Caring for the Child with a Life-Threatening Condition: Challenges in Regional Analgesia and Palliative Medicine

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Objectives

• Indications for regional techniques in PPC

• Patient assessment and selection

• Examine management and complications / side effects of various regional techniques

• Recognize ethical challenges in regional analgesia and EOL care
Pediatric Palliative Care Patients: A Prospective Multicenter Cohort Study

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Pediatrics 2011

- PPC teams currently serve a diverse cohort of children and young adults with life-threatening conditions.

- Most PPC patients are alive for more than a year after initiating PPC.
Palliative Care

- specialized medical care for people with serious illnesses.
  - High risk of death over one year, but cure may remain possible
  - Negative impact on quality of life and function
  - Highly burdensome to patient and family

- Focus on relief of symptoms, pain, and stress of serious illness

- Goal: improve quality of life both for patient and their family
Symptoms of Dying Children

• The mean # of symptoms per patient in the last week of life = 11

Symptoms and Suffering in Children with Cancer at the End Of Life

Wolf, J. *NEJM* 2000

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**A**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage of Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue from fatigue</td>
<td>100%</td>
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<tr>
<td>Pain</td>
<td>80%</td>
</tr>
<tr>
<td>Suffering from pain</td>
<td>80%</td>
</tr>
<tr>
<td>Dypnea</td>
<td>80%</td>
</tr>
<tr>
<td>Suffering from dyspnea</td>
<td>80%</td>
</tr>
<tr>
<td>Poor appetite from poor appetite</td>
<td>80%</td>
</tr>
<tr>
<td>Suffering from nausea and vomiting</td>
<td>80%</td>
</tr>
<tr>
<td>Constipation from constipation</td>
<td>80%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>80%</td>
</tr>
<tr>
<td>Suffering from diarrhea</td>
<td>80%</td>
</tr>
</tbody>
</table>

**B**

- Symptom treated
- Treatment successful

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**Cincinnati Children's**
Prevalence of Pain in Pediatric Cancer

- Chemotherapy: 56%
- Tumor itself: 21%
- Inflammation: 13%
- Procedural/Operative: 11%
- Radiation: 4%

Mechanisms of Cancer Pain

• Nociceptive pain
  – Somatic pain from highly innervated skin, bone and soft tissues
  – Visceral pain from differently innervated inner organs

• Neuropathic pain
  – Peripheral nervous system (direct invasion by tumor or neuropathy)
  – Central nervous system (brain or spinal cord lesion)
Considerations in Treating the Patient with Cancer Pain

• Understand the family
  – Family-centered communication lead to “shared decision making”
  – Respecting the developing role of the adolescent
  – Level of support, fear, anxiety
  – May have “different treatment goals”

• Understand “Culture of Cancer”
  – Some therapies seen as “giving up”
Considerations in Treating the Patient with Cancer Pain

• Unique risk/benefit assessment in the terminal patient

• Increasing survival rates → chronic cancer pain
Multiple Dimensions of Pain

Physical:
- Constipation
- Nausea
- Breathlessness
- Vomiting
- Muscle spasm
- Incontinence
- Fitting
- Insomnia

Pain:
- Loss of income
- Loss of support
- Cough
- Fear of death
- Guilt

Psychological:
- Family: What will they do without me?
- After life separation
- Purpose of lost life
- Loss of hope

Spiritual:
- Meaning of disease

Social:
- Guilt
A Successful Palliative Care Intervention for Cancer Pain Refractory to Intrathecal Analgesia

Fig. 1. Morphine equivalent daily dose from the day of M. D. Anderson registration

Reddy A, Hui D, Bruera E, J Pain Symptom Manage 2012
Role of Anesthesiologist in Pain Relief for Life-Threatening Conditions

Perioperative and post-operative pain management for patient with a life-threatening illness.

