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Lipid Emulsion and the Management of Local Anesthetic Systemic Toxicity

Randall Hagemeister

LIPID EMULSION AND THE MANAGEMENT OF LOCAL ANETHESTIC SYSTEMIC TOXICITY

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Randall Hagemeister

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ABSTRACT

Title: Lipid Emulsion and the Management of Local Anesthetic Systemic Toxicity

Background: Local anesthetic systemic toxicity (LAST) is a rare but serious complication that can occur after the use of local anesthetics.

Purpose: This case study involves a patient who received local anesthetic injections around incision sites as well as a lidocaine infusion as part of an enhanced recovery after surgery (ERAS) protocol. With the concurrent use of more than one local anesthetic, the patient is at an increased risk for LAST.

Process: In practice settings where local anesthetics are used, proper precautions and an understanding of LAST as well as management can help to improve patient outcomes and prevent complications. The database PubMed was searched, and case report reviews, current recommendations on LAST management, and individual case reports were attained. Around 5,000 articles were returned in the search, and by utilizing specific keywords, the results were refined to 19. Six were utilized for the discussion, as well as reference lists from articles to find case studies for the literature review section. Initial findings were limited to within the last 5 years and then increased to the last 10 years to allow for adequate sources of information. The findings were reviewed and recommendations were made based on the literature.

Results: Through a review of several case reports involving LAST, the use of lipid emulsion was effective in either terminating or limiting the CNS and cardiovascular effects of the toxicity.

Implications: LAST is a life-threatening complication that can arise with local anesthetic use. With proper precautions and readiness should LAST occur, ASRA guidelines and the use of lipid emulsion can to help treat LAST episodes and improve patient outcomes.

Keywords: local anesthetic, anesthesia, LAST, management, treatment, lipid

Lipid Emulsion and the Management of Local Anesthetic Systemic Toxicity

Local anesthetic systemic toxicity (LAST) is an extremely rare, but very serious complication that can occur when local anesthetics are utilized. The complication can occur from accidental intravascular injection or from absorption into the vasculature of local anesthetics when large volumes are used (Nagelhout & Elisha, 2018). The incidence of LAST varies depending on the source. According to Dickerson and Apfelbaum (2014), the incidence is approximately 2.5 per 10,000 peripheral nerve blocks, whereas Nagelhout and Elisha (2018) reported an estimated incidence as low as 0.4 per 10,000 peripheral nerve blocks and 4 per 10,000 epidurals. Increased safety measures such as ultrasound use, aspiration prior to injection, and utilizing a test dose, have been implemented over the past years and played an integral role in decreasing the incidence rate (Nagelhout & Elisha, 2018). Nevertheless, poor recognition and improper management can lead to dire consequences for the patient should a LAST event occur.

It is important for anesthesia professionals to remain current on the diagnosis and management of LAST. The American Society of Regional Anesthesia and Pain Medicine (ASRA) released a checklist for LAST management in 2018, an update to the 2012 version. Although the incidence of LAST is low, patient safety should always remain a top priority. The purpose of this paper is to review the mechanism of action for local anesthetics and LAST as well as the current recommendations for LAST management.

Case Report

A 41-year-old, 170 cm, 126 kg female presented to the operating room for laparoscopic gastric bypass. The patient's past medical history included Hashimoto's thyroiditis, rheumatoid arthritis, morbid obesity, and peripheral neuropathy. Her past surgical history included a hysterectomy and a laparoscopic cholecystectomy, which were performed without any anesthetic

or surgical complications. Her home medications included ferrous sulfate, hydroxychloroquine, a multivitamin, vitamin D, and valacyclovir. The patient was given an ASA physical status classification of 2 and had baseline vital signs of BP 125/84, HR 76, RR 16, SpO2 96% on room air, and a temperature of 97.5-degrees Fahrenheit. An airway evaluation was performed and revealed a Mallampati class I, full neck mobility, and full dentition with adequate mouth opening. An 18-guage peripheral IV of Lactated Ringers (LR) was placed preoperatively.

The patient was transported to the operating room and standard monitors were applied. The patient was pre-oxygenated by mask with 10 LPM O2 for 5 minutes. General anesthesia was induced with the following intravenous (IV) medications: midazolam 2 mg, fentanyl 100 mcg, propofol 200 mg, ketamine 50 mg, and rocuronium 40 mg. The patient was uneventfully intubated with a MAC 3 blade and 7.0 endotracheal tube (ETT). ETT placement was confirmed with bilateral breath sounds upon auscultation and the presence of an end tidal CO2. Sevoflurane was titrated to an inspired concentration of 1.8-2% with flows of 1 L air and 1 L O2. A dexmedetomidine infusion at 0.4 mcg/kg/hr and a lidocaine infusion at 2 mg/min were initiated post induction prior to surgical incision. The patient received clindamycin 900 mg and ciprofloxacin 400 mg as her preoperative antibiotics. She received enoxaparin sodium 40 mg subcutaneously. An orogastric tube was also placed to help decompress the stomach for the surgery.

During the case, the patient received rocuronium 30 mg and ephedrine 15 mg, in divided doses, as well as phenylephrine 50 mcg. PONV prophylaxis was provided with ondansetron 4 mg and dexamethasone 5 mg. She received a total of LR 1,550 mL with an estimated blood loss of 25 mL. Her neuromuscular blockade was reversed with glycopyrrolate 0.8 mg and neostigmine 5 mg. Once incisions were sutured, the surgeon injected 0.5% bupivacaine with

1:200,000 epinephrine 30 mL around the surgical incisions. The patient was extubated in the operating room without complication and was transferred to the Post Anesthesia Care Unit (PACU) on 4 LPM O2 via nasal cannula.

