ISSN:2790-167X DOI: 10.56028/aehssr.4.1.151.2023

Intravenous lipid emulsion for the treatment of acute lipid-soluble anesthetic drug toxicity in pediatric patients

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Abstract. Clinical studies on the use of lipid emulsions for the treatment of lipid-soluble anesthetic drug intoxication in children are relatively absent. Since children are not shrinking versions of adults, the therapeutic efficacy of lipid emulsions for the treatment of lipid-soluble anesthetic drug intoxication in pediatric patients is uncertain. This paper investigates the therapeutic efficacy and therapeutic mechanism of intravenous lipid emulsion for reversing acute narcotic drug intoxication in pediatric patients based on clinical data from west China Hospital of Sichuan University. The clinical data of 106 pediatric patients with acute lipid-soluble drug intoxication admitted to an inpatient center in the past 3 years were retrospectively analyzed and randomly divided into an observation group and a control group. The cardiac function indexes and blood gas indexes of patients in both groups were compared before and after treatment. After treatment, the left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD) values and plasma B-type natriuretic peptide (BNP) in the observation group were lower than control group, and the left heart ejection fraction (LVEF) was higher than those in the control group, with statistically significant differences ($P<0.05$). The arterial oxygen saturation (SaO_2), partial pressure of oxygen (PaO_2) and acid-base (pH) values were higher in the observation group than in the control group, and the partial pressure of carbon dioxide ($PaCO_2$) values were lower than in the control group. And these differences were statistically significant ($P<0.05$). Therefore, intravenous lipid emulsion has a positive effect in reversing acute fat-soluble anesthetic drug intoxication in pediatric patients, and is effective in promoting recovery of cardiac function, reversing respiratory failure, and improving blood gas indexes. The results of the study demonstrated the effectiveness of intravenous lipid emulsion in reversing pediatric lipid-soluble anesthetic drug intoxication and enrich the clinical research on this issue.

Keywords: Lipid emulsion, pediatric patients, lipid-soluble anesthetic, toxicity.

1. Introduction

Lipid emulsions originated from research on parenteral nutrition support which appeared in experiments back in the 18th century. In 1712, William Courten injected olive oil into the veins of a dog, but the dog died a few hours after the injection with symptoms of respiratory distress, caused by an embolism of the fat to the lungs [1]. In 1873, Edward Hodder injected fat in the form of milk into three cholera patients, of whom one did not survive, while the others recovered completely [1]. Several other studies similarly show that milk injection can lead to adverse effects [2]. These events support Sir William Coulton's early observations and conclusions that intravenous injection of pure oil is fatal. Breaking down lipid sources into smaller droplets, known as emulsions before the injection is necessary. It was not until 1962 that the first safe injectable lipid emulsion was prepared by Arvid Wretlind of Sweden using egg phospholipids as an emulsifier mixed with soybean oil [3]. Over the next few decades, lipid emulsions as parenteral nutritional support were gradually refined. Since complications of excessive intake of parenteral glucose as a sole energy source were identified (e.g., respiratory insufficiency, hepatic steatosis, hyperglycemia-related immunosuppression), intravenous lipid emulsions as parenteral nutritional support became more acceptable in clinical treatment and more researchers pay attention to relative studying [4]. With further research, lipid emulsions have also been found to be effective in the treatment of toxicity caused by lipid-soluble drugs. In 1962, Enhanced recovery from barbiturate-induced neurological

