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Two for One: A Case Report of Intravenous Lipid Emulsion to Treat Local Anesthetic Systemic Toxicity in Term Pregnancy

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Abstract

Combined spinal–epidural (CSE) analgesia is a frequently used method of labor analgesia. Although it is considered safe and effective, CSE can be complicated by local anesthetic systemic toxicity (LAST), a potentially life-threatening condition. We present a case of LAST that developed in a primigravida 50 minutes after uneventful placement of a CSE. Her symptoms resolved within 10 minutes of administering intralipid emulsion. She subsequently underwent cesarean delivery under spinal anesthesia for failure to progress without sequelae in the mother or infant. LAST in pregnancy can occur at traditionally subthreshold dosing; anesthesiologists must be vigilant to ensure prompt and effective treatment.

Combined spinal–epidural (CSE) analgesia is widely used as a safe and effective method of labor analgesia. Many regional anesthetic procedures, however, are associated with the risk of local anesthetic systemic toxicity (LAST). LAST is a well-known complication of regional anesthesia with an estimated incidence of up to 1 per 500 peripheral nerve blocks.¹ The incidence of LAST during epidural anesthesia has been estimated at 4 per 10,000 epidural procedures.^{2,3} Furthermore, pregnancy is known to increase sensitivity to local anesthetics and thus increase the risk of LAST.^{1,4} Pregnancy is associated with decreased protein binding of local anesthetics (and thus increased free fraction), increased risk of arrhythmias as a result of hormonal effects on cardiomyocytes, and increased neuronal

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sensitivity to local anesthetics.¹ Engorgement of epidural veins can lead to an increased risk of systemic absorption and/or accidental intravascular injection of local anesthetic. Because the rarity and severity of LAST make its study difficult, case reports provide a valuable opportunity to further characterize risk factors for LAST and guide its management.

We present a case of LAST on the obstetric floor that presented 50 minutes after uneventful placement of a CSE. Neurologic symptoms promptly subsided after administration of intralipid emulsion, and no adverse effects developed in the mother or the fetus. Our institution maintains a secure procedure log and quality assurance database where procedure-related complications are reported. Since the implementation of this database 10 years ago, this is the first reported case of LAST in a parturient who received a CSE for labor analgesia at our facility. All other reported events of LAST have been related to peripheral nerve block placement. Written consent to report this case was obtained from the patient.

CASE DESCRIPTION

A 29-year-old primigravid woman with a history of congenital renal malformation presented to our hospital for scheduled induction of labor at 39 weeks 3 days of gestation. Her medical history and obstetric history were otherwise unremarkable. She denied any earlier problems or complications with anesthesia. Her allergies included latex, levofloxacin, and ceftriaxone. Her vital signs were within normal limits, and she was 5 ft 4 in tall and weighed 87.3 kg. On physical examination, she was in no acute distress and exhibited the normal physical changes of pregnancy. Her prenatal laboratory values were unremarkable except for a mildly elevated serum creatinine level of 1.00 mg/dL (normal range 0.4–0.8 mg/dL during pregnancy), an albumin level of 1.9 g/dL (reference range 3.9–5.0 g/dL), and a total protein of 3.9 g/dL (reference range 6.3–8.2 g/dL).

The patient requested an epidural as a result of labor pain and was assessed by the anesthesia team for CSE placement. Standard monitors were placed, sodium citrate was administered orally for aspiration prophylaxis, and an IV infusion of crystalloid was started for intravascular preloading. The patient was placed in a sitting position. Her back was cleansed with 2% chlorhexidine and draped in a sterile fashion. The skin and subcutaneous tissue overlying the L4–L5 interspace were infiltrated with 2 mL of 1% lidocaine. A 17-gauge Tuohy needle was advanced and loss of resistance was appreciated at 5.5 cm with a technique utilizing air. A 26-gauge Gertie Marx needle (International Medical Development, Huntsville, UT) was advanced beyond the dura into the subarachnoid space. After confirmation of flow of cerebrospinal fluid (CSF) through the spinal needle, a mixture of 0.5 mL of 0.25% bupivacaine and 0.3 mL of fentanyl 50 µg/mL was administered intrathecally. The spinal needle was withdrawn and a 19-gauge flexible spring wound epidural catheter (Arrow FlexTip Plus Epidural Catheter; Teleflex, Research Triangle Park, NC) was advanced into the epidural space to a depth of 11 cm at the skin. The patient was repositioned supine immediately after catheter fixation. Sensory testing with ice revealed an upper extent of her analgesia at the T10 level. After negative aspiration for heme or CSF with a 3-mL syringe and a negative 3-mL test dose (lidocaine 1.5% and epinephrine 1:200,000), a patient-controlled epidural anesthetic (PCEA) infusion of bupivacaine 0.1%

