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Research Article

Intraoperative Cardiac Arrest: Management of Systemic Toxicity by Local Anesthetics: A Literature Review

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Received: June 28, 2019; **Published:** August 06, 2019

Abstract

Introduction: Cardiac arrest in operating room is a rare, but catastrophic event, with high mortality. The causes are different than other in-hospital settings and they have a specific treatment. One of these is represented by cardiac arrest due to systemic toxicity from local anesthesia. A cardiac toxicity can occur related to dose or site of injection and the consequences can be dramatic, with alterations of neurological status, with convulsions, until Cardiocirculatory collapse and cardiac arrest. The cardiopulmonary resuscitation is characterized by long efforts, with a dilation time of resuscitation and applying alternative techniques as extracorporeal membrane oxygenation (ECMO). The specific treatment to systemic toxicity from local anesthetics is the infusion of lipid emulsion with boles of intralipid.

Material and Methods: A literature review about the phenomenon was conducted in PubMed and in the principal Resuscitation and Anesthesiologist Guidelines. A free-word research had "INTRALIPID" AND "CARDIC ARREST" as keywords, while a second research had as search strategy ("soybean oil, phospholipid emulsion" [Supplementary Concept]) AND "Heart Arrest"[Mesh] From literature review, the pediatric population was excluded due to small cases.

Results: A totally of 36 articles were identified in the first strategy, while 10 in the second. Different international anesthesiologist guidelines were identified.

The results demonstrated that intralipid can be used to more pharmacological reactions not only local anesthetics, increasing cardiac output and blood pressure.

Discussion: In operating room, many causes occur respect other setting. For examples from the 4H-4T of reversible causes of European Council of Resuscitation, the intraoperative cardiac arrest (ICA) causes increase to 8H-8T. In relation to the setting of operating room, the multidisciplinary approaches, the technology, a specific course of crisis resource management in operating room has been created during Master I level in "Infermiere di Sala Operatoria" - University of Insubria.

Keywords: *LAST: Local Anesthetic Systemic Toxicity; CPR: Cardiopulmonary Resuscitation; ICA: Intraoperative Cardiac Arrest; OR: Operating Room*

Introduction

The incidence of cardiac arrest and death attributable to anesthesia is very low, however, anesthesiologists consider it as a perioperative catastrophes [1].

Cardiac Arrest is a rare event (Rukewe., *et al.* 2014) with high mortality and different causes (Goswami., *et al.* 2012; Berry 2012); its rate is lower than other in-hospital or out-hospital setting and the pathophysiology is different than those settings (Sebbag., *et al.* 2013).

In fact, in developed countries, there is a reduced percentage of cardiac arrest during anesthesia: an estimated between 0.2 and 1.1 cases per 10,000 anesthetized adults [2]. In a prospective and retrospective study, the incidence of cardiac arrest anesthesia-related was of 19.7 per 10.000 anesthetic procedures [3]. Moitra., *et al.* (2017, 2002) analyzed the intraoperative cardiac arrest and they identified 16 causes (Figure 1) of cardiac arrest during Perioperative period, with a focus on neuraxial and local anesthesia.

Hypoxia	Toxins (anaphylaxis/anesthesia)
Hypovolemia	Tension pneumothorax
Hyper-/Hypokalemia	Thrombosis/Embolus, pulmonary
Hydrogen ion (acidemia)	Thrombosis coronary
Hypothermia	Tamponade
Hypoglycemia	Trauma (hemorrhagic shock, CV injury)
Malignant Hyperthermia	qT prolongation
Hypervagal	Pulmonary hyperTension

CV = cardiovascular

Figure 1: *Moitra., et al. 2012.*

The incidence of cardiac arrest during neuroaxial anesthesia is about 1.3 - 18 per 10.000 patients, with a major incidence during spinal anesthesia (2.9 vs 0.9), but the pathophysiology of cardiac arrest neuroaxial anesthesia-related is unclear. From the studies conducted by Li., *et al.* in the United States between the years 1999 - 2005, it was possible to observe that 46.6% of the 2211 deaths due to anesthesia correlated with an overdose of anesthetic drugs, while 42.5% was due to adverse effects from anesthetics used for therapeutic purposes (Li., *et al.* 2009).

The principal etiology of cardiac arrest during spinal anesthesia is represented by brady-asystole during the procedure, but another risk is present during neuraxial and local anesthesia: local anesthetic toxicity.

Materials and Methods

A Literature review was conducted on PubMed, with association of "lipid emulsion" AND "intraoperative cardiac arrest". In addition, filters as "full text" and "previous of 10 years" were applied to the research. Paediatric population was excluded.

The principal societies of resuscitation, American Heart Association and European Council of Resuscitation, and the Guidelines by American Society of Anesthesiology and European Society of Anesthesiology were consulted.

