Update on Local Anesthetic Systemic Toxicity

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Objectives

• Participants will be able to describe a number of changes to practice which may result in a reduced incidence of Local Anesthetic Systemic Toxicity (LAST) to patients receiving nerve blocks.
• Participants will be able to describe how LAST may present in their patient.
• Participants will be familiar with the current LAST guidelines published by the American Society of Regional Anesthesia.
• Participants will be able to describe possible mechanisms of action for intravenous lipid emulsion (ILE) when used in patients who are experiencing LAST.
• Participants will be able to describe possible adverse effects of ILE.
Workflow

• Pre-block phase
  – Planning: equipment, drugs, patient selection

• Block phase
  – Execution of block: checklist, monitoring, symptoms

• Local Anesthetic Systemic Toxicity (LAST)
  – Guideline for resuscitation and reasons, checklist use, mechanisms of lipid emulsion (ILE), toxicity of ILE
Pre-Block phase

• Available Resuscitation Equipment
  – “We strongly advise that those using local anesthetics (LA) in doses sufficient to produce LAST establish a plan to manage this complication. Making a LA toxicity kit and posting instructions for its use are encouraged”\(^1\)
  – Lipid Emulsion and a Checklist
    • Use of the ASRA checklist improved medical management and performance during simulated LAST \(^2\)
    • Academic OB units\(\rightarrow 88\%\) has ILE on unit, 95% had it available within less then 30 minutes\(^3\)

• Standard ACLS drugs and equipment
Pre-Block Phase

• Equipment used to perform block
  – 2010 Joseph M. Neal
    • “Although there is evidence for Ultrasound guided regional anesthesia (UGRA) reducing the occurrence of vascular puncture.....as yet there is at best inconclusive scientific proof that these surrogate outcomes are linked to actual reduction of their associated complications, such as LAST....”


Pre-Block Phase

• 2013, Joseph M. Neal
  – “Slowly but surely, emerging data have proven that ultrasound guidance reduces the rate of not only unintended vascular puncture, but LAST events as well—that is ultrasound-guidance affects the true outcome$^5$”
  – “The positive benefit of ultrasound guidance has now been solidified, but it does not absolve us from mindfulness of total local anesthetic dose, careful post block monitoring, judicious use of intravascular markers, incremental aspiration and injection, and availability of checklists and ILE when LAST occurs despite our best efforts$^5$”
Pre-Block Phase

• **Why the change?**
  – Sites et al, 2012^6^
    • 8 yr period, 12,668 patients receiving peripheral nerve blocks
    • LAST=“any event in which patient experienced unconsciousness, arrhythmias, seizure or cardiac arrest associated with the injection of local anesthetic”
    • 1 LAST event in 12,668 ultrasound guided +/- nerve stim blocks
    • .08/1000 (95% CI 0.0/1000 to 0.4/1000)
  – Orebaugh et al, 2012^7^
    • Data from departmental QI database for adverse outcomes associated with peripheral nerve blocks, billing records for denominator
    • ISB, axillary, femoral, sciatic, popliteal-sciatic
    • 2006-2011
    • LAST: neuro → tonic clonic motion of patient during or within 60 minutes of peripheral block, with LOC. CV → hypotension requiring pressors or inotrope, appearance of ventricular dysrhythmia or cardiac arrest during that time.
    • **Landmark-nerve stim technique:** 6/5436 cases of LAST
    • **UGRA-nerve stim:** 0/9238 cases of LAST (p=.006)
Pre-Block Phase

– Barrington et al, 2013
  • Multicenter prospective study, 20 hospitals, Australian Regional Anaesthesia Collaboration
  • Jan 2007-May 2012
  • LAST:
    – Minor- CNS features like agitation, confusion, tinnitus
    – Major- seizures, LOC
    – Cardiac arrest
  • 22 episodes of LAST
    – No ultrasound : 10/4745 cases of LAST
    – Ultrasound +/- stim: 12/20,401 (p=.004)
    – Risk of LAST was reduced by greater than 65% with ultrasound guidance
Pre-Block Phase

• Choice of drugs, dose and additive
  – Use of epinephrine as intravascular marker controversial but within the 2012 guideline → “Consider use of a....test dose e.g. epinephrine 5mcg/ml of LA”\(^1\)
  – ASRA Practice Advisory, 2010\(^9\)
    • “...use of an intravascular marker is recommended....its benefits likely outweigh the risks in the majority or patients."
  – “Use the least dose of LA necessary to achieve the desired extent and duration of block”\(^1\)
    • Barrington et al, 2013\(^8\) → LA dose, dose per kg were predictors of LAST
Pre-Block Phase

