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Lipid Emulsion Therapy as Treatment for Local Anesthetic Systemic Toxicity

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LIPID EMULSION THERAPY AS TREATMENT FOR LOCAL ANESTHETIC SYSTEMIC TOXICITY

by

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Abstract

Local anesthetic systemic toxicity, due to misapplication of local anesthetic in an otherwise routine procedure, can result in deleterious effects. Although improved regional anesthesia techniques, effective test-dosing, and availability of less toxic local anesthetics have resulted in a decline in local anesthetic toxicity rates, adverse events do occur. A comprehensive review of literature was conducted and current research findings and documented case studies were systematically reviewed. The "lipid sink" phenomenon is the most widely accepted theoretical framework surrounding intravenous lipid emulsion treatment for local anesthetic induced cardiovascular collapse (Rothschild, Bern, Oswald, & Weinberg, 2010). Current evidence suggests that immediate infusion of lipid emulsion should be considered when clinical signs of local anesthetic toxicity manifest. By relaying information surrounding practice guidelines on local anesthetic systemic toxicity, anesthesia practitioners will have an improved understanding of local anesthetic systemic toxicity clinical diagnosis and lipid emulsion infusion as a treatment modality.

Keywords: intravenous lipid emulsion, local anesthetics, local anesthetic systemic toxicity, local anesthetic toxicity, lipid sink, lipid infusion

Lipid Emulsion Infusion as Treatment for Local Anesthetic Systemic Toxicity

Emerging technologies in regional anesthesia and the increasing popularity of perioperative regional anesthesia technique renders importance of anesthesia provider vigilance in both detection and treatment of potentially catastrophic complications of regional anesthesia. Although serious side effects associated with local anesthetic administration are rare, it is prudent that anesthesia providers remain up-to-date with the latest research and guidelines in resuscitation of local anesthetic systemic toxicity (LAST) with intravenous lipid emulsion.

Purpose

Because local anesthetic toxicity remains a clinical concern when performing regional anesthesia, it is imperative that Certified Registered Nurse Anesthetists (CRNAs) are vigilant in recognizing signs and symptoms of LAST and are able to demonstrate both effective and efficient administration of lipid emulsion therapy in resuscitation of significant local anesthetic toxicity.

The purpose of this independent project is to improve clinical practice by providing current and future anesthesia practitioners medical literature involving the seriousness of local anesthetic toxicity and the institution of intravenous lipid emulsion therapy as a beneficial treatment modality. The information gathered was presented to clinicians and ancillary operating room staff at local anesthetic toxicity workshops conducted at Sanford Health, Fargo, North Dakota, and will be delivered at the North Dakota Association of Nurse Anesthetists bi-annual meeting in Bismarck, North Dakota.

The ultimate goal for the delivery of current, reputable evidence combined from the literature is to guide anesthesia professionals in the execution of rapid problem recognition and

efficiency in the resuscitation process, including guidelines for an appropriate lipid emulsion therapy regimen.

Significance

Although emerging technologies in regional anesthesia may potentially improve the efficacy and safety of regional anesthesia, the reduction in the number of clinically important LAST events have not been correlated. Unfortunately, local anesthetic toxicity continues to be a major contributing source of morbidity and mortality in regional anesthesia practice. According to Varela and Burns (2010), the incidence of local anesthetic toxicity ranges from 7.5 to 20 per 10,000 peripheral nerve blocks and about 4 per 10,000 epidural blocks, however, the incidence may be underreported (Varela & Burns, 2010, p. 361). An American Society of Anesthesiologists closed claim analysis report recently attributed one-third of claims for death or brain damage associated with regional anesthesia to local anesthetic systemic toxicity (Lee, Posner, Chaney, Caplain, & Domino, 2008). As evidenced by the statistics relayed above, LAST is a rare and potentially fatal complication of regional anesthesia. A recent survey conducted by Corcoran et al. (2006) concluded "wide variability in preparedness for local anesthetic toxicity and lack of consensus for treatment" (p. 1326) among anesthesiology departments in the United States. In order to appropriately manage a local anesthetic induced cardiac toxicity crisis, clinicians must be relevant in practice in effectively treating one of the most devastating complications of regional anesthesia.

Theoretical Framework

Initially devised in 1998 by Guy Weinberg, MD, the "lipid sink" phenomenon is the most widely accepted mechanism of action for lipid infusion as a treatment for local anesthetic toxicity (Rothschild et al., 2010). Weinberg, VadeBoncouer, Ramaraju, Garcia-Amaro and Cwik

(1998), provided direct evidence that lipids had the ability to counteract the toxic effects of bupivacaine in the bloodstream in a rat model (as cited in Manavi, 2010). The observations made by this group of investigators suggested the potential for treatment of bupivacaine induced cardiotoxicity (Weinberg et al., 1998).