The pediatric population was excluded from the review due to the hypersensitivity inherent in this group in relation to the complications of regional anesthesia with cardiotoxic local anesthetics.

Results

A total of 36 articles were founded in PubMed by "free words" research, while 10 were by "MeSH" research. All of these articles were included in the literature review.

About Guidelines, were founded all about the theme without data restrictions; in addition, International Guidelines for Resuscitation were included about the lipid emulsion use.

An interest site was consulted by http://lipidrescue.org/.

Discussions

Story

In the early 1960s, unwanted cardiac effects related to etidocaine and bupivacaine were already known, however they were attributed to expected physiological effects or to involuntary subarachnoid injection [4].

In 1979 there was a turning point: a young adult showed sudden seizures and ventricular fibrillation resistant to standard therapy, later the caudal administration of 25ml of 1% etidocaine. From here the first doubts began to arise about the potential long-term toxicity of the myocardium, in the same year there were five other cases similar to the one just described [5,6].

In 1997 Weinberg., *et al.* [7] during the intervention of a patient with metabolic disorder, they observed unexpected cardiotoxicity due to bupivacaine.

Driven by curiosity, they did experiments in which they used lipid infusions in animal models, thinking to reduce the toxicity threshold; in fact they discovered the protective effect of lipids, proving that clinically relevant concentrations of bupivacaine interrupt mitochondrial function [7-9].

Already in 1998, thanks to the laboratory of Guy Weinberg, we have the first reports about the use, and its success, of the intravenous lipid emulsion with the sole purpose of improving local anesthetic toxicity [9].

Subsequently, in 2006, ILE was used for the first time as a rescue therapy for refractory cardiotoxicity associated with local anesthetic [10].

Symptom

The risk of local anaesthetic toxicity is difficult to predict. Symptoms such as metallic taste in the mouth, ringing in the ears, dysphagia, confusion and premature ventricular contractions should not be underestimated as they are anticipatory expressions of the toxicity of the local anesthetic at the level of the nervous system [11].

From the literature, the risk of systemic toxicity is difficult to predict, but it's related to site of injection and dose. Related to dose, the local anesthetics depress the heart, with symptomatic bradycardia evolving to asystole, with hypotension and lower contractility. The results by decreasing of heart rate and stroke volume, by depressed myocardial contractility, reduce the cardiac output, with a systemic hypoperfusion. [12].

Related to site of injection, an intravascular injection shows immediately the systemic toxicity whereas in well-vascularized tissue, as pleuras, may occur delayed.

From the anesthetics family, bupivacaine represents the agent most associated with cardiac arrest.

The principal manifestations described by literature were neurological symptoms (dysphasia, confusion, unconscious state), dyspnea, hypotension, wide QRS with ventricular extrasystoles, bradycardia to asystole [13].

Intralipid increases aortic flow, arterial blood pressure, heart rate, contributing to lipid rescue effect in bupivacaine and ropivacaine [14].

Other effects of lipid emulsion are increasing of calcium infusion in verapamil intoxication [15], cardioprotection against ischemia - reperfusion injury [16,17] and against tricyclic antidepressant as amitriptyline [18].

From a literature review, Cave G and Harvey M [19] identified some articles about experimental animal tests using different agents, while on human population there are more case report than human studies.

There are many studies supporting a benefit if ILE is used: experimenting on a rat model in bupivacaine-induced asystole, demonstrated greater survival using epinephrine plus lipid emulsion administered after 10 minutes of BLS; the major result in metabolic recovery was with lipid administration alone [20].

Also, Rosenblatt is on affirms the same positive result, namely a circulatory return, both with the sole injection of lipids, and in combination with epinephrine [10].

Although there are few explanations regarding the pathophysiology of cardiac arrest related to neuroaxial anesthesia, it remains an area to investigate as it is a sudden and significant cause of morbidity and mortality in the perioperative period [21].

What interaction is present between lipid emulsion and local anesthetics? Ruan., *et al.* answered this question: analyzing *in vitro* the main local anesthetics (bupivacaine, ropivacaine and mepivacaine) were able to observe how these are sequestrated to lipid-spiked plasma consistent with their intrinsic octanol: water partition constants Moreover, a characteristic of local anesthetics is to have affinity for both lipid environments and aquatic environments: this allows it to go beyond the plasma membrane and the intracellular membranes, thus producing a series of toxic effects in various types of tissue (brain, heart and skeletal muscle) [22].

What remains to be done today?

Multiple clinical cases have occurred in recent years, increasingly reinforcing the use and treatment with lipid emulsion, confirming its clinical efficacy, so that anesthetic societies around the world, supported by toxicological forums, consent ILE as an adjuvant for resuscitation in case of lipophilic drug intoxication Further, the new guidelines give a shift to lipid bypass on cardiopulmonary bypass: it is a clear recommendation to administer lipids in cardiac arrest due to local anesthetic intoxication [12].