Advise and initiate, when indicated, interventional techniques for pain management

Manage acute and chronic cancer pain in the setting of a pain service
Phantom Limb Pain (PLP)

- Incidence 76%
- Pain typically occurs early and diminished over time (10% w pain at one year)
  
  Burgoyne, LL et al *Clin J Pain* 2012

- Management of Phantom Limb Pain
  “Preemptive analgesia”
  Perioperative local anesthetic block

  Niikolajsen *Br J Anaesth.* 2001

- Morphine (IV/Po), gabapentin and ketamine demonstrate trends towards short-term analgesic efficacy

  Cochrane Database Syst Rev. 2011 Dec 7
Optimized Perioperative Analgesia Reduces Chronic Phantom Limb Pain Intensity, Prevalence, and Frequency

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Description</th>
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<tbody>
<tr>
<td>Epi/Epi/Epi</td>
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<tr>
<td>PCA/Epi/Epi</td>
<td></td>
</tr>
<tr>
<td>PCA/Epi/PCA</td>
<td></td>
</tr>
<tr>
<td>PCA/GA/PCA</td>
<td></td>
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<tr>
<td>CONTROL</td>
<td>prn IM opioid</td>
</tr>
</tbody>
</table>

Incidence PLP at 6 mo. w PCA+/or Epi 28% vs opioid 75%

Karanikolas, M. *Anesthesiology* 2011
Continuous Nerve Block for Limb Salvage Procedures

- Two young men (13yr and 19yr) w distal femur osteogenic sarcoma underwent limb salvage procedures

- Preoperative chemotherapy (cisplatin/methotrexate/doxorubicin)

- Post-operative analgesia w Ropivacaine 0.2% at 4-6 ml /hr through femoral/sciatic catheter placed under ultrasound guidance

- Loss of dorsiflexion and painful paresthesia in the peroneal nerve distribution w leg weakness persisting 9 to 12 months post surgery
"Double Crush" Phenomenon

Potential contributors to injury
1. chemotherapy
2. tourniquet
3. joint manipulation
4. acute blood loss
5. needle trauma
6. LA toxicity
"Double Crush" Phenomenon

Fig. 1 Intraoperative neuromonitoring performed during femur osteosarcoma resection in our third patient (Case 3). Lower extremity cortical potentials were recorded from a subdermal electrode affixed to Cpz and referenced to Fpz (International 10-20 system). Subcortical potentials were recorded between electrodes over the third cervical vertebra and Fpz. Cortical (A) and subcortical (B) somatosensory-evoked potentials (SSEPs) recorded from the peroneal nerve on the surgical and nonsurgical sides are shown. Compared with the baseline (open arrow), significant attenuation of peroneal SSEP amplitude (opaque arrow) was noted 20 minutes after internal rotation of leg to facilitate wound closure. SSEPs returned to baseline within 6 minutes of repositioning the leg to neutral position.
Modification of WHO Step Ladder

Step 1
Mild/Moderate Pain
Acetaminophen
NSAIDS
Adjuvant Analgesics

Step 2
Moderate/Severe Pain
Opioids
NSAIDS
Adjuvant Analgesics

Step 3
Refractory Pain
Nerve block
Neurolysis/Ablation
Spinal Opioids
+ alpha-2 agonist
+ local anesthetic
Total Analgesia
Subanesthetic Ketamine
IV local anesthetics
Total Sedation
e.g. Propofol, etc.

Fine P, Anesth Analg 2005;100:183
Regional Anesthesia for Intractable Pain Associated with Terminal Pediatric Malignancy

- Retrospective - 199 children
  - 12 children (6%) required > 3 mg/kg/h morphine
  - 11/12 with tumor spread to nerves or spinal cord

- Retrospective – 11 cases of RA in Terminal CA
  - Pain localized to one area
  - Satisfactory pain control w epidural/subarachnoid infusions or neurolytic block
  - 5 patients cared at home
Analgesic Interventional Pain Management Techniques for Difficult to Manage Pain

• Peripheral nerve blocks
• Sympathetic blocks
• Neuroaxial techniques
Peripheral Nerve Blocks Continuous Techniques

