Optimizing nontraditional pain management strategies in the pediatric population

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The Multimodal Plan

- Enhance or achieve analgesia with additive or synergistic effect
- Limit the duration and intensity of pain
- Reduction in doses to minimize or prevent side effects
- Attack different portions of the pain pathway

Prevalence of moderate–severe pain in hospitalized children
The Bottom Line

Incidence of pain is common among neonates, infants, and children with an estimated 33-82% of hospitalized patients having moderate to severe pain poorly assessed and under treated or mismanaged.
Historically Speaking

- 1997 – Recommendations from the American Academy of Pediatrics
- 2006 – Warnings about potential danger and lack of efficacy
- 2006 – American College of Chest Physician recommendations
- 2012 – WHO removes from analgesic ladder
- 2012 – FDA issues black box warning
- 2013 – Canadian Ministry of Health and European Medicines Agency restricts use

Historically Speaking

- Well controlled trials are lacking
- 1978 study in pediatrics
  - 5mg/kg single dose produced > 1 symptom
  - 8/234 suffered respiratory depression with subsequent death
- Little knowledge of relationship of serum levels to effects or duration
- 1984–2010: 18% death claims following tonsillectomies due to opioids
- 1969–2012: 10 deaths and 3 overdoses in children treated with codeine

Where Were You in 1978?
What has changed?
• 1997 Warnings from AAP
• 2006 Recommendations against use
• 2007
  – Product Label Change and
  – FDA Public Health Advisory issued

PRECAUTIONS
Ultra-rapid Metabolizers of Codeine
Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regiments, individuals who are ultra-rapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion or shallow breathing.

2012
World Health Organization removes from analgesic ladder

2012
FDA Safety Communication (August 15, 2012)

2013
Restricted use to >12 years old

Codeine phosphate should be deleted from the WHO Model List of Essential Medicines for Children for its use as an analgesic. The rationale for the recommendation not to use codeine for relief of persistent pain in children is applicable and valid for acute and procedural pain. Furthermore, the WHO Model List already includes morphine, which is now recommended by WHO for relief of moderate to severe persisting pain in children.
Some opioids are converted by CYP2D6 to an active metabolite (codeine, hydrocodone, oxycodone).

<table>
<thead>
<tr>
<th>Allele Variant</th>
<th>Drug Metabolizing Phenotype</th>
<th>Incidence - Population</th>
<th>Incidence - Ethnic Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two nonfunctioning alleles</td>
<td>Poor metabolizer (PM)</td>
<td>-5 – 10%</td>
<td>African-American: 2 - 8% Asian: &gt; 1% Caucasian: 5 – 10%</td>
</tr>
<tr>
<td>One reduced functioning allele</td>
<td>Intermediate metabolizer (IM)</td>
<td>-2 – 11%</td>
<td></td>
</tr>
<tr>
<td>At least one functional allele</td>
<td>Extensive metabolizer (EM)</td>
<td>-77 – 92%</td>
<td>Asian: 1% Ethiopian: 28% Northern Europeans: 1 - 2% Southern Europeans: 10%</td>
</tr>
</tbody>
</table>
| Multiple copies of a functional allele | Ultrarapid metabolizer (UM) | -1 – 2% |}

PRECAUTIONS

Ultra-rapid Metabolizers of Codeine

Some individuals may be ultra-rapid metabolizers due to a specific CYP2D6*2x2 genotype. These individuals convert codeine into its active metabolite, morphine, more rapidly and completely than other people. This rapid conversion results in higher than expected serum morphine levels. Even at labeled dosage regiments, individuals who are ultrarapid metabolizers may experience overdose symptoms such as extreme sleepiness, confusion or shallow breathing.

