2.5 ANCC Contact Hours

Abstract

Local anesthetic systemic toxicity (LAST) is a life-threatening event caused by elevated local anesthetic plasma concentration. It is often unrecognized or misdiagnosed. Peripartum women are at increased risk for toxicity due to pregnancy-related physiological changes. Rising serum drug levels can cause cellular level impairment of mitochondria and voltage-gated ion channels leading to a cascade of symptoms that can end in cardiac arrest. Local anesthetic systemic toxicity can mimic other maternal pathologies but may be considered if local anesthetics have been used. Published treatment guidelines for this event include lipid emulsion which is approved for use in pregnant women. We review LAST in the maternity care setting, published treatment protocols, management of maternity patients with toxicity, and recommendations to increase awareness among maternity care clinicians for this medical emergency.

Key words: Clinical protocols; Emulsion; Lipids; Local anesthetic; Pregnancy; Pregnant women.

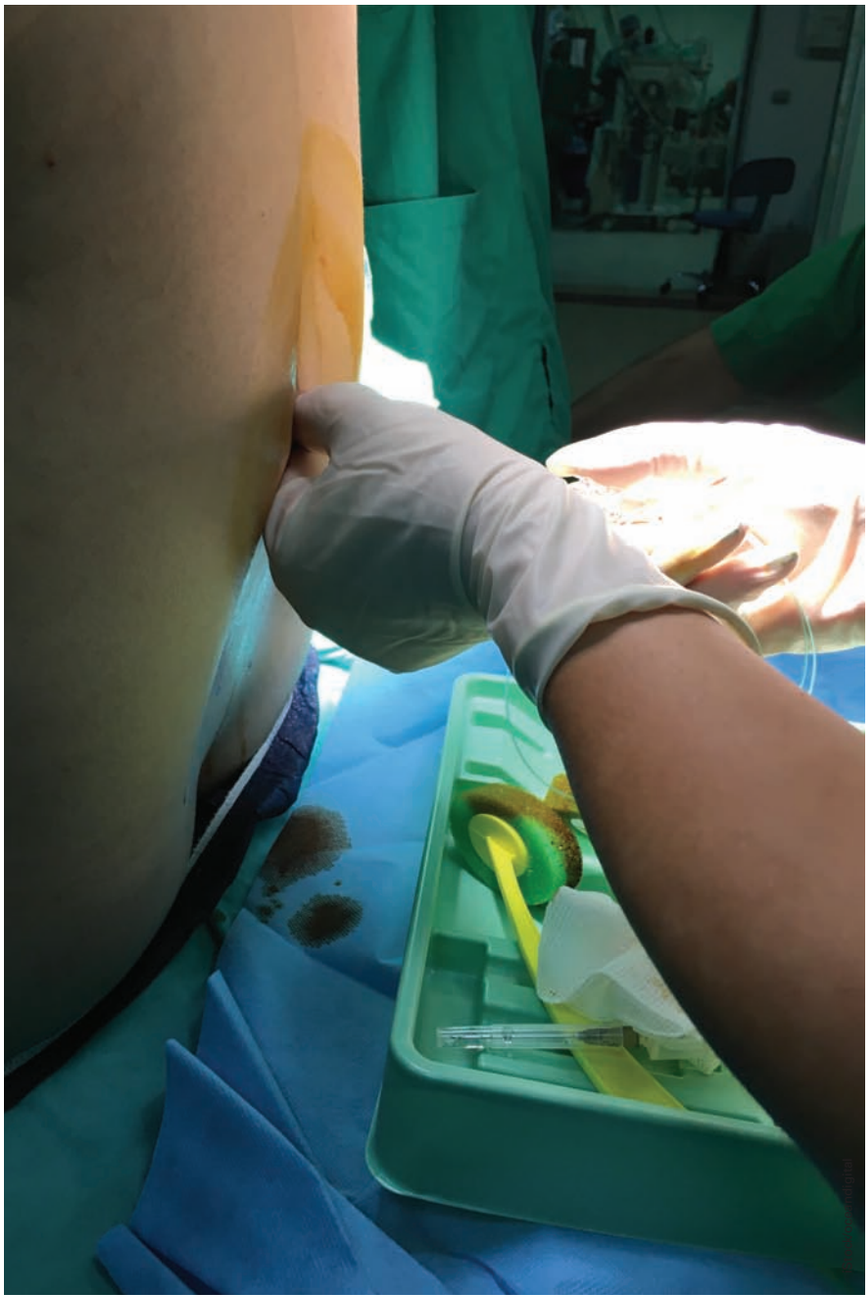
LOCAL ANESTHETIC SYSTEMIC TOXICITY DURING LABOR, BIRTH, AND IMMEDIATE POSTPARTUM: CLINICAL REVIEW