Infusion of lipid emulsion therapy can be instrumental in the resuscitation of local anesthetic induced systemic toxicity theoretically by acting as a "lipid sink" that draws down the content of the lipid-soluble local anesthetics from within the cardiac tissue, ultimately improving cardiac conduction, contractility, and coronary perfusion (Neal et al., 2010). More simply described, the "lipid sink" theory postulates that infusion of a lipid emulsion creates a separate lipid compartment within plasma into which local anesthetics are drawn (Manavi, 2010).

The clinical efficacy of lipid emulsion therapy can be attributed to the binding property of the emulsion. According to Rothschild et al. (2010), the "lipid sink" theory suggests that a large serum lipid phase extracts local anesthetics from the plasma. Lipophilic drugs, such as local anesthetics, are drawn into the "lipid sink" and a concentration gradient develops between tissue and blood which cause the local anesthetic to move away from the heart or brain to the "lipid sink" (Rothschild et al., 2010, p. 8).

Undoubtedly, the "lipid sink" theory has taken precedence in providing an explanation for the mechanism of action of intravenous (IV) lipid emulsion therapy in local anesthetic toxicity. However, historically another theory is that lipid infusions may have metabolic effects by inhibiting mitochondrial metabolism of lipids, reducing tissue acidosis, and decreasing carbon dioxide production during times of myocardial ischemia. It has also been suggested that local anesthetics impair fatty acid production of mitochondria. Infusion of lipid emulsions may work

to saturate the impaired delivery of fatty acids to restore further production of energy (Felice & Schumann, 2008).

Definitions

Concepts surrounding local anesthetic induced cardiac toxicity and lipid infusion therapy can be difficult to comprehend. Although case reports of LAST depict variability in presentation, the American Society of Regional Anesthesia (ASRA) and Pain Medicine Practice advisory states the classic description of the clinical diagnosis of systemic toxicity includes "subjective symptoms of central nervous system excitement such as auditory changes, circumoral numbness, metallic taste and agitation that progresses to seizures and/or central nervous system depression" (Neal et al., 2010, p. 155). It is important to note that in the classic presentation of local anesthetic systemic toxicity, central nervous system toxicity precedes cardiac toxicity. Patients presenting with LAST seem to follow a common clinical course of symptoms including tachycardia, followed by a widening QRS pattern on the electrocardiogram, seizure activity and ultimately asystole (Manavi, 2010). If clinicians familiarize themselves with this consistent pattern, local anesthetic toxicity may be recognized and intervened in a stage before it becomes disastrous.

Because the commercial intravenous lipid emulsion products are available in various concentrations, it is important to define the specifications for lipid emulsions suitable in the treatment of local anesthetic toxicity. Human case reports predominantly documented commercial preparation of a 20% lipid emulsion formulation. The 20% formulation of lipid emulsion contains 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and the remainder is water (Felice & Schumann, 2008, p. 186). According to the ASRA guidelines published in 2010, there is no evidence that one trade name formulation of lipid emulsion is

superior to another (Neal et al., 2010). The recommendations importantly state propofol is not to be considered as a substitute for lipid emulsion therapy because of its low lipid content, the large volumes required for resuscitation, and the direct cardiac depressant effects associated with administration (Neal et al., 2010, p. 158).

Process

A comprehensive review of literature was conducted using major literature search engines such as Cumulative Index to Nursing and Allied Health Literature (CINAHL) and National Library of Medicine's PubMed, Ovid, and Google Scholar databases. American Association of Nurse Anesthetists journal publications and relevant citations from retrieved articles were studied to provide supplemental documentation. In addition to peer reviewed journal articles and a systematic literature review, an online lipid rescue organization was utilized to investigate and convey clinically relevant data. After the first case of successful resuscitation using lipid emulsion infusion was published in 2006, Dr. Guy Weinberg created a website, www.lipidrescue.org, dedicated to informing healthcare providers on the methodology surrounding lipid emulsion infusion. This online forum provides a means for the anesthesia community to review and post case reports, medical literature, research data, and guidelines all aimed toward the prevention, recognition, and treatment of local anesthetic systemic toxicity.

Key search words and phrases included: intravenous lipid emulsion, local anesthetics, local anesthetic systemic toxicity, local anesthetic toxicity, lipid sink, lipid infusion. The systematic literature review was geared toward gaining relevant medical literature and case reports surrounding the mechanisms, diagnosis, and treatment of life-threatening local anesthetic overdose.