In PACU, the patient received fentanyl 50 mcg and a hydromorphone PCA was initiated. The patient was admitted to an inpatient medical-surgical floor for observation overnight and was successfully discharged to home the next day.

Methodology

A literature search was performed using the PubMed database through the University of North Dakota Health Sciences Library. Keywords including local anesthetic, anesthesia, management, treatment, LAST, and lipid were used. The results were filtered for English language, full-text, and within the last 5 years. Due to limited results, the filter was expanded to the last 10 years. The primary form of literature retrieved was limited to case reports. The mechanism of action for LAST along with treatment has only been tested on animal subjects in a larger population. Human studies involving LAST mechanisms and treatment are not feasible due to the nature and severity in can encompass.

Discussion

Local Anesthetics

Local anesthetics exist in two forms, amides and esters. Ester local anesthetics exhibit a higher chance of causing an allergic reaction versus amide local anesthetics. The potential for a cross allergy exists between local anesthetics within the ester class, but not between the ester and amide classes. Esters are typically shorter acting due to rapid metabolism while amides are typically longer acting due to increased lipophilicity and protein binding. This is why bupivacaine, a long-acting amide, exhibits such prolonged cardiotoxic effects at high plasma

levels. Although esters are metabolized by tissue cholinesterase and amides are metabolized by the liver, both classes of local anesthetics work through the same mechanism of action (Nagelhout & Elisha, 2018).

Local anesthetics have been used for means of anesthesia and more recently, their use has been increased in post-operative pain management (Nagelhout & Elisha, 2018). The benefits of local anesthetic use are numerous and they can be thought of as a cornerstone to multimodal analgesia (Dickerson & Apfelbaum, 2014). Local anesthetics work by binding reversibly to voltage-gated sodium channels (Nagelhout & Elisha, 2018; El-Boghdadly, Pawa, & Chin, 2018; Dickerson & Apfelbaum, 2014). After binding to voltage-gated sodium channels, they "inhibit neuronal ion transfer and depolarization, and prevent neuronal transmission" (El-Boghdadly et al., 2018, p. 36).

Local anesthetics are able to bind to the sodium channels in their open or inactive state and do not bind in their closed state (Nagelhout & Elisha, 2018). Local anesthetics work quicker when the channel is frequently depolarized, which allows for the channel to predominantly be in the open and inactive states (Nagelhout & Elisha, 2018). Local anesthetics can exist in both ionized and nonionized forms according to their pKa and pH (Nagelhout & Elisha, 2018). Local anesthetics utilize their nonionized, lipid soluble, fraction to transfer across the cell membrane to reach the receptor inside the neuron. Inside the neuron, the local anesthetic utilizes the ionized, water soluble, fraction to bind to the sodium channel (Nagelhout & Elisha, 2018). Once the local anesthetic exerts its action, loss of autonomic function occurs, followed by loss of superficial pain perception, touch, temperature, motor function, and proprioception (Nagelhout & Elisha, 2018). Different local anesthetics can be utilized depending on desired duration of action ranging from short, 15-30 minutes, to long, 180-600 minutes (Nagelhout, & Elisha, 2018).

Mechanism of LAST

Presentation of LAST can vary, but it typically begins with central nervous symptoms (CNS) that can develop into severe cardiovascular symptoms as increased toxic plasma levels are reached (Dickerson & Apfelbaum, 2014). Prodromal symptoms, such as dizziness, drowsiness, tinnitus, circumoral numbness, and a metallic taste usually present rapidly, while more severe CNS symptoms, such as seizures, loss of consciousness, and agitation can follow (Nagelhout & Elisha, 2018; Dickerson & Apfelbaum, 2014). Other CNS symptoms including visual disturbances, muscle twitching, coma and respiratory arrest may ensue as further depression occurs (Nagelhout & Elisha, 2018; El-Boghdadly & Chin, 2016). Cardiovascular symptoms, which usually occur at increased levels of toxicity, include bradycardia or asystole, tachycardia, hypotension or hypertension, wide-complex arrhythmias, and ventricular tachycardia or fibrillation (Dickerson & Apfelbaum, 2014). Arrhythmias are the most common cardiovascular complication (Nagelhout & Elisha, 2018; El-Boghdadly & Chin, 2016).

Prevention is the most important step to take in order to avoid LAST. Measures that can be taken to help prevent LAST include utilizing ultrasound, aspirating prior to injection, using test doses, injecting in increments, using the lowest possible local anesthetic dose, and reviewing guidelines (Nagelhout &Elisha, 2018; Dickerson & Apfelbaum, 2014). It is also important to consider that "concurrent administrations of multiple local anesthetics contribute to a single systemic toxic threshold" (Dickerson & Apfelbaum, 2014, p. 1114). Certain risk factors for developing LAST have also been identified and include extremes of age, renal dysfunction, cardiac disease, hepatic dysfunction, pregnancy, and choice of block site and technique (El-Boghdadly & Chin, 2016).