Nicole D. Mock, DNP, CRNA, Kellie M. Griggs, DNP, MSN-Ed, RNC-OB, and Lisa A. Mileto, DNP, CRNA

In 2004, following an uneventful pregnancy, a healthy 30-year-old nurse gave birth at 0847. She had an epidural placed for analgesia during labor that was removed following the birth. Fifteen minutes into the postpartum period a fluid bolus was required for mild hypotension. The intravenous line was connected, and the bolus initiated. Within minutes the woman experienced seizures and cardiac arrest. Despite an extensive resuscitation attempt, she was pronounced dead at 1027. Following this tragic event, it was discovered that the bupivacaine infusion for her epidural had inadvertently been connected to her IV, and 150 mL of bupivacaine was infused intravenously (Sud & Szawarski, 2018; Tran, 2009).

Maternity in-patient deaths are rare, occurring in 0.012% of hospitalized pregnant women annually (Mogos et al., 2020). The Centers for Disease Control and Prevention (CDC, 2019) monitors indicators of in-patient severe maternal morbidity that can lead to poor outcomes. Local anesthetic systemic toxicity (LAST) has been implicated as a contributor to maternal morbidity (CDC) because pregnancy increases the risk for LAST and local anesthetics are frequently used in the maternity care setting.

Local anesthetic systemic toxicity is a low-frequency/high-risk event that results from increased plasma concentration of local anesthetic. A treatment exists today that was not available in 2004. This event is a medical emergency but can be successfully managed if recognized early. The purpose of this article is to discuss LAST, its causes, risk factors, and clinical manifestations,



Pregnancy-related physiological changes can increase the risk for local anesthetic systemic toxicity.

and to review evidence-based treatment guidelines, management of the maternity patient with toxicity, and recommendations to increase awareness.

Overview

Local anesthetics are pH-sensitive lipophilic solutions that penetrate the cell membrane to block sodium channels and can potentially block potassium and calcium channels. Depolarization of the target nerve cell is prevented, blunting sensory and/or motor function. The diameter of the nerve determines the effect of the local anesthetic as small fibers conducting pain or temperature signals are rapidly blocked; and larger fibers conducting pressure signals and muscle tone are affected later. Local anesthetics are categorized as short-acting, intermediate, or long-acting based on pharmacodynamics (Butterworth, 2021). Some of the most frequently used local anesthetics in maternity care are lidocaine and bupivacaine, followed by levobupivacaine, ropivacaine, and chloroprocaine. These drugs bind to alpha-1 glycoprotein in serum and are metabolized by the liver. Epinephrine added to local anesthetics causes localized vasoconstriction slowing absorption of the drug into the vascular system (Butterworth). Local anesthetics can be safely used within limits based on ideal body weight, but these limits are centered on healthy individuals absent of other risk factors (Table 1).

Toxicity occurs when peak plasma levels of the local anesthetic exceed its specified limits by inadvertent intravascular injection or infusion, accelerated absorption in highly vascularized peripheral tissue, large volume dosing, decreased serum protein-binding, and/or delayed drug clearance (El-Boghdadly & Chin, 2016). Early signs of toxicity can include tinnitus, dysgeusia, or mild confusion. If left unchecked, symptoms can progress to seizures, loss of consciousness, cardiac depression, ventricular arrhythmias, and cardiac arrest (Butterworth, 2021).

Incidence

Millions of local anesthetic blocks are performed yearly. Toxicity occurs as transient prodromal symptoms in as many as in 1:500 peripheral nerve blocks, with resuscitation required in 1:1,000 of these cases and 4:10,000 epidurals; however, the true incidence of LAST is unknown (Macfarlane et al., 2021; Mörwald et al., 2017; Toledo, 2011). Misdiagnosis and underreporting result in underestimating true occurrence (Macfarlane et al.).