2012

World Health Organization removes from analgesic ladder

2012

FDA Safety Communication (August 15, 2012)

Using genetic markers to identify individuals at high risk for adverse effects or therapeutic failures

Frequency of One or More Symptoms of Codeine Poisoning

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>0-30min</th>
<th>31-60min</th>
<th>61-120min</th>
<th>121-360min</th>
<th>&gt;360min</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>1/12</td>
<td>1/14</td>
<td>5/11</td>
<td>0/3</td>
<td>2/2</td>
<td>9/42</td>
</tr>
<tr>
<td>2-6</td>
<td>5/40</td>
<td>16/43</td>
<td>16/32</td>
<td>24/35</td>
<td>12/14</td>
<td>73/164</td>
</tr>
<tr>
<td>6-10</td>
<td>9/24</td>
<td>23/38</td>
<td>31/33</td>
<td>44/51</td>
<td>7/10</td>
<td>114/156</td>
</tr>
<tr>
<td>&gt;10</td>
<td>3/8</td>
<td>7/9</td>
<td>17/18</td>
<td>26/28</td>
<td>5/5</td>
<td>58/68</td>
</tr>
<tr>
<td>TOTAL</td>
<td>18/84</td>
<td>47/104</td>
<td>69/94</td>
<td>94/117</td>
<td>26/31</td>
<td>254/430</td>
</tr>
</tbody>
</table>

Populations at High Risk

- Pediatric Tonsillectomies and Adenotonsillectomies
- Upper Respiratory Infections
- Obesity
- History of Sleep Apnea

Childhood obesity and OSA: strong link between obesity and SDB. For every unit increase in BMI for age/gender, the incidence of OSA increases by 12% (Am J Respir Crit Care Med 2005;13:1175–1179).

Worldwide Obesity Issues in Children

Figure 1. Trends in obesity among children and adolescents: United States, 1963–2008

NOTE: Obesity is defined as a body mass index (BMI) greater than or equal to sex- and age-specific 95th percentiles from the 2000 CDC Growth Charts.

What Has Changed?

• Cross sectional analysis from 2001-2010 of pediatric emergency room visits
• Assessment of prescribing changes since 2006 recommendations
• N=189 million visits
• Children 3-17 yo

Adjusted codeine prescription rate for cough/URI before and after guidelines.

Frequency of codeine and opiate prescription during pediatric emergency department visits, 2001 to 2010.
Analgesic Prescribing Practices Can Be Improved by Low-Cost Point-of-Care Decision Support

UMHS Outpatient Analysis of Codeine Prescribing

<table>
<thead>
<tr>
<th>Month</th>
<th>Percent of total prescriptions that were codeine each month</th>
<th>Percent of codeine prescriptions each month that were pediatric*</th>
<th>Percent of total prescriptions that were codeine prescribed to pediatric* each month</th>
</tr>
</thead>
<tbody>
<tr>
<td>November</td>
<td>0.16%</td>
<td>23.33%</td>
<td>0.04%</td>
</tr>
<tr>
<td>December</td>
<td>0.28%</td>
<td>29.31%</td>
<td>0.08%</td>
</tr>
<tr>
<td>January</td>
<td>0.28%</td>
<td>25.42%</td>
<td>0.07%</td>
</tr>
<tr>
<td>February</td>
<td>0.28%</td>
<td>19.20%</td>
<td>0.05%</td>
</tr>
<tr>
<td>March</td>
<td>0.21%</td>
<td>10.87%</td>
<td>0.03%</td>
</tr>
<tr>
<td>April</td>
<td>0.21%</td>
<td>8.70%</td>
<td>0.02%</td>
</tr>
</tbody>
</table>

*Includes children <12 years of age

Pediatric UMHS Codeine Use
November 2013 - April 2014
Recommended Alternatives (UMHS)

- Hydrocodone-based
- Hydrocodone/Acetaminophen liquid 7.5 mg/325 mg per 15mL
- Hydrocodone/Acetaminophen tablet 5 mg/325mg
- Hydrocodone/Acetaminophen tablet 10 mg/325mg
- Oxycodone-based
- Oxycodone-elixir 1 mg/mL
- **ALERT: Also available in 20 mg/mL concentration – not available at UMHS**
- Oxycodone IR tablet 5 mg
- Oxycodone SR tablets in 10 mg, 20 mg, 30 mg, 40 mg
- Oxycodone/Acetaminophen tablet 5 mg/325 mg

What Can You Do?