- Any peripheral or plexus block possible
- Localized analgesia
- Decrease systemic analgesics
- May use to temporize pain until other palliative treatments begin to treat pain
- May facilitate physiotherapy or wound care
- Typically infusions – bupivacain or ropivacain ± clonidine adjunct
- Tunneled catheters reported duration as long as 88 days
Case: 17 yr Male with Osteogenic Sarcoma Involving L Humerus

- Technique ultrasound placement under sedation
- Interscalene catheter tunneled and sterile preparation of infusion by pharmacy changed every 5-7 days
- Continuous infusion of 0.2% Ropivacaine 6 ml/hr
- Decrease in systemic opioid use
Sympathetic Blocks

• Celiac plexus and splanchnic nerves

• Lumbar sympathetic

• Superior hypogastric plexus

• Ganglion impar
Celiac Plexus Block

- Favorable evidence for upper abdominal malignancy
  - Pancreas
  - Stomach
  - Liver and biliary
  - Intestinal tract to splenic flexure
14 yr Male with Recurrent Adrenocortical Carcinoma

- Recurrence of tumor
- Morphine equivalent/day 180 mg
- VAS 8/10 w Karnofsky Performance Status 60%
- CPB – 40 ml absolute alcohol + LA
- Decrease VAS 4/10 + decrease~ 50 % MED
- Able to make a memorable trip with mother
Celiac Plexus Block

- Meta-analysis suggesting efficacy in 70-90% efficacy
- Unrelated to specific technique

- Suggestion of superiority of CT vs fluoroscopic guidance
Retrocural Approach to Celiac Plexus
Diagnostic Celiac Plexus Block

- Yuen-Retrospective analysis of 59 patients
  - 32 diagnostic block $\rightarrow$ 28 neurolytic $\rightarrow$ 85%+
  - 27 direct to neurolytic $\rightarrow$ 79%+
- Positive predictive value- 85%
- Negative predictive value- 58%
- NNT= 16.7
- Trend moving away from diagnostic blocks

Common Adverse Effects

- Local pain (96%)
- Diarrhea (44%)
- Hypotension (38%)

Eisenberg, Anesth Analg 80:290-295, 1995
Complications

- PERSISTENT Hypotension or Diarrhea
- Paresis from somatic neurolysis
- Pneumothorax
- Abscess/discitis
- Retroperitoneal bleeding
- Paraplegia
  - Subarachnoid neurolysis
  - Anterior cord infarction
  - Case series 4 of 2730 (0.15%)
Celiac Plexus and Splanchnic Nerve Block

• Chronic pancreatitis and abdominal pain
  Attila, T et al, Gastrointest Endosc 2009

• Mitochondrial disease w intestinal dysmotility

  MNGIE Syndrome
  Teitlebaum, JE et al J Pediatr Gastroenterol Nutr 2002
  Celebi, N et al Paediatr Anaesth 2006
13 yr Female with SLE and Necrotizing Vasculitis
Lumbar Sympathetic Block

Transitioned from IV to PO meds
Lumbar Sympathetic Block

- Refractory pain in lower extremity
- Extending from L2-L4
- Single or multiple needle techniques
- Risk of somatic block if injecting psoas
- Risk of injury to genitofemoral nerve, greatest risk if approaching L4
Neuroaxial Analgesia

- Epidural
- Intrathecal
Indications for Neuroaxial Analgesia

• Patient selection is important
  – Cancer survivor versus terminal phase of life-shortening disease process

• Pain unrelieved with systemic analgesics/adjuvants or intolerable side effects prevent dose escalation

• Procedural / operative analgesia

• Goals:
  – decrease pain
  – decrease opiate-related side effects
  – improve functional status when possible
  – improve quality of life
Patient Assessment

• Pain and symptom history
• Cancer history (location of mets, prognosis, planned therapy)
• Psychosocial history (R/O non–nociceptive factors)
  o depression, anxiety, chemical coping
• Did the patient have an adequate trial of opioid titration and rotation along with addition of adjuvants
• Goals for Care
• A recent magnetic resonance imaging of the spine?
• Are there logistic concerns?
Contraindications to Neuroaxial Interventions