Most cases are encountered within the surgical suite yet can go unrecognized even by anesthesia professionals (Edwards et al., 2018). Recent data reflect increasing trends in LAST outside of the surgical setting and among nonanesthesia clinicians. Of 36 in-hospital cases reported in peer-reviewed articles between December 2017 and May 2020, 32% occurred in maternity care, radiology, intensive care units, and interventional cardiology (Macfarlane et al., 2021). Of these, 14% occurred during intraurethral or intravaginal injection or perineal nerve block. Another 14% occurred during neuraxial blocks (epidural or paravertebral). One case was reported from transabdominal plane block (Macfarlane et al.). Lidocaine has been implicated in 66% of these reported cases, used individually or mixed with another local anesthetic. Ropivacaine and bupivacaine account for 11% each of reported incidents. The remaining 12% of cases involve other local anesthetics (Macfarlane et al.).

Risk Factors

Both single bolus injections and continuous infusions have caused toxicity. No drug delivery method appears to be safer than another. Risk is influenced by injection site, drug properties, and patient factors.

Injection Site

To achieve the desired effect, some blocks require injection of local anesthetic near nerves in highly perfused tissues. The increased blood flow accelerates absorption of the drug into the central circulation. Local anesthetics absorbed into serum are then delivered to well-perfused organs such as the heart and brain. The propensity for toxicity according to injection site blood flow is Tracheal > Intercostal > Caudal/Epidural/Brachial Plexus > Spinal/Subcutaneous.

Certain injection sites pose a risk for unintentional breach of a blood vessel by the terminal end of the needle. Ultrasound guidance has reduced risk of inadvertent intravascular injection in recent years (Macfarlane et al., 2021), but is not feasible for all injection sites (Christie et al., 2015; El-Boghdadly et al., 2018).

Drug Properties

Concentration of the preferred anesthetic influences the volume used. Higher concentration anesthetics should be used in lower volumes. Local anesthetic toxicities are additive when combined or injected separately within a short time frame. Dosage ratios should be calculated for the toxicity levels of each drug and adjusted downward when more than one local anesthetic is used.

Some anesthetics, such as bupivacaine, have inherent vasodilating properties that can accelerate drug absorption rates (Christie et al., 2015). Bupivacaine is also more lipophilic than other local anesthetics and can accumulate in cardiac tissue and cellular mitochondria at a ratio of 6:1 relative to plasma. This accumulation results in cardiotoxicity and symptoms occurring at plasma levels lower than expected (Gitman et al., 2021).

TABLE 1. LOCAL ANESTHETIC DOSING LIMITS

Local Anesthetic	Maximum Dose without Epinephrine (mg/kg)	Maximum Dose with Epinephrine (mg/kg)
Lidocaine	4.5	7
Bupivacaine	2	3
Levobupivacaine	2	3
Ropivacaine	3	3
Chloroprocaine	11	14

Note. Dosages are based on ideal body weight and nonspecific injection site (University of Iowa Health Care, 2019).

Patient Factors

Among reported cases of LAST, more were related to patient predisposition than to drug overdose or injection site (Macfarlane et al., 2021). Patient-related risk factors for toxicity include extremes of age, low muscle mass, renal, hepatic, or cardiac dysfunction, conduction disorders, acidosis, and pregnancy (El-Boghdadly & Chin, 2016; Macfarlane et al.).

Maternity patients are at an increased risk due to pregnancy-related physiological changes. Decreased alpha-1 glycoprotein levels contribute to increased availability of unbound local anesthetic. Cardiac output is elevated during pregnancy leading to higher tissue perfusion and drug absorption. Expanded blood volume causes epidural venous engorgement increasing drug uptake and poses a risk for catheter migration into the intravascular space (Bern & Weinberg, 2011; Macfarlane et al., 2021). Pregnancy-induced changes in estradiol and progesterone increase cardiac irritability and create a propensity for dysrhythmias. Cardiomyocytes are then more easily aggravated by the sodium channel blocking action of local anesthetics (El-Boghdadly et al., 2018). Advanced maternal age, obesity, or other comorbidities such as preeclampsia can affect drug clearance and compound the risk of toxicity (Bern & Weinberg; El-Boghdadly & Chin, 2016).

Pregnant women receive local anesthetics through epidural infusions or boluses, pudendal or paracervical blocks, and/or subcutaneous injections of the perineum (Choi et al., 2020). Transabdominal plane nerve blocks may be used for postoperative pain control for women who have undergone cesarean birth (El-Boghdadly et al., 2018). Peripheral nerve blocks, epidural bolus dosing, and long-term epidural infusions can result in large volumes of different local anesthetics being used in the presence of existing risk factors and can precipitate toxicity. Resuscitation of pregnant women with LAST is inherently challenging and can be further complicated by gastric reflux with aspiration, limited lung expansion, aortocaval compression, and difficult airway management (Bern & Weinberg, 2011).