The information gathered was presented to clinicians and ancillary operating room staff at three local anesthetic toxicity workshop sessions at Sanford Health, Fargo, North Dakota, and will be delivered to attendees of the North Dakota Association of Nurse Anesthetists bi-annual meeting in Bismarck, North Dakota.

Review of Literature

With data from various animal studies and several case reports to testify the effectiveness of lipids, lipid emulsion therapy is gaining international clinical acceptance as a treatment for LAST. However, an inconsistency among practices in the management of catastrophic local anesthetic toxicity remains. Numerous documented animal studies have been conducted to aid in the formulation of lipid emulsion therapy guidelines as an appropriate intervention for treatment in the clinical realm. Published case reports, editorials, research, and reviews of lipid emulsion therapy in the medical literature further aid in both recognizing and treating life threatening local anesthetic toxicity.

The foundation for sparking interest among anesthesia professionals for lipid emulsion infusion for treatment of LAST is based on published studies involving animal models. In 1998, Weinberg and colleagues reported the first laboratory observation suggestive of supporting lipid infusion in both prevention and treatment of bupivacaine overdose. The case involved a pretreatment protocol and resuscitation protocol experiment in rat models. In the pretreatment group, the rats received pretreatments of saline or lipid emulsion and then received a 0.75% bupivacaine hydrochloride dose to induce asystole for a period of 10 seconds. In the resuscitation protocol experiment, rat models were administered a range of bupivacaine bolus doses followed by either a saline or lipid emulsion dose, and then a continuous infusion. The results of this study showed bupivacaine doses to produce asystole in rats are increased when pretreated with lipids.

As in pretreatment, lipid emulsion improved mortality from large boluses of bupivacaine at doses producing asystole compared to saline treated control rats (Weinberg et al., 1998). The resuscitation data relayed in this publication support limited explanation especially when attempting to link the findings with relevance to clinical practice. The phenomenon surrounding the mechanism of action in lipid emulsion treatment, as well as optimal dosing or concentration of the lipid infusion was not determined by this research. This study only evaluated immediate, short term cardiovascular outcomes and did not consider long term survival rates, neurological function, or cardiac performance (Weinberg et al., 1998).

Weinberg and investigators continued to search explanations for the mechanisms in which lipid emulsion treats severe bupivacaine cardiac toxicity. In 2006, a study was conducted in isolated rat hearts to better validate the hypothesis that lipid resuscitation reduces cardiac bupivacaine content in bupivacaine induced asystole (Weinberg et al., 2006). The experiment compared controls without lipid infusion and hearts getting lipid immediately after an infusion of bupivacaine. Both cardiac tissue and bupivacaine efflux from hearts with and without lipid infusion were compared. First heart beat and hemodynamic recovery was evaluated with subsequent findings of a more rapid return of spontaneous circulation and full recovery of cardiac function in hearts receiving lipid emulsion doses. Although this animal study does not rule out alternate mechanisms to which lipid emulsion infusion works, the findings are consistent with today's most accepted hypothesis of "lipid sink."

Another animal study evaluated the effectiveness of lipid emulsion infusion using saline as a control group and experimental lipid infusion following local anesthetic induced toxicity in dogs by injection of large doses of bupivacaine. Lethal doses of bupivacaine were administered to dogs and resuscitation was initiated by internal cardiac massage followed by either a saline or

lipid infusion. Both the control and experimental groups developed hemodynamic changes; however, dogs treated with saline led to progressing asystole and eventually death. Rapid hemodynamic recovery was observed among all the lipid treated dogs. Further trials included in the study introduced a 10 minute lag time between the symptomatic presentation of cardiac toxicity and subsequent lipid infusion therapy. The delay in infusion initiation is to better simulate a typical clinical scenario where the antidote may not be readily available or where practitioners may delay lipid treatment due to failure in rapidly recognizing LAST symptoms (Bern, Akpa, Kuo, & Weinberg, 2011). The study using non-rodent models helped to determine the effectiveness of lipid emulsion infusion in larger species as well as providing basis to the value lipids exhibit in aiding to the return of normal hemodynamics in acute bupivacaine toxicity (Weinberg, Ripper, Feinstein, & Hoffman, 2003).

