Pain Relief and Analgesic Grief: From the ED to ICU
Disclosure

Asad Patanwala
AcelRx: Advisory Board

John Radosevich
AcelRx: Advisory Board

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.
Objectives

• Assess optimal analgesic options for pain given a patient case scenario in the emergency department (ED).
• Compare optimal analgesic options for pain given a patient case scenario in the intensive care unit (ICU).
• Apply guidelines and an evidence-based approach for opioid use in the ED and ICU.
Pain in the ED

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Associate Professor
The University of Arizona, College of Pharmacy
Tucson, Arizona
A long time ago . . . in a land far away

Can repeat? How often?

Cumulative or single dose?

2 - 20 mg IV

morphine
What is your pain score?

0 1 2 3 4 5 6 7 8 9 10

No Pain

Worst Possible Pain

Pulling your arms out of their sockets
What is your Pain score?

Whatever score gets me morphine
Patient-Driven Protocol

- Prospective cohort (n=207)
- Hydromorphone 1mg given every 30 min if patient desires
- Satisfactory analgesia in 99% of patients
- ADE – 9 desaturations,
- 2 ↓RR, 2 ↓HR

So Many Choices

MORPHINE
HYDROMORPHONE
KETOROLAC
LIDOCAINE
FENTANYL
ACETAMINOPHEN
IBUPROFEN
CYCLOBENZAPRINE
A 50 y/o M is in the ED with flank pain and hematuria. He says the pain comes in waves and he is also nauseous. CT scan indicates that he has a kidney stone. He says that morphine gives him nausea and itching.
# Ketorolac

<table>
<thead>
<tr>
<th>RCT – ED patients with renal colic</th>
<th>Morphine 5 mg (n=43)</th>
<th>Ketorolac 15 mg (N=43)</th>
<th>Morphine 5 mg + Ketorolac 15 mg (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses could be repeated at 20 min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Pain</td>
<td>8.7</td>
<td>8.8</td>
<td>8.9</td>
</tr>
<tr>
<td>Dose repeated at 20 min</td>
<td>84%</td>
<td>88%</td>
<td>70%</td>
</tr>
<tr>
<td>Pain 40 min</td>
<td>3.7</td>
<td>4.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Change</td>
<td>4.0</td>
<td>4.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Rescue morphine</td>
<td>42%</td>
<td>33%</td>
<td>16%</td>
</tr>
</tbody>
</table>

Combination vs. morphine (difference in change 1.8, 95% CI 0.1-3.3)
Combination vs. ketorolac (difference in change 2.2, 95% CI 0.5-3.7)

Ketorolac Dose

RCT (n=240): Patients in the ED with moderate to severe acute pain

Dose

10 mg  
Baseline Pain  7.7  
Pain at 30 min  5.1

15 mg  
Baseline Pain  7.5  
Pain at 30 min  5

30 mg  
Baseline Pain  7.8  
Pain at 30 min  4.8

## Lidocaine

**RCT (n=240)**  
Patients with renal colic in the ED [Iran]

<table>
<thead>
<tr>
<th>Pain Score</th>
<th>Lidocaine 1.5 mg/kg IV</th>
<th>Morphine 0.1 mg/kg IV</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>9.65 ± 0.88</td>
<td>9.74 ± 0.63</td>
<td>0.365</td>
</tr>
<tr>
<td>15 min</td>
<td>1.83 ± 1.59</td>
<td>2.55 ± 1.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>30 min</td>
<td>1.13 ± 1.15</td>
<td>2.23 ± 1.57</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Soleimanpour et al. BMC Urology 2012;12:13
Lidocaine

- RCT (n=41)
- Patients with radicular back pain in the ED
- Lidocaine 100 mg IV vs. Ketorolac 30 mg IV

Tanen et al. JEM 2014;47:119-124
A 35 y/o M is in the ED with severe back pain. He took 2 tablets of his wife’s oxycodone/APAP and it did not help

A. Give him more oxycodone/APAP
B. Give him hydromorphone instead
C. Give him a non-opioid
Guideline: **Acute Back Pain**

1st
- **Non-Pharmacological therapy**

2nd
- **NSAIDS**
- **Skeletal muscle relaxants**

**Insufficient evidence or not effective**
- Antidepressants
- Benzodiazepines
- Opioids
- APAP
- Steroids

So what is most commonly used for back pain in the ED?

