Retrospective Review of Lidocaine Infusion Therapy in the Treatment of Refractory Neuropathic Pain Conditions

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Research Study Staff for this Project

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No conflict of interest with any study staff

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- Tammy Ortiz, Research Administrative Assist

Educational Objectives

- At the conclusion of this activity participants should be able to:
  - Identify why lidocaine infusion might be an appropriate option to consider for refractory neuropathic pain
  - Be able to define most common side effects and pre-emptive testing to obtain
  - Identify quality measures used to evaluate this therapy
  - Summarize the benefit noted from this retrospective review of this therapy (2013-2018)
Indications for Lidocaine Use

- 1st marketed in 1948 for tx of ventricular tachycardia
- Now used as a local anesthetic and anti-arrhythmic suitable for infiltration, block and surface anesthesia
- IV use for tx of ventricular arrhythmia (post MI, digitalis poisoning, cardioversion or cardiocath); for refractory status epilepticus & with various pain conditions
- Topically for management of allodynic post-herpetic neuralgia. (lidoderm patches)

Lidocaine

- Lidocaine can be used as an agent for multimodal analgesic therapy
- Peripheral and Central Mode of action
  - Peripherally
    - Localized anti-inflammatory response
  - Centrally
    - Selectively decrease C-fiber activity

Neuropathic Pain & Lidocaine

- Neuropathic pain is related to damage or diseased nociceptive pathway of the central or peripheral nervous system.
- Pathophysiology of neuropathic pain is not clearly defined
- It is hypothesized that an up-regulation of sodium channels may cause neurons to depolarize more quickly. This increases nociceptive signaling and increases neuropathic pain
Mechanism of Action: Lidocaine

- Lidocaine, a local anesthetic, antiarrhythmic (Class Ib) alters signal conduction in the neurons by blocking the fast voltage gated sodium (Na) channels in the cell membrane that are responsible for signal propagation.

- With sufficient blockage of Na channel the membrane of the postsynaptic neuron will not depolarize and then fails to transmit an action potential.

- Voltage gated K channels also blocked by lidocaine (K involved in repolarization)

- This creates the anesthetic effect by preventing pain signals from prohibiting transmission to the brain before it begins.

Local Anesthetics

- Protein binding is related to the duration of action. The site of action (the Na channel) is primarily protein in a lipid environment.

- Binding affinity will thus affect duration of action.

- Protein binding also plays a part in the availability of the drug as local anesthetic binds to lipoproteins in the blood stream.

- * can transfer to fetus via blood stream

Lidocaine Metabolism

- Approximately 95% metabolized (dealkylated) in the liver by CYP3A4 and CYP450 to an active metabolite monoethylglycinexylidide (MEGX) then to inactive glycinexylidide.

- MEGX has a longer ½ life than lidocaine but is a less potent sodium channel blocker.

- Drugs that affect hepatic blood flow can raise plasma concentration of lidocaine (eg, phenytoin, beta-blockers, antibiotics, antifungals, SSRI antidepressants)

- Addition of vasoconstrictor medications, such as epinephrine or phenylephrine can prolong duration of action of local anesthetics, decrease their absorption (and the peak plasma level) and enhance the blockade.
**IV Lidocaine Infusion Therapy**

- Used in clinical practice since the 1950’s

- Documented benefit noted for post-herpetic neuralgia, complex regional pain syndrome, diabetic neuropathy, central pain and spinal cord injury.

- However dosing, frequency of infusion, duration of therapy and other quality measures have not been well studied.

