IV Lidocaine: Show Me The Evidence

Robert H. Thiele, M.D.
Assistant Professor, Departments of Anesthesiology and Biomedical Engineering
Divisions of Cardiac, Thoracic, and Critical Care Anesthesiology
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Director, Technology in Anesthesia & Critical Care Group
Co-Director, UVA Enhanced Recovery after Surgery (ERAS) Program
University of Virginia School of Medicine

Know Thy Enemy (sort of)

- A variety of insults can lead to the manifestation of pain and include:
  - Mechanical stimuli
    - Nociceptors (free nerve endings without barriers)
  - Chemical mediators
    - In particular, inflammatory mediators
      - Bradykinin, free H⁺ (low pH), serotonin (5-HT), histamine, substance P (neurogenic inflammation), prostaglandins, thromboxanes, leukotrienes, adenosine, ATP, protein kinase C (PKC), nerve growth factor, cytokines, excitatory amino acids, capsaicin (TRPV1 receptors)
  - Damaging temperature (> 45°C)
Inflammation is a significant contributor to the development of perioperative pain. Agents which decrease the magnitude of inflammation can potentially attenuate the experience of pain perioperatively.

**Steroids**

**NSAIDs**

**Local anesthetics**
- Neuraxially
- Regionally
- Locally
- Intravenously

### The Anti-Inflammatory Hypothesis

- Local anesthetics have *many* effects
  - Anti-nociceptive
    - Sodium channel blockade (also K⁺, dopamine, and pre-synaptic muscarinic receptors [GPCRs])
  - Anti-inflammatory effects *(partial list)*
    - Blockade of leukotriene release (e.g. LTB₄, which induces margination at endothelial cells, degranulation, diapedesis, superoxide generation, increases vascular permeability)
    - Inhibition of thromboxane receptor signaling
    - Inhibition of IL-1α (stimulates phagocytosis, respiratory burst, chemotaxis, and degranulation) release
    - Decreased neutrophil accumulation in injured tissue (decreased chemotactic factors (C3a, C5a, TNF-a, IL-1B))
    - Reduced microvascular permeability and albumin extravasation

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Thoracic Epidural: Gold Standard?

- Epidural versus
  - **Nothing**: epidural wins *(we assume)*
  - IV opioid prn: epidural wins
  - **PCA**: epidural wins (but not as much)
    - VA study
      - 1021 abdominal surgical patients
      - No overall difference in death or major complications
      - Less opioid, better pain control with EDC
    - Australian study
      - 915 abdominal surgical patients
      - No overall difference in any outcome other than respiratory failure
      - NSAIDs, acetaminophen in some patients


**Thoracic Epidural: Gold Standard?**

- Epidural versus
  - **Nothing**: epidural wins *(we assume)*
  - IV opioid prn: epidural wins
  - **PCA**: epidural wins (but not as much)
  - Multimodal analgesia: ???

**WE DON’T KNOW**
The Good, The Bad, and The Ugly

- Randomized controlled trial
- Thoracic, abdominal, major vascular (n = 53)
  - **Group 1**: either...
    - \( \text{N}_2\text{O} + 35 \text{ ucg/kg fentanyl} \)
    - "Balanced" technique of \( \text{N}_2\text{O} \), < 35 ucg/kg fentanyl and either low dose volatile or paralysis
  - Both groups: parenteral opioids in ICU
  - **Group 2**: epidural + \( \text{N}_2\text{O} \) and "small" doses of opioids, epidural used in ICU

![Comparison of "Traditional" Anesthesia to Epidural Supplementation in 1987](chart.png)

Yeager MP et al. Anesthesiology 66: 729, 1987

Thoracic Epidural: Gold Standard?

- 5094 patients
- Thoracic and abdominal surgery
  - OR of pneumonia 0.54 (95% CI 0.49-0.83)
  - Less impactful when PCA is used
  - Improvement has declined over time

![Thoracic Epidural: Gold Standard?](chart.png)

Popping DM. JAMA Surgery 143: 990, 2008
Thoracic Epidural: Gold Standard?

