From Myths, Magic, and Morphine: Advanced Pain Treatment in Hospitalized Children

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Learning Objectives

- Critically review risks & safety of analgesic under-treatment versus over-treatment in hospitalized children
- Evaluate assumptions about opioid use in children
- Discuss how multiple agents, interventions, rehabilitation, psychological & integrative therapies act synergistically for more effective pediatric pain control with fewer side effects than a single analgesic or modality - and improves patient experience
5-year old Marius: Procedural Pain Management


Don't have enough staff for pediatric pain control...?

Funny, how there is always enough staff to restrain a child.

Pediatric Analgesia in 1985

“Papoose Boards”

4 Sizes to Fit All Ages

- Small Size
- Regular Size
- Large Size
- Extra Large Size

- Infants and toddlers 3 to 24 months
- Small children 2 to 6 years
- 6 to 10 years
- Teenagers and adults

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So, how do we treat the individual pain patient in front of us?

Hmhh...

Spoiler Alert: Crystal-clear answer on 3rd last slide!

Pediatric Pain - Status Quo

- Under treatment of pain in children
- Parents expect pain to be relieved
- Priorities of parents of hospitalized children “Taking care of pain” rated as second highest priority (1st: getting right diagnosis)
- Parents’ greatest distress: failing to protect their child from pain
- Assumption: everything possible is done

Pediatric Pain - Status Quo

- USA: adults receive more than two - three times as many analgesic doses as children (with identical diagnoses)
- Compared to adults, pediatric patients receive fewer and/or incorrectly dosed analgesics in daily routine
- The younger children are, the less likely they receive appropriate analgesia

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Parents’ greatest distress: failing to protect their child from pain
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Inappropriate Analgesia: Why Bother...?

- Children with persistent pain suffer more physical symptoms in adult life, more anxiety and more depression. (1946 Medical Research Council and 1958 National Child Development Study)

Myths and Barriers to Using Opioids

Case Scenario:

- You are taking care of a child in a hospital with severe acute somatic nociceptive pain. It crosses your mind to administer a strong opioid such as morphine, fentanyl, or hydromorphone.
- What would be the most common concerns you might hear from your colleagues or parents arguing against opioid use in this child?

Common Opioid Assumptions

- Addiction: "chronic relapsing condition characterized by persistent, compulsive dependence on a behavior or substance despite adverse consequences"
  - Tolerance ≠ addiction
  - Pseudo-addiction
- Over Sedation / Respiratory Depression
- Ileus / Constipation
- Medication “Too strong”
- Masking symptoms
- Abdominal Pain
- Opioids after major cranial surgery in children do NOT result in altered mental status nor respiratory depression.
- As always... Think first! (e.g. compartment syndrome?)... analgesia second...
Safety of Analgesics

“Dr. Cox, I am worried about drug safety….would it be okay not using analgesia for children in acute pain?”

Opioid Safety & Long-Term Outcome

- Studies in neonatal rats suggest potential adverse effects of opioids (changes in behavior and brain functioning)

- NEOPAIN multicenter trial: Detailed secondary analysis: Although morphine associated with hypotension among ventilated preterm neonates, it does NOT increase the risk of severe IVH, any IVH, or death

- Higher cumulative fentanyl dose in preterm infants correlated with higher incidence of cerebellar injury, lower cerebellar diameter: No correlation was detected between cumulative fentanyl dose and development at 2 years of age.

- Long-term outcome at 5-6 years among formerly preterm babies exposed to continuous morphine infusion: No adverse effect of morphine on intelligence, motor function, or behavior

- Continuous morphine infusion of 10 mcg/kg/h during the neonatal period does not harm general functioning and may even have a positive influence on executive functions at 8 to 9 years.

Long-Term Outcome

- Low-dose morphine analgesia received on NICU associated with early alterations in cerebral structure, short-term neurobehavioral problems; did not persist into childhood: at 7 years no detrimental impacts of morphine on neurobehavioral outcome observed

- Long-term outcome at 5-6 years among formerly preterm babies exposed to continuous morphine infusion: No adverse effect of morphine on intelligence, motor function, or behavior
Does analgesia improve outcome?

- Yes, in animal model
  (Suellen Walker, PhD, London)


How Do We Manage Acute Pain in Children?

WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (2012)

- Data suggests that applying the World Health Organization (WHO) principles of pain management result in good pain relief for a large majority of children with cancer.

- In addition there is emerging evidence, that these principles are equally effective in acute pediatric pain management for non-malignant conditions.

Available online at: http://who.int/bcdoc/who.int/publications/2012/9789241548130_Guidelines.pdf
WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (2012)

- Dosing at regular intervals (“By the Clock”)
- Adapting treatment to the individual child (“With the Child”)
- Using the appropriate route of administration (“By the appropriate route”)
- Using a two-step strategy (“By the Analgesic Ladder”)

WHO Principle 1: Dosing at Regular Intervals

- PRN (“as needed”)
- PRN = Patient Receives Nothing
- When pain is constantly present, analgesics should be administered, while monitoring side-effects, at regular intervals
- “By the clock” and NOT as an “as needed” (or pro re nata “PRN”) basis

WHO Principle 2: Adapting Treatment to the Individual Child

- Treatment should be tailored to the individual child and opioid analgesics should be titrated on an individual basis
- At analgesic dosing: no sedation expected
- The effective dose is what relieves the pain
- Different children may respond differently to same dose
- Effective dose must be adjusted to child’s needs
- Dose of strong opioids: only the sky is the limit

- Regular scheduling ensures a steady blood level, reducing the peaks and troughs of PRN (“as needed”) dosing
- PRN (as needed) only:
  - May take several hours & higher opioid doses to relieve pain
  - Results in cycle of undermedication and pain, alternating with periods of overmedication and drug toxicity

Regular (!) Pain Assessment

- One-dimensional self-report scores
- Multi-dimensional rating scores

What are we measuring...

(1) Nociceptive Pain: arises from the activation of peripheral nerve endings (nociceptors) that respond to noxious stimulation
  - Somatic (for example, muscles, joints)
  - Chronic somatic pain typically well localized & often results from degenerative processes (such as arthritis)
  - Visceral (internal organs)

(2) Neuropathic Pain: resulting from injury to, or dysfunction of, the somatosensory system.
  - Central pain: caused by a lesion or disease of the central somatosensory nervous system

(3) Psycho-social-spiritual-emotional Pain / Total Pain

(4) Chronic Pain
  - Pain beyond expected time of healing

Pain in children with impaired communication

- Non-communicating Children's Pain Checklist - Revised (NCCPC-R); postoperative Version (NCCPC-PV) (Breau, 2002)

- Pediatric Pain Profile (PPP) (Hunt, 2003)

- r-FLACC (Malviya 2006)
Measuring pain alone…?

High specificity, low sensitivity…? Don’t forget:

- **Withdrawal**: WAT-I score
  
  
  [http://familynursing.ucsf.edu/research-and-clinical-tools](http://familynursing.ucsf.edu/research-and-clinical-tools)

- **Neonatal Abstinence Scoring Tool (Finnegan)**
  

- **Delirium**: CAPD
  

- **Sedation**: SBS score
  

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**WHO Principle 3: Route of Administration**

- **oral**
- **i.v. / s.c.**
- **intranasal** (MAD device)
- **nebulization?**
- **i.m.**
- **sublingual**
- **transmucosal**
- **transdermal**
- **suppository**

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**WHO Principle 4: Using a Two-Step Strategy**

WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses (2012)

**WHO Step 1**

**Mild Pain**

Ibuprofen

and/or

Acetaminophen (Paracetamol)

Other NSAIDs?

Cox-2 Inhibitor?
A δ or C fiber Injury

Thalamus

NSAIDs

Acetaminophen (Paracetamol)

2nd Neuron

Nociceptive Pathways & Primary Sites of Action of Analgesics

Citius, Altius, Fortius...

• Ibuprofen salts: fast-acting formulations
  e.g. Advil® Film-Coated Tablets: 266 mg ibuprofen sodium (≈ 200 mg of standard ibuprofen)
  • Produced significantly better analgesia over 6h, fewer re-medications than standard formulations
  • 200 mg fast-acting ibuprofen (NNT 2.1, 95% confidence interval 1.9-2.4) was as effective as 400 mg standard ibuprofen (NNT 2.4, 95% CI 2.2-2.5), with faster onset of analgesia.
  • More rapid absorption, faster initial pain reduction, good overall analgesia in more patients at the same dose, and probably longer-lasting analgesia, but with no higher rate of patients reporting adverse events.
  • However, earlier onset preferred in other pain conditions, such as chronic nociceptive or neuropathic pain? Peloso, P.M., Faster, higher, stronger: to the gold medal podium? Pain, 2014. 155(1): p. 4-5.

