typically associated with the introduction of newly manufactured medications. There have been several recent high-quality systematic reviews on this issue. The purpose of this narrative review is to examine recent literature with a specific focus on advances in understanding of the mechanism of ILE, particularly in pediatric patients, and to evaluate the evidence supporting ILE administration, in order to determine whether any changes to current recommendations for ILE administration are warranted. This study seeks to provide an overview of the research on the use of ILE as an antidote, along with recommendations for its administration in cases of drug overdose in pediatric patient's possible mechanisms of action, and safety profile.

Physico-Chemical Characteristics of ILE

ILE stands for oil-in-water emulsion. It's made up of triglyceride-rich oils, a phospholipid emulsifier, and glycerin [21]. The first commercially accessible fat source in parenteral feeding was a pure soybean oil emulsion, which is still used today. Newly developed fat emulsions for parenteral usage include mixed lipid emulsions comprising soybean oil, medium-chain triglycerides, olive oil, and fish oil, as well as pure fish oil emulsion [15, 22]. The emulsifying ingredient is commonly egg yolk phospholipid at a concentration of approximately 1%, and the emulsion contains particles with a mean diameter of less than 50 m. The phospholipid emulsifier stabilizes the lipid compartment created by these fat droplets by acting as both a mechanical and an electrically charged barrier. Oil droplets scattered in the internal phase of the emulsion are electrostatically attracted to one another by the negatively charged oil-water contact, preventing coalescence and a growth in droplet size [16]. When a

fat emulsion is injected intravenously, an enlarged intravascular lipid phase develops. When a lipophilic drug, such as local anesthetics, is partitioned into this lipid phase, its plasma concentration decreases. Target tissues and the aqueous plasma phase gradually diverge in the concentration of the lipophilic substance, which causes the substance to be redistributed to the plasma and eventually to the lipid plasma phase. The so-called "lipid sink" effect is the primary mechanism supporting the use of ILE as an antidote for drug toxicity [23].

Mechanism of Action of ILE

Lipid Sink Phenomenon:

The solubility of long-acting local anesthetics in lipid emulsions, as well as the emulsions' high binding capacity, presumably explain the clinical effectiveness when lipid is immediately administered in cases of LAST [4]. The 'lipid sink' phenomenon, first described by Weinberg in 1998, is the most commonly acknowledged mode of action for ILE. Infusion of a lipid emulsion expands the lipid phase, and the resultant balance pushes hazardous drugs from the tissue to the aqueous plasma phase, then to the lipid phase. While the precise mechanisms of action of lipid emulsion infusion to cure LAST are unknown, the important component is most likely the emulsion's binding capability [24].

20% Intra-lipid emulsion contains 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, water, and sodium hydroxide. When injected into an aqueous media such as blood, emulsified fat droplets produce a lipid compartment into which lipophilic molecules are theoretically partitioned. Lipophilic chemicals, such as local anesthetics, are attracted into the "lipid sink" and a concentration gradient forms between tissue and blood which cause local anesthetics to flow away from the heart or brain (areas of high concentrations) to the "lipid sink". Weinberg et colleagues revealed in an experimental rat model that radiolabeled bupivacaine injected in vitro to lipid-treated rat plasma preferentially flows to the lipid phase with a partition value of 11 [4]. In later investigations employing an isolated heart model of bupivacaine toxicity, Weinberg et colleagues demonstrated that infusion of lipid emulsion accelerated the clearance of radiolabeled bupivacaine from myocardial tissue compared to controls [25].

Alternate Mechanisms:

Lipid emulsion might theoretically enhance intracellular fatty acid levels, overcoming the lower ATP generation caused by LA blockage of fatty acid transit and oxidation. It's likely that the higher intracellular fatty acid level leads to better ATP generation in the cardiomyocyte. Under typical aerobic circumstances, fatty acids are the primary substrate for myocyte oxidative phosphorylation, accounting for approximately 80-90% of cardiac adenosine triphosphates production (ATP) [26]. If fatty acid transport is disrupted, ATP generation falls, reducing myocyte lifespan and potentially leading to heart damage. Van de Velde *et al.,* [20] demonstrated in a dog model that infusion of 20% lipid emulsion enhances contractility due to enhanced fatty acid oxidation. Eledjam *et al.,* [27] discovered that pre-incubating isolated myocardium strips with ATP inhibits bupivacaine-induced contractility depression. As a result, ILE may raise intracellular fatty acid levels sufficiently to counteract or overcome the reduction in cardiac ATP generation. Interestingly, lipid emulsion was originally discovered to respond faster in vivo than expected based on a basic lipid sink mechanism, hinting that direct cardio-tonic effects may possibly be at work [28]. Stehr *et al.,* [19] showed that lipid emulsion restores bupivacaine-induced contractile depression at concentrations too low to offer a lipid sink effect, implying a metabolic explanation for the beneficial impact. Infusion of lipid emulsions may also directly enhance intra- myocyte calcium levels, resulting in a direct positive inotropic impact [29].