- Systemic lidocaine at 2–4 mg/min
- Systemic lidocaine at 2–4 mg/min

Epidural vs. Intravenous LA

- Randomized, prospective trial in open colorectal surgical patients (n = 42)
- Control group: thoracic epidural (bupivacaine + hydromorphone) continued until the day after bowel function returned
- Intervention group: IV lidocaine at 1-3 mg/min, continued until the day after bowel function returned
- Both groups: morphine PCA as the primary analgesia agent post-operatively


Epidural vs. Intravenous LA

- Randomized, prospective trial in laparoscopic colorectal surgical patients (n = 60) as part of an ERAS protocol
- Control group: thoracic epidural (bupivacaine + morphine)
  - No opioid rescue
- Intervention group: IV lidocaine at 1 mg/kg/hr for 48 hours post-operatively
  - Rescued with morphine PCA

TABLE 3. Daily Opioid Consumption

<table>
<thead>
<tr>
<th>Daily Morphine Consumption</th>
<th>Op. Day</th>
<th>POD 1</th>
<th>POD 2</th>
<th>POD 3</th>
<th>POD 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural group median, mg</td>
<td>25</td>
<td>57</td>
<td>49</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>25% Interval</td>
<td>11</td>
<td>27</td>
<td>12</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>75% Interval</td>
<td>56</td>
<td>100</td>
<td>74</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Lidocaine group median, mg</td>
<td>17</td>
<td>48</td>
<td>23</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>25% Interval</td>
<td>30</td>
<td>17</td>
<td>14</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>75% Interval</td>
<td>30</td>
<td>17</td>
<td>14</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

P = 0.883 0.883 0.057 0.111

Op. Day indicates operative day; POD, postoperative day.

FIGURE 2. Median average daily pain scores by postoperative day. Whiskers represent the interquartile range. Day 1 = day of operative procedure.

**Epidural vs. Intravenous LA**

- Randomized, prospective trial of placebo vs. IV lidocaine vs. epidural in open colonic surgery
- **Placebo group:** saline through IV and epidural
- **Systemic group:** IV lidocaine at 2 mg/kg/hr *intraoperatively*
- **Epidural group:** epidural lidocaine at 2 mg/kg/hr
- Opioid/Analgesic use (all groups)
  - Intraoperative *remifentanil*
  - Bolus of opioid + LA via epidural at end of case
  - Rescue: acetaminophen (up to 4 g/day) and lornoxicam (NSAID)

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**TABLE 4.** VRS Pain at Rest, on Walking, and on Coughing
In the 2 Subgroups, Column and Row

<table>
<thead>
<tr>
<th></th>
<th>TEA (n = 15)</th>
<th>IL (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRS no rest Ac 24 hrs</td>
<td>2 (0-3)</td>
<td>2 (0-2)</td>
<td>0.798</td>
</tr>
<tr>
<td>Ac 48 hrs</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>0.799</td>
</tr>
<tr>
<td>Ac 72 hrs</td>
<td>1 (0-2)</td>
<td>1 (0-1.5)</td>
<td>0.426</td>
</tr>
<tr>
<td>VRS no walking Ac 24 hrs</td>
<td>2 (0-3)</td>
<td>0 (0-2)</td>
<td>0.614</td>
</tr>
<tr>
<td>Ac 48 hrs</td>
<td>2 (0-3)</td>
<td>0 (0-3)</td>
<td>0.731</td>
</tr>
<tr>
<td>Ac 72 hrs</td>
<td>1 (0-2)</td>
<td>0 (0-1)</td>
<td>0.783</td>
</tr>
<tr>
<td>VRS no coughing Ac 24 hrs</td>
<td>4 (0-5)</td>
<td>0 (0-3)</td>
<td>0.569</td>
</tr>
<tr>
<td>Ac 48 hrs</td>
<td>1 (0-3)</td>
<td>0 (0-2)</td>
<td>0.219</td>
</tr>
<tr>
<td>Ac 72 hrs</td>
<td>2 (0-3)</td>
<td>2 (0-4)</td>
<td>0.344</td>
</tr>
</tbody>
</table>

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**TABLE 5.** Clinical Data of Postoperative Period