Clinical Manifestations

Circulating local anesthetics can affect voltage-gated ion channels of the central nervous system (CNS) and cardiovascular (CV) system. This leads to an evolving constella-

tion of symptoms that can occur in one or both systems, in sequence and in tandem.

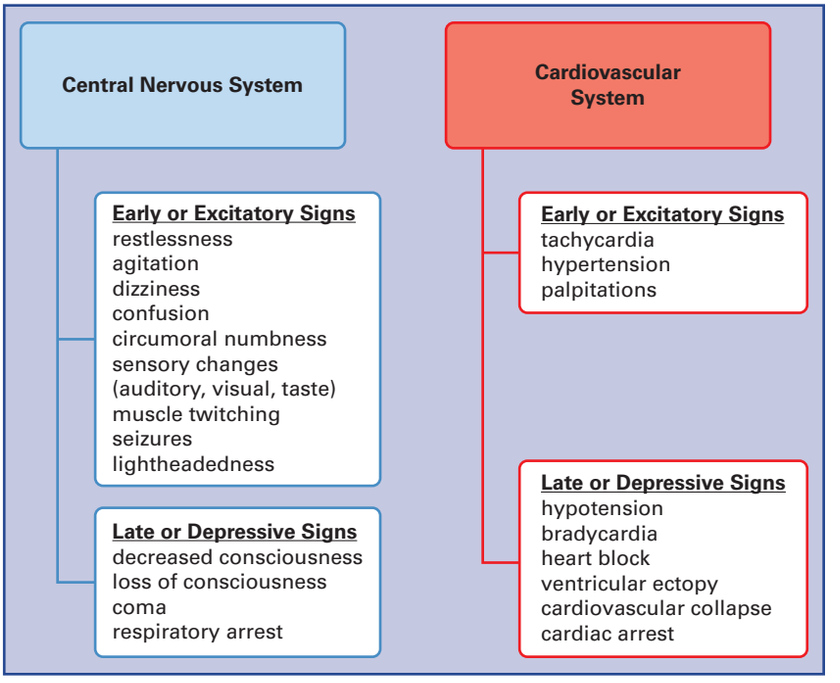
Toxicity has classically been described as manifesting in two phases, early or excitatory and late or depressive phases (Figure 1). Early or excitatory signs within the CNS can include agitation, restlessness, sensory disturbances (visual, auditory, taste), muscle twitching, seizures, or vague complaints of dizziness, circumoral numbness, or confusion (Christie et al., 2015). Late or depressive CNS signs are decreased level of consciousness, loss of consciousness, and respiratory arrest (Christie et al.). Toxicity worsens as hypoxia leads to acidosis and more offending drug becomes available in the plasma as pH drops. Central nervous system signs can be obscured by sedating medications or preexisting neurologic deficits.

The same excitatory and depressive phases can occur in the CV system. Early or excitatory signs of CV toxicity are tachycardia and/or hypertension. Late or depressive signs appear as sodium channels, and sometimes potassium and calcium channels, within the heart are blocked leading to dysrhythmias, conduction blocks, ventricular ectopy, and ensuing myocardial depression with blood pressure instability. These can devolve to profound hypotension, bradycardia, CV collapse, and asystole (Christie et al., 2015; Macfarlane et al., 2021).

Although these phases are described separately, moving from early to late phases may not be well delineated in individual clinical cases. Symptoms may seem to occur simultaneously in a quickly evolving event. Manifestations of both CNS and CV signs are indicative of probable mitochondrial impairment resulting in cellular adenosine triphosphate depletion, a sign of severe toxicity (Macfarlane et al., 2021).

Immediate onset of symptoms of toxicity from direct intravascular injection can manifest within 5 minutes or less. However, symptoms can be delayed by up to an hour or more through prolonged absorption of local anesthetic deposited into peripheral tissues or by continuous infusions. Reporting from the 36 published cases from 2017 to 2020 shows 53% of cases occurred within 10 minutes of injection. Nineteen percent appeared within the first hour and 16% occurred in 1 to 12 hours or more (Macfarlane et al., 2021).