• Absolute - raised intracranial pressure
• Relative - balanced against Goals for Care
  – Chronic infection
  – Anticoagulation
  – Concurrent chemotherapy/radiation
  – OSA – close monitoring
    - IT Ziconotide monotherapy?
19 mo Male w Malignant Melanocytic Nevus

- Escalation of pain necessitating PICU management with analgesia / sedation
- percutaneous tunneled lumbar epidural catheter
Tunneled Epidural Catheter for Long-Term Management

Figure 1. A, A 19G epidural catheter is inserted into the lumbar or thoracic epidural space through a 17G Tuohy needle and threaded 3–6 cm into the epidural space; a 2-mm horizontal incision is made at the catheter exit site. B, The Tuohy needle is reinserted 9-cm lateral to the initial entry site and the tip is brought out through the previous incision. C, The catheter is threaded retrograde through the Tuohy needle, and the Tuohy needle is removed, allowing the catheter to exit the skin distally from the insertion site over the spine. D, Steps (2) to (4) are repeated another one to two times to bring the catheter exit site to the anterior abdominal or thoracic wall.
Tunneled Epidural Catheter for Long-Term Management

- 25 pediatric patients with pain unresponsive to systemic opioids - 8 w malignant pain
- Duration 4-240 days
- No serious complications: systemic infection, epidural or spinal infection or neurologic complications

Arum L, Anesth Analg 2001:1432
Differences Between Epidural Infusions used in Traditional Areas Compared to Palliative Setting

<table>
<thead>
<tr>
<th>Traditional</th>
<th>Epidural</th>
<th>Palliative Epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal coagulation</td>
<td>May be abnormal</td>
<td></td>
</tr>
<tr>
<td>No septic focus</td>
<td>May have infected areas nearby</td>
<td></td>
</tr>
<tr>
<td>Frequent monitoring of vital signs</td>
<td>Monitoring less intense</td>
<td></td>
</tr>
<tr>
<td>Skilled resuscitators constantly available</td>
<td>Cardio-respiratory resuscitation less likely</td>
<td></td>
</tr>
<tr>
<td>Duration &lt; 72 hrs</td>
<td>May be used for months</td>
<td></td>
</tr>
</tbody>
</table>

Chambers, WA. Br J Anaesth 2008
Port-ACATH Epidural System
(Smiths Medical)

Intrathecal Drug Delivery

• Life expectancy > 3 months ??

• Can be IT catheter w percutaneous exit or IT catheter w implantable reservoirs/pump

• Intrathecal superior to epidural
  – Improved pain relief
  – Lower rates of treatment failure
  – Lower rates of system replacement
  – Lower rates of catheter-related complications (obstruction or dislodgement)

  Dahm, P et al; *Clin J Pain* 1998
Cost Comparison of Two Neuroaxial Delivery Systems

Bedder, M et al 1991 J Pain Symptom Manage
CASE:  9 yr old boy – Osteogenic Sarcoma LLE

- Metastatic disease to lungs and spinal cord
- Spinal cord compression pain unresponsive to opioids, steroids, anticonvulsants
- Percutaneous Intrathecal catheter – bupviacaine, clonidine, fentanyl
- Lived 6 wks at home, returned to school part-time, took piano lesson 3 days prior to his peaceful death
Implanted Intrathecal Drug Delivery System
19 yr Female with Metastatic Ependymoma
Study Design

Eligible

Randomize

IT/Ep Screen

Pass

Yes

IT morphine

No

CMM

CMM

Intrathecal

Crossover: allowed 1 month after enrollment either arm

Intention to Treat: patients analyzed with group to which they were randomized

Smith, TJ et.al. J Clin Oncol 2002

Cincinnati Children's
Reduction in VAS From Baseline to 4 Weeks (As Randomized and As Treated) Difference Between CMM and CMM + IDDS Significant ($P = .007$)

Error bars are +/- 2 standard errors

Smith, et al., 2002
Reduction in Toxicity from Baseline to 4 Weeks (As Randomized and As Treated; \( P = .008 \))

Error bars are +/- 2 standard errors

Smith, et al., 2002
Reduction in Toxicity

Fig 2. Reduction in individual toxicities from baseline to 4-week follow-up. *P < .05.