ILE in Non-LA Drug Toxicity

Lipid emulsion therapy is not only used to alleviate local anesthetic toxicity. Recent human case reports of successful resuscitation have heightened interest in the potential efficacy of lipid emulsion in cardiac arrests caused by lipophilic, non-LA medications [30, 31]. Two extensive reviews of the literature describe the use of ILE in the setting of non-LA overdoses [32, 33]. Recent case reports of successful resuscitation imply that lipid emulsion infusion is effective for treating non-local anesthetic overdoses of a wide range of medications, including beta blockers, calcium channel blockers, parasiticides, herbicides, and numerous types of psychiatric substances. Toxicities produced by tricyclic antidepressants and other psychiatric medicines, calcium channel blockers, and beta blockers are likely to be the most clinically relevant. These drugs, like local anesthetics, have sodium channel blocking characteristics and are often lipophilic. With these lipophilic medicines, ILE is likely to have the similar "lipid sink" effect, lowering the quantity of active drug in the target tissue and minimizing toxicity [34].

Calcium Channel Blockers:

Multiple animal studies have shown that ILE is superior than placebo in the treatment of verapamil toxicity [35]. Tebbutt *et al.,* [35] demonstrated in rats that using lipid emulsion nearly quadrupled the LD50 and reduced bradycardia caused by hazardous dosages of verapamil. In a canine model of verapamil poisoning, Bania *et al.,* [36] compared lipid emulsion to normal resuscitation approaches and discovered that ILE-treated animals had substantially higher MAPs at 30, 45, and 60 minutes post rescue compared to control dogs. Young *et al.,* [37] presented the first human case of verapamil toxicity successfully treated with lipid emulsion, providing proof of effectiveness for ILE in

treating CCB overdose. The patient was already in shock that was resistant to normal resuscitation care but was alleviated with intravenous lipid emulsion delivery; no side effects were seen, and the patient recovered completely. Other case reports describe comparable hemodynamic improvements in calcium channel blocker overdose patients [38, 39].

Beta Blocker:

In both the rat and rabbit models, ILE reduces propranolol induced QRS prolongation and bradycardia [40, 41]. A comparable model investigating ILE in the treatment of atenolol toxicity in rabbits revealed no significant changes in MAP following lipid administration [42]. While this raises concerns regarding the use of ILE in the presence of beta-blocker intoxication, the findings may be explained by the fact that atenolol is not nearly as lipophilic as other beta- blockers, such as propranolol. One case report described hemodynamic recovery following ILE treatment in a patient who had been intoxicated by both ethanol and atenolol. However, it is unclear if these benefits were caused by ILE, atropine, glucagon, or saline [43].

Psychotropic Drugs:

Yoav *et al.*, [44] found that administering clomipramine in a lipid infusion vehicle rather than saline reduced mortality in rats. Harvey and Cave employed a rabbit model to investigate the effects of lipid infusion on clomipramine toxicity and discovered that lipid-treated rabbits recovered from hypotension quicker than saline or sodium bicarbonate-treated controls. A rat model of amitriptyline toxicity found no statistically significant variations in hemodynamic parameters or survival; however this may be due to the limited sample size [45]. Sirianni *et al.*, [46] published the first account of the effective application of lipid emulsion in a person as a remedy for a lipophilic, non-local anesthetic toxicity. They report the resuscitation of a 17-year-old female who had taken enormous amounts of lamotrigine and bupropion, two medications used to treat depression and bipolar illness. Ten hours later, the patient's circulatory system collapsed, resulting in ventricular fibrillation and pulseless electrical activity. After seventy minutes of failed resuscitation with normal ACLS plus sodium bicarbonate injection, 20% ILE was administered as a last resort to regain hemodynamic stability. Vital indicators returned to normal after a minute following ILE administration. She healed and was able to leave the hospital with just minor neurologic abnormalities.