OPIOIDS

Friedman et al. Spine 2010;35(24):E1406-11
## Radicular Back Pain

<table>
<thead>
<tr>
<th>RCT (n=58) – Low back pain with radiculopathy</th>
<th>Dexamethasone 8mg IV</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS change at 24 hours</td>
<td>-2.63 (-3.63 to 1.63)</td>
<td>-0.77 (-2.04 to 0.51)</td>
</tr>
<tr>
<td>Straight leg raise angle improvement</td>
<td>20.2 degrees</td>
<td>5.5 degrees</td>
</tr>
<tr>
<td>ED length of stay</td>
<td>3.5 hours</td>
<td>18.8 hours</td>
</tr>
</tbody>
</table>

A 40 y/o M is in the ED after an ATV accident. He has an open fracture of his lower extremity. PMH includes heroin use. He is screaming in pain. After receiving 250 mcg IV (50 + 100mcg + 100 mcg) of fentanyl he is still screaming.
Ketamine Effectiveness

Systematic review of low-dose ketamine in emergency settings (6 trials, 438 patients)

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Std. Mean Difference on NRS</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>-0.35</td>
<td>-1.13 to 0.42</td>
<td>0.37</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>-0.09</td>
<td>-0.59 to 0.40</td>
<td>0.71</td>
</tr>
</tbody>
</table>

Dose = 0.2 to 0.3 mg/kg IV

Lee et al. PLoS ONE 2016;11(10):e0165461
# Ketamine Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>1.10</td>
<td>0.65 to 1.84</td>
<td>0.73</td>
</tr>
<tr>
<td>Neurological</td>
<td>2.17</td>
<td>1.37 to 3.42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychological</td>
<td>13.86</td>
<td>4.85 to 39.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major cardiopulmonary</td>
<td>0.22</td>
<td>0.05 to 1.01</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Lee et al. PLoS ONE 2016;11(10):e0165461
Ketamine

RCT (n=116)

- Convenience sample of ED patients with refractory pain (≥6/10) after 1st opioid dose
- Randomized to ketamine 0.1 mg/kg versus saline
- Morphine for breakthrough pain

Bowers et al. Acad Emerg Med 2017;24:676–685
A 45 year old male with abdominal pain (10/10). Would you change his opioid dose if his weight was different?

A. Decrease dose
B. Same dose
C. Increase dose

Weight: 70 kg

Weight: 140 kg
Weight-Based Dosing

- Prospective cohort (n=50)
- Adult patients with severe abdominal pain Pain measured before, 15 min post, and 30 min post morphine 4 mg IV

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (95% CI)</th>
<th>R²</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial pain score</td>
<td>0.54 (0.13-1.06)</td>
<td>0.081</td>
<td>0.045</td>
</tr>
<tr>
<td>Race (white)</td>
<td>−0.9 (−2.37-0.56)</td>
<td>0.031</td>
<td>0.222</td>
</tr>
<tr>
<td>Pain location (abdominal)</td>
<td>0.47 (−1.01-1.95)</td>
<td>0.008</td>
<td>0.526</td>
</tr>
<tr>
<td>Age, y</td>
<td>−0.007 (−0.05-0.04)</td>
<td>0.002</td>
<td>0.76</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>0.12 (−1.36-1.61)</td>
<td>&lt;0.001</td>
<td>0.867</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>0.002 (−0.03-0.03)</td>
<td>&lt;0.001</td>
<td>0.907</td>
</tr>
<tr>
<td>Height, cm</td>
<td>−0.002 (−0.08-0.07)</td>
<td>&lt;0.001</td>
<td>0.946</td>
</tr>
</tbody>
</table>

Obesity

• Retrospective cohort (n=300)
• Includes 100 patients with BMI $\geq 40$ kg/m$^2$
• All given morphine 4 mg IV

An obese patient is brought to the ED after a motor cycle collision. He has a femur fracture and is in a lot of pain. IV access has not been obtained after 3 attempts.