Local anesthetics block voltage-gated sodium channels (Nagelhout & Elisha, 2018; El-Boghdadly & Chin, 2016; Dickerson & Apfelbaum, 2014). CNS symptoms occur due to the local anesthetic also blocking intracellular sodium channels located in neuronal tissue (Nagelhout & Elisha, 2018; El-Boghdadly & Chin, 2016). The inhibitory cerebral pathways are blocked initially, which evidences as excitatory CNS symptoms including seizures, visual and sensory disturbances, and muscle twitching (Nagelhout & Elisha, 2018; El-Boghdadly & Chin, 2016). As toxic plasma levels of local anesthetic increase, CNS excitatory pathways are also blocked, which exhibits as loss of consciousness, coma, and respiratory arrest (El-Boghdadly & Chin, 2016). Plasma levels of lidocaine are considered to be around 2 mcg/mL to act as an antiarrhythmic and 4 mcg/mL to provide positive inotropy. Toxic effects including circumoral numbness, tinnitus, and lightheadedness can occur at levels of 5 mcg/mL or less. As plasma levels reach 10 mcg/mL, symptoms of visual disturbances, convulsions, and muscular twitching can occur. Unconsciousness and coma can be seen when plasma levels reach 15 mcg/mL. Respiratory arrest can be encountered at levels around 20 mcg/mL and cardiovascular collapse when levels reach around 25 mcg/mL (Rooyen, 2010).

Cardiovascular compromise occurs from local anesthetic interference with cardiac ion channels, including potassium and calcium (El-Boghdadly & Chin, 2016). This blockade of ion channels in the cardiac tissue results in "dysrhythmias, myocardial depression, and changes in systemic vascular resistance" (El-Boghdadly & Chin, 2016, p. 331). Blockade of cardiac ion channels "affect initiation and propagation of the contraction and repolarization" (Nagelhout & Elisha, 2018, p. 119). Sodium channels in cardiac conducting cells are also blocked and can lead to dysrhythmias (El-Boghdadly & Chin, 2016). The sodium channel blockade produces myocardial depression as well. Bradycardia occurs most commonly and ventricular fibrillation is

the most detrimental arrhythmia in LAST episodes (Nagelhout & Elisha, 2018). Severe cardiac collapse occurs through "suppression of the baroreceptor reflex as well as a direct reduction in vascular tone" (El-Boghdadly & Chin, 2016, p. 331). Shorter acting local anesthetics such as lidocaine are often much less cardiotoxic that longer acting local anesthetics such as bupivacaine (Nagelhout & Elisha, 2018).

Lipid Emulsion and Management of LAST

Lipid emulsion therapy has different proposed mechanisms of action. One is thought that lipid emulsion exhibits a scavenging effect to the local anesthetic. Specifically, the lipid emulsion binds to the local anesthetic itself and allows for redistribution of the drug away from cardiac and CNS tissues (Fettiplace & Weinberg, 2018). Fettiplace and Weinberg (2018) noted that the binding of lipid molecules to local anesthetics, such as bupivacaine, can restore the function of voltage-gated sodium channels as well as other ion channels. The binding effect of lipid molecules is not thought to be enough to combat toxicity but also lies with the redistribution effects of the lipid molecules. Redistribution occurs from organs that are more sensitive to local anesthetic toxicity, such as CNS and cardiac tissue, to organs, such as the liver and kidneys that help metabolize the local anesthetics (Fettiplace & Weinberg, 2018).

Lipid emulsion therapy can also directly support cardiac function through improving contractility, cardiac output, and blood flow and pressure (Fettiplace & Weinberg, 2018). The direct cardiac effects may be attributed to the elevated free fatty acids, which are used by the cardiac tissue as fuel, interfering with signaling of nitric oxide, and modifying adrenergic sensitivity (Fettiplace & Weinberg, 2018). It is also thought that lipid emulsion therapy provides a postconditioning benefit and cardiac protection, but the mechanism for this is untested in human models and lacks support (Fettiplace & Weinberg, 2018).

ASRA has created a checklist and guideline for the management of LAST. The newest version came out in 2018 and contains updates from the 2012 version (Neal, Woodward, & Harrison, 2018b). The 2018 ASRA checklist update has some key differences from other cardiac arrest situations. One update includes administering lipid emulsion at the first significant sign of LAST. Monitoring times based of symptoms experienced were also added in the update. Another update involves the maximum dose of lipid emulsion reaching 12 mL/kg (Neal et al., 2018b). It is recommended to avoid vasopressin, calcium channel blockers, beta blockers, and local anesthetics as well as limiting epinephrine doses to less than 1 mcg/kg. Epinephrine doses are limited in order to avoid compromised pulmonary gas exchange and increased afterload and vasopressin was found to be counterproductive. (Neal et al., 2018a; Dickerson & Apfelbaum, 2014). Calcium channel blockers and beta blockers are to be avoided as they can lead to further myocardial depression (Dickerson & Apfelbaum, 2014). As local anesthetics are the culprit of LAST, further use of local anesthetics for the treatment of arrhythmias is not recommended (Dickerson & Apfelbaum, 2014).

The checklist begins with stopping the local anesthetic administration and to get help. Lipid emulsion is to be administered at the first serious sign of LAST as soon as able, and the LAST management kit should be obtained, if available. The nearest facility with cardiopulmonary bypass capability should also be notified in the event of prolonged resuscitation efforts. Airway management should occur with 100% oxygen with avoidance of hyperventilation. Seizures are to be controlled with benzodiazepines with caution to avoid propofol in the incidence of hemodynamic instability. Cardiopulmonary resuscitation (CPR) efforts should be initiated if the patient becomes pulseless. Lipid emulsion dosing for patients greater than 70 kg begins with a 20% lipid emulsion 100 mL bolus over 2-3 minutes and a bolus

of 20% lipid emulsion 1.5 mL/kg if the patient weighs less than 70 kg over 2-3 minutes. Infusions for patients over 70 kg occur should contain 200-250 mL over 15-20 minutes and should be 0.25 mL/kg/min for patients less than 70 kg. In the case of sustained LAST, the bolus dose can be given up to two additional times and the infusion rate can be doubled. Up to 1 L of lipid emulsion can be utilized for severe LAST incidences. ASRA recommends monitoring the patient for at least 4-6 hours after a cardiac event or 2 hours after a CNS event. It is also recommend to not exceed a total lipid emulsion dose of 12 mL/kg. There are recommendations for healthcare facilities that routinely use local anesthetics. Facilities are encouraged to develop "LAST Management" kits that include the following: 20% lipid emulsion 1 L, several syringes and needles, IV tubing, and a copy of the ASRA LAST checklist (Neal et al., 2018b).