WHO Principle 1:
Using a Two-Step Strategy

WHO Step 1
Mild Pain

Ibuprofen
and/or
Acetaminophen (Paracetamol)

Other NSAIDs?
Cox-2 Inhibitor?

WHO Step 2
Moderate to Severe Pain

Morphine
or fentanyl, hydromorphone, oxycodone, methadone
CDC Guideline for Prescribing Opioids for Chronic Pain — United States, 2016
http://www.cdc.gov/mmwr/volumes/65/rr/rr6501e1.htm

- **Scope:** “patients aged ≥ 18 years with chronic pain outside of palliative and end-of-life care” and “treating patients with chronic pain (i.e., pain lasting >3 months or past the time of normal tissue healing) in outpatient settings”
- “recommendations do not address the use of opioid pain medication in children or adolescents aged <18 years”
- 12 recommendations, including:
  1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain
  4. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting opioids
  6. Acute pain opioid prescribing: Three days or less will often be sufficient; more than seven days will rarely be needed
  12. Evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder

### Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

### Integrative Therapies
- Massage
- Distraction
- Deep Breathing
- Biofeedback
- Hypnosis

### Multimodal (Opioid-sparing) Analgesia

#### Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

#### Opioids
- Tramadol (“weak”)
- Morphine (“strong”)

#### 4 WHO-Principles
- “by the clock”

Integrative Pain Management

State of the art pain management in the 21st century demands that pharmacological management must be combined with supportive and integrative, non-pharmacological therapies to manage a child’s pain.

- Physical methods (e.g. cuddle/hug, massage, comfort positioning, heat, cold, TENS)
- Cognitive behavioral techniques (e.g. guided imagery, hypnosis, abdominal breathing, distraction, biofeedback)
- Acupuncture, acupressure, aromatherapy
6-year-old Cassandra with severe pain due to chest tube insertion

Fentanyl PCA “the pump” and blowing bubbles “going to bubble land”

Integrative Pain & Symptom Management

- A Pediatrician’s Top 10 Apps for Distraction & Pain Management
  [Link to NoNeedlessPain.org]

Nociceptive Pathways & Primary Sites of Action of Analgesics

- Periaqueductal grey (endorphins)
- Integrative (non-pharmacological) therapies
  - Thalamus
  - Opioids
  - Acetaminophen (Paracetamol)
  - NSAIDs

Descending pathways that mediate transmission of nociceptive input originate in periaqueductal grey layer and modulate pain transmission via descending pathways. Transmitters involved include norepinephrine, 5-hydroxytryptamine (serotonin), dopamine, and endogenous opioids.
How does this stuff work...?


- Distraction significantly increased activation of cingulo-frontal cortex including orbitofrontal & perigenual anterior cingulate cortex (ACC), as well as periaqueductal gray (PAG) & the posterior thalamus.

Non-Opioids
- Acetaminophen / Paracetamol
- NSAIDs

Opioids
- Tramadol ("weak")
- Morphine ("strong")

4 WHO-Principles
- "As the clock"

Regional Anesthesia
- Neuraxial infusion
- Peripheral/Plexus Nerve block
- Intrathecal port/pump

Integrative Therapies
- Massage
- Distraction
- Deep Breathing
- Biofeedback
- Aromatherapy
- Hypnosis

Psychology
- CBT

Rehabilitation
- Exercise
- Physical Therapy
- Sleep Hygiene
- Occupational Therapy
- Speech Therapy

Adjuvants
- Alpha-Agonists
- Gabapentinoids
- TCA/Antidepressants
- NMDA-Antagonists
- Na-channel blockers

Neurolytic Sympathectomy
- Regional Sympathectomy
- Peripheral Sympathectomy
- Intrathoracic Sympathectomy
- Intraventricular opioids