A. Give morphine IM
C. Give fentanyl IN
D. Wait for IV access
Intranasal Opioids

- ↑Lipophilicity → ↑Absorption (fentanyl preferred)
- Ideal volume = <1 ml
  (↑volume → drug run-off into pharynx)

Intra-Nasal Fentanyl PK/PD

• Bioavailability 89% (inter-patient absorption variability 29%)
• Time to peak concentration 13 min (lag of ~5 min before enters systemic circulation)
• Mean duration of action 58 ± 24 min
• Mean time to rescue medication 71 ± 32 min

Sublingual Sufentanil

- Sufentanil 30 mcg SL
- Multicenter, open-label study (n=76) in adults with acute pain due to trauma or injury

Key Takeaways

• Key Takeaway #1
  – Treat the patient rather than pain scores -“Do you want pain medication?”

• Key Takeaway #2
  – Use non-opioids when possible and consider the diagnosis

• Key Takeaway #3
  – Patient size is not the only factor to consider when dosing opioids in adults
Thank You
Pain in the ICU

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Clinical Pharmacy Specialist – Medical ICU
St. Joseph’s Hospital and Medical Center
Phoenix, Arizona
Patient Case

- Hospital day 3 for a 38 year old male on ventilator s/p debridement x2 of left lower extremity for necrotizing fasciitis, currently having issues with ventilator dysynchrony, mild tachycardia and hypertension
  - Analgosedation regimen
    - Fentanyl 50 mcg/hr + propofol 40 mcg/kg/min
    - RASS score is -2
    - Not on any other adjunct pain medications
What is our next step with this patient?

A. Increase fentanyl infusion rate
B. Assess CPOT/BPS
C. Increase propofol infusion rate and target RASS of -3 to -5
D. Add cisatracurium
How is his pain?

Vitals are okay, he is fine....
Pain Assessment in the ICU

- Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit
  - Recommend pain be routinely monitored
  - Behavioral Pain Scale (BPS) and Critical Care Observation Tool (CPOT) are the most valid and reliable behavior pain scales for monitoring pain in adult ICU patients who are unable to self report

Pain Assessment in the ICU

- Critical Care Observation Tool (CPOT)

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial Expressions</td>
<td>0 – 2</td>
<td>(0) Relaxed; (1) Tense; (2) Grimacing</td>
</tr>
<tr>
<td>Body Movements</td>
<td>0 – 2</td>
<td>(0) Absence of movement; (1) Protection; (2) Restlessness/agitation</td>
</tr>
<tr>
<td>Compliance with ventilator or Vocalization</td>
<td>0 – 2</td>
<td>(0) Tolerating vent/normal talking: (1) Coughing but tolerating/sighing or moaning; (2) Fighting ventilator/Crying or sobbing</td>
</tr>
<tr>
<td>Muscle Tension</td>
<td>0 – 2</td>
<td>(0) Relaxed; (1) Tense/rigid; (2) Very tense/rigid</td>
</tr>
</tbody>
</table>

## Pain Assessment in the ICU

- **Behavioral Pain Scale (BPS)**

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial Expressions</td>
<td>1 – 4</td>
<td>(1) Relaxed; (2) Partially tightened; (3) Full tightened; (4) Grimacing</td>
</tr>
<tr>
<td>Upper Limb Movements</td>
<td>1 – 4</td>
<td>(1) No movement; (2) Partially bent; (3) Fully bent with finger flexion; (4) Permanently retracted</td>
</tr>
<tr>
<td>Compliance with ventilator</td>
<td>1 – 4</td>
<td>(1) Tolerating movement; (2) Coughing but tolerating most of the time; (3) Fighting ventilator; (4) Unable to control ventilation</td>
</tr>
</tbody>
</table>

Pain Assessment in the ICU

- Are we using CPOT/BPS?

**ESICM**
- 101 ICUs throughout Europe
  - 30% of ICUs used a validated tool for MV patients

**Norway**
- 2 ICUs in Norway
  - When patients were unable to communicate, nurse made an assessment on their behalf

**Canada**
- 51 ICUs throughout Canada
  - 47.1% of ICUs reported pain assessment tool
  - 19.1% of patients had pain assessed with validated tool

Pain Assessment in the ICU

- Are we using CPOT/BPS?