<table>
<thead>
<tr>
<th></th>
<th>TEA (n = 15)</th>
<th>IL (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first drink</td>
<td>4.2 (2-8)</td>
<td>3.7 (2-8)</td>
<td>0.215</td>
</tr>
<tr>
<td>Time to first full drink</td>
<td>38 (22-51)</td>
<td>38 (22-46)</td>
<td>0.894</td>
</tr>
<tr>
<td>Time walking out of bed, min</td>
<td>98 (28-130)</td>
<td>120 (27-240)</td>
<td>0.803</td>
</tr>
<tr>
<td>Day 2</td>
<td>98 (28-130)</td>
<td>120 (50-348)</td>
<td>0.526</td>
</tr>
<tr>
<td>Day 3</td>
<td>125 (39-336)</td>
<td>120 (30-375)</td>
<td>0.801</td>
</tr>
<tr>
<td>Day 4</td>
<td>11 (2-12)</td>
<td>9 (1-15)</td>
<td>0.788</td>
</tr>
<tr>
<td>Day 5</td>
<td>22 (10-40)</td>
<td>15 (10-46)</td>
<td>0.870</td>
</tr>
<tr>
<td>Day 6</td>
<td>39 (12-40)</td>
<td>29 (14-40)</td>
<td>0.817</td>
</tr>
<tr>
<td>Readmission to days, d</td>
<td>3 (3-4)</td>
<td>3 (3-4)</td>
<td>0.574</td>
</tr>
<tr>
<td>Hospital stay, d</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>0.764</td>
</tr>
</tbody>
</table>

**Note:** Data are presented as median (interquartile range) or absolute number (%).


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**TABLE 6.** VRS Pain at Rest, on Walking, and on Coughing
In the 2 Subgroups, Column and Row

<table>
<thead>
<tr>
<th></th>
<th>TEA (n = 15)</th>
<th>IL (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRS no rest Ac 24 hrs</td>
<td>0 (0-2)</td>
<td>3 (1.5-3)</td>
<td>0.047</td>
</tr>
<tr>
<td>Ac 48 hrs</td>
<td>0 (0-2)</td>
<td>3 (1.5-3)</td>
<td>0.047</td>
</tr>
<tr>
<td>Ac 72 hrs</td>
<td>0 (0-2)</td>
<td>3 (1.5-3)</td>
<td>0.047</td>
</tr>
<tr>
<td>VRS no walking Ac 24 hrs</td>
<td>3 (0-4)</td>
<td>4 (2.5-5)</td>
<td>0.207</td>
</tr>
<tr>
<td>Ac 48 hrs</td>
<td>3 (0-4)</td>
<td>4 (2.5-5)</td>
<td>0.207</td>
</tr>
<tr>
<td>Ac 72 hrs</td>
<td>3 (0-4)</td>
<td>4 (2.5-5)</td>
<td>0.207</td>
</tr>
<tr>
<td>VRS no coughing Ac 24 hrs</td>
<td>4 (0-4)</td>
<td>6 (2.5-4)</td>
<td>0.984</td>
</tr>
<tr>
<td>Ac 48 hrs</td>
<td>4 (0-4)</td>
<td>6 (2.5-4)</td>
<td>0.984</td>
</tr>
<tr>
<td>Ac 72 hrs</td>
<td>4 (0-4)</td>
<td>6 (2.5-4)</td>
<td>0.984</td>
</tr>
</tbody>
</table>

**Note:** Data are presented as median (interquartile range) of absolute number (%).

Epidural vs. Intravenous LA

- Pain scores: lower in IV group initially, then higher
  - Systemic LA was only used intraoperatively
  - Post-operative analgesic requirements: no difference

![Graph showing pain scores comparison between epidural (EDC) and intravenous (IV) groups.]


UVA (unpublished) Experience

- Complications per day were significantly higher in the epidural group
- IV lidocaine group:
  - Bowel movement 23 hours earlier (p = 0.019)
  - Foley's removed 24 hours earlier (p < 0.001)
  - Discharged home 24 hours earlier (p = 0.081)

![Graph showing retrospective comparison of epidural vs. IV Lidocaine in abdominal surgery.]