An experimental case report was published in 2010 in anticipation of gaining a more concrete understanding of the resuscitation effects surrounding administration of vasoactive drugs in conjunction with lipid emulsion therapy in treatment of cardiac arrest and cardiovascular collapse secondary to local anesthetic toxicity. The investigation involved rabbit models undergoing bupivacaine induced cardiac arrest. Twenty sedated rabbits received a 10mg/kg IV bupivacaine bolus to produce asystole. Ventilation was controlled mechanically and a nonintervention period of 30 seconds after asystole was instituted to mimic clinical practice and response time. Chest compressions were initiated after the lag period commenced. At 1 minute, all twenty subjects received 20% lipid emulsion and either epinephrine or saline was administered over the subsequent 10 seconds. Four experimental groups were designed, comprising of the following treatments: a control group receiving saline; low dose epinephrine group given 2.5 μg/kg; intermediate-dose epinephrine animals administered 10 μg/kg; and a 100

μg/kg high dose epinephrine group. A repeat injection of lipids was administered to all groups at the 4 minute interval. Chest compressions, mechanical ventilation, and hemodynamic monitoring was continued for 15 minutes or until spontaneous circulation returned. The animals in the control, lipid only group were given high dose epinephrine treatment after the 15 minute resuscitation phase and were monitored for 20 minutes. Results showed epinephrine's capability of attaining return of spontaneous circulation at immediate and high doses. The correlation of return of spontaneous circulation and epinephrine administration was further evident in circulatory recovery after late high dose epinephrine administration in the models initially treated with lipids alone. However, animals treated with epinephrine subsequently demonstrated hemodynamic measurements threatening survival. Whereas, lipid emulsion alone resulted in a less rapid return of circulatory function but sustained viability. The association between the epinephrine response and compromised outcomes in the experimental animals receiving vasoactive medication provides laboratory data supporting retention of epinephrine use. With the conclusion of this research, the authors suggest conducting further studies to better define the role of epinephrine in lipid emulsion therapy (Harvey, Cave, Prince, & Lahner, 2010).

The *AANA Journal* recently published a study that evaluated the effectiveness of combined lipid emulsion and advanced cardiac life support (ACLS) following LAST and hypoxia induced cardiovascular collapse in unanesthetized swine. Twenty four swine were observed following administration of lethal doses of bupivacaine in conjunction with mechanical airway obstruction with a period of hypoxia. Following complete cardiovascular collapse, ACLS was initiated and the animals were randomized to receive either 20% lipid emulsion or saline. The lipid emulsion or saline was administered as a bolus injection of 4 mL/kg over 2 minutes, followed by a continuous infusion with concurrent ACLS resuscitation. Resuscitation efforts

continued until return of spontaneous circulation or for 25 minutes. Hemodynamic variables suggestive of viability were compared, as well as the period of time required to achieve return of spontaneous circulation. The results of this study failed to demonstrate the effectiveness of lipid emulsion therapy in a combined bupivacaine and hypoxia induced cardiovascular collapse in an awake, unanesthetized swine model (Bushey, Auld, Volk, & Vacchiano, 2011).

This unique study combined 2 distinctive criteria from previous animal data: bupivacaine toxicity in an unanesthetized animal subject further exacerbated with a period of hypoxia. This design was significant in gaining perspective of a clinical scenario involving an awake patient receiving a major plexus block who experiences respiratory and cardiac compromise secondary to inadvertent intravascular injection of local anesthetic (Bushey, Auld, Volk, & Vacchiano, 2011). Research data relays conflicting animal studies regarding the efficacy of lipid emulsion therapy. Laboratory research continues to be conducted to better define the treatment guidelines for lipid emulsion therapy.

Approximately eight years after the first animal model of lipid rescue was documented, the first case report detailing a successful rescue using lipid emulsion in a patient with LAST was published. This clinical translation was very suggestive of the reported observations in animal experiments, thereby gaining significant ground in the acceptance of lipids as an antidote for local anesthetic toxicity. Rosenblatt and colleagues published the first case report detailing the successful resuscitation of local anesthetic toxicity using intravenous lipid emulsion therapy (Rosenblatt et al., 2006). This human case report involved a 58 year-old male who developed neurological and cardiovascular symptoms, ultimately leading to prolonged cardiac arrest immediately following the placement of an interscalene block with bupivacaine and mepivacaine. After appropriately identifying the brachial plexus using the nerve stimulator

technique, injection of 40 mL local anesthetic solution (20 mL, 0.5% bupivacaine and 20 mL, 1.5% mepivacaine) in 5 mL increments took place without aspiration of blood, report of pain, or parasthesia. The patient was awake and alert throughout the procedure; however, approximately 30 seconds after removing the stimulator needle the patient became incoherent and developed a tonic-clonic seizure. Immediate resuscitation using ACLS failed. Additionally, propofol was administered throughout initial resuscitation efforts without clinical response. Approximately 20 minutes after the onset of cardiovascular collapse, a 20% lipid emulsion bolus was administered and preparation for cardiopulmonary bypass was underway. Within 15 seconds, the cardiac rhythm was restored to normal sinus rhythm and hemodynamic stability was achieved. A lipid infusion was started and continued for 2 hours in duration. The patient recovered without neurological deficits or adverse effects from lipid infusion therapy. The favorable outcome in this event built the cornerstone for lipid emulsion as a potential therapeutic modality.