and fentanyl 2.5 µg/mL was started at a basal rate of 6 mL/h with a bolus of 6 mL, a lockout period of 10 minutes, and a maximum bolus frequency of 3 boluses per hour. A single 6-mL bolus was delivered through the epidural pump immediately after the test dose. Vital signs remained stable and fetal heart tones were reassuring throughout the procedure.

Fifty minutes after administration of the first local anesthetic, the patient reported symptoms of tinnitus and metallic taste. She exhibited a narrow-complex sinus tachycardia at 130–140 beats per minute and maintained a normal blood pressure. She was positioned in left uterine displacement and was given supplemental oxygen. Her clinical course was reviewed, and it was determined that no other medications had been administered since CSE placement. She began to experience palpitations, stating that “something was off” and that she was “having an out-of-body experience.” A presumptive diagnosis of LAST was made on the basis of her rapidly evolving symptoms. The PCEA infusion was stopped, and 1.5 mL/kg of 20% intralipid emulsion was given as a bolus with an infusion started afterward at 0.25 mL/kg/min. The patient’s symptoms resolved within 10 minutes of intralipid emulsion administration, which was continued for an hour after symptom resolution. The pre-existing epidural catheter was subsequently removed and the tip was noted to be intact but blood-tinged. Review of the epidural pump record revealed a total of 24 mL of bolus deliveries. Fetal heart tones throughout this period were normal, and the decision was made to continue with induction of labor.

Two hours later, the patient underwent an urgent primary cesarean delivery for arrest of active descent. A repeat CSE was performed successfully at the L3–L4 level with 1.4 mL of 0.75% bupivacaine administered intrathecally without complications. An epidural catheter was advanced into the epidural space but was never dosed. The patient delivered a healthy female neonate with Apgar scores of 9, 9, and 9 and was transferred to the recovery room in stable condition. As per the American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines, she was monitored overnight in the recovery room and the next morning she was transferred to the hospital floor. Her hospital course thereafter was uneventful, and she was ultimately discharged home with her baby on hospital day 5.

DISCUSSION

Our differential diagnosis initially included drug allergy, pulmonary embolism, hemodynamically stable supraventricular tachycardia, anxiety, and LAST. We were able to rule out drug allergy, because the patient did not manifest any of the typical signs of type 1 hypersensitivity or anaphylaxis (eg, urticaria, bronchoconstriction, hypotension). The patient’s presentation was compatible with the remaining diagnoses. Pulmonary embolism may present with normoxia, altered mental status, tachypnea, tachycardia, and hypertension; supraventricular tachycardia is relatively common in pregnancy as a result of the cardiovascular demands of labor and the effects of circulating catecholamines; and anxiety may also present similarly. However, given the nature and progression of her symptoms in the context of a PCEA infusion, we established a working diagnosis of LAST.

A number of measures were taken in this case to minimize the risk of LAST. First, a CSE was used. An intrathecal bolus dose of local anesthetic is significantly smaller than an

epidural dose and if accidentally injected intravascularly would not be sufficient to exceed the toxic threshold for LAST. Second, dilute concentrations of bupivacaine were used. Third, attention was paid to aspirating both the spinal needle as well as the epidural catheter to avoid accidental intravascular administration of local anesthetic. Fourth, the PCEA setup was limited to 3 boluses an hour with a 10-minute lockout to help minimize the local anesthetic dose. Finally, a flexible spring wound catheter was used to avoid vascular trauma. Nevertheless, this case exhibited pathognomonic prodromal symptoms of LAST.