Terkawi AS et al. ASRA 2015 (abstract)
Epidural and VTE (unpublished)

- Retrospective analysis of 431 gyn-onc patients before and after administration of a thromboprophylaxis protocol (goal = SQH within 1 hour of placement)

Thoracic Epidural: Gold Standard?

- **Question 1**: what is the relative contribution of systemic local anesthetic absorption to epidural efficacy?

- **Question 2**: in a multimodal / regional analgesia, early ambulation around the clock acetaminophen world, do epidurals still offer a benefit?
Lidocaine as an Analgesic

- **Systemic lidocaine reduces pain** after:
  - Prostate surgery, ambulatory surgery, major abdominal surgery
- **Systemic lidocaine reduces opioid needs** after:
  - Laparoscopic colectomy, major abdominal surgery, ambulatory surgery
- Particularly relevant for chronic pain patients
  - Reduced hyperalgesia in humans in multiple models
    - Interdigital web pressure
    - Heat trauma
    - Forearm incision


Lidocaine and Length of Stay

- 8 RCTs including 320 patients
  - Estimated reduction in LOS by 0.8 days

<table>
<thead>
<tr>
<th>Reference</th>
<th>Lidocaine</th>
<th>Placebo</th>
<th>WMD (random)</th>
<th>Weight (g)</th>
<th>WMD (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Street et al.</td>
<td>0.08 (0.73)</td>
<td>0.10 (2.89)</td>
<td>17.02</td>
<td>(-1.10 (-1.11, -0.50)</td>
<td>0.45</td>
</tr>
<tr>
<td>McKenzie et al.</td>
<td>0.06 (0.71)</td>
<td>0.08 (3.00)</td>
<td>22.48</td>
<td>(-1.02 (-1.01, -0.92)</td>
<td>0.56</td>
</tr>
<tr>
<td>Kaba et al.</td>
<td>0.08 (0.45)</td>
<td>0.10 (1.77)</td>
<td>20.44</td>
<td>(-1.02 (-1.01, -0.92)</td>
<td>0.56</td>
</tr>
<tr>
<td>Koppert et al.</td>
<td>0.08 (3.00)</td>
<td>0.08 (3.15)</td>
<td>4.08</td>
<td>(-1.02 (-1.01, -0.92)</td>
<td>0.56</td>
</tr>
<tr>
<td>Kühn et al.</td>
<td>0.06 (0.45)</td>
<td>0.10 (0.80)</td>
<td>30.46</td>
<td>(-0.80 (-0.79, -0.80)</td>
<td>0.56</td>
</tr>
<tr>
<td>Total</td>
<td>0.08 (0.73)</td>
<td>0.10 (2.89)</td>
<td>19.68</td>
<td>(-1.02 (-1.01, -0.92)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Test for heterogeneity: χ² = 7.94, d.f. = 4, p = 0.01, I² = 40.1%
Test for overall effect: Z = 3.01, p = 0.002

The UVA Experience

- **Intraoperative Protocol:**
  - Intrathecal morphine
  - **NO INTRAVENOUS OPIOID**
  - Induction includes magnesium, ketamine, dexamethasone
  - Ketamine and **lidocaine infusion**
  - "Goal-directed fluid therapy" (GDT)
    - Favors vasopressor for hypotension

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### Differences in Pre and Post ERAS (All Cases)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Pre-ERAS</th>
<th>Post-ERAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid Balance</td>
<td>2734</td>
<td>4410</td>
</tr>
<tr>
<td>Fluid Balance (Total)</td>
<td>895</td>
<td>0.30</td>
</tr>
<tr>
<td>MSO4 in OR</td>
<td>21.7</td>
<td>283</td>
</tr>
<tr>
<td>Total MSO4</td>
<td>6.9</td>
<td>2.24</td>
</tr>
<tr>
<td>LOS</td>
<td>1.48</td>
<td>39</td>
</tr>
<tr>
<td>Date first bowel movement</td>
<td>2.24</td>
<td>-931</td>
</tr>
</tbody>
</table>
Pain Scores (Days 0-3) For Open Cases

![Graph showing pain scores for Days 0-3 for open cases, with bars indicating Pre-ERAS and Post-ERAS, and p < 0.05 significance.]