FIGURE 1. PROGRESSION OF SIGNS AND SYMPTOMS OF LOCAL ANESTHETIC SYSTEMIC TOXICITY



Evidence-Based Treatment Guidelines

Prior to 2010 the standard treatment for local anesthetic toxicity was cardiopulmonary bypass, an intervention not available to all patients. In 2010, the American Society of Regional Anesthesia and Pain Medicine (ASRA) first established the evidence-based treatment guidelines for LAST using modified advanced cardiac life support (ACLS) paired with intravenous lipid emulsion (ASRA, 2020; Weinberg, 2012).

Modified ACLS

Advanced cardiac life support is modified for this specific event by limiting vasopressin or epinephrine to small doses. Suppression of cellular activity by high plasma concentrations of local anesthetics render these standard resuscitative medications only slightly effective and they can hinder the beneficial action of lipid emulsion (Macfarlane et al., 2021). The intense vasoconstriction caused by vasopressin can lead to pulmonary edema and reduced tissue perfusion hampering resuscitation efforts (Neal et al., 2010; Toledo, 2011). Calcium channel blockers, beta blockers, and local anesthetics used to treat arrhythmias, such as lidocaine, should be avoided (ASRA, 2020). Amiodarone is the preferred antidysrhythmic agent. Seizures should be treated using a benzodiazepine.

Lipid Emulsion Therapy

Lipid emulsion therapy, sometimes referred to as lipid rescue, is the prescribed antidote for LAST. Lipid emulsion is a 20% solution that creates a concentration gradient that extracts local anesthetics from plasma and reverses toxicity through several mechanisms. Positively charged local anesthetics in vulnerable tissues of the heart and brain are drawn by the negatively charged lipid particles

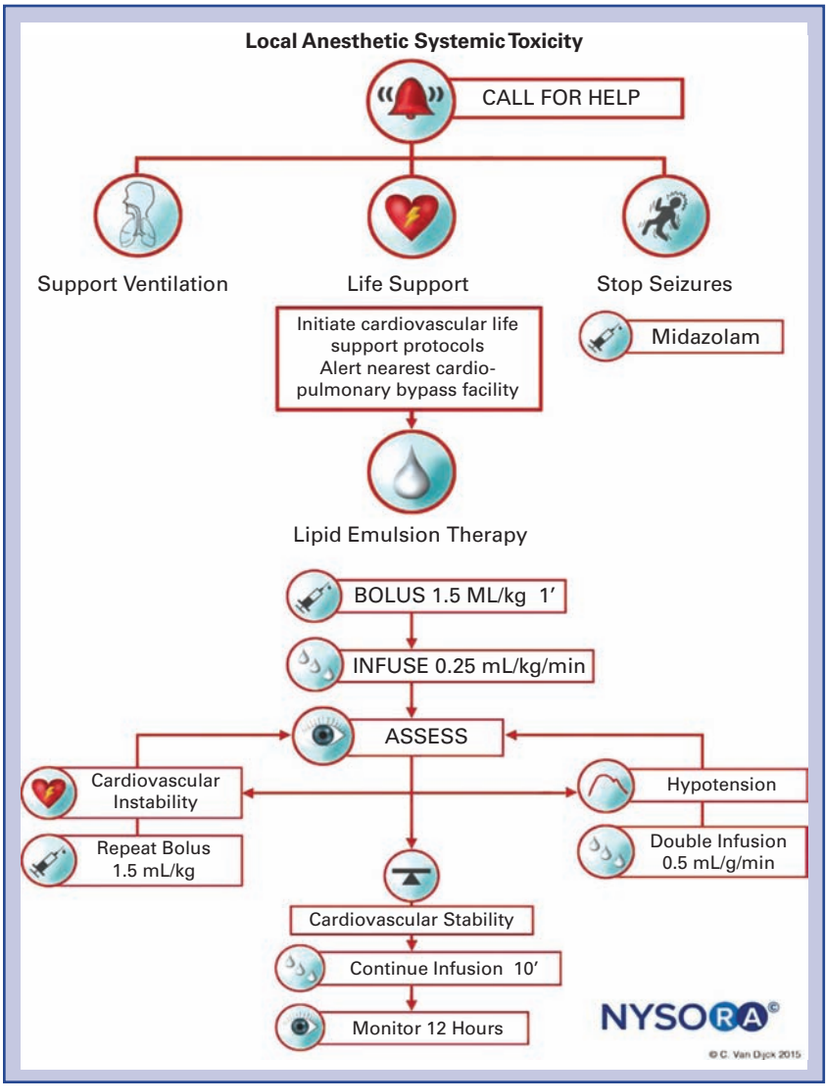
to be redistributed to other high blood flow organs such as the liver and skeletal muscle. Lipid emulsion acts in reversing mitochondrial impairment and sodium channel blockade. Resuscitation outcomes are improved as it has also shown to increase cardiac contractility and block reperfusion injury (Macfarlane et al., 2021).