Other Non-LA Drugs:

Other toxins, such as herbicides and pesticides, have been treated using ILE as an unique therapy method. In a recent example of verified moxidectin poisoning in a puppy, treatment with intravenous lipid over four hours resulted in a significant decrease in recovery time [47]. Since there are no current standards for the treatment of non-LA toxicities, the dosage of ILE was based on therapeutic recommendations for bupivacaine toxicity. The use of ILE in treating a patient with refractory hypotension brought on by the herbicide glyphosate-surfactant (GlySH) has drawn a lot of interest. The patient's condition was not improved by aggressive fluid and vasopressor treatment, but a 100 mL lipid bolus and subsequent 400 mL infusion induced a quick and dramatic recovery to normal blood pressure. Because GlySH is typically resistant to standard therapy, the authors recommend that ILE be evaluated in situations of refractory hemodynamic instability [48].

Dosing of ILE in Pediatric Patients

The most commonly reported dose procedure is an intravenous bolus of 1-1.5 mL/kg of 20% ILE solution delivered over one minute [37, 49]. If there is no reaction, the same amount may be repeated every 3-5 minutes in the event of cardiac arrest (maximum total of 3 boluses). Although there is no maximum time of ILE therapy indicated in the literature, the treatment typically lasts 30-60 minutes. Following the bolus, an infusion of 0.25-0.5 mL/kg/minute is begun until hemodynamic variables recover to normal ranges. To prevent hypotension, the infusion rate can be adjusted. The US Food and Drug Administration recommend a maximum dose of 15 mL/kg over 24 hours in children [50].

There has been little published evidence on dose recommendations for children with local anesthetic toxicity. The median bolus dosages published in Presley and Chyka's [51] assessment of pediatric series of lipid emulsion for resuscitation ranged from 0.8 to 3 mL/kg of a 20% lipid emulsion, which are significantly lower than the values previously reported in acute lipid emulsion overdoses [52]. The American College of Medical Toxicology (ACMT) recommends ILE for inebriated individuals with hemodynamic compromise who are not responding to traditional resuscitation therapy. To guarantee medication safety, intravenous lines for drug delivery, flow rates, and dosages should be double-checked in the context of resuscitation attempts [53].

Only a few cases involving children have been mentioned in published case reports on the issue. The first pediatric case report involving ILE therapy in the treatment of acute poisoning was reported in 2011. It described a 20- month-old girl who consumed a big dose of Tricyclic antidepressants (TCA) and had convulsions and hemodynamic instability. She did not react to the standard poisoning care procedure; intravenous lipid emulsion therapy was performed, resulting in the patient's complete recovery [54].

An research published in 2013 examined all case studies on the use of ILE treatment in children and adolescents. It was determined that virtually all of the

cases demonstrated a favorable impact of ILE treatment, with only one case report exhibiting negative effects. However, the dosing regimens were not clearly established [38].

TCA is a lipophilic medication with cardiovascular and central nervous system adverse effects when taken in large doses. Neurotoxicity was seen in two documented instances [55]. Lipid emulsion treatment was employed in both cases, and it resulted in quick recovery. Although it is impossible to attribute the success in saving lives solely to Lipid Emulsion therapy due to the multi-agent poisoning and multiple therapies administered, the sequence of events observed in toxicity reversal proves a significant role of ILE in the favorable outcome observed in both cases [55].

Risk of Accidental ILE Overdose in Pediatric Patients

Premature newborns may benefit from adequate protein and calorie intake by PN in terms of postnatal growth, cognitive function, and neurologic prognosis [56-58]. According to the 2018 pediatric PN recommendations, preterm newborns should be given at least 45-55kcal/kg/day on their first day of life. In this demographic, it is also suggested that ILE begin promptly after delivery [59]. A previous instance documented a fatal unintentional lipid overdose in a newborn child on the second day of life, which for the first time involved a composite lipid emulsion [60].

A case clearly recorded the source of this iatrogenic incident as well as the clinical and biological progression, particularly after ET, but the absence of an autopsy prevents us from confirming the pathophysiological hypothesis regarding what caused the patient's death [2].