- Provide education and recommendations for alternative analgesics
- Utilize clinical decision support
- Facilitate changes in insurance reimbursement
- Remove from formulary

Taming the Tiger
The Power of One

- Ketamine properties include
  - Sedation
  - Analgesia
  - Amnesia
- Key disadvantage
  - Psychomimetic side effects

A Local Discovery

- First described in 1965 by Parke Davis/UM researchers
- Phencyclidine derivative
- N-methyl D-aspartate (NMDA) receptor antagonist
  - Inhibits serotonin and dopamine reuptake
  - Inhibits voltage-gated Na⁺ and K⁺ channels

Ketamine Mechanisms of Action

Advantages Over Opioids

– Does not suppress cardiovascular function
– No histamine release
– Airway reflexes preserved
– Less respiratory depression
– Less prolonged sedation than with opioids and benzodiazepines

Incidence of CNS Side Effects

<table>
<thead>
<tr>
<th>Study</th>
<th>Ketamine + Opioid</th>
<th>Opioid Alone</th>
<th>RR (95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV PCA Ketamine + Morphine</td>
<td>27/146</td>
<td>20/135</td>
<td>1.27</td>
</tr>
<tr>
<td>IV Ketamine Cont. Inf.</td>
<td>15/149</td>
<td>9/140</td>
<td>1.31</td>
</tr>
<tr>
<td>IV Ketamine single IVP</td>
<td>38/444</td>
<td>16/322</td>
<td>1.61</td>
</tr>
</tbody>
</table>

Subramaniam K et al. Anesth Anal. 2004

Incidence of PONV

<table>
<thead>
<tr>
<th>Study</th>
<th>Ketamine + Opioid</th>
<th>Opioid Alone</th>
<th>RR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV Ketamine Cont. Inf.</td>
<td>15/106</td>
<td>27/117</td>
<td>0.58</td>
</tr>
<tr>
<td>IV Ketamine single IVP</td>
<td>74/391</td>
<td>75/258</td>
<td>0.76</td>
</tr>
<tr>
<td>Epidural Ketamine</td>
<td>70/229</td>
<td>76/224</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Subramaniam K et al. Anesth Anal. 2004
What to Watch For…

- Random movements of head and extremities
  - Tonic/clonic movements
  - Nystagmus
- Mildly increased BP and HR from endogenous catecholamine release
- Increased oral and tracheobronchial secretions
- Vomiting during recovery
- Metallic taste on injection

Opioid Sparing

- Useful and safe additive to standard practice opioid analgesia
- Cumulative morphine consumption at 24 hours: 3 of 4 trials report statistically significant reduction from 9% to 47% (median 32%)
- No reduction in opioid side effects such as PONV, pruritus and respiratory depression

Subramaniam K et al Anesth Analg 2004;99:482-95

Correlation of Ketamine to Reduction in Pain

Elements of a Successful Low Dose Ketamine Protocol

- Define the dose
  - $\leq 0.3\text{mg/kg/hr}$ up to a maximum of $30\text{mg/hr}$ – Adults
  - $\leq 5\text{mcg/kg/min}$ up to a maximum of $500\text{mcg/min}$ – Pediatrics
- Standardize concentrations
  - $5\text{mg/ml}$ Adults, $2\text{mg/ml}$ Pediatrics
- Standardize nursing monitoring
- Limit prescribing to select groups

Patient Selection

- When anticipated VAS is greater than 7/10
- Opioid tolerant patients
- Selected surgical procedures
- Patients at risk for postoperative nausea/vomiting
- No history of urinary tract infection
Questions still to be answered