Lipid emulsion is delivered intravenously in an initial weight-based bolus of 1.5 mL/kg over 1 minute, followed by an infusion of 0.25 mL/kg/min. The goals are seizure cessation, neurologic recovery, and cardiac/hemodynamic stability. If symptoms persist after initial bolus, a second bolus may be delivered. The infusion may be titrated upwards for continuing hypotension and is continued for at least 15 minutes beyond stabilization. The additional infusion time helps avoid recurrence of symptoms caused by residual circulating local anesthetic not removed by the initial bolus(es). A limit of 12 mg/kg of lipid emulsion is suggested. Monitoring of vital signs, cardiac rhythm, and neurologic status will continue for several hours postevent (ASRA, 2020). See Figure 2 for Local Anesthetic Systemic Toxicity treatment checklist (Gitman et al., 2021).

Lipid Emulsion Side Effects

Potential side effects of lipid emulsion include allergic reaction, hyperamylasemia, interference with certain lab values, bronchospasm, and chest pain (Gitman et al., 2021). Despite the possibility of these side effects better outcomes have been associated with early lipid administration. Local anesthetic plasma concentrations continue to rise as more time passes, so experts recommend not waiting until other traditional resuscitative measures have failed. Lipid emulsion should be administered concurrently with airway management (Macfarlane et al., 2021; Ozcan & Weinberg, 2011). This treatment has been approved for use in pregnant women by the American Heart Association and international committees (Lavonas et al., 2015; Neal et al., 2018), and is recommended to be accessible to maternity care clinicians (Bowsher et al., 2018).

FIGURE 2. CHECKLIST FOR MANAGEMENT OF LOCAL ANESTHETIC SYSTEMIC TOXICITY



Toxicity in the Maternity Care Setting

Maternity Case Reports

Few maternal cases of LAST are published in current literature, although experts believe reporting in this population is likely skewed low (Lin et al., 2017). This event can go unrecognized in this group, misdiagnosed, or may go unreported; and local anesthetic toxicity in pregnant women has not been part of randomized clinical trials (Edwards et al., 2018). Lipid emulsion has been used in several cases involving pregnant women resulting in positive mother and baby outcomes (Table 2).

Management of Maternal Local Anesthetic Systemic Toxicity

Initial Actions

Assessment, situational awareness, timely response, and communication are important to promote optimal outcomes in this maternal high-risk event (Griggs & Woodard, 2019). Assessment should include vital signs, maternal heart rate/rhythm/regularity, fetal heart rate changes, subjective patient information, and objective signs noted. Local anesthetic systemic toxicity can evolve rapidly and assessment should be continuous if suspicion is high. Initial actions

TABLE 2. PUBLISHED CASE REPORTS OF LAST IN MATERNITY CARE

First Author and Date	Context	Clinical Presentation	Treatment	Outcome
Castro-Lalin (2020)	26 weeks pregnant, fetal thoracentesis procedure under lidocaine infiltration	Dizzy, short of breath, slurred speech, loss of consciousness, seizures, respiratory arrest	Lipid emulsion bolus and infusion, advanced airway management, intensive care unit	Cesarean performed for preterm labor; patient awakened after surgery neurologically intact and stable
Lin (2017)	29-year-old woman; combined spinal and epidural	50 minutes later, tinnitus, dysgeusia, tachycardia, "out of body" perception	Lipid emulsion following 2010 guidelines	Symptoms resolved within 10 minutes; healthy mother and baby
Ozcan (2011)	Active labor, epidural with bupivacaine	Not specified	Lipid emulsion, following 2010 guidelines, basic life support	Full recovery and birth of healthy baby
Singh (2019)	28-year-old woman in active labor; epidural with bupivacaine bolus and continuous infusion	15 minutes later, twitching, hypertension, tachycardia, fetal heart rate decelerations	Lipid emulsion following 2018 guidelines, cesarean birth	Symptoms resolved within minutes, healthy mother and baby
Spence (2007)	18-year-old woman, hypertension, proteinuria, induction of labor, epidural with bupivacaine bolus and continuous infusion	15 minutes later, severe hypertension, tachycardia, agitation, confusion, twitching, unresponsiveness, fetal bradycardia	Lipid emulsion, benzodiazepine, basic life support, cesarean	Return of consciousness in less than 1 minute, healthy mother and baby discharged in usual time frame
Sud (2018)	1-hour postpartum, inadvertent intravascular infusion of bupivacaine	Grand mal seizures, ventricular fibrillation, cardiac arrest	Standard resuscitation measures, no lipid emulsion	Death
Weiss (2014)	Postoperative cesarean, transabdominal plane block with levobupivacaine for postoperative pain control	10 minutes later, tonic-clonic seizures	Lipid emulsion, supportive care	Recovered within minutes
Weiss (2014)	Postoperative cesarean, transabdominal plane block with ropivacaine for postoperative pain control	25 minutes later, generalized seizures	Lipid emulsion, assisted ventilation with Bag-Valve-Mask	Successfully resuscitated and fully recovered