**UK**
- 45 ICUs in London and Southeast England
  - 37.4% of patients had a physician reported pain assessment
  - 71.4% of patients had nurse reported pain assessment

**Belgium**
- 95 ICUs throughout Belgium
  - 11% (n=16) of ICUs use validated pain assessment tool
  - 88% of MDs/RNs used physiological parameters to assess pain

**Netherlands**
- 84 ICUs throughout Netherlands
  - 19% (n=16) of ICUs use validated pain assessment tool
  - Validated pain assessment tool was used in 11% of patients

Pain Assessment in the ICU

• Barriers to effective pain management in the ICU

Provider
- Managing pain is low priority
- Failure to assess, evaluate, and adjust pain regimen
- Concern about tolerance or dependence

Healthcare System
- Underemphasized
- Logistical hurdles
- Lack of accountability for unsatisfactory outcomes

Patient
- Inability to report
- Fear of side effects
- Fear of consequences of reporting pain
- Feeling that pain is inevitable

Pain Assessment in the ICU

- Benefits of routine assessment of pain with CPOT/BPS

  - Reduced Pain
  - Reduced Agitation
  - Reduced Infections
  - Reduced Duration of MV

Payen et al. *Anesthesiology* 2009;111:1308-16.
Pain Assessment in the ICU

- Validated pain assessment tools are underutilized
- Provider, system, and patient related barriers to pain assessment exist and must be overcome
- Using validated pain assessment tools improves outcomes
Hospital day 5 for our 38 year old male s/p debridement x2 of left lower extremity for necrotizing fasciitis, remains on ventilator, vasopressors are being weaned down

- Analgosedation regimen
  - Fentanyl 200 mcg/hr + propofol 20 mcg/kg/min
  - RASS score is -1
  - CPOT score is 6 (indicating significant pain)
- Adjunctive agents
  - Acetaminophen 1000mg FT q8hrs
What is our next step with this patient?

A. Increase fentanyl infusion rate
B. Assess CPOT/BPS
C. Start ketamine infusion
A. Increase propofol infusion rate
Adjunctive Pain Agents

• Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit
  – Acetaminophen, NSAIDs, or **Ketamine** maybe used in addition to opioids for non-neuropathic pain
  – Carbamazepine or gabapentin maybe used in addition to opioids for neuropathic pain

Ketamine

• Pharmacology
  – Opioid receptor augmentation (delta, kappa, and mu)
  – NMDA receptor blockade (antinociception and psychosis)
  – CNS anticholinergic (psychic and sedative effects)
  – GABA inhibition (involved in anesthesia)
  – Hyperadrenergic (increased release and reduced uptake of mediators)

Ketamine

- Limited data regarding analgosedation outcomes
  - Randomized, prospective studies in MV patients

<table>
<thead>
<tr>
<th>Citation</th>
<th>Design</th>
<th>Ketamine Dosing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillou et al. <em>Anesth Analg</em> 2003;97:843-7.</td>
<td>Double blind, n=93 SICU s/p abdominal surgery</td>
<td>0.5mg/kg bolus Then 1 – 2 mcg/kg/min x 48hrs</td>
<td>Opioid Utilization</td>
</tr>
<tr>
<td>Mogahd et al. <em>Ann Card Anaesth</em> 2017;20:182-7.</td>
<td>n=70 CABG</td>
<td>1mg/kg bolus Then 0.25 mg/kg/hr</td>
<td>Opioid Utilization</td>
</tr>
</tbody>
</table>
Ketamine

• Limited data regarding analgosedation outcomes
  – Retrospective studies in MV patients

<table>
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<th>Design</th>
<th>Ketamine Dosing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smith et al. <em>Crit Care Med</em> 2016;97:853.</td>
<td>n=24 Mixed ICU</td>
<td>1 – 60 mcg/kg/min</td>
<td>Sedative Utilization</td>
</tr>
</tbody>
</table>
Ketamine

- Limited data regarding analgosedation outcomes
  - Retrospective study in MV patients; mixed ICU
  - No difference was noted in opioid requirements

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ketamine (n=39)</th>
<th>Non-ketamine (n=40)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [median, IQR]</td>
<td>59 (53-68)</td>
<td>54 (43-67)</td>
<td>0.322</td>
</tr>
<tr>
<td>SOFA score [median, IQR]</td>
<td>7 (4-11)</td>
<td>7 (6-10)</td>
<td>0.630</td>
</tr>
<tr>
<td>Percent CPOT at goal [median, IQR]</td>
<td>99 (93-100)</td>
<td>91 (77-96)</td>
<td>0.044</td>
</tr>
<tr>
<td>Ventilator days [median, IQR]</td>
<td>8 (4-18)</td>
<td>7 (3-11)</td>
<td>0.171</td>
</tr>
</tbody>
</table>