Dr. Rosenblatt and colleagues reported case demonstrated the clinical efficacy of lipid rescue, while leaving some questions unanswered. Dr. Weinberg wrote an editorial review commenting on the application of lipid emulsion therapy in the above case scenario. Although it was recognized that research still be conducted to determine the optimal dose, rate, duration of infusion, and upper safety dosing limit, he emphasized the importance of Rosenblatt and her team in providing evidence in support of lipid emulsion use. He further commentated on the importance of having 20% lipid emulsion readily available for use in all operating rooms, regional anesthesia block rooms, obstetric units, and other surgical suites where local anesthetics are administered (Weinberg, 2006).

This initial case report sparked publication of cases detailing rapid recovery of patients presenting with LAST. A report of an elderly female who inadvertently received 40 mL 1%

ropivacaine for a brachial plexus block soon appeared after the first published case. Fifteen minutes after injection, the patient complained of dizziness and drowsiness which progressed into a generalized tonic-clonic seizure, followed by cardiac arrest. After 10 minutes of unsuccessful cardiopulmonary resuscitation efforts, a 20 % lipid emulsion infusion was injected as a bolus followed by a continuous drip. Electrical activity was restored after a total dose of 200 mL. The patient was transferred to the intensive care unit and extubated shortly after. The patient was discharged home after 4 days without negative sequelae. Upon further review of this scenario, it was reported that the incident occurred due to a misunderstanding between the anesthesiologist and the nurse anesthetist as 1 % ropivacaine was injected instead of 40 mL of 0.5 % ropivacaine. The cardiovascular collapse described was attributed to ropivacaine absorption following accidental overdose. The case not only reiterated the importance of effective communication, it also provided evidence to consider lipid infusion in cases of local anesthetic toxicity when conventional resuscitation has been unsuccessful (Litz, Popp, Stehr, & Kock, 2006).

An interesting case report, published in 2007, described a 75 year old female who received levobupivacaine for surgical repair of a fractured femur neck. Foxall, McCahon, Lamb, Hardman, & Bedford (2007), described a case in which a lumbar plexus block was placed after several unsuccessful attempts at placing a subarachnoid block. The lumbar plexus block was performed using 20 mL total of levobupivacaine 0.5% injected slowly into the psoas muscle after several negative aspirations. Seconds following administration of the local anesthetic, the patient was unresponsive, experienced a tonic-clonic seizures, and widening QRS complex with a palpable carotid pulse. The patient's airway was managed and secured with endotracheal tube intubation. Within 4 minutes of the levobupivacaine injection, she received 100 mL of 20% lipid

emulsion bolus over 5 minutes. During the lipid infusion bolus, her electrocardiogram morphology normalized with return of a stable arterial blood pressure and heart rate. 10 minutes following administration of the lipid emulsion bolus, the patient proceeded with the surgical procedure. The patient had an uneventful postoperative recovery phase and regained consciousness after the two hour surgical procedure.

Foxall et al. (2007) reported the first case report of the successful use of lipid emulsion in situation where a patient received the bolus to reverse local anesthetic toxicity that had not progressed to cardiac arrest. Prior human case reports demonstrated the importance in initiating a lipid emulsion infusion only after unsuccessful resuscitation measures. Although it is impossible to predict whether the patient's outcome would be unchanged if intravenous lipid emulsion therapy hadn't been initiated until cardiovascular collapse occurred, this case report provides beneficial evidence to clinicians to use lipids in a near cardiac-arrest situation.