are similar to those in other medical emergencies and include: (1) Stop any local anesthetic infusion, (2) call for help, (3) apply 100% oxygen and support ventilation, (4) ensure adequate intravenous access, and (5) have resuscitation equipment available. This is a potentially fatal event that requires a team effort to treat. At least one member should remain with the patient, ensuring adequate ventilation and safety in the event of seizure activity. Others should call for the rapid-response or resuscitation team and retrieve lipid emulsion. Contextual information is important to communicate in this event (Figure 3). Close the information gap for responding team members and suggest assessing for local anesthetic toxicity as it can mimic other maternal pathologies such as preeclampsia. In the context of preeclampsia, seizures from LAST versus eclampsia are indistinguishable. If LAST is suspected, proceed with lipid emulsion which quickly reverses symptoms if local anesthetic toxicity is the root cause.

Next Steps

Lipid emulsion should be administered as soon as it is available. Using a large syringe, an initial bolus administration should be delivered intravenously over 1 minute while another team member prepares the infusion set/pump. Continuous lipid infusion can begin once the bolus has been given. Clinical presentation will dictate other necessary interventions such as benzodiazepines for seizures or cardiopulmonary resuscitation. Follow the LAST Treatment Guidelines (Figure 2). Prepare for rapidly changing conditions. Anticipate a possible emergency transfer to the operating room for a surgical birth. The maternity patient who has been treated for LAST may be monitored in intensive care and/or may have additional medical providers collaborating in her care, such as cardiologists or intensivists.

Patient Teaching

Early recognition leads to early treatment. Initial signs of LAST can be easily dismissed by the patient or obscured

Credit / Photo Credit

Toxicity can mimic other high-risk conditions of pregnancy and may be considered if local anesthetics have been used.

by the dynamics of labor. Women should be instructed to report any of the following when local anesthetics are being used: sensory changes (auditory, visual, taste); confusion, agitation, uneasiness, or dread; muscle twitching; numbness around the mouth; dizziness or lightheadedness; and palpitations.

Impacts

Lipid emulsion has emerged as the definitive treatment for this event, but deaths still occur despite lipid administration. This happens if local anesthetic plasma concentrations are beyond what can be reversed, if lipid emulsion is given too late, or following other measures that hinder its action. Cardiac dysfunction from toxicity or other preexisting conditions can inhibit delivery of lipid solution to the capillary level where it is needed; and other comorbidities may prevent successful resuscitation (Macfarlane et al., 2021).

Although the focus of this article is on maternity patients, it is important to be aware of possible toxicity occurring in newborns related to local anesthetics crossing the placental membrane. Toxicity in newborns has been reported following nerve blocks of the perineum or cervix. Newborns with high serum levels of local anesthetics have experienced seizures, bradycardia, heart block, and apnea (Demeulemeester et al., 2018). Treatment for neonates has been reported to be successful using lipid emulsion therapy (Gitman et al., 2021). When local anesthetics have been used, it is important to monitor both the mother and baby for any adverse effects.

Recommendations

Maternity nurses are frontline experts positioned to identify and respond to subtle or worsening changes in patients (Gillespie et al., 2021; Mhyre et al., 2014). Optimal outcomes in cases of LAST depend on early recognition of signs and symptoms and timely administration of lipid emulsion. Interprofessional education is important to fostering awareness and knowledge of LAST. Opportunities for shared educational experiences between maternity nurses and anesthesia clinicians may include interdepartmental in-services, unit meetings, planned educational days, or invitational shadowing.