Radoevich et al. *Submitted to SCCM Congress February 2018.*
Ketamine

- Role in therapy
  - Adjunctive agent
    - May improve pain scores
    - May reduce opioid/sedative utilization
- Dosing
  - Pain: 1 – 20 mcg/kg/min; titrate by up to 1 mcg/kg/min q15min
  - Sedation: 5 – 50 mcg/kg/min; titrate by up to 5 mcg/kg/min q15min

Patient Case

• Hospital day 12 for our 38 year old male s/p debridement x2 of left lower extremity for necrotizing fasciitis, remains on ventilator, vasopressors are off...
  – Analgosedation regimen
    • Fentanyl 200 mcg/hr + ketamine 10 mcg/kg/min
    • RASS score is 0
    • CPOT score is 2 (indicating no pain)
  – Facility patient is getting transferred will not take him with IV drips
What is our next step with this patient?

A. Stop fentanyl and ketamine now
B. Transition to oral methadone
C. Wean fentanyl and ketamine over the next 3-5 days
D. Transition to bolus fentanyl and ketamine
Enteral Methadone

• Methadone
  – Pharmacology
    • mu opioid receptor agonist
    • NMDA receptor antagonist
    • Inhibits serotonin reuptake
  – Adverse effects
    • prolonged QT interval, serotonin syndrome
  – Dosage forms: tablet, oral solution, intravenous (2:1 oral→IV conversion)

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>70 – 80 %</td>
</tr>
<tr>
<td>Protein Binding</td>
<td>85 – 90 %</td>
</tr>
<tr>
<td>Half-life</td>
<td>7 – 65 hrs</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>3.6 L/kg</td>
</tr>
</tbody>
</table>

Enteral Methadone

- Limited data regarding analgosedation outcomes
  - Studies in MV patients

<table>
<thead>
<tr>
<th>Citation</th>
<th>Design</th>
<th>Methadone Dosing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wanzueta et al. Critical Care 2012; 16:R49</td>
<td>n=68 Mixed ICU Randomized, DB</td>
<td>10mg enterally q6hrs</td>
<td>No difference in MV duration, opioid withdrawal, or ICU los</td>
</tr>
<tr>
<td>Al-Qadheeb et al. Ann Pharmacother 2012;46:1160-6.</td>
<td>n=24 Medical ICU Case-control</td>
<td>~10 – 15 mg enterally q8hrs</td>
<td>Reduced time to fentanyl discontinuation, no difference in MV duration, or ICU LOS</td>
</tr>
</tbody>
</table>
Enteral Methadone

- Limited data regarding analgosedation outcomes
  - Studies in MV patients

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<th>Citation</th>
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<th>Methadone Dosing</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones et al.</td>
<td>n=70 Burn ICU</td>
<td>Medial initial Dose 15mg/day</td>
<td>Increased ventilator free days</td>
</tr>
<tr>
<td><em>J Burn Care Res</em></td>
<td>Randomized, DB</td>
<td>Median Max Dose 30mg/day</td>
<td>(16.5 vs 11.5; P=0.03)</td>
</tr>
</tbody>
</table>
Enteral Methadone

- Potential benefits include:
  - Increase number of ventilator free days
  - Facilitate transfer to outside facility
  - Reduce the number of invasive lines
  - Reduce the fluid load associated with infusions
  - Reduced risk of developing delirium

Enteral Methadone

• Role in therapy
  – May facilitate earlier ventilator weaning and increase ventilator free days
  – May reduce opioid/sedative utilization

• Dosing
  – Initial: 5 – 10 mg enteral q8 – 12 hours
  – Titrate: 5 – 10 mg enteral q8 – 12 hours every 3 – 5 days

• Reassess and monitor

Key Takeaways

• Key Takeaway #1
  – Validated pain assessment tools are underutilized despite having been shown to improve numerous clinical outcomes

• Key Takeaway #2
  – Continuous infusion ketamine may improve pain scores and reduce opioid/sedative utilization

• Key Takeaway #3
  – Enteral methadone and other opioid analgesics may play a role in facilitating discontinuation of continuous infusion analgesics