ISSN:2790-167X DOI: 10.56028/aehssr.4.1.151.2023
depression in rats was demonstrated [5]. This was the first successful case of lipid emulsions counteracting drug toxidrome. Weinberg et al discovered that low doses of subcutaneous bupivacaine induce cardiotoxic effects in a patient with carnitine deficiency [6]. The results of these early trials illustrate that lipid preconditioning was protective against local anesthetic toxicity. The suppression of local anesthetic toxicity through the method of intravenous lipid emulsions led to significant developments in clinical practice. In later clinical trials, lipid emulsion as an antidote was not only effective for local anesthetic agents, but its therapeutic scope also included the treatment of other lipid-soluble drug toxicities. Sebnem et al reported several cases of intravenous lipid emulsions as antidotes to treat lipid-soluble drug poisoning [7]. The results demonstrate the effectiveness of intravenous lipid emulsions for the treatment of lipid-soluble drug poisoning. Although clinical familiarity with intravenous lipid emulsions is increasing, there is still uncertainty as to the precise mechanism of action. Therefore, experimental clinical studies have become particularly important. In recent years, intravenous lipid emulsions have been used clinically to treat acute toxicity caused by several local anesthetics and other drugs mainly in adults. However, data on the indications for children are currently inadequate. As the renal function and endocrine system of children are still developing, the pharmacokinetics and pharmacodynamics of the drugs in their bodies may differ significantly from adults, and the therapeutic effects of the drugs may likewise vary. To solve this issue, clinical data from pediatric patients with lipid-soluble anesthetic drug intoxication at an inpatient center over three years were collected and screened. Subsequently, patients were grouped according to the use of intravenous lipid emulsions or not. The cardiac function and blood gas indices of both were compared and analyzed before and after treatment. Also, the mechanism of the changes in the indicators was speculated based on the recurrent research. Finally, it found that the patients in the observation group recovered on average more than the control group in the same period. Intravenous lipid emulsions in reversing acute drug toxicity in pediatric patients have positive effects.

2. Lipid emulsion therapy

Before analyzing the relevant clinical data, the theories on the detoxification mechanism of lipid emulsions in recent years were collected. A widely accepted theory of the detoxification mechanism of lipid emulsions is the lipid sink theory, which states that when lipid emulsions enter the blood system, a lipid phase in plasma can absorb the lipid-soluble drug. Weinberg et al supported the lipid sink theory by studying lipid emulsions for bupivacaine in rats [8]. But the results did not rule out other mechanisms. The adsorption of lipid molecules to lipid-soluble drugs through electrical actions can also serve to accelerate drug metabolism and redistribution [9]. At the same time, the lipid shuttle theory suggests that the back-and-forth movement of lipid emulsions enhances the binding and redistribution of lipid-soluble drugs to reduce toxicity in drug-sensitive organs [10]. Since the cardiac and blood-brain systems are sensitive to decreases in blood oxygen content and the natural metabolic process of lipid-soluble drugs that cause intoxication is relatively slow. Patients are prone to clinical manifestations of intoxication in the form of a weakened heartbeat and coma. The shuttle process of lipid emulsions facilitates the binding of lipid molecules to lipid-soluble drugs and their redistribution to the liver and muscle, and the binding and redistribution process is much faster than the natural metabolism, thus accelerating the removal of drugs from organs metabolism of drugs by the liver [11]. In a study by Litonius et al on the therapeutic effects of lipid emulsions on the lipid-soluble drug bupivacaine, it was found that the half-life of bupivacaine in plasma concentration decreased from 45 minutes to 25 minutes after the use of intravenous lipid emulsions [12]. Therefore, lipid emulsions are an effective option for acute lipid-soluble drug poisoning.

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3. Method

A retrospective study analyzed the clinical data of 106 pediatric patients with acute lipid-soluble drug intoxication in an inpatient centre for three years until July 30, 2022. These data were randomly divided into an observation group and a control group of 53 patients for each. In the observation group, there were 27 males and 26 females aged 6-12 years, and the duration of poisoning was 2-6 h. In the control group, there were 27 males and 26 females aged 5 - 14 years. The duration of poisoning for all patients was 3-7 h. No statistically significant differences were found between the two groups (P > 0. 05). Clinical data are from West China Hospital of Sichuan University and this study consists with 《Declaration of Helsinki》 and informed patient consent.