PN adequately fulfilled the infant's energy requirements; nonetheless, certain irregularities in the prescription are worth mentioning. Premedication with propofol, a chemical synthesized in a lipid emulsion, was given to the newborn patient in this case before surfactant treatment. His clinical trajectory, as well as certain pharmacological considerations, show that propofol treatment had little, if any, influence on the emergence of clinical and laboratory symptoms. The pharmacodynamics results found in neonates during laryngoscopy imply that the vast majority of newborns recover from sedation within 15-30 minutes following various dosages (1-2.5mg/kg) of intravenous propofol [61-65]. From a biological standpoint, 1mg/kg propofol administration corresponds to a relatively modest lipid intake, 5mg soybean oil, which cannot explain the very high blood triglyceride level found 39-40h following propofol administration.

With the exception of individuals at the extremes of age, notably newborns and babies, adverse effects related with ILE are uncommon and typically non-life threatening [66]. Triglyceride levels rise in fat overload syndrome, which is accompanied by fever, cholestasis, hepatosplenomegaly, and coagulopathy. It has been described in individuals who have received large doses of ILE [67] for a lengthy period of time [68]. Another reason is unintentional lipid overdose as a result of a high infusion rate. Four cases of Intralipid 20%, a pure soybean oil emulsion, have been described in the neonatal literature [69]. Medialipide is a 20% emulsion of medium-chain triglycerides and soybean oil. Four more occurrences of overdose with this medicine due to an administration error were found in both the national pharmacovigilance database and VigiBase [70], including three preterm neonates who experienced minor and resolving symptoms once ILE was discontinued for a few days. The most prevalent symptom was hypertriglyceridaemia, however one infant also had transient tachycardia and polypnoea.

Another example was a more severe overdose in a 23-month-old male kid with a history of severe lung disease. He quickly developed a temperature (39°C), sweating, polypnoea, desaturation, and severe respiratory distress, necessitating transfer to a pediatric critical care unit to give breathing support. After 10 days, the severe hypertriglyceridemia and general health improved [71].

One of the most common side effects of ILE overdose is respiratory distress, which can have several causes. Infusion rate errors might result in volume overflow [72]. Premature newborns' lethargy and apnea have been linked to changes in cerebral perfusion, which may involve fat emboli in brain capillaries and arterioles [73].

Another cause of ventilation perfusion mismatch was changes in vascular tone, which resulted in PH, increased pulmonary vascular resistance, and ductal right-left shunting. According to observations, a peak tricuspid regurgitant jet velocity of 3m/s corresponds to about twice the velocity typically recorded in preterm children [74]. A research in stable low birth weight newborns found increased pulmonary vascular resistance with a 2h infusion of 0.6g/kg of a pure soybean oil emulsion using a relevant M-mode echocardiography parameter [75]. During continuous infusion of the same emulsion in preterm babies with respiratory distress, dose- and time-dependent increases in pulmonary vascular resistance were identified using the same device. Serum triglyceride levels were normal, indicating that variations in pulmonary resistance may be connected to the synthesis of vasoactive eicosanoid lipid metabolites generated from long- chain polyunsaturated fatty acids [76].

Treatment of ILE Overdose

It is not conventional practice to treat intravenous lipid emulsion overdose in neonates beyond halting it and providing supportive care. Exchange

transfusion (ET) is a method that was first used in the mid-1990s to treat newborn hemolytic disease mortality. ET was first established in the late 1940s. Experience with ET in preterm babies is limited, especially given the recent significant reduction in the number of ETs done during the previous two decades [77]. This lack of knowledge extends to our medical and nursing staff, raising the possibility that our patient's prognosis was influenced, at least in part, by an ET-related adverse effect. Several writers, however, have expressed concern about attributing difficulties to this treatment in children who were already critically sick when it was initiated [77-80].

ET was chosen and then conducted on a patient who was already suffering from ARDS and severe shock. The technique was extremely successful in lowering triglyceride levels in these situations but gave no therapeutic benefit. This finding contradicts two case studies that found remarkable improvements with this technique. A 5-day-old preterm baby weighing 2160g who was delivered at 32 weeks gestation was the first example. This baby's triglyceride level was more than double what we had previously noted (129g/L). The second was a pair of twins that was delivered at 25 weeks and 6 days gestation and weighed 920 g at birth but whose triglyceride levels could not be determined. Although an ET was conducted in both instances with two blood volumes, the authors did not state how long it took for the ET to be finished after a lipid overdose. In addition, a 3-month-old male child who accidentally overdosed on ILE and had serum triglyceride levels of 48g/L was reported to have fully recovered after receiving a single-volume blood exchange transfusion [1].