- Are effects in absence of opioid administration due to sedative or analgesic effect
- Failure to reduce post-op pain relative to single dose studies
- Efficacy has been inconclusive
- Definition of “low dose” is inconsistent

**IV Acetaminophen**

- Available in Europe since 2002
- Approved by FDA in November 2010 for:
  - Mild to moderate pain
  - Moderate to severe acute pain with an opioid
  - Reduction of fever
- Central mechanism of action:
  - Passive diffusion; highly dependent on concentration gradient ($C_{max}$)

**Iv acetaminophen Pharmacokinetics**

(vs. oral and rectal in healthy male volunteers)

Earlier and higher peak plasma and CSF concentrations with IV route
• Less variability in plasma concentration with IV route (vs. oral and rectal)
• 100 children undergoing tonsillectomy
  – Plasma concentration > 10.6 mg/L was analgesic for 75% of children
  – Ceiling analgesic effect at 19.7 mg/L

Anesth Intens Care 1996;24:669
Pain Practice 2012 Apr 24 doi: 10.1111/j.1533-2500.00556.x

Oral absorption before surgery
• 106 adults undergoing ENT or orthopedic surgery randomized to receive IV or oral acetaminophen pre-op
  • Plasma concentrations > 10 mg/L achieved in:
    • 96% of patients who received IV
    • 67% of patients who received oral (P<0.0001)

Anaesth Intensive Care 2011;39:242

Effects of IV Acetaminophen on PONV
• Prospective, placebo controlled RDB
• 86 children between 2-14 yr old
• Saline vs Paracetamol 15mg/kg IV
• Outcome was PONV within 24 hours postop
  – Nausea: 33% placebo, 14.6% APAP
  – Vomiting: 24.4% placebo, 7.3% APAP
  – Opiate use higher in the placebo grp

COK OY. et.al. Euro J Anaesth. 2011
Pain Medications Prescribed for Mod-Severe Pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Overall (N = 88)</th>
<th>Medical (N = 22)</th>
<th>Surgical (N = 66)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not used</td>
<td>22 (25)</td>
<td>10 (45)</td>
<td>12 (18)</td>
<td>.011</td>
</tr>
<tr>
<td>PRN</td>
<td>47 (53)</td>
<td>8 (36)</td>
<td>39 (59)</td>
<td></td>
</tr>
<tr>
<td>Scheduled</td>
<td>19 (22)</td>
<td>4 (18)</td>
<td>15 (23)</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not used</td>
<td>70 (80)</td>
<td>18 (82)</td>
<td>52 (79)</td>
<td>.760</td>
</tr>
<tr>
<td>PRN</td>
<td>8 (9)</td>
<td>2 (9)</td>
<td>6 (9)</td>
<td></td>
</tr>
<tr>
<td>Scheduled</td>
<td>10 (11)</td>
<td>2 (9)</td>
<td>8 (12)</td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not used</td>
<td>21 (24)</td>
<td>8 (36)</td>
<td>13 (20)</td>
<td>.012</td>
</tr>
<tr>
<td>PRN</td>
<td>35 (40)</td>
<td>9 (41)</td>
<td>26 (40)</td>
<td></td>
</tr>
<tr>
<td>Scheduled</td>
<td>32 (36)</td>
<td>5 (23)</td>
<td>27 (41)</td>
<td></td>
</tr>
</tbody>
</table>

1. Patients with moderate-severe pain. Data are presented as N (%).
2. The percentage of patients receiving the given medication (either PRN or Scheduled) was compared between medical and surgical admissions using the chi-square test.
3. NSAIDs, nonsteroidal anti-inflammatory drugs.