**Lidocaine Infusions**

<table>
<thead>
<tr>
<th>Possible Adverse Effects</th>
<th>Blood Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lightheadedness</td>
<td>1 mcg/ml</td>
</tr>
<tr>
<td>Peri-oral numbness</td>
<td>2 mcg/ml</td>
</tr>
<tr>
<td>Metallic Taste</td>
<td>2-3 mcg/ml</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>5-6 mcg/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Reactions – Stop Immediately</th>
<th>Blood Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blurry vision</td>
<td>6 mcg/ml</td>
</tr>
<tr>
<td>Twitching</td>
<td>8 mcg/ml</td>
</tr>
<tr>
<td>Seizures</td>
<td>10 mcg/ml</td>
</tr>
<tr>
<td>Bradycardia; HR&lt;50</td>
<td>20-25 mcg/ml</td>
</tr>
</tbody>
</table>
Guidelines for Lidocaine Infusion Treatment

Guidelines for Lidocaine Infusion Treatment

- RN should decrease the infusion rate by 50% if signs of early toxicity:
  - ringing in ears, metallic taste in mouth, circumoral numbness/tingling
  - notify Pain Provider (available in clinic suite)
- Discontinue infusion if any progressive side effects occur
- Availability of 20% Lipid emulsion per provider orders

Guidelines for Lidocaine Infusion Tx in UR Outpatient Setting

- Guidelines provide standardized approach for provider training (ie RN/MD) and management of clinical care; overall improvement of pt safety
- Pre-procedure assessment, history, physical, consent & post-procedural discharge instructions should be developed per organization's framework
- Use of programmable infusion pump; IV access no smaller than 20 gauge
- Infusion administered at a steady rate over 60-90 minute timeframe (Max dose 5mg/kg)

Guidelines for Lidocaine Infusion Tx in UR Outpatient Setting

- RN assess at 15 minute intervals throughout infusion and 60 minutes post infusion:
  - blood pressure, heart rate, pO2
  - Sedation / agitation level
  - Pain level reported by patient using NRS (0=no pain, 10=worst pain possible)
Lidocaine Safe for Use

- With experienced trained staff administering
- In decreasing intraoperative and postoperative analgesic requirements
  
  - No Toxicity reported in clinical trials when doses of 3 mg/kg/hr infusions used
  
  - Reduction in postoperative ileus noted in 4 clinical trials, lowering hospital stay and overall hospital costs

Retrospective Review of Lidocaine Infusion Therapy in the Treatment of Refractory Neuropathic Pain Conditions

- University of Rochester Pain Treatment Center
- Multiple dx: Complex Regional Pain; Abdominal /Pelvic pain; Post-herpetic Neuralgia; Central post-stroke pain; Fibromyalgia
- Failed multiple therapies (stellate/LSB, facets/RFA, TPI, stim trials, acupuncture); medication trials of neuromodulators, muscle relaxants, opioids)

Retrospective Review of Lidocaine Infusion Therapy in the Treatment of Refractory Neuropathic Pain Conditions

- 265 infusion encounters were tabulated during study timeframe (1/2013- 5/2018)
- 51 pts ranging from 2 -45 infusions over study timeframe
- 16 pts (3%) had significant relief however 6 of 16 either had short duration of benefit (12 days or less) or were unable to obtain insurance (WC) coverage & remained with prior tx options.
- 10 pts (20%) continued ongoing intermittent infusion therapy at 4, 8, 12 or 16 week intervals for an extended period of time.
Retrospective Review of Lidocaine Infusion Therapy in the Treatment of Refractory Neuropathic Pain Conditions

<table>
<thead>
<tr>
<th>Dx</th>
<th>Inf Dose in mg</th>
<th>Num infusion during study timeframe</th>
<th>Freq of infusions</th>
<th>Duration of Benefit</th>
<th>% Pain reduced</th>
<th>Sleep/Fx Imp</th>
<th>Mod Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>myalgia; s/p mults</td>
<td>200</td>
<td>retired</td>
<td>10 days</td>
<td>90%</td>
<td>50%</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Central Pain post MVA</td>
<td>350</td>
<td>Retrial</td>
<td>4 days</td>
<td>50%</td>
<td>25%</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Abd/Pelvic</td>
<td>350</td>
<td>2x per day</td>
<td>4 days</td>
<td>75%</td>
<td>25%</td>
<td>Oxy, preg MND</td>
<td>no change</td>
</tr>
<tr>
<td>Phantom Limb</td>
<td>350</td>
<td>Retrial</td>
<td>11 days</td>
<td>75%</td>
<td>25%</td>
<td>Oxy, preg MND</td>
<td>no change</td>
</tr>
<tr>
<td>CRPS</td>
<td>350</td>
<td>retired</td>
<td>8 days</td>
<td>55%</td>
<td>25%</td>
<td>Oxy, preg MND</td>
<td>no change</td>
</tr>
</tbody>
</table>

Retrospective Review Cont.