Smith, et al., 2002
Overall Survival Curves (Kaplan-Meier)

![Graph showing overall survival curves with Kaplan-Meier method.](image)

**Survival (%)**

- **Days:** 0, 30, 60, 90, 120, 150, 180

**Survival Curves**
- IDDS
- CMM

**P-value:** 0.04

**No. at Risk**

<table>
<thead>
<tr>
<th>Days</th>
<th>CMM</th>
<th>IDDS</th>
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<tr>
<td>0</td>
<td>99</td>
<td>101</td>
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<tr>
<td>30</td>
<td>74</td>
<td>85</td>
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<tr>
<td>60</td>
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<td>90</td>
<td>51</td>
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<tr>
<td>120</td>
<td>39</td>
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<tr>
<td>150</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>180</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

Smith, et al., 2002
Analgesic Agents for Intraspinal Drug Delivery

- **Opioids**
  - Morphine sulfate
  - Hydromorphone
- **Alpha-2 agonists**
  - clonidine
  - dexmetatomidine
- **Local Anesthetics**
  - bupivacaine
- **Ziconotide**
- **Baclofen**

- **Adenosine**
- **Neostigmine**
- **Nonsteroidal antiinflammatory drugs**
  - ketorolac
- **Midazolam**
- **Amitriptyline**
- **NMDA antagonists**
- **Glycine antagonists**
- **Gabapentin**
- **Butamben**
- **Adrenal chromaffin cells**
- **Aspirin**
Dosing Considerations for IT Medications

Morphine 100 mg IV = 10 mg Epidural = 1 mg IT

Neuropathic Pain
- Morphine + bupivacaine/clonidine
- Ziconotide

Nociceptive Pain
- Morphine
- Hydromorphone
- Ziconotide

Ziconotide

- Cleared rapidly: $t_{1/2} = 4.5$ hr
- Requires a significant titration window to reach therapeutic effect
- Side effect incidence high (95% experience at least one side effect):
  - Abnormal gait
  - Nystagmus
  - Dizziness
  - Nausea
  - Amblyopia
  - Contraindicated w/ history of psychosis
- Side effects are dose and titration related and can be avoided with slow titration

Rauck RL, et al *JPSM* 2006
Intrathecal combination of ziconotide and morphine for refractory cancer pain

VAS change from baseline: p<0.001 at all times
Side Effects of Long-Term Neuroaxial Analgesia

- Postdural puncture headache
- Rare respiratory depression
- Secondary effects: motor or sensory block, sympathetic blockade, interference with urination
- Peripheral edema
- Infection
- Granuloma formation
Peripheral Edema
Infection Risk of Long-Term Neuroaxial Analgesia

<table>
<thead>
<tr>
<th>Study</th>
<th>Infection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stafford, M et al. Anesth Analg 1995</td>
<td>2.4 % (1.4-3.4 %)</td>
</tr>
<tr>
<td>Dupen, SL et al Anesthesiology 1990</td>
<td>23.7 % (350 pts)</td>
</tr>
<tr>
<td>Rauck, RL et al Anesthesiology 1993</td>
<td>1 %</td>
</tr>
</tbody>
</table>

Risk factors for infection:

- Immunocompromised
- Concomitant steroids
- Distal skin infection
- Diabetes
- Sepsis
Granuloma Formation

- Inflammatory cells - spinal cord compression
- Rare (0.04% at 1 yr)
- Associated with hydrophilic opioid
- No case report w lipophilic opioid
- Co-administration of clonidine may protect
- Most frequent symptom – decrease in therapeutic response/inadequate pain relief or onset of new pain (eg, thoracic spine)

Majority regress spontaneously when change drug
Checklist Prior to Initiating Neuroaxial Analgesia

1. Is the pain expression because of nociception?  Yes
   R/O non-nociceptive factors: somatization? No
depression,
anxiety,
delirium,
chemical coping

2. Did the patient have an adequate trial of opioid titration and rotation along with addition of adjuvants? Yes

3. Are there logistic problems? No
Thank You