We theorize that in the 50 minutes that elapsed between the placement of the CSE and her symptoms, the epidural catheter either migrated or was accidentally placed intravascularly. Thus, the PCEA infusion of local anesthetic was absorbed intravascularly and caused the patient to develop symptoms of LAST. The patient also activated her PCEA the maximum number of times within the 50-minute time period that led to maximal dosing of local anesthetic. Moreover, the patient exhibited mild renal insufficiency and profound hypoalbuminemia. The combination of these effects (decreased renal clearance and protein binding) may have increased her serum-free fraction of bupivacaine beyond the toxic threshold, contributing to the development of LAST at an unusually low dose. Of note, aspiration of the catheter before its removal was negative for blood, CSF, or local anesthetic, but this test is not sensitive for intravascular placement of an epidural catheter. The patient's prompt response to intralipid emulsion and the blood-tinged appearance of the epidural catheter tip on removal may support our hypothesis but cannot confirm it.

We believe that this case highlights some of the potential prodromal signs of LAST in the context of the heightened sensitivity of parturients to local anesthetics. First, the symptoms were primarily central nervous system manifestations of LAST without cardiovascular progression despite the narrow margin between cerebral and cardiovascular toxicity for bupivacaine.⁵ Since publication of the ASRA guidelines, a review of LAST cases by Vasques et al⁶ suggests that more patients have been presenting in a delayed fashion with only neurologic symptoms, possibly as a result of heightened recognition of the signs and symptoms of LAST. Second, the patient developed LAST despite receiving a small dose of bupivacaine. Knudsen et al⁷ reported an average maximum tolerated dose of 103 mg bupivacaine in healthy male volunteers, in which 0.5% bupivacaine was infused IV at a rate of 10 mg/min. In our case, the patient received a 45-mg lidocaine test dose and 29.25 mg bupivacaine over 50 minutes (four 6-mL boluses of 0.1% bupivacaine, 40 minutes of a 6-mL/h continuous infusion of 0.1% bupivacaine, and an intrathecal dose of 1.25 mg), resulting in an average rate of administration of 0.5 mg bupivacaine per minute. This supports the notion that pregnancy sensitizes the parturient to the effects of local anesthetic.

Our case report does have several limitations. First, we were unable to draw serum bupivacaine levels during the event to confirm the diagnosis. Because of the relative rarity of these events on our labor and delivery floor, we did not have the resources to obtain confirmatory laboratory testing. Nevertheless, the patient's constellation of signs and symptoms as well as her response to treatment are suggestive of LAST. Second, although we did note her excitatory cardiovascular signs (eg, tachycardia, hypertension), we were unable to rapidly obtain a 12-lead electrocardiogram during the patient's LAST event. Acknowledging that a formal electrocardiogram could elucidate the precise nature of the

patient's tachydysrhythmia, we opted for empiric diagnosis and treatment to avoid delay. Third, recent studies in volunteers suggest that intralipid emulsion administration may not affect the severity or duration of purely neurologic symptoms of LAST.^{8,9} This would seem to challenge our presumptive treatment of the patient's neurologic symptoms with intralipid emulsion. However, in a rapidly evolving clinical setting, it is not possible to determine whether the symptoms of LAST are purely neurologic; furthermore, the decreased threshold for LAST in pregnancy clouds the picture. Indeed, rapidly developing central nervous system symptoms accompanied by tachycardia, hypertension, tachypnea, and altered mental status are red flags suggesting impending LAST that should not go ignored. Akin to other medical emergencies such as tension pneumothorax, LAST is a clinical diagnosis, and its treatment cannot be delayed by laboratory confirmation. Because we could not predict the likelihood of severe maternal or fetal toxicity, we promptly administered intralipid emulsion in accordance with the ASRA checklist on the management of LAST.¹⁰