In 2008, *Anesthesia & Analgesia* published the first case report of lipid rescue therapy in a child. Ludot, Tharin, Belouadah, Mazoit, & Malinovsky (2008) relayed events of a 13 year old child scheduled for knee surgery with placement of a posterior lumbar plexus block under general anesthesia. After an uncomplicated anesthetic induction, the posterior lumbar plexus block was achieved using a 20 mL total volume of mixture containing equal amounts of 1% lidocaine with added epinephrine 1:200,000 and 0.75% ropivacaine. Vital signs remained unchanged throughout administration and the solution was administered in divided doses of 3 mL after negative aspiration. A ventricular arrhythmia occurred 15 minutes after the end injection of the local anesthetic mixture. Her blood pressure remained stable, end-tidal carbon dioxide unchanged, and her arterial oxygen saturation decreased to 92%. The anesthesia practitioner quickly suspected local anesthetic toxicity and 20% lipid emulsion was rapidly

injected over 3 minutes. Within 2 minutes her electrocardiogram returned to normal complex QRS with noted ST depression, which persisted for approximately 30 minutes. The clinicians elected not to initiate an infusion due to her hemodynamic stability.

Not only did this case provide clinical evidence of the effectiveness of lipid emulsion infusion for LAST in the pediatric patient population, it also gained precedence for the theory suggesting one formulation of lipid emulsion superior over another. In this particular scenario, a pediatric 20% lipid emulsion routinely used for intravenous nutrition of pediatric patients was used. The lipid formulation described in previous human case reports differed from this unique case, therefore suggesting effectiveness among a variety of preparations.

The only obstetric case published to date of a parturient receiving lipid reversal for bupivacaine toxicity was reported in 2007 by Andrew G. Spence. An 18 year old primagravida, presenting at 38 weeks gestation, received lipid emulsion therapy for signs and symptoms suggestive of LAST. Epidural anesthesia was requested and was performed in the sitting position, at the L1-L2 interspace utilizing the loss of resistance to saline technique. The patient received a 4 mL lidocaine 2% test dose with negative response for intravenous or spinal effects after 5 minutes. An initial bolus injection of bupivacaine 0.25% was given with good pain relief within 10 minutes. The epidural catheter was later injected with 100 μg fentanyl and 10 mL of bupivacaine 0.5% in anticipation of cesarean delivery. The patient responded with agitation, restlessness, and eventually became unresponsive with noted twitching of her face and extremities. The practitioner again aspirated the epidural catheter, revealing obvious venous blood and confirming inadvertent intravascular injection of bupivacaine. Two lipid emulsion therapy boluses of 50 mL 20% lipid, were initiated in a timely response, with return of consciousness within 30 seconds. The remaining 400 mL of lipid infusion was administered and

an emergency cesarean delivery was performed under general anesthesia. The neonate and mother were discharged home without further complications. This report provides both clinical evidence and reaffirmation in the proposed clinical efficacy of lipid emulsion therapy, as local anesthetic toxicity in pregnancy remains a critical issue (Spence, 2007).

It has been proposed that with the emerging technologies of ultrasound guided regional anesthesia a decrease in the overall incidence of local anesthetic toxicity will occur. The use of ultrasound has the potential to provide a more precise local anesthetic deposition at the neural target, ultimately leading to a decreased required dose of drug. However, evidence is inconclusive in determining a reduction in local anesthetic toxicity when ultrasound guidance for regional anesthesia is employed (Dillane & Tsui, 2010). In fact, recent research has been conducted and relayed that ultrasound guidance may reduce, but not eliminate the most common complications associated with regional anesthesia: blood vessel puncture, inadvertent intravascular injection, or intraneural injection of local anesthetic (Hadzic, Salla-Blanch, & Xu, 2008).

Case studies have been published specifically surrounding adverse events of vascular puncture occurring under ultrasound guided regional anesthesia blockade. A 82 year old women scheduled for an excision of toe osteophytosis experienced cardiac arrest during a combined ultrasound guided and nerve stimulation sciatic nerve block. The clinician performing the block documented ultrasound guidance visualization of the main landmarks as well as observing an appropriate neurostimulation response. Following multiple negative aspiration tests, 20 mL 0.5% ropivacaine and 50 μg clonidine were injected over approximately 90 seconds. Within seconds of injection, the patient became unconscious and experienced a tonic clonic seizure. Her airway was immediately secured and the seizure was stopped with the administration of thiopental and

suxamethonium. One minute following the seizure activity, ventricular fibrillation occurred and chest compressions were initiated. Two defibrillations were required to return to the patient's initial rhythm of atrial fibrillation and obtain hemodynamic stability. Amiodorone and a 20% lipid emulsion infusion were administered upon transfer to the intensive care unit. The patient had an uneventful recovery and was discharged without negative neurologic sequelae (Gnaho, Eyrieux, & Gentili, 2009).