• Block choice and patient selection
  – Traditional teaching: highest blood levels of LA seen after intercostals, lumbar epidural, brachial plexus, sciatic/femoral
  – Lumbar Plexus has been shown to impart higher risk of LAST then upper and lower limb blocks
  – Barrington et al, 2013
    • Paravertebral (which included lumbar plexus) and upper limb blocks highest risk for LAST compared with lower limb and trunk blocks
Pre-Block Phase

• Block choice and patient selection
  – “Factors that increase the likelihood of LAST include: advanced age, heart failure, ischemic heart disease, conduction abnormalities, metabolic disease, liver disease, low plasma protein concentration, metabolic or respiratory acidosis, medications that inhibit sodium channels\(^1\)”
  – *Modify dose and possibly site of injection to mitigate some of the increased risk in these types of patients*
• Mulroy, Weller and Liguori, 2014\textsuperscript{10}
  – 3 senior ASRA members asked to create a checklist *incorporated multiple organizational requirements and practice advisories*, while *seeking input* from the membership to keep the product as streamlined as possible
Pre-procedure checklist, Block Phase

<table>
<thead>
<tr>
<th>Regional Block Preprocedural Checklist</th>
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<tbody>
<tr>
<td>1) Patient is identified, 2 criteria</td>
</tr>
<tr>
<td>2) Allergies and anticoagulation status are reviewed.</td>
</tr>
<tr>
<td>3) Surgical procedure/consent is confirmed.</td>
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<tr>
<td>4) Block plan is confirmed, site is marked.</td>
</tr>
<tr>
<td>5) Necessary equipment is present, drugs/solutions are labeled.</td>
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<tr>
<td>6) Resuscitation equipment is immediately available: airway devices, suction, vasoactive drugs, lipid emulsion.</td>
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<tr>
<td>7) Appropriate ASRA monitors are applied; intravenous access, sedation, and supplemental oxygen are provided, if indicated.</td>
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<tr>
<td>8) Aseptic technique is used: hand cleansing is performed, mask and sterile gloves are used.</td>
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<tr>
<td>9) “Time out” is performed before needle insertion for each new block site if the position is changed or separated in time or performed by another team.</td>
</tr>
</tbody>
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What are we looking for in cases of LAST?

- ASRA checklist, 2012
  
  “Consider LAST in any patient with altered mental status, neurological symptoms, or cardiovascular instability after a regional anesthetic.”
  
  CNS: excitation, depression, non-specific
  
  CV: hyperdynamic, progressive hypotension, conduction block, ventricular arrhythmia
Gregorio et al, 2009 Clinical Presentation of LAST
Block

The frequency of symptoms and signs referable to CV, CNS, or both is given for the 93 cases in this review\textsuperscript{11}
Block\textsuperscript{11}

Spectrum of Central Nervous System Signs

- Dizziness, Drowsiness, Tinnitus, Perioral, Confusion, Dysphonia, Dysarthria (18%)
- Loss of Consciousness (7%)
- Agitation (11%)
- Seizure (68%)
Spectrum of Cardiovascular Signs

- Bradycardia / Asystole (27%)
- Tachycardia (16%)
- Hypotension (18%)
- Wide Complex (12%)
- Ventricular Ectopy (5%)
- ST Changes, Pain, Dyspnea, Hypertension (9%)
- VT / VF (13%)
The Pharmacologic Treatment of Local Anesthetic Systemic Toxicity (LAST) is Different from Other Cardiac Arrest Scenarios

- Get Help
- Initial Focus
  - Airway management: ventilate with 100% oxygen
  - Seizure suppression: benzodiazepines are preferred; AVOID propofol in patients having signs of cardiovascular instability
  - Alert the nearest facility having cardiopulmonary bypass capability
- Management of Cardiac Arrhythmias
  - Basic and Advanced Cardiac Life Support (ACLS) will require adjustment of medications and perhaps prolonged effort
  - AVOID vasopressin, calcium channel blockers, beta blockers, or local anesthetic
  - REDUCE individual epinephrine doses to <1 mcg/kg
- Lipid Emulsion (20%) Therapy (values in parenthesis are for 70kg patient)
  - Bolus 1.5 mL/kg (lean body mass) intravenously over 1 minute (~100mL)
  - Continuous infusion 0.25 mL/kg/min (~18 mL/min; adjust by roller clamp)
  - Repeat bolus once or twice for persistent cardiovascular collapse
  - Double the infusion rate to 0.5 mL/kg/min if blood pressure remains low
  - Continue infusion for at least 10 minutes after attaining circulatory stability
  - Recommended upper limit: Approximately 10 mL/kg lipid emulsion over the first 30 minutes
- Post LAST events at www.lipidrescue.org and report use of lipid to www.lipidregistry.org
• Why avoid vasopressin\textsuperscript{12,13}?  
  – Mechanism of LA toxicity
    • Inhibition of cellular signaling within the myocardium (\textit{v.g} sodium, potassium and calcium channels\textrightarrow ultimately leading to impaired cellular function)
    • Impairs mitochondrial metabolism
    • Result\textrightarrow “poisoned” heart, toxic cardiomyopathy
  – In setting of heart contracting POORLY, intense systemic vasoconstriction will decrease cardiac output
  – For this reason it is also recommended that you avoid drugs that may impair cardiac contractility.
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LAST