Literature Review

Nedialkov, Umadhay, Valdes, and Campbell (2018) performed a literature review of case studies involving animal and human reports. They noted that human studies on a larger population are not feasible due to potential adverse outcomes. The authors also noted that potential side effects of lipid emulsion use are not commonly reported although they can occur. Side effects can include allergic reactions due to the soy component, hyperthermia, hypercoagulability, pancreatitis, elevated liver enzymes, and fat embolism. Conclusions from the literature review included the safe and effective use of lipid emulsion in LAST situations and how important early recognition of CNS and cardiovascular symptoms is. Recommendations from the authors included availability of lipid emulsion where regional anesthesia is performed, education, reporting of LAST events, and the development of an international guideline for LAST management with lipid emulsion.

Nguyen and White (2012) presented a case report of a 19-year-old male patient receiving an ultrasound guided supraclavicular block for an ulnar medial collateral ligament repair. The block was initiated with 0.5% ropivacaine 5 mL after a negative aspiration. The provider had trouble visualizing the spread on ultrasound so the needle was repositioned and an additional 10 mL of local anesthetic was injected. The patient quickly became disoriented and began thrashing his head back and forth. He became tachycardic and hypertensive. The provider gave a bolus of 20% lipid emulsion 100 mL over 1 minute as well as supplemental oxygen and midazolam 2 mg IV. After 2 minutes, the patient was reoriented and his vital signs returned to baseline. The authors pointed out that the first 5 mL of local was probably injected intravascularly and no more severe CNS symptoms occurred due to the patient receiving midazolam 2 mg IV prior to the block.

Ludot, Tharin, Belouadah, Mazoit, and Malinovsky (2008) presented a case report of a 13-year-old female undergoing a meniscectomy of her left knee. This patient received a posterior lumbar plexus block under general anesthesia. The anesthesia provider used a neurostimulator and insulated needle to place the block. Once the correct position was found, a negative aspiration occurred and 1% lidocaine with epinephrine and 0.75% ropivacaine 2 mL was injected. A total of 20 mL of the local anesthetic solution was injected in divided doses over a 2 minute period. After supine positioning about 15 minutes after local anesthetic administration, the patient developed ventricular tachycardia at 150 bpm. The patient's blood pressure remained stable and her oxygen saturation fell to 92%. She was manually ventilated and a 20% lipid emulsion 150 mL bolus was administered over 3 minutes. Two minutes into the lipid bolus, the heart rate fell to 100 bpm at sinus rhythm and oxygen saturation increased to 97%. The patient displayed no more complications and the surgery was performed uneventfully.

Espinet and Emmerton (2009) presented a case report of a 36-year-old male patient undergoing a fasciotomy and myomectomy of his gastrocnemius after an injury. The patient received a local anesthetic solution containing 1% lignocaine with epinephrine 10 mL and 0.5% bupivacaine 20 mL into his soleus and extensor hallucis longus muscles for analgesia. About 1 minute after injection, the patient displayed perioral tingling, headache, dizziness, lightheadedness, diplopia, as well as hypertension and tachycardia. The patient was treated with 100% oxygen per mask and within five minutes of symptom onset, two 20% lipid emulsion 100 mL boluses were given. Shortly after lipid emulsion bolus initiation, the heart rate and blood pressure decreased as well as improved neurological symptoms. An infusion of 20% lipid emulsion 100 mL was given over a period of 1 hour and the patient was admitted to the intensive care unit. The patient's symptoms completely resolved after treatment with lipid emulsion.

Marwick, Levin, and Coetzee (2009) presented a case report of a 33-year-old male patient undergoing a debridement of a right humeral fracture. The patient received an infraclavicular paracoracoid block under nerve stimulation with 0.375% bupivacaine 30 mL in 5 mL increments with aspiration in between. Immediately after injection, the patient complained of dry eyes and mouth, began having convulsions, and experienced respiratory arrest. The patient received two doses of thiopental IV, 100 mg and 150 mg, which ended the convulsions. The patient was then found to be in sinus tachycardia with ORS-complexes that began to appear wide leading into asystole. A 20% lipid emulsion 150 mL bolus was initiated and finished right before the patient experienced asystole. The patient then received epinephrine 1 mg IV, and after 3 minutes of lipid emulsion bolus completion, the patient displayed a rhythm of sinus tachycardia and hypertension. An infusion of 20% lipid emulsion 350 mL was given over 30 minutes and an epinephrine infusion was initiated. In this case, they decided to complete the surgery. About 40

minutes after the lipid emulsion infusion, the patient experienced another episode of sinus tachycardia with runs of ventricular tachycardia. The facility was unable to obtain additional lipid emulsion and it was decided to give a loading dose of amiodarone 300 mg. After admission to the intensive care unit, the patient was extubated several hours later and was discharged a few days later.