Another example implies that the clinical success of its approach would have necessitated more fast application, maybe at the detection of high blood lactate levels a few hours after the overdose, in order to avert the progression to multiple organ failure. Our patient had many susceptibility factors that were both prenatal and postnatal in nature. Intrauterine growth restriction, an inadequate prenatal corticosteroid regimen, perinatal hypoxia, caesarean delivery, delivery of an out born child, extremely low birth weight, and very preterm baby delivery were among them. It is possible that the tissue fragility of this vulnerable neonate had a role in the unfavorable evolution. Indeed, the amino acid profile demonstrated that various indications of neonatal asphyxia-related liver damage, such as increased alanine and a lower ratio of branched-chain amino acids/(phenylalanine + tyrosine), were present prior to the ILE overload. A bolus of 1g/kg over 15min of a soy-based ILE elevated triglyceride levels to 10g/L in stable eutrophic preterm neonates after a few days of life, with the level thereafter stabilizing within 2h of the start of infusion [81].

Rapid infusion of ILE has been proposed as a treatment for the toxicity of local anesthetics and other medicines. The mechanism of action of ILE appears to be mostly connected to the emulsion's binding characteristic. Various ILEs have been employed, and this method has also been extended effectively to the pediatric population [51, 82]. Regional anesthesia is utilized in about one-third of all neonatal surgical operations and has shown beneficial in improving postoperative pain management and minimizing the usage of systemic analgesics such as opioids [83]. While problems are uncommon and typically mild, some examples may encourage doctors to exercise extreme caution while utilizing an ILE to revive a newborn with a cardiac arrest caused by local anesthesia [84].

ILE Safety

Particularly in infants, the use of ILE for parenteral nourishment has been associated with severe pulmonary adverse effects, with the coalescence of oil droplets, which increased their size, and subsequent fat embolization proving to be the primary contributing reason [85]. Exposures to divalent and trivalent cations, as well as an acid pH, are regarded possible determinants of emulsion instability, although exposure to high temperatures does not appear to be as important [86]. Nonetheless, total disintegration necessitates sustained exposure to these harsh circumstances. Headaches, jaundice, hepatosplenomegaly, and spontaneous bleeding may occur in addition to respiratory distress, forming the so-called fat overload syndrome, a well-known consequence of ILE delivery in parenteral nutrition [22].

In contrast, the use of ILE for medication toxicity inversion has not been linked to such complications [87]. Furthermore, despite a faulty conception of therapeutical protocol that led in an excessive administration of 2 liters of ILE in an unusual instance of amlodipine poisoning, cardiac consequences were not indicated [88]. Two occurrences of acute asystole following ILE infusion, on the other hand, have been reported. Despite the chronological link, no clear cause explanation has been identified [89].

Recent studies have investigated ILE-related side effects in attempt to determine the maximum safe dosage. Hiller *et al.*, [90] employed the "Dixon-up-down" approach in a mouse investigation to calculate the median lethal dosage (LD_{50}) of ILE 20% at 67 ± 11 ml/kg. Although the LD_{50} is not the ultimate criteria for determining medication safety, it was much higher than the normal dose. Histological examination of major organ tissue revealed no abnormal findings in the myocardial, central nervous system, pancreas, or kidneys. Although ILE had temporary effects on lung and hepatic tissues, these findings were only found after substantial dosages of ILE (> 60 ml/kg). ASRA, on the

other hand, advises ILE at a dosage of 10-12 ml/kg in 30 minutes [91].

One of the well-accepted underlying causes of acute pancreatitis is hyperlipidemia in the form of hypertriglyceridemia or chylomicronemia. Chylomicrons are triglyceride-rich lipoprotein particles that circulate when triglycerides exceed 900 mg/dl and are big enough to occlude pancreatic capillaries, resulting in inflammation. Pancreatic lipase release and increased lipolysis mediate inflammation, edema, and necrosis [92]. Despite the fact that lipid emulsions are meant to mimic natural chylomicrons, there has only been one instance of severe pancreatitis related with ILE administration, with reports of chemical hyper-amylasemia without symptoms being more common [93, 94]. Furthermore, lipemia impedes blood sample analysis, particularly when spectrophotometric methods are used for laboratory evaluation.