Gnaho and colleagues (2009) postulated accidental intravascular injection associated with nerve stimulation and patient motor movement. Additionally, they suggested the possibility of the ultrasound probe compressing the vascular structures causing an obstructed view of an intravascular placement of the insulated needle. Although a clear understanding of what the exact fault in technique may have been was not established from this case study, it provides further evidence of the beneficial effects of lipid emulsion therapy as treatment for LAST.

Amongst case reports of successful use of lipid emulsion therapy in resuscitation for local anesthetic systemic toxicity, ineffectiveness of lipid infusion administration has been published. A 51 year old female, 57 kg, planned for left hallux valgus surgery under an ultrasound guided sciatic nerve block suffered from neurological symptoms after injection of 30 mL of a 50/50 mixture of lidocaine 20 mg mL and ropivacaine 7.5 mg mL solution. Five minutes later, a saphenous nerve block was achieved by administering 100 mg of lidocaine. Aveline, Cognet and Bonnet (2010) report the patient experienced agitation, confusion, and jerking movements thirty minutes after the sciatic nerve block injection (Aveline, Gognet, & Bonnet, 2010). Cardiovascular collapse did not occur; however, two minutes following timely administration of 100 mL lipid emulsion bolus, the patient remained unresponsive with persisting jerky movements. A second bolus was administered without apparent change in patient status. Elective

tracheal intubation was performed with thiopental and suxamethonium and immediate improvement of neurological symptoms resulted. The patient underwent extensive metabolic and electrolyte evaluations, as well as a thorough neurological examination; findings were concluded to be normal.

Unique considerations arise with the documentation of this case report. It describes an incidence of unsuccessful reversal of LAST with lipid therapy, as well as addresses the use of ultrasound guidance with resulting toxicity. Discussion provided by the clinicians hypothesized the ineffective use of lipid emulsion therapy in reversal of lidocaine induced toxicity as lidocaine is less lipid soluble than ropivicaine or bupivacaine. The patient's current medical regimen was also discussed as she was taking carbamazepine for treatment of trigeminal neuralgia. They concluded with recommendations of instituting lipid emulsion therapy only in an event where lipid-soluble local anesthetic intoxication occurs.

An editorial in response to Aveline et al. (2010) was published in the *European Journal of Anaesthesiology* in 2011. Undoubtedly both authors agreed that the patient exhibited symptomology suggestive of LAST, however speculations of the ineffective result of lipid emulsion therapy differed. Uncles, Willers, Samuels, & Chaklader (2011) acknowledged the timely recognition and accurate diagnosis of LAST, but suggested possible explanations for the failure of lipid treatment in the case report. Calculation of the cumulative administered dose of lidocaine injected with the combination sciatic and saphenous nerve block overcomes the recommended maximum dose of plain lidocaine with a total of 7.02 mg/kg. Central nervous system signs of LAST may be explained by both the systemic absorption of the increased dosing regimen, as well as the additive effect of the ropivacaine component in the mixture (Uncles, Willers, Samuels, & Chaklader, 2011). The editorial further discussed the possibility of drug

interference and protein binding in relation to the combined administration of carbamazepine, lidocaine, and ropivacaine. Due to the risk of competition for protein binding sites leaving a higher amount of free, unbound local anesthetic, a larger volume of lipid emulsion administration may have been necessary.

Discussion

Local anesthetic toxicity and lipid rescue resuscitation remains on the forefront of discussion surrounding anesthesia clinical practice. Intravascular injection of local anesthetics remains a major risk of regional anesthesia and peripheral nerve blocks even considering the emerging technological advances of ultrasound guidance. Animal studies, ongoing clinical research, and case reports have demonstrated the effectiveness of lipid infusion in treating cardiovascular collapse due to LAST. With the increasing use of local anesthetics in perioperative regional anesthesia and labor suites, anesthesia providers who deliver potentially dangerous doses of local anesthetics must be able to rapidly recognize and effectively manage LAST in order to facilitate recovery.

Interpretation

Although promising animal research conducted in the 1990s and the first human case reports of lipid rescue emerged in the mid-2000s, the appropriate management and technique of resuscitation remains an evolving topic. Discussion continues surrounding the mechanism of action in lipid resuscitation as well as variations in methods for treating LAST. However, the evidence of benefits and lack of apparent risk continues to guide an overall acceptance of lipid emulsion therapy administration in the setting of LAST.