Yamane and Kagawa (2015) presented a case report involving a 6-year-old female patient undergoing a permanent pacemaker implantation under thoracotomy. She was uneventfully placed under general anesthesia and then an ultrasound guided thoracic paravertebral block was performed. The anesthesia provider injected 0.375% ropivacaine 7 mL incrementally into the paravertebral space through a catheter. Approximately two minutes after injection, the patient experienced asystole. The patient was given CPR and epinephrine 0.1 mg IV. A pulse was regained in less than two minutes and approximately 7 minutes after local anesthetic injection, a 20% lipid emulsion 20 mL bolus was administered. A transesophageal pacemaker was placed and infusions of epinephrine, dobutamine, and dopamine were started. The surgery was performed uneventfully and upon removal of the block catheter, it was found to contain blood and intravascular injection more than likely had occurred. The patient was admitted and successfully discharged 13 days post-surgery.

Vadi, Patel, and Stiegler (2014) presented a case report of an 88-year-old female undergoing a right hip fracture repair after a fall. The patient received a posterior psoas compartment block with 0.25% bupivacaine with epinephrine 10 mL and 1.5% mepivacaine 15 mL in increments with aspiration prior to each injection. After completion of the block, a right sciatic nerve block was also performed under ultrasound guidance. A total of 1.5% mepivacaine 15 mL was injected in increments for the sciatic nerve block. Approximately 15 minutes after

block placement, the patient became unresponsive and displayed a fixed gaze. Initially, she was suspected to have experienced a cerebrovascular accident. Around 5 minutes later, the patient experienced a grand mal seizure and was given midazolam 2 mg IV and the airway was secured. Surgery was cancelled and the patient was admitted to the intensive care unit. Approximately 40 minutes after block placement, the patient displayed bradycardia and was given atropine 0.4 mg IV. Shortly after, the patient went into pulseless electrical activity and was given epinephrine 1 mg IV and CPR was initiated. The patient was given additional doses of epinephrine, atropine, and vasopressin. Forty-five minutes after block placement was completed, LAST was suspected and a bolus of 20% lipid emulsion 1.5 mL/kg was given as well as an infusion at 0.25 mL/kg/min following ASRA guidelines. The providers re-dosed the lipid bolus twice and also doubled the infusion rate due to sustained arrest. The patient was declared dead after 1 hour of resuscitation efforts. The authors reviewed ASRA guideline and further discussed the diagnostic delay of LAST in this situation. The authors noted that this particular presentation of LAST did not fit the typical picture as 15 minutes had elapsed from time of block placement to first noted symptom. The patient was also noted to have other neurological and cardiovascular risk factors leading to believe a cerebrovascular accident was the cause of the neurological and hemodynamic compromise. “Anchoring” was also discussed as symptoms of the patient were fixated upon as well as the diagnosis of a cerebrovascular accident.

Tsang, Okullo, Field, and Mamo (2016) presented a case report of a 66-year-old male undergoing a left mini-thoracotomy for biopsies. The patient received a thoracic paravertebral block and a catheter was advanced for continual infusion. Local anesthetic of 0.25% bupivacaine was used in divided doses for a total of 50 mg. Surgery was completed uneventfully and the patient was extubated. A continuous infusion of 0.2% ropivacaine was started at 10 mL/hr per

the catheter. Approximately 37 hours post block initiation, the patient became agitated, had convulsions of the extremities, and a burning sensation in his legs. Consciousness was never lost and he became hypertensive and tachycardic. The provider immediately suspected LAST and the continuous infusion was stopped. The patient received midazolam 2.5 mg IM and a 20% lipid emulsion 150 mL bolus was given as well as an infusion at 1500 mL/hr for a total dose of 1000mL. After an hour, limb movements ceased and within 7 hours, the tachycardia and hypertension were resolved. He remained stable and was discharged home a few days later.

Kamel, Trehan, and Barnette (2015) presented a case report of a 51-year-old female patient undergoing a posterior colpoperinerorrhaphy and transobturator sling insertion. The surgery was completed uneventfully and prior to the end of the surgery, the surgeon injected 0.5% bupivacaine with epinephrine 80 mL around the surgical incision. After arrival to the PACU, the patient became agitated, dizzy, and started posturing. She lost movement of her left lower extremity and after 20 minutes in PACU, LAST was suspected by the provider. 20% lipid emulsion was given as a bolus of 100 mL, followed by a 20-minute infusion of 400 mL. After the bolus was given, the patient reported improvement of symptoms as well as displayed resolution of neurological symptoms. She received one dose of phenylephrine 100 mcg prior to lipid emulsion for hypotension. The patient was successfully discharged the next day.

Weiss et al. (2014) presented two separate case reports, which both involved the patient experiencing convulsions. The first patient was a 36-year-old female undergoing a cesarean delivery. The patient received a spinal block with bupivacaine 10 mg and sufentanil 5 mcg. After the delivery was performed, a transversus abdominis plane block was performed under ultrasound guidance. Injection of 0.375% levobupivacaine in increments after aspiration was used for a total of 40 mL. Ten minutes after block completion, the patient developed

unresponsiveness and experienced a generalized tonic-clonic seizure. The patient's breathing was supported and a 20% lipid emulsion 100 mL was given. An infusion of 20% lipid emulsion 0.25 mL/kg/min was started after the bolus, and after 5 minutes, the patient began spontaneously breathing again. The patient experienced another seizure and was given clonazepam 2 mg IV. Seizures were terminated and vital signs remained stable. The patient received a total of 20% lipid emulsion 200 mL for the episode. She was discharged 3 days later.