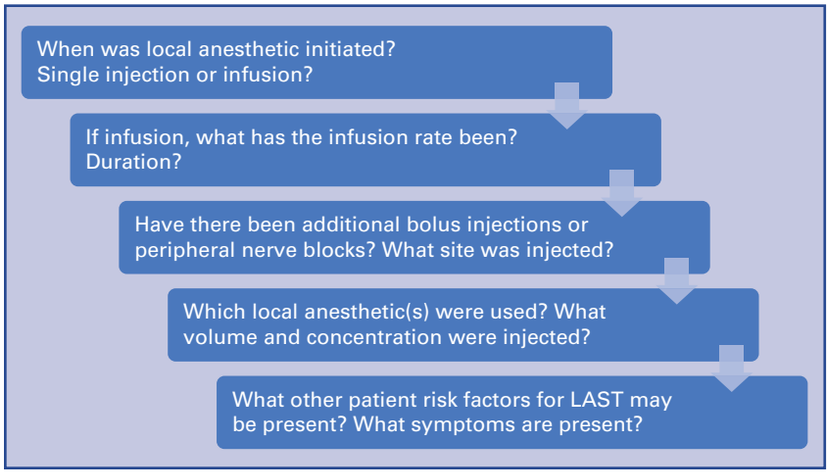
Continuing education is vital to maintaining readiness. Interprofessional annual drills may help to reinforce knowledge for infrequent/high-risk events such as this. It is recommended that all maternity care team members participate in LAST simulations focused on education, identification, and treatment.

Access to lipid emulsion solution is key. There is no standardized protocol among hospitals for the location of lipid rescue kits (Toledo et al., 2013). If it is stored outside the maternity care unit, additional time will be needed for retrieval. A plan should be formulated for quick access to this medication for maternity patients (Toledo et al.). A collaborative approach that includes maternity nurses, anesthesia providers, pharmacists, physicians, and risk management professionals can result in effective safety protocols guiding lipid emulsion storage, resuscitation planning, and policy development.

Clinical Implications

Local anesthetics are important pharmacological tools to aid in the care and comfort of maternity patients yet

FIGURE 3. SITUATIONAL INFORMATION ASSESSMENT



SUGGESTED CLINICAL IMPLICATIONS

- Evidence-based treatment guidelines for local anesthetic systemic toxicity include lipid emulsion which is approved for pregnant women.
- Local anesthetic toxicity is a rapidly evolving event requiring a team to initiate life-saving interventions.
- LAST can mimic other conditions and should be considered if local anesthetics have been used.
- Toxicity can occur in mothers or neonates and both should be monitored for adverse effects if using local anesthetics.
- Maternity patients should be instructed about what symptoms to report, and maternity nurses should be aware of subtle early warning signals of toxicity.
- Increased plasma concentrations of local anesthetics are potentially fatal yet easily treated if recognized early.
- Interdisciplinary collaboration and education is the most effective approach for developing policies for anesthetic complications in maternity care.

do carry the risk of systemic toxicity. Physiological changes inherent to pregnancy increase the chances of LAST, which can be misdiagnosed or go unidentified in this group. Maternity nurses should be aware of subtle warning signs of LAST and patient teaching is vital for early reporting of possible symptoms. Local anesthetic toxicity is a rapidly evolving, potentially fatal event that may be easily and effectively reversed with prompt recognition and use of lipid emulsion.

Interdisciplinary collaboration is the most effective strategy for developing safeguards and policies for anesthetic complications in maternity care. Such policies should address lipid emulsion accessibility and a LAST treatment plan specific to the maternal patient. Ongoing interprofessional education fosters sustainability of awareness and proficiency in responsiveness. This multidisciplinary approach can increase the chances of successful maternal outcomes in cases of LAST. ✣

Dr. Nicole D. Mock is a Nurse Anesthetist, Department of Anesthesiology, Harnett Health, Dunn, NC. Dr. Mock can be reached via email at ndmock@outlook.com

Dr. Kellie M. Griggs is an Assistant Professor, Department of Academic Nursing, Wake Forest University School of Medicine, Winston-Salem, NC.

Dr. Lisa A. Mileto is Director for Doctoral Education, and Assistant Professor, Department of Academic Nursing, Wake Forest University School of Medicine, Winston-Salem, NC.

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