LOS relative to Medical Center

![Graph showing reduced length of stay post-ERAS implementation, with data from Thiele RH et al. JACS 2015 [ePub ahead of print].]
Actual vs. NSQIP Predicted LOS

2.2 day reduction in actual and adjusted LOS

<table>
<thead>
<tr>
<th>Question</th>
<th>Pre-ERAS (n = 48)</th>
<th>Post-ERAS (n = 47)</th>
<th>Pre-ERAS %ile</th>
<th>Post-ERAS %ile</th>
</tr>
</thead>
<tbody>
<tr>
<td>How well your pain was controlled</td>
<td>86.7</td>
<td>91</td>
<td>43</td>
<td>98</td>
</tr>
<tr>
<td>Staff addressed emotional needs</td>
<td>83.9</td>
<td>90.2</td>
<td>23</td>
<td>98</td>
</tr>
<tr>
<td>Response concerns/complaints</td>
<td>84.6</td>
<td>88.9</td>
<td>39</td>
<td>92</td>
</tr>
<tr>
<td>Staff include decisions re:trtmnt</td>
<td>85.6</td>
<td>90.2</td>
<td>49</td>
<td>97</td>
</tr>
<tr>
<td>Overall Assessment Section</td>
<td>88.1</td>
<td>92.2</td>
<td>29</td>
<td>81</td>
</tr>
<tr>
<td>Staff worked together care for you</td>
<td>89.4</td>
<td>90.8</td>
<td>36</td>
<td>54</td>
</tr>
<tr>
<td>Likelihood recommending hospital</td>
<td>87.5</td>
<td>92.9</td>
<td>32</td>
<td>89</td>
</tr>
<tr>
<td>Overall rating of care given</td>
<td>87.2</td>
<td>92.9</td>
<td>17</td>
<td>85</td>
</tr>
</tbody>
</table>
Tentative Conclusions

- In the pre-ERAS era, our institution (UVA) significantly over-utilized opioids
- The anti-inflammatory effect of multimodal agents (NSAIDs, steroids, systemic LA) provides a significant reduction in the manifestation of pain
- We find it increasingly difficult to justify the use of epidural catheters if systemic LA is an option
  - Compared to epidural catheters, systemic lidocaine is associated with fewer complications
  
- Patient satisfaction has very little to do with the numerical pain score
  - Focus should probably be on function
Special Thanks To...

Marcel Durieux, M.D., Ph.D.
Professor of Anesthesiology and Neurological Surgery

John Rowlingson, M.D.
Cosmo A. DiFazio Professor of Anesthesiology
Director, Acute Pain Services

APPENDIX
Lidocaine as an Anesthetic

The Anesthetic Potency of Lidocaine in the Rat

COSMO A. DIFAZIO, PHD, MD*
JAMES R. NIEDERLEHNER, MD†
ROBERT G. BURNEY, MD‡
Charlottesville, Virginia§

The anesthetic effect of lidocaine was evaluated in rats by determining the change in anesthetic requirement of cyclopropane MAC that was produced by blood concentrations of lidocaine in the clinically useful range. A linear reduction in anesthetic requirement was produced with concentrations up to 1 µg/ml. Further increases in lidocaine up to 5.5 µg/ml resulted in no further decrease in cyclopropane requirement. Lidocaine was found to contribute a maximum MAC fraction of 0.4.


Lidocaine as an Anesthetic

- Rodent cyclopropane anesthesia
- IV lidocaine at 200-1000 ucg/kg/min
- MAC measured using tail clamping technique
- Results:
  - Up to 40% reduction in MAC
  - Ceiling effect noted
Lidocaine as an *Anesthetic*

- *Intravenous* Lidocaine and MAC reduction
  - Animal Studies
    - Reduces MAC of volatile anesthetics in rats by approximately 40%
    - Reduces MAC in cats by as much as 59%
    - Reductions of 23-40% in dogs (and up to 63% when combined with ketamine)
  - Human Studies
    - IV lidocaine reduced MAC requirements by 10-28%
    - Maintenance of BIS scores from 40-50 required 29% less propofol