• Why only low dose epinephrine\textsuperscript{12}?  
  – Epinephrine has been shown to have dose dependent adverse effects
    • At higher doses it promoted arrhythmia’s, impairs lipid emulsion efficacy, and worsens arterial pH
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• What are the proposed mechanisms of ILE in reversing LAST?
  – Acts as lipid “sink” such that LA partition into lipid phase\(^1\)
    • This is likely how ILE reverses neurologic toxicity as brain does not utilize fatty acids for energy
    • Supported by efficacy of ILE in treating other lipophilic drug overdoses
  – Direct inotropic effect\(^1\)
  – Interfere with bupivacaine binding of sodium channels (competition)\(^1\)
LAST

• How does ILE work? Continued....
  – Augment mitochondrial fatty acid metabolism$^{12,13,14,15}$
    • Lipid is preferred energy source for myocardium
    • Specific mechanism controversial
    • ILE “...might increase the intracellular myocardial fatty acid content, overwhelm bupivacaine inhibition of carnitine exchange, thereby augmenting the mitochondrial fatty acid metabolism, and replenishing tissue ATP stores”$^{14}$
  – Cytoprotective effects$^{12,15}$
    • “Lipid attenuates cardiac ischemia reperfusion injury$^{12}$”
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– What are the “overdose” or side effects of ILE?
  • Interference with clinical laboratory measurements
  • Cave et al, 2014\textsuperscript{16}
    – 10 cases of LAST, received ILE, 1 complication
      » Bronchospasm, IV steroids, negative tryptase
    – 38 cases of use of ILE for other drug OD
      » Elevated amylase, no clinical signs of pancreatitis
      » Interference with labs
      » 8 were given ILE for CV collapse, of those 3 died
LAST

• What are the “overdose” or side effects of LE?
  – Fettiplace et al, 2015 ¹⁷
    • Editorial/review of recent cases of ILE
    • Patient receiving ILE 42ml/kg developed lipemia and elevated amylase, recovered and d/c
    • Patient who received 3,220 ml of ILE over 4 hrs who developed ARDS, eventually recovered
    • Patient who received apx 79ml/kg ILE over 5 hour period experienced clogging of continuous renal replacement filter and eventually died (in RATS LD50 of 20% Intralipid is 67.7ml/kg)
    • American College of Medical Toxicology guidelines on ILE use 1.5ml/kg bolus, infusion 0.25ml/kg/min AND suggest that with enteral OD there is likely prolonged absorption of drug and need for high doses therefore no upper limit is provided for dosing
LAST

• Cao et al, 2015<sup>18</sup>
  – Total of 19 cases reports of adverse events attributable to lipid emulsion
    • Lipemic serum interfering with lab results, up to 39 hrs
    • Acute pancreatitis and ARDS in 13 yr old with TCA OD receiving ASRA dose of ILE
    • Elevated amylase levels
    • 2 cases of bupropion/metoprolol and diltiazem/propanolol OD, received ILE, asystolic arrests
  – Cevike et al, 2014<sup>19</sup>
    • 10 cases in ED who received ILE
    • 2 cases with side effects
      – Elevated amylase and urine color change(reddish)
      – ILE related infiltration in lungs and urine color change
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• After patient is stable and intralipid off
  - “Prolonged monitoring (>12hrs) is recommended after ANY signs of systemic LA toxicity, since cardiovascular depression due to local anesthetics can persist or recur after treatment”¹
Workflow

• Pre-block phase
  – Planning: equipment, drugs, patient selection

• Block phase
  – Execution of block: checklist, monitoring, symptoms

• Local Anesthetic Systemic Toxicity (LAST)
  – Guideline for resuscitation and reasons, checklist use, mechanisms of lipid emulsion (ILE), toxicity of ILE
References


Case Scenario
Anesthesiology 120(4):987-996, 2014
Vadi MG, Patel N, Steigler MP

- 88 yo woman, 45 kg, ASA IV
- Hip fracture repair
- HTN, CAD, PVD, CVA, hypothyroid, renal artery stenosis, subdural hematoma in past
- Pre-syncope with BP less than 150 per patient
- TTE 5 months ago-LVEF 55-60%, mod AS, mod to severe MR, no pulmonary HTN
- No obstructive disease of carotids
Case cont.

• A line pre-block

• Surgical anesthesia planned via psoas compartment block and sciatic block
  – Lumbar plexus: 10 ml 0.25% bupivacaine with epi and 15 ml of 1.5% mepivacaine plain, - aspiration q3ml
  – Sciatic with 15ml of 1.5% mepivacaine plain