3.1 Inclusion criteria

Patients with a confirmed diagnosis of acute lipid-soluble anesthetic drug intoxication on hospital examination; Patients who have not taken any emergency measures before receiving this treatment; Patients who have been admitted to the intensive care unit for at least 6 hours and have received two or more intravenous lipid emulsions; Patients are under the age of 15 years.

3.2 Treatment

The treatment for the control group was based on the use of conventional antidotes, i.e., treatment with the appropriate traditional antidote based on the type of lipid-soluble drug poisoning. In the observation group, patients were treated with lipid emulsions in combination with the treatment of the control group. In both groups, cardiac and hepatic and renal function parameters were observed before and 24 h after treatment.

3.3 Drug description.

The drug used is fat emulsion Injection (C14~24), produced by Anhui Fengyuan Pharmaceutical Co. in China. The size of the drug specification is 100ml:20g:1.2g/bottle. It is a sterilized emulsion made of soybean oil emulsified with lecithin for injection and glycerin for injection. Each 100ml contains 20g of soybean oil for injection, 1.2g of lecithin for injection and 2.2g of glycerin for injection.

3.4 Evaluation indexes

Echocardiography was used to detect the changes in left ventricular end-systolic diameter (LVESD) and left ventricular end-diastolic diameter (LVEDD) indexes of the patients. The left heart ejection fraction (LVEF) level was measured by cardiac ultrasound. The plasma B-type natriuretic peptide (BNP) level was measured by the automatic biochemical analyzer in both groups. Blood indexes of the patients in both groups were measured by blood analyzer, including arterial oxygen saturation (SaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2), acidity and alkalinity (pH).

3.5 Statistical methods

The screened data were statistically analyzed by spss pro. t-test was used for comparison between groups for quantitative data ($x \pm s$) conforming to normal distribution. The x^2-test was used for comparison between groups for generally qualitative data (%). If P<0. 05, a statistically significant for this difference should be included in the consideration.

4. Result

After statistical processing, the results of plasma BNP and cardiac function indices before and after treatment for patients in the control and observation groups are shown in Table I. Before treatment, the p-values for all parameters were greater than 0.05, indicating that the differences in

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the data were not statistically significant. However, the p-value tests for all parameters after treatment were less than 0.05, thus making the data statistically significant after lipid emulsion treatment. This indicates that the combination of intravenous lipid emulsion has a different degree of effect on plasma BNP and cardiac function parameters in patients compared to traditional therapy.

The blood gas indices of the patients in both groups are outlined in Table II. Before treatment, the p-value of the data in the two groups was larger than 0.05, indicating no morphological differences were obtained between the two groups. After treatment, the patients in the observation group showed more positive changes in blood indices compared to the control group. In particular, SaO2 rose more in the observation group compared to the control group, reaching the normal range (95%-100%). The observation group had higher blood oxygen levels and higher blood PH concurrently. All blood indicators of the patients were less than 0.01. This indicates that the combination of intravenous lipid emulsions in conjunction with traditional therapy had an additional effect on the recovery of patients.

Time	Gender	Number	LVESD (mm)	LVEDD (mm)	Plasma BNP (mg·L-1)	LVEF (%)
Before treatment	Control group	53	57.57±4.19	64.23±3.19	304.03±38.34	46.24±3.31
	Observation group	53	57.76±4.29	64.43±3.22	304.23±37.39	46.29±3.34
	t-value		0.154	0.162	0.132	0.098
	p-value		0.98	0.956	0.992	0.912
After treatment	Control group	53	50.65±7.01	60.55±4.12	202.35±30.12	54.67±8.01
	Observation group	53	45.45±6.67	53.69±4.32	184.65±21.12	60.02±8.20
	t-value		3.767	6.453	5.768	3.914
	p-value		0.0037	0.0056	0.0058	0.005