Summary of Opioid Sparing Effects

Reduction in opioid consumption

Literature review of placebo-controlled trials (6 h)

- Study et al. 2008 (intrathecal lidocaine)
- Hovnanian et al. 2008 (bupivacaine)
- Knecht et al. 2008 (bupivacaine)
- Miller et al. 2009 (acetaminophen)
- Milne et al. 2009 (epinephrine-free)
- Ansell et al. 2009 (acetaminophen)
- Ansell et al. 2009 (acetaminophen)
- Kaiser et al. 2009 (acetaminophen)

% reduction in opioid consumption for IV paracetamol vs. placebo

* P < 0.05
** P < 0.01
NS = not significant

Visual Analog Scores ≥ 6: Acetaminophen vs. Placebo

* P < 0.05
Opioid Reduction with Non-opioids in Children


Analgesic effectiveness of acetaminophen for primary cleft palate repair in young children

Pediatric Anesthesia
Volume 24, Issue 6, pages 574-581, 2 APR 2014 DOI: 10.1111/pan.12393

Beyond Opioid Sparing Effects

- Wininger S. Clin Ther 2010
  Abdominal Laparoscopy 200pts
  Patient Satisfaction 70% Placebo/ 87% APAP
- Sinatra RS. Anesth. 2005
  Total Hip and Knee 101pts
  Patient Satisfaction 23% Placebo/ 41% APAP
- Gimbol. AAPM Mtg. 2008
  Total Hip 61pts
  Patient Satisfaction 39% Placebo/ 86% APAP
Elastomeric Pumps for Analgesia Management

Overview: Continuous Peripheral Nerve Blocks

- Definition
  - Regional anesthetic
    - Anesthesia affecting a large part of the body, such as a limb or the lower half of the body
  - Elastomeric pumps are made to deliver a continuous infusion of local anesthetics directly through a catheter placed at the surgical site
  - Indicated for subfascial/subcutaneous localized delivery of anesthetics and delivery of anesthetic to peripheral nerves
  - Disposable infusion devices designed for temporary, one-time use
  - NOT for use via epidural, spinal or caudal anesthesia access or intravenous access

How do they work?

- Reservoir of local anesthetic to infuse over 5 days
- Required pressure comes from the elastomeric layer molded inside the cassette
- Accuracy is controlled by a flow restrictor molded into the tubing or reservoir
- Wide range of flow rates
- Nationwide Children’s Hospital study
  - 15 pumps, 5 of each, On-Q, Ambu, and Baxter
  - 12ml/hr for 10 hours of Ropivacaine 0.1%
  - Ambu the most consistent
  - Baxter the most accurate
Approved Elastomeric Pumps

**ON-Q® PainBuster®**
B. Braun
Nominal fill volume of 400 ml
3 different fixed flow rates (5, 8, 10 ml/h)
Completely silent without any complicated electronics
OnDemand unit for Patient Controlled Analgesia
One bolus of 5 ml per hour (60 mins refill time) at a basal rate of 5 ml/h (fixed flow rate)
Select-A-Flow unit
Adjusted flow rate within a range of 2 ml/h to 14 ml/h (2 ml increments)
Detachable key and the lockable cover

**Ambu® ACTion™**
Block Pain Pump
Available in 100 mL or 275 mL syringe reservoirs made of rigid polypropylene reducing the concern of bursting or damage
6 psi nominal pressure helps maintain catheter patency
Flexible: Features a wide range of flow sets (0.6 to 250 ml/hr)

**Accufuser**
Patented mechanical infusion technology ensures precise and reliable delivery to prevent over or under infusion. Can be used from 1 to 5 days. Delivers 0.5 to 10 mL/hr. Offers 7 basal rates with 5 drug delivery options (both 2 basal intervals).