The second patient case report presented by Weiss et al. (2014) involved a 33-year-old female undergoing a cesarean delivery. She received a spinal block including bupivacaine 10 mg and sufentanil 5 mcg. After the delivery was completed, a transverse abdominis plane block was completed under ultrasound guidance. The patient received 0.75% ropivacaine 40 mL for the block in increments after negative aspiration. A generalized tonic-clonic seizure was experienced by the patient 25 minutes after block completion. Respirations were supported and a 20% lipid emulsion 100 mL bolus was initiated immediately followed by an infusion at 0.25 mL/kg/min. After 2 minutes, the patient began breathing and after 15 minutes, the patient was conscious again. She received a total of 20% lipid emulsion 250 mL lipid for the episode. Hypertension was present and was treated with urapidil IV as well as oral agents. The patient had an uneventful hospital stay and was discharged home on postoperative day 8.

Recommendations

After a thorough review of the current literature regarding LAST, recommendations can be formed. Anesthesia professionals utilizing local anesthetics should always verify the facility they are practicing at has a LAST management kit, or at the least, 20% lipid emulsion 1 L. Even though LAST is a rare complication, adequate preparation and prevention can help to decrease complications. The risk of LAST with ultrasound-guided techniques is decreased, although not

erased, and it is recommended that ultrasound be used for all peripheral nerve blocks when able. Education utilizing the most current evidence for LAST prevention, recognition, and management should be completed regularly. ASRA recommends reporting LAST events on lipidrescue.org to help track incidence and treatment of LAST (Neal et al., 2018b). High quality studies, such as random control trials, on human populations regarding LAST and lipid emulsion use for management would be helpful in supporting its use, although these types of studies are not feasible due to the potential risk to study participants. Future research focusing on the optimal bolus dose, infusion dose, and maximum dose of lipid emulsion could potentially help to treat LAST more effectively.

Conclusion

LAST continues to be a very serious, yet rare complication of local anesthetic use. Local anesthetics offer many benefits to patients, but their use does not come without risks. Anesthesia professionals need to remain up to date on education, take proper precautions, and act quickly in situations where LAST is suspected to increase positive patient outcomes. Through a review of numerous case studies involving LAST, the use of 20% lipid emulsion is supported and should be considered whenever LAST is suspected. In addition, anesthesia professionals are highly encouraged to utilize the ASRA checklist for LAST management.

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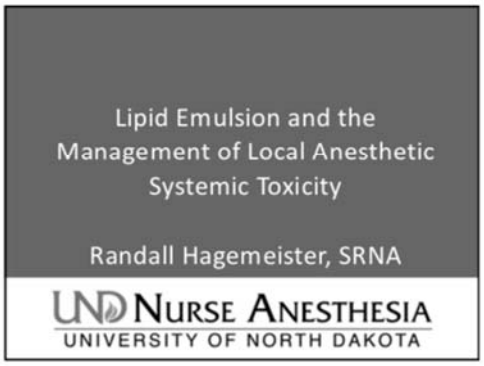
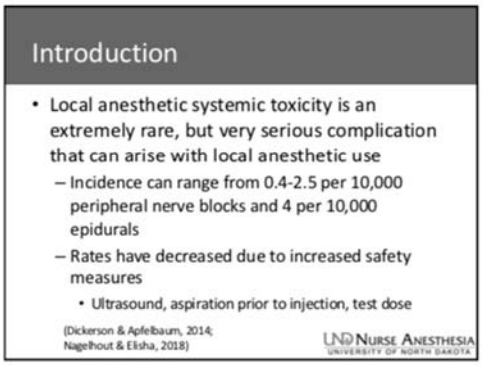
Appendix A


Lipid Emulsion and the Management of Local Anesthetic Systemic Toxicity
Randall Hagemeister, SRNA
UND Nurse Anesthesia
University of North Dakota