Table.1 Plasma BNP and cardiac function indices before and after treatmen

Table.2 The blood gas indices

Time	Gender	Number	SaO2 (%)	PaCO2 (mmHg)	PaO2 (mmHg)	pH
Before treatment	Control group	53	84.44±0.21	67.31±5.21	51.45±7.26	7.11±0.09
	Observation group	53	84.54±0.17	67.26±5.78	51.37±7.19	7.13±0.10
	t-value		0.765	0.34	0.347	0.451
	p-value		0.445	0.821	0.843	0.887
After treatment	Control group	53	89.34±1.15	46.35±3.56	79.49±3.26	7.24±0.05
	Observation group	53	97.56±1.52	38.75±3.66	91.32±3.20	7.37±0.05
	t-value		18.469	10.547	8.674	8.421
	p-value		0.0076	0.0061	0.0045	0.0049

5. Discussion

Acute lipid-soluble anesthetic drug poisoning is a common clinical condition, although cases of lipid-soluble anesthetic drug poisoning have decreased with improved drug management and administration. However, due to the immaturity of children's organs and the relative lack of clinical data in this area, lipid-soluble anesthetic poisoning in children still occurs from time to time. In this work, we screened appropriate clinical data on lipid-soluble anesthetic drug poisoning in children,

ISSN:2790-167X DOI: 10.56028/aehssr.4.1.151.2023
categorized and compared the data according to two groups, investigated the mechanism and effect of intravenous lipid emulsion on reversing acute lipid-soluble anesthetic drug poisoning in pediatric patients. According to the data on cardiac parameters, there was an increase in the left ventricular end-systolic and diastolic internal diameter during poisoning and an abnormal decrease in the ejection fraction. These clinical manifestations were related to the effect of the anesthetic drugs on the cardiomyocytes. Lipid-soluble anesthetic drugs attach to the intracellular junctional domains of cellular sodium channels and inhibit the flow of sodium ions, affecting the depolarization and transfer of neuronal ions [13]. When the drug concentration is too high, the drug may likewise affect potassium ions, calcium channels, sodium-potassium particle ATPase channels et. At the same time, it will interfere with intracellular and transmembrane cell signaling. This interference inhibits the metabolic processes of stimulated kinases such as protein kinase B (Akt), cyclic adenosine monophosphate and adenosine 5-monophosphate activated protein kinase (AMPK) [14]. Related studies have shown that lipid-soluble drugs, exemplified by local anesthesia, affect the inhibitory sarcoplasmic reticulum of cardiac myocytes by inhibiting ryanodine receptors and reducing the Ca2+ sensitivity of myofilaments [15-16]. This leads to a reduction in the patient's cardiac systolic function, an increase in both end-systolic and diastolic internal diameter of the left ventricle and a lower-than-normal ejection fraction. Abnormalities in cardiac function led to abnormal elevation of plasma BNP. In a study by Iwanaga et al on the correlates of factors affecting plasma BNP, they found a high correlation between left ventricular end-diastolic wall stress (EDWS) and plasma BNP in patients [17]. Also, other cardiac function indices such as end-diastolic pressure (EDP) and ejection fraction (EF) have some correlation with plasma BNP [18]. And the abnormal cardiac function caused by lipid-soluble anesthetic drug intoxication leads to the mechanism of stimulating BNP, which in turn leads to the elevation of BNP in patients. Maisel et al showed in a related study that plasma BNP is an important indicator in response to heart failure [19]. Combined with the clinical data from this study, the abnormal elevation of plasma BNP reflects the level of myocardial impairment by lipid-soluble anesthetic drugs. However, in combination with treatment with intravenous lipid emulsions, lipid emulsions bind lipid-soluble anesthetics in the heart and translocate them to the liver and redistribute them to other muscle cells. The process of transport and redistribution is much faster than the natural metabolism of the drug. When lipid emulsions are used clinically with conventional antidotes, this process will have more efficient detoxification. Michael et al demonstrated that intravenous lipid emulsion has a rapid inotropic and lusitropic effect on the heart, which has significant implications for the clinical treatment of reversal of heart failure due to acute intoxication [20]. In figure 1, three histograms from left to right show the cardiac parameters of the patient before treatment, the cardiac parameters after treatment and the percentage change before and after.