<table>
<thead>
<tr>
<th>Dx</th>
<th>Inf Dose in mg</th>
<th>Num infusion during study timeframe</th>
<th>Freq of infusions</th>
<th>Duration of Benefit</th>
<th>% Pain reduced</th>
<th>Sleep/Fx Imp</th>
<th>Mod Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRPS</td>
<td>250</td>
<td>2x per day</td>
<td>120 days</td>
<td>90 days</td>
<td>50%</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Central pain C6 paraplegia</td>
<td>200</td>
<td>2x per day</td>
<td>120 days</td>
<td>42 days</td>
<td>50%</td>
<td>↓ oxy 20mg MDD - 10mg MDD</td>
<td></td>
</tr>
<tr>
<td>CRPS</td>
<td>350</td>
<td>4x per day</td>
<td>42 days</td>
<td>30 days</td>
<td>75%</td>
<td>↓ muscle relax &amp; neuromod</td>
<td></td>
</tr>
<tr>
<td>Central pain post CVA</td>
<td>300</td>
<td>6x per day</td>
<td>30 days</td>
<td>18 days</td>
<td>50%</td>
<td>↓ oxy IR 30mg MDD - 10mg MDD</td>
<td></td>
</tr>
<tr>
<td>substernal chest pain</td>
<td>300</td>
<td>2x per day</td>
<td>120 - 180 days</td>
<td>150 days</td>
<td>75%</td>
<td>Neuromod</td>
<td></td>
</tr>
<tr>
<td>CRPS</td>
<td>300</td>
<td>2x per day</td>
<td>120 - 180 days</td>
<td>160 days</td>
<td>90%</td>
<td>↓ Oxy 140mg MDD to 0</td>
<td></td>
</tr>
<tr>
<td>CRPS</td>
<td>325</td>
<td>12x per day</td>
<td>30 days</td>
<td>26 days</td>
<td>75%</td>
<td>↓ Vicodin 30mg - 0mg, 2 wks Qinf</td>
<td></td>
</tr>
<tr>
<td>CRPS</td>
<td>350</td>
<td>4x per day</td>
<td>35 days</td>
<td>25-33 days</td>
<td>75%</td>
<td>↓ Oxy IR 30mg MDD - 0</td>
<td></td>
</tr>
</tbody>
</table>

Retrospective Review of Lidocaine Infusion Therapy in the Treatment of Refractory Neuropathic Pain Conditions

- Of the 10 pts who continued infusions, the Fx Assessment / PROMIS questionnaires and NRS indicated: improved sleep, functional improvement, reduction of pain and reduction of medication use (opioids and neuromodulators).
- Pain NRS reduced 50-90% with improved ability to care for self, household tasks, exercise, remain out of hospital as emergent pain flares absent
- Sleep improved by 50-75% thru duration of benefit
- Medication changes were variable; 2 pts discontinued all opioids, 7 pts reduced opioid use overall & with each infusion duration of benefit, 4 reduced dosing of neuromodulators and muscle relaxants.
Retrospective Review of Lidocaine Infusion Therapy in the Treatment of Refractory Neuropathic Pain Conditions

- Circum-oral tingling & metallic taste were infrequent AE's (13 / 265 encounters) & were limited to infusion time

- No side effects that lasted beyond infusions

- In conclusion, select pts with severe neuropathic pain refractory to multiple other modalities (medications, injections, stimulator implants, acupuncture) may do very well with intermittent lidocaine infusions to manage their pain symptoms.