Protocol

The Guidelines for Resuscitation by European Council of Resuscitation 2015 [23] identified a dose of 15 ml/kg/h of intralipid emulsion 20% during advanced life support, with boles each 5 minutes until a maximum of 12 ml/kg of intralipid.

So, currently infusion of lipid emulsion is considered the primary treatment for local anesthetic toxicity: example, if local anesthetic toxicity is assumed, treatment with intravenous infusion a 20% lipid emulsion of a loading dose of 1.5 ml/kg is started, followed by a constant infusion rate or by repeated boluses [24,25].

Association of Anaesthetists of Great Britain and Ireland (AABGI) [26] did safety guidelines in 2010 (Figure 2) to management of severe local anaesthetic toxicity. By steps:

1. Recognition of symptoms.
2. Immediate management with stopping of LA injection, call for help, give adequate ventilation, establish an intravenous access, blood analysis.
3. Treatment: from cardiopulmonary resuscitation, to intravenous lipid emulsion.
4. Follow-up in intensive care unit with focus to exclude pancreatitis.

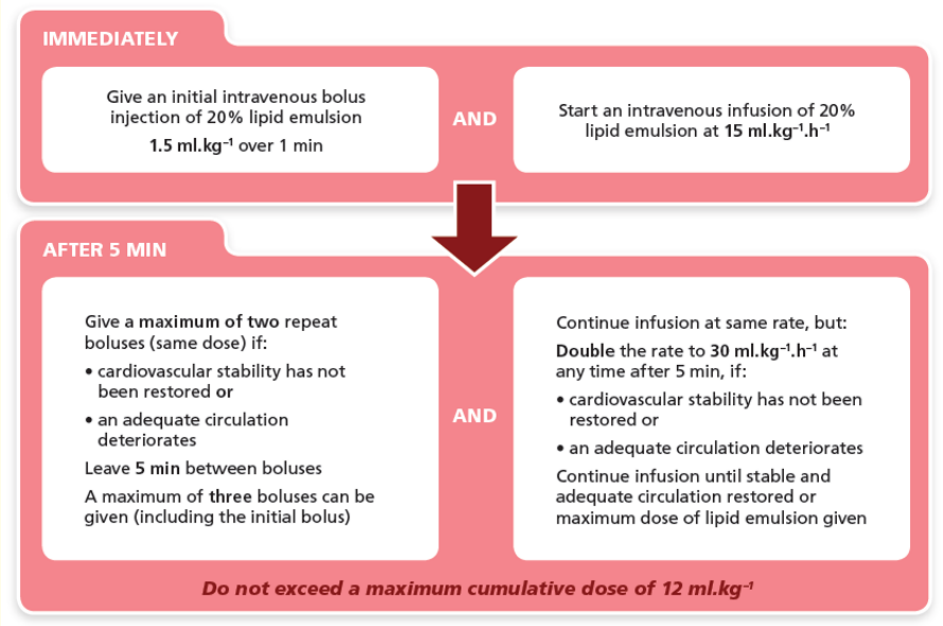

Figure 2: *AABGI Guidelines.*

Conclusion

Unfortunately, much of ILE still remains unknown. Despite the research commitments of the last decade, it has recently begun to understand the exact mechanism of action of ILE It should be remembered that, fortunately, we are dealing with a rare problem, but this involves having not much information about it given the protective effects, a new type of study is expected to work on patients with ischemic heart disease [27-34].

Related to operating room setting (i.e. sterile dressing, abdomen opened), patient variables, high level of technology, multidisciplinary figures (i.e. surgeons, anesthesiologists, nurses), anesthesiologist techniques contribute to specific management of ICA. Those variables are different from each surgical operation, causes can be different and the management must be oriented to rhythm, etiology, surgical operation (i.e. thorax or abdomen closed or open) with specific treatment (i.e. intralipid) or alternative techniques as open chest cardiopulmonary resuscitation, with direct internal cardiac massage, or ECMO.

During the Master I level of "Infermeire di Sala Operatoria" (Nurse of Operating Room), III edition, in University of Insubria, a specific course about Cardiac arrest in operating theatre has been created, with theory founded on principal Guidelines of Society of Resuscitation (AHA, ERC), of global society of Anesthesiologist, Surgeons and Trauma Care (i.e. Advanced Trauma Life Support), and high fidelity simulation in which non-technical skills and technical skills can be improved.

Conflict of Interest

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Acknowledgement

In memory of Roberto Perugini, MD anesthetist and intensivist "Erba - Rinaldi" Menaggio Hospital, an example as professionist, father and man.

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Volume 3 Issue 9 September 2019