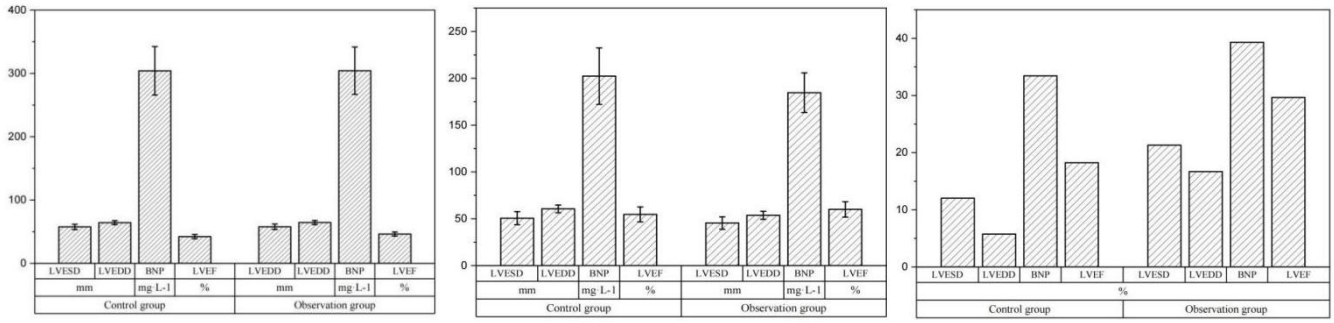

Fig. 1 Cardiac indicators before and after treatment

The histograms reflect that the changes in the cardiac parameters of the patients in the observation group were greater than those in the control group during the same period, which indicates that patients in the observation group had a higher average degree of recovery of cardiac function and a lower risk of cardiac arrest due to acute drug intoxication.

ISSN:2790-167X DOI: 10.56028/aehssr.4.1.151.2023

According to the patient's blood indicators, the data showed that the blood oxygen levels were lower in patients with lipid-soluble narcotic drug intoxication before treatment. This mainly stems from the effect of narcotic analogues on the respiratory system of the patients. Although the mechanism of the effect of different anesthetic drugs on the respiratory system varies, in most cases, it affects the muscle cells of the respiratory system and thus the blood oxygen level. Lennart et al explained the effect of anesthesia on the respiratory system. Under the influence of anesthetic drugs, lung muscle tone is reduced or even lost, leading to a decrease in resting lung volume (functional residual capacity). In turn, the reduction in FRC may lead to altered ventilation distribution and impaired blood oxygenation [21]. The most obvious is the indirect or persistent closure of the airways due to the decrease in resting inspiratory lung volume, and the rapid absorption of oxygen from the closed airways tends to trigger pulmonary atelectasis or more severe respiratory failure [22]. According to the graded criteria for respiratory failure, patients have a mean arterial partial pressure of oxygen less than 60 mmHg and a mean arterial partial pressure of carbon dioxide greater than 50 mmHg before treatment, which indicates that most patients have type II respiratory failure. This was accompanied by hypercapnia, i.e., a blood PH significantly below the normal level. The mechanism of the effect of the intravenous lipid emulsion approach on blood oxygen changes does not have a definitive explanation due to the different mechanisms of drug action. Although the mechanism of detoxification of intravenous lipid emulsions remains uncertain, in conjunction with the prevailing detoxification mechanism, it may be that lipid emulsions bind some of the lipid-soluble anesthetic drugs in the respiratory system, accelerating the redistribution and metabolic process of the drugs and thus accelerating the patient's respiratory recovery. Regardless of the specific mechanism, intravenous lipid emulsion is highly effective in reversing respiratory failure due to acute lipid-soluble narcotic drug intoxication in children. The three histograms in Figure 2 show, from left to right, the blood gas indices of the patient before treatment, the blood gas indices of the patient after treatment and the percentage change in blood gas indices before and after treatment, respectively.