Regional anesthesia approaches to pain management in PC

- Regional anesthesia: pediatric knowledge limited to case reports and case series
- Neurolytic Sympathectomy
- RCT (n=109) inoperable abdominal or pelvic cancer: better pain control, less opioid consumption, and better quality of life
Multimodal Analgesia

No Needless Pain

- Pain lasting > 3-6 months: Time definition arbitrary
- Pain that extends beyond the expected period of healing
- Hence lacks the acute warning function of physiological nociception


Chronic Pain in Children

- Pain lasting > 3-6 months: Time definition arbitrary
- Pain that extends beyond the expected period of healing
- Hence lacks the acute warning function of physiological nociception

Chronic-on-acute Pain

- Approximately 5% of children and teenagers in general population have significant pain related dysfunction
- In USA: > 3.7 million children
- At least (!) 5% of children with sickle cell disease, inflammatory bowel disease, rheumatoid arthritis, congenital heart disease, or cancer are expected to display chronic pain in addition to their underlying somatic pain episodes

Communication with Patient / Family

- Pain is real!
- First “function” gets better, then “pain” (not other way around)
- Positive Expectation = Self-fulfilling prophecy

Physical Therapy
- Daily home exercise

Integrative Medicine
- Self-Hypnosis
- Biofeedback
- Progressive Muscle relaxation
- Daily home exercise
- Passive Massage, Acupuncture

Psychology (...if missing school)

Normalize Life
- Sports/Exercise
- Sleep-hygiene
- Social: Having daily fun
- School: Attending full-time (or school-re-entry plan)

Family Coaching

Medications...???
**Multimodal Analgesia**

- Multimodal (opioid-sparing) analgesia: Multiple agents, interventions, rehabilitation, psychological and integrative therapies act synergistically for more effective pediatric pain control with fewer side effects than single analgesic or modality

**Multimodal = Awesome!**


- (Adults): Multimodal analgesia therapy (versus PCA only) reduces length of hospitalization in patients undergoing surgery


Opioids in the absence of tissue injury or inflammation not indicated!
Do you remember Marius...?
How about a Plan B?

LET Anesthesia

- Sitting upright
- Distraction
- Topical Anesthesia
- 3mL LET-gel: Lidocaine 4% - Epinephrine 0.18% - Tetracaine 0.5%


So, how do we treat the individual pain patient in front of us?

Crystal clear answer:
"It Depends"
-Socrates
Conclusions

- Withholding evidence-based analgesia from hospitalized children in pain suffering from serious hematologic/oncologic diseases not only unethical, but causes immediate and long-term harm
- Potential risks in safety of analgesics are real, but manageable; cannot justify denying administration of pain medications to pediatric patients
- Opioids (outside end-of-life) usually short term only - contraindicated for chronic pain
- Use multimodal (opioid-sparing) analgesia: Multiple agents, interventions, rehabilitation, psychological and integrative therapies act synergistically for more effective pediatric pain control with fewer side effects than single analgesic or modality

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- Tracey Cossall
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Just say stop!
http://pediatric-pain.ca/it-doesnt-have-to-hurt
Further Links

- The New York Times (Dec 16, 2015) essay by Dr. Stefan Friedrichsdorf “When a Baby Dies” [Link]
- Video: Kiran Stordalen and Horst Rechelbacher Pediatric Pain, Palliative and Integrative Medicine Clinic Tour [Link]
- “Children’s Comfort Promise: Doing everything possible to treat and prevent pain.” Eliminating Needle Pain in children (Feb 2015) Staff video [Link]
- Short Movie: Meet the Interdisciplinary Chronic Pain Clinic Team at Children’s Minnesota: Lea & Deirdre’s TV [Link]
- Video: Tour of the Kiran Stordalen and Horst Rechelbacher Pediatric Pain, Palliative and Integrative Medicine Clinic at Children’s Hospitals and Clinics of Minnesota and an overview of the three programs that are offered at Children’s under this clinic. [Link]
- Short Movie: LittleStarsFilm ‘Kali’s Story - Beyond the NICU’: This amazing pediatric palliative care short movie (7 min) features 8-year-old Kali’s journey at Children’s Hospitals and Clinics of Minnesota from NICU to today, receiving care by the Pain & Palliative & Integrative Medicine program while inpatient, in the clinic, and at home. (Jan 22, 2015) [Link]