Following a thorough critique of published case reports, there is evidence of clear discrepancies between the recommended guidelines and management set forth by ASRA and

what is actually being translated into clinical practice. Controversies surrounding the underlying mechanisms of action of lipid emulsion, the risks associated with administering intravenous lipid emulsion therapy, delay of administration, and the optimal lipid emulsion dose remains. Because there is no ethical way to conduct clinical trials involving local anesthetic toxicity, further case reports and animal studies are warranted. With continued lab investigation and further study of the outcomes of patients who received lipid emulsion therapy for LAST, clarification of the ideal timing of lipid emulsion therapy, along with identification of adverse events and long term effects may certainly be achieved.

Outcome/Dissemination

Following a comprehensive review of literature, the information was gathered and organized into a both a formal presentation and clinical reference brochure. The clinical literature data and treatment guidelines were provided to CRNAs and ancillary operating room staff at three local anesthetic toxicity workshop sessions at Sanford Health, Fargo, North Dakota, and will be delivered to attendees of the North Dakota Association of Nurse Anesthetists bi-annual meeting in Bismarck, North Dakota. Effectiveness of the workshop was evaluated by a participant course examination at the end of the session. An evaluation tool was distributed at the North Dakota Association of Nurse Anesthetists fall meeting to assess the quality of the PowerPoint presentation.

Implications for Nursing

In 2010, the ASRA and Pain Medicine Practice Advisory on LAST made a streamline effort in providing evidence-based recommendations and guidelines regarding the prevention, diagnosis, and treatment of local anesthetic toxicity. A constant amongst the majority of recent clinical case reports is the guidelines set by ASRA. Recommendations for treatment of LAST

begin with timely recognition of symptoms followed by prompt, effective airway management. Benzodiazepine administration is appropriate if seizure activity is to occur. However, if benzodiazepines are not readily available, a small dose of propofol may be administered. If cardiac arrest occurs, standard ACLS treatment should be followed with appropriate modifications including: smaller (10-100 μg) epinephrine boluses for the adult, avoid the use of vasopressin, calcium channel blockers and β-adrenergic blockers, and finally, initiate amiodorone for the treatment of ventricular arrhythmias. The use of lidocaine or procainamide is not recommended. Lipid emulsion dosing guidelines, as outlined by ASRA, recommend administering a 1.5 mL/kg 20% lipid emulsion bolus at the first signs of LAST, after airway management. A subsequent infusion of 0.25 mL/kg per minute should be continued for 10 minutes after cardiovascular stability has been achieved. If refractory circulatory arrest occurs, a repeated bolus and increased infusion rate to 0.5 mL/kg per minute may be considered. The upper limit for initial dosing is defined as 10 mL/kg lipid emulsion for 30 minutes (Neal et al., 2010). Cardiopulmonary bypass remains an appropriate treatment modality in the occurrence of an unsuccessful resuscitation attempt with lipid emulsion and vasopressor therapy.

With the addition of guidelines for optimizing the treatment of LAST and the growing number of clinical case reports documenting lipid infusion for patients with local anesthetic toxicity, a couple of clinical pearls have been identified. Recent case reports support initiation of lipid emulsion therapy at onset of local anesthetic toxicity symptoms rather than delaying administration until standard resuscitation measures fail (Weinberg, 2008). Additionally, the advisory council does not favor one formulation of lipid emulsion solution over another. However, it is important to refrain from using propofol as a substitute for lipid emulsion therapy due to its low lipid content and high cardiac depressant effects (Neal et al., 2010).

Based upon the successful data reported from both animal studies and case reports, lipid emulsion therapy remains an effective treatment of toxic overdose from local anesthetics and reversal of associated cardiovascular symptoms. Lipid emulsion therapy can be instrumental in the resuscitation of a toxic event and should be employed at the onset of neurological or cardiovascular symptoms. In the event of local anesthetic toxicity, early recognition and timely administration requires the availability of lipid emulsion therapy in arenas where local anesthetics are commonly used. Operating rooms, obstetric suites, and areas where regional blocks are conducted should keep an IV lipid emulsion supply and dosing protocol readily available. Proficient and effective resuscitation efforts require prompt intervention and vigilance by anesthesia clinicians in instituting both timely ACLS and lipid emulsion therapy.

Summary

Although rare, local anesthetic toxicity remains a potentially fatal complication of regional anesthesia that cannot be solely prevented by any single measure (Bern et al., 2011). Symptoms of LAST initially manifest primarily through neurological excitation and cardiovascular dysfunction, and eventually progress to refractory cardiovascular arrest. Treatment of local anesthetic toxicity is aimed at providing adequate oxygenation, instituting ACLS, and prompt administration of lipid emulsion therapy. Guidelines for the use of lipid emulsion therapy in treatment of severe local anesthetic toxicity have paved the way for a promising treatment modality and reliable reversal of local anesthetic toxicity.

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