Introduction
• Local anesthetic systemic toxicity is an extremely rare, but very serious complication that can arise with local anesthetic use
– Incidence can range from 0.4-2.5 per 10,000 peripheral nerve blocks and 4 per 10,000 epidurals
– Rates have decreased due to increased safety measures
• Ultrasound, aspiration prior to injection, test dose
(Dickerson & Apfelbaum, 2014; Nagelhout & Elisha, 2018)
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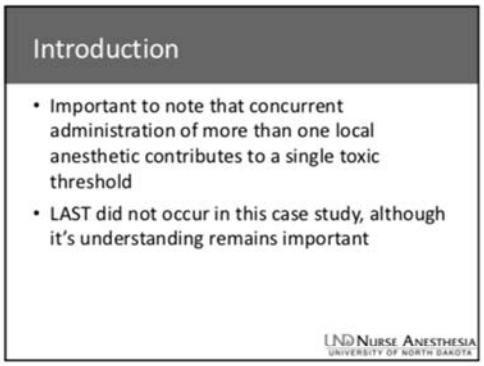
Introduction
• Important to note that concurrent administration of more than one local anesthetic contributes to a single toxic threshold
• LAST did not occur in this case study, although it's understanding remains important
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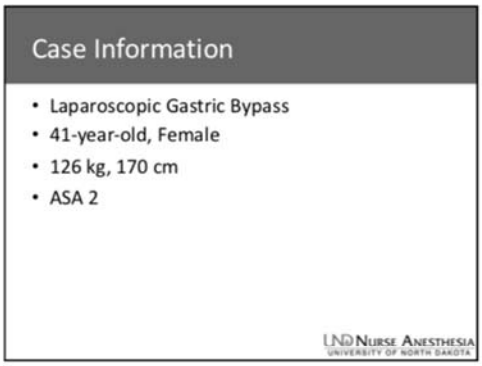
Case Information
• Laparoscopic Gastric Bypass
• 41-year-old, Female
• 126 kg, 170 cm
• ASA 2
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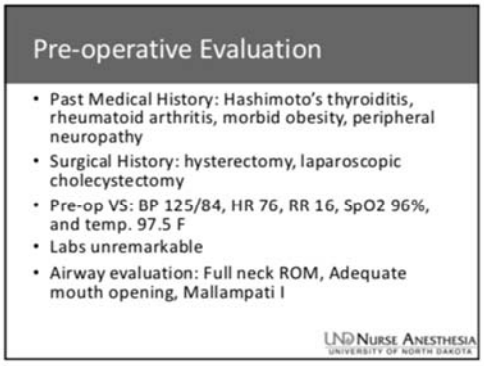
Pre-operative Evaluation
• Past Medical History: Hashimoto's thyroiditis, rheumatoid arthritis, morbid obesity, peripheral neuropathy
• Surgical History: hysterectomy, laparoscopic cholecystectomy
• Pre-op VS: BP 125/84, HR 76, RR 16, SpO2 96%, and temp. 97.5 F
• Labs unremarkable
• Airway evaluation: Full neck ROM, Adequate mouth opening, Mallampati I
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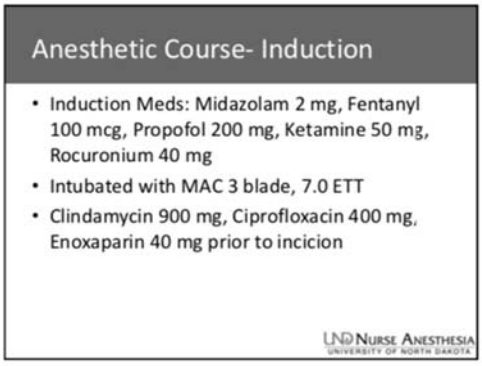
Anesthetic Course- Induction
• Induction Meds: Midazolam 2 mg, Fentanyl 100 mcg, Propofol 200 mg, Ketamine 50 mg, Rocuronium 40 mg
• Intubated with MAC 3 blade, 7.0 ETT
• Clindamycin 900 mg, Ciprofloxacin 400 mg, Enoxaparin 40 mg prior to incicion
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Anesthetic Course- Maintenance

- Maintained with 1 MAC Sevoflurane with 1 L O2 and 1 L Air FGF
- Dexmedetomidine 0.4 mcg/kg/hr and Lidocaine 2 mg/min infusions
- Rocuronium 30 mg to maintain ¼ TOF
- Ephedrine 15 mg (divided doses) and Phenylephrine 50 mcg for hypotension

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Anesthetic Course- Emergence

- Lidocaine and Dexmedetomidine infusions stopped when surgeon began closing
- Reversed with Glycopyrrolate 0.8 mg and Neostigmine 5 mg
- LR 1550 mL for intake and EBL of 25 mL
- 0.5% Bupivacaine with 1:200,000 Epinephrine 30 mL injected per surgeon upon closing
- Extubated uneventfully, placed on 4 LPM per NC and transferred to PACU

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PACU

- Uneventful PACU course
- Hydromorphone PCA initiated
- Admitted to inpatient floor
- Discharged to home the following day

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Discussion

- Review LAST management and mechanism
- Explain role and mechanism of lipid emulsion in the treatment of LAST
- Discuss LAST case reports and outcomes

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Presentation

Central Nervous System (CNS)

- Dizziness and drowsiness
- Tinnitus
- Circumoral numbness
- Seizures
- Loss of consciousness
- Agitation
- Visual disturbances
- Respiratory arrest

Cardiovascular System

- Bradycardia or asystole
- Tachycardia
- Hypo- or hypertension
- Wide-complex arrhythmias
- Ventricular tachycardia or fibrillation
- Cardiovascular collapse

(Dickerson & Apfelbaum, 2014; El-Boghdadly & Chin, 2016; Nagelhout & Elisha, 2018)

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Risk Factors

- Extremes of age
- Renal dysfunction
- Hepatic dysfunction
- Cardiac disease
- Pregnancy
- Choice of block site and technique

(El-Boghdadly & Chin, 2016)

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Prevention

- Ultrasound use
- Aspiration prior to injection
- Test dose
- Lowest effective local anesthetic dose use
- American Society of Regional Anesthesia and Pain Medicine (ASRA) guideline use

(Nagelhout & Elisha, 2018)

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Mechanism of LAST

- Local anesthetics also block sodium channels in CNS tissue
  - Initially inhibitory pathways followed by excitatory pathways as plasma levels increase
- Ion channels, including potassium and calcium, in cardiac tissue are blocked and produce symptoms
  - Conducting cells affected, dysrhythmias
  - Myocardial depression at high plasma levels
  - Long-acting amides, bupivacaine, most cardiotoxic

(Dickerson & Apfelbaum, 2014; El-Boghdadly & Chin, 2016; Nagelhout & Elisha, 2018)

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LAST Management

- Management checklist created by ASRA
  - Stop LA use immediately and get help
  - Administer 20% lipid emulsion at first sign of LAST
  - Manage airway with 100% O2, no hyperventilation
  - Avoid Propofol, calcium channel blockers, large epinephrine doses, beta-blockers, other LA's, and vasopressin
  - CNS events monitored for 2 hours, CV events monitored for 4-6 hours
  - CPR when pulseless, cardiopulmonary bypass for prolonged arrest