As a result, even at low triglyceride levels, hematological and biochemistry parameters are frequently impacted following lipid infusion. Hemoglobin and platelet values may be raised, as may liver and coagulation tests [95]. In order to reduce the potential impact of ILE on treatment choices and patient care, blood can be drawn prior to the administration of ILE and quickly high-speed centrifuged serum can be utilized [96].

Although just one incidence of bronchospasm has been described among patients who received ILE for drug intoxication, hypersensitivity and allergy side effects are also possible consequences of ILE treatment [66].

The ILE-drug interaction is not well understood. In the presence of atropine, bicarbonate, or calcium, no adverse effects were seen. On the other hand, studies from a rat model of bupivacaine overdose show that care should be used when including adrenaline into a lipid emulsion therapy regimen, since it was hypothesized that epinephrine beyond a threshold level hampered lipid resuscitation [97]. Through the induction of hyper-lactatemia and acidosis. Based on these findings, ASRA underlined that the pharmacological management of local anesthetic systemic toxicity differs from other cardiac arrest situations and advised avoiding epinephrine dosages more than 1 mcg/kg. A recent experimental investigation shows that taking levosimendan with it may be advantageous [98].

Administration of ILE According to Current Guidelines

The 2015 European Resuscitation Council (ERC) Guidelines on Resuscitation prescribe a 1.5 ml/kg intravenous bolus over 1 minute, followed by a 15 ml/kg/h continuous infusion. In the event of prolonged cardiovascular collapse, the bolus should be given twice more at 5-minute intervals. The infusion should be maintained at least until hemodynamic recovery is achieved or until the maximum dosage of 12 ml/kg is reached. Standard resuscitation should be carried out in accordance with ALS recommendations [99].

These instructions address the specific situation of circulatory collapse and cardiac arrest caused by LAs poisoning, but ILE is also discussed in beta-blocker intoxication [99]. The American Heart Association extends the suggestion to LA neurotoxicity and advises that it may be permissible to provide ILE to patients who are failing routine resuscitation procedures due to other kinds of drug toxicity. Despite the limited and contradictory evidence, the prognosis of patients who fail traditional resuscitation techniques is dismal, and empiric use of ILE in this scenario may be prudent [13].

In situations of acute poisoning with lipophilic substances where a particular antidote is not available, lipid emulsion treatment is a promising and less expensive option. Jeffrey Brent a prominent medical toxicologist, offered a stunning comment in this respect in an editorial published few years ago " It is fair to say that based on what we known so far, no patient dying of cardio toxic drug poisoning should do so without a trial of lipid rescue " [30]. More study is needed on the matter, and adequate recommendations for pediatric use must be devised.

Future Research Questions

It is hoped that randomized controlled trials would be conducted to provide for a more informed assessment of the involvement of ILE in specific poisonings. Efforts in animals should be aimed on establishing controlled experiments examining the time of delivery, with the toxin administered orogastrically. It is also critical to investigate the dosage- response relationship for the loading dose and the infusion, while explicitly reporting on the presence or absence of side effects. Ideally, it would also concentrate on establishing the best end point for ILE therapy. In vitro investigations may be adequate to assess the possible interferences of ILE on typical co-ingestant tests or binding affinity with other medications. To establish the relative effectiveness of the products that are now on the market, it is also important to compare the effectiveness of the lipid emulsions that are readily accessible for purchase [100].

CONCLUSION

ILE treatment is a well-known method in clinical toxicology. The lack of randomized clinical trials appears to be unavoidable, and ILE administration recommendations are mostly based on animal research and case reports. ILE is a relatively new treatment with a limited understanding of its effectiveness, modes of action, safety, and related analytical interferences.

Clinical recommendations for the use of ILE in poisoning were only viable in a few cases due to the very poor quality of evidence, risk-benefit balance, and resource consumption. Nonetheless, ILE treatment has been broadened to include drug intoxication with substances other than local anesthetics. In attempt to explain this vast range of ILE effectiveness, not only the lipid sink phenomena, but also molecular explanations, have been proposed. Because of its good safety profile, ILE empiric delivery in cases of failed conventional resuscitation may be prudent. ILE treatment, on the other hand, is a well-established method in clinical toxicology. Future bigger prospective or registry- based research may shed light on the genuine therapeutic effects of ILE in medication toxicity.

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