To our knowledge, this is only the third case report on the successful use of intralipid emulsion to manage LAST in a parturient.^{11,12} Spence¹¹ reported a case of LAST in 2007 in which symptoms of LAST developed immediately after epidural bolus administration of 50 mg bupivacaine (preceded by administration of an 80-mg lidocaine test dose and 15 mg bupivacaine 15 minutes before).¹⁰ The patient slowly developed tachycardia and hypertension over the 15-minute period, and after the epidural bolus injection, she subsequently developed restlessness, agitation, seizures, and ultimately lost consciousness; she also developed fetal bradycardia necessitating emergent cesarean delivery. The patient regained consciousness within 30 seconds of treatment with intralipid emulsion. Diaz et al¹² reported a case of LAST in 2012 in a term parturient that developed approximately 45 minutes after epidural bolus injection with 340 mg lidocaine for cesarean delivery (preceded by 34.25 mg levobupivacaine administered epidurally over 3 hours 30 minutes).¹¹ Over a period of 5 minutes, the patient became progressively hypotensive and nauseated, accompanied by drowsiness, hand tremors, nystagmus, and then loss of consciousness. The patient regained consciousness within 3 minutes of treatment with intralipid emulsion. In both cases, the signs and symptoms of LAST progressed to the point of loss of consciousness, which was rapidly reversed with intralipid emulsion therapy, and in both cases, no adverse effects were reported. We are happy to report that in our case, both the neonatal and obstetric outcomes were optimal. No short- or long-term adverse outcomes were observed with the administration of intralipid emulsion, and the baby did not manifest any postnatal symptoms of LAST or developmental issues over the 2.5 years that elapsed since the event.

In conclusion, LAST is a rare and potentially devastating complication of regional anesthesia. Although it is now more commonly seen with peripheral nerve blocks than neuraxial blocks, a high degree of vigilance for the signs and symptoms of LAST is recommended during epidural or CSE placement.⁶ In the case of a possible LAST event, the timing of intralipid emulsion administration should be based on the severity and evolution of the symptoms, in accordance with the ASRA checklist on the management of LAST.¹⁰ In our case, the patient exhibited rapidly evolving symptoms of LAST; early administration of intralipid emulsion was likely critical to the outcome.

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REFERENCES

1. Bern S, Weinberg G. Local anesthetic toxicity and lipid resuscitation in pregnancy. *Curr Opin Anaesthesiol* 2011;24:262–267. [PubMed: 21494132]
2. Toledo P, Nixon HC, Mhyre JM, Wong CA, Weinberg G. Brief report: availability of lipid emulsion in United States obstetric units. *Anesth Analg* 2013;116:406–408. [PubMed: 23267002]
3. Mulroy MF. Systemic toxicity and cardiotoxicity from local anesthetics: incidence and preventive measures. *Reg Anesth Pain Med* 2002;27:556–561. [PubMed: 12430104]
4. Griffiths JD, Le NV, Grant S, Bjorksten A, Hebbard P, Royse C. Symptomatic local anaesthetic toxicity and plasma ropivacaine concentrations after transversus abdominis plane block for Caesarean section. *Br J Anaesth* 2013;110:996–1000. [PubMed: 23454825]
5. de Jong RH, Ronfeld RA, DeRosa RA. Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. *Anesth Analg* 1982;61:3–9. [PubMed: 7198411]
6. Vasques F, Behr AU, Weinberg G, Ori C, Di Gregorio G. A review of local anesthetic systemic toxicity cases since publication of the American Society of Regional Anesthesia Recommendations: to whom it may concern. *Reg Anesth Pain Med* 2015;40:698–705. [PubMed: 26469367]
7. Knudsen K, Beckman Suurkula M, Blomberg S, Sjövall J, Edvardsson N. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. *Br J Anaesth* 1997;78:507–514. [PubMed: 9175963]
8. Heinonen JA, Litonius E, Salmi T, et al. Intravenous lipid emulsion given to volunteers does not affect symptoms of lidocaine brain toxicity. *Basic Clin Pharmacol Toxicol* 2015;116:378–383. [PubMed: 25207682]
9. Dureau P, Charbit B, Nicolas N, Benhamou D, Mazoit JX. Effect of Intralipid® on the dose of ropivacaine or levobupivacaine tolerated by volunteers: a clinical and pharmacokinetic study. *Anesthesiology* 2016;125:474–483. [PubMed: 27404223]
10. Neal JM, Mulroy MF, Weinberg GL; American Society of Regional Anesthesia and Pain Medicine. American Society of Regional Anesthesia and Pain Medicine checklist for managing local anesthetic systemic toxicity: 2012 version. *Reg Anesth Pain Med* 2012;37:16–18. [PubMed: 22189574]
11. Spence AG. Lipid reversal of central nervous system symptoms of bupivacaine toxicity. *Anesthesiology* 2007;107:516–517.
12. Diaz J, Bernasinski M, Malinovsky JM. Reversal of neurologic symptoms related to lidocaine toxicity with a lipid emulsion administration. *Ann Fr Anesth Reanim* 2012;31:647. [PubMed: 22749556]