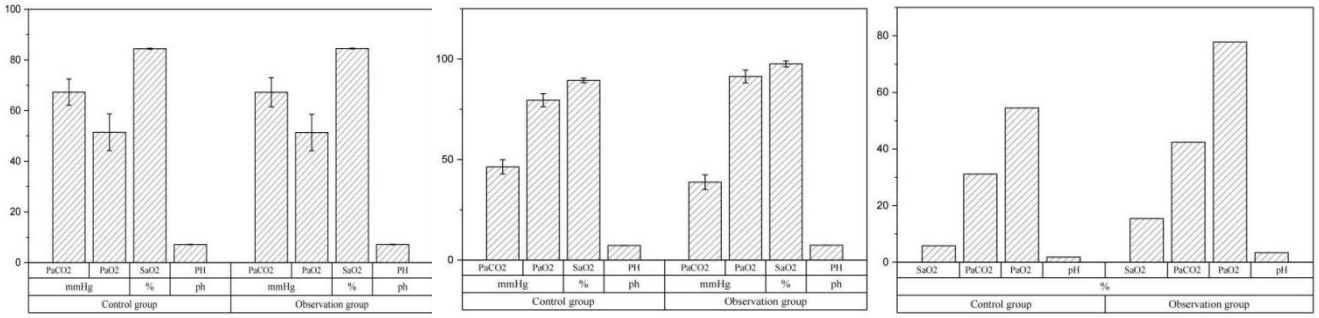

Figure .2. Patient's blood gas index before and after treatment

From the clinical data, the percentage change in blood indexes before and after treatment was greater in the observation group. the therapy of intravenous lipid emulsions in conjunction with the same period resulted in a more pronounced recovery of the patient's blood indices. Although the above data imply that lipid emulsions are effective in reversing acute lipid-soluble anesthetic drug intoxication in pediatric patients, the exact mechanism still needs experimental validation. At the same time, since the relative lack of clinical data on pediatric patients, the conditions of clinical trials, and ethical restrictions, the lack of relevant studies in the pediatric field is still a severe shortage. The effect of intravenous lipid emulsion on other organs or tissues in pediatric patients is still worth exploring. This paper focuses on the study of the therapeutic effects of patients involved in intravenous lipid emulsions, and the respiratory effects in the data can be studied in more depth based on specific drug principles and more accurate clinical test data. This is important for clarifying the relevant mechanisms and the clinical reference.

ISSN:2790-167X DOI: 10.56028/aehssr.4.1.151.2023

6. Conclusion

This paper focuses on the investigation of the effect of intravenous lipid emulsions on reversing acute lipid-soluble anesthetic drug intoxication in pediatric patients. Since the specificity of the pediatric patient population, there is a relative paucity of relevant studies. This paper has significant meaning in enriching clinical references. According to the retrospective analysis of clinical data combined with relevant mechanisms, intravenous lipid emulsion has a positive effect on reversing pediatric fat-soluble anesthetic drug intoxication, which can enhance cardiac function index, reverse respiratory failure and improve blood index. However, due to the lack of clinical data and the limitation of experimental conditions, the mechanism of drug action on specific organs is still vague. This paper lays the foundation for future organ-specific pharmacokinetic analysis and provides a reference for more in-depth clinical studies.

Acknowledgments

I would like to thank Beijing Jiaotong University for supporting this project and West China Hospital of Sichuan University for supporting the data. Project ‘reversal of acute drug toxicity in pediatric patients by intravenous lipid emulsion’ supported by National Training Program of Innovation and Entrepreneurship for Undergraduates. Project ID: 202310004008.

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