(Neal, Woodward, & Harrison, 2018)

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20% Lipid Emulsion Dosing

< 70 kg

- 1.5 mL/kg bolus over 2-3 minutes
- 0.25 mL/kg/min infusion

> 70 kg

- 100 mL bolus over 2-3 minutes
- 200-250 mL infusion over 15-20 minutes
  - If LAST continues, boluses can be repeated two additional times and infusion rate doubled
  - 1 L total may be used, limit total dose to 12 mL/kg

(Neal et al., 2018)

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20% Lipid Emulsion Mechanism

- Scavenging effect
  - Binds to LA and redistributes to less sensitive tissue
- Direct cardiac effects
  - Improved contractility, cardiac output, and blood pressure
- Provides postconditioning effect and cardiac protection
  - Support for these mechanisms lack support

(Fettiplace & Weinberg, 2018)

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Literature Review

- PubMed database through the UND Health Sciences Library
- Keywords: local anesthetic, anesthesia, LAST, management, treatment, lipid
- Due to the lack of studies on human subjects regarding LAST and treatment, only case reports available for review
- 10 case reports were included in the review

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Discussion

- Nedialkov, Umadhay, Valdes, and Campbell (2018)
  - Literature review of LAST cases involving animal and human reports
  - Concluded lipid emulsion is a safe and effective treatment for LAST
  - Mentioned importance of considering side effects of lipid emulsion
    - Allergic reactions, hypercoagulability, hyperthermia, elevated liver enzymes, pancreatitis, fat embolism

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Lipid Treatment with CNS Symptoms

- Nguyen and White (2012)
  - Supraclavicular block, CNS symptoms successfully treated after lipid emulsion bolus
- Kamel, Trehan, and Barnette (2015)
  - LA injected around incisions, CNS symptoms in PACU treated with lipid emulsion

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Lipid Treatment with CNS Symptoms

- Weiss et al. (2014) two separate case reports
  - Spinal with TAP block for C-section, seizure treated with lipid emulsion
  - 2nd report with spinal and TAP block for C-section, seizure treated with lipid emulsion

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Lipid Treatment with CNS/CV Symptoms

- Espinet and Emmerton (2009)
  - LA injected into soleus and extensor hallucis longus muscles for analgesia, CNS symptoms occurred initially followed by hypertension and tachycardia, symptoms treated with lipid emulsion
- Marwick, Levin, and Coetzee (2009)
  - Infraclavicular paracoracoid block, immediately CNS symptoms with wide-complex arrhythmia leading to asystole, symptoms resolved with bolus and infusion, CV symptoms recurred later and treated with amiodarone

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Lipid Treatment with CNS/CV Symptoms

- Vadi, Patel, and Stiegler (2014)
  - Posterior psoas compartment block and sciatic nerve block, 15 minutes post block became unresponsive with fixed gaze, 40 minutes post block developed bradycardia, initially treated as a cerebrovascular accident, 45 minutes post block LAST suspected, lipid emulsion given but patient had sustained arrest and expired
- Tsang, Okullo, Field, and Mamo (2016)
  - Thoracic paravertebral block with catheter, 37 minutes post block CNS symptoms with hypertension and tachycardia occurred, symptoms resolved with lipid emulsion bolus and infusion

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Lipid Treatment with CV Symptoms

- Yamane and Kagawa (2015)
  - Thoracic paravertebral block, 2 minutes post block, asystole occurred, CPR performed and lipid emulsion initiated 7 minutes post block, symptoms resolved
- Ludot, Tharin, Belouadah, Mazoit, and Malinovsky (2008)
  - Posterior lumbar plexus block, 15 minutes post block VT occurred, symptoms resolved 2 minutes after lipid emulsion initiation

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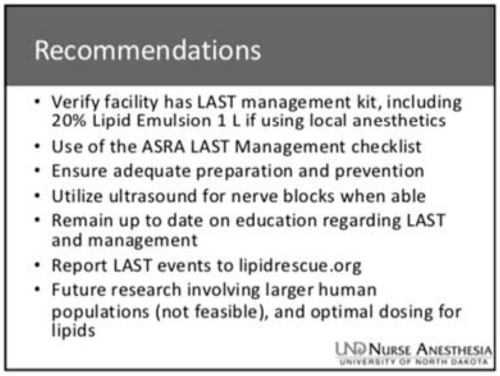
Recommendations
• Verify facility has LAST management kit, including 20% Lipid Emulsion 1 L if using local anesthetics
• Use of the ASRA LAST Management checklist
• Ensure adequate preparation and prevention
• Utilize ultrasound for nerve blocks when able
• Remain up to date on education regarding LAST and management
• Report LAST events to lipidrescue.org
• Future research involving larger human populations (not feasible), and optimal dosing for lipids
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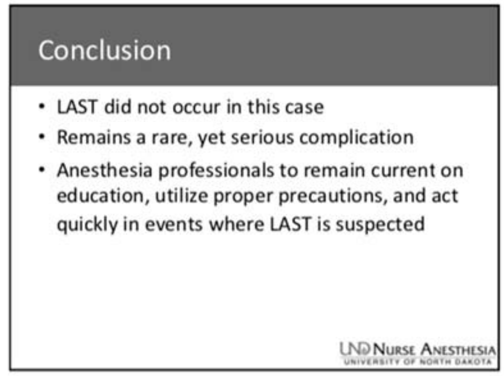
Conclusion
• LAST did not occur in this case
• Remains a rare, yet serious complication
• Anesthesia professionals to remain current on education, utilize proper precautions, and act quickly in events where LAST is suspected
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