**Why Pediatric Regional Anesthesia**

- Low complication rate
- Children at risk for opioid induced respiratory depression and/or tolerance to effects
- Ideal psychological conditions
- Potential of neuroprotective effects
- Reduced sensitization of the nociceptive pathways
- Ultrasound guided placement techniques

Rosenberg A. Ped Anesth. 22, 2012
Feasibility of CPNB’s in Children

- 292 children age 0.6-17 yo
- Primarily orthopedic surgeries
- Ropivacaine/bupivacaine
  - Median duration 61.6hrs
  - Median infusion 0.11mg/kg/hr
- Minor adverse effects
  - Catheter issues
  - Nausea and vomiting
**Electronic Order Sets**

Pediatric Order Set Example:

<table>
<thead>
<tr>
<th>Pump Size</th>
<th>Preferred Agent*</th>
<th>Preferred Agent**</th>
</tr>
</thead>
<tbody>
<tr>
<td>5—6 kg</td>
<td>Bupivacaine 0.125% 1 mL/hr</td>
<td>200 mL</td>
</tr>
<tr>
<td>&gt;6—10 kg</td>
<td>Bupivacaine 0.25% 1 mL/hr</td>
<td>200 mL</td>
</tr>
<tr>
<td>&gt;10—20 kg</td>
<td>Bupivacaine 0.25% 2 mL/hr</td>
<td>200 mL</td>
</tr>
<tr>
<td>&gt;20—25 kg</td>
<td>Bupivacaine 0.25% 4 mL/hr</td>
<td>400 mL</td>
</tr>
<tr>
<td>&gt;25 kg</td>
<td>Bupivacaine 0.25% 5 mL/hr</td>
<td>400 mL</td>
</tr>
</tbody>
</table>

*Recommended dose for neonates and infants < 4 months: 0.2—0.25 mg/kg/hr
**Recommended dose for infants >4 months and children: 0.4—0.5 mg/kg/hr

*Notes:
- Recommended dose for neonates and infants < 4 months: 0.2—0.25 mg/kg/hr
- Recommended dose for infants >4 months and children: 0.4—0.5 mg/kg/hr
- Recommended dose for children >2 years: 5—20 mg/hr
- The above datasets are compliant with recommended dosing parameters
*Note: 1 mL/mL solution includes preservative free
Ropivacaine Dosing

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Infusion Rate</th>
<th>Pump Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5—5 kg</td>
<td>1 mL/hr</td>
<td>200 mL</td>
</tr>
<tr>
<td>&gt;5—7.5 kg</td>
<td>1 mL/hr</td>
<td>200 mL</td>
</tr>
<tr>
<td>&gt;7.5—12.5 kg</td>
<td>2 mL/hr</td>
<td>200 mL</td>
</tr>
<tr>
<td>&gt;12.5—15 kg</td>
<td>3 mL/hr</td>
<td>400 mL</td>
</tr>
<tr>
<td>&gt;15—25 kg</td>
<td>4 mL/hr</td>
<td>400 mL</td>
</tr>
<tr>
<td>&gt;25 kg</td>
<td>5 mL/hr</td>
<td>400 mL</td>
</tr>
</tbody>
</table>

Notes:
- Recommended dose for children 4 months—7 years: 0.4 mg/kg/hr
- Recommended dose for adults: 12-28 mg/hour
- The above infusion rates correspond with recommended dosing parameters
- **Dilute with 0.9% sodium chloride preservative free

Precautions:
- Increases in pain
- Redness, swelling, pain at catheter site
- Blurred vision, dizziness, tinnitus
- Nausea/vomiting
- Metallic taste
- Temperature > 38°C
- Catheter tip is not black and rounded at time of removal

Peripheral Nerve Catheter Tip

Khabiri B et al. Open J Anesth. 2013
Potential Safety Concerns

• Unlabeled devices
• Lack of staff education
• Use without pharmacy involvement
• No pharmacy ordering process
• Use of local anesthetics in combination with other drugs
• Non-standard concentrations
• Refilling of cassette/reservoir

Sterility and Stability

• Bupivacaine 0.25% and Ropivacaine 0.1%
• Drug Purity at 30 days – pure
• Drug Potency at 30 days – no change
• Drug Appearance at 30 days – clear, colorless
• Sterility at 30 days – sterile

• Key is proper aseptic technique employed at time of drug preparation and fill

Moog Medical Devices Product Information 2011

Conclusion and Questions