Implanted Ports and Pumps and Other Interventional Approaches to Management of “Intractable” Pain for Children in Pediatric Palliative Care

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Aims of the Lecture
• To summarize patterns of pain and symptoms in children with life-limiting illnesses
• To outline decision-making around when to consider interventional approaches
• What qualifies as “intractable”?
• Technical aspects of placing and managing implanted ports and pumps and other interventions in pediatric palliative care.
• Review of available case series and some selected cases.
• Future directions
Note:

Some of the slides in this handout are for reference and discussion purposes, and will not be presented in detail during the lecture. Additional graphics will be shown in the lecture.
Pain and Symptoms in Adults with Cancer

• Development of palliative care movement in 1970s-90s
• World Health Organization development of analgesic ladder approach
Overview

• Some aspects of adult palliative care extrapolate well to children, some may not.
• Some approaches based on patients with cancer can be extrapolated to children with other illnesses, some cannot.
Overview

• “Intractable” or “refractory” is open to interpretation
WHO Pain Ladder

- simple, well-validated, and effective method for assuring the rational titration of therapy for cancer pain has been devised by WHO
- shown to be effective in relieving pain for ~ 90% of patients with cancer and > 75% of cancer patients who are terminally ill
Opioid Dosing and Escalation
Textbook Principles from the 1980s-90s

• “Opioid dosing can be escalated without limit.”
• “Tolerance is never a problem, you just keep escalating as needed.”
• “If dose escalations are required, it is usually due to disease progression.”
Problems with this view

- Sometimes, opioid dose escalation becomes logarithmic, not linear.
- Some side-effects emerge with massive dosing (e.g. myoclonus, dysphoria, confusion, ….)
- Opioid-induced hyperalgesia
- Opioid tolerance is more rapid in younger subjects (see below).
- Prognosis is imprecise and clinical course vary: a child may have pain and/or require opioids for a very long period of time.
Initial Approach to Apparent Increase in Opioid Dose Requirement:

Consider, Confirm or Reject Some Provisional Diagnoses
• New, acute, and sometimes treatable sources of nociception and neuropathy, e.g. tumor spread, nerve involvement, new fractures, spinal cord compression, bowel obstruction, urinary tract obstruction,....
Some of these conditions have specific treatments:
- fractures can be stabilized
- local anti-tumor therapies, e.g. radiation
- steroids or decompressive surgery for spinal cord compression
- “kinder-gentler” palliative chemotherapy
- decompression or drainage for bowel obstruction, ascites, pleural effusions, or obstructed urinary tracts…
• Existential/spiritual suffering, fear, anxiety and failure of communication expressed in the language of physical pain.
  - seen most commonly in the family where parents say
    “we can’t talk about cancer or dying…”
• Delirium and other mental status changes presenting with distress.
  - consider consequences of metabolic derangements, polypharmacy, ….
Exclude “trivial causes” of apparent opioid analgesic failure

- Medication not being given by parents or rejected by adolescents, due to fear of opioids or due to unreported or unmanaged side-effects.
- Prescriptions rejected by local pharmacies.
- Opioid diversion by family members (rare, but it happens…)
- Impaired delivery or absorption, doses refused, emesis, diarrhea, ….
Next, try some dose escalation

- Don’t quit too soon.
- Don’t make excessively wimpy steps.
- Make a formal oral or IV titration until:
  - side-effects that are not readily managed
  - signs of narcotization, somnolence, relative hypoventilation
  - analgesia improves
Other Interventions to Try

- Steroids
- Medications for neuropathic pain
- Stimulants
- Low dose ketamine (orally or IV)
- Opioid switching
- Palliative sedation
Low-Dose IV Ketamine

• Analgesic dosing, rather than sedative-hypnotic-dissociative dosing.
• Typical range 0.1 – 0.2 mg/kg/hr IV
• Steady-state oral/parenteral ratio unclear, estimated at 3:1.
• Variability in limiting dose that generates dysphoria or dissociation
• J. Finkel et al pediatric case series J. Pain 2007 8:515-21
Opioid Switching: Stated Rationale

- Incomplete cross-tolerance
- Individual differences in side-effect profiles
- Do side-effects tend to track with drug classes? If you get similar side-effects with 3 phenanthrene alkaloids, is it time to chose a synthetic opioid?
- Unique differences in sites of action, e.g. methadone’s NMDA blocking activity.
Opioid Tolerance:
the downside of neuroplasticity

This problem is worse in younger subjects than in older subjects.
• Adults with chronic pain: 70 year olds develop tolerance slowly, 30 year olds develop tolerance more rapidly.
• Young rats develop tolerance more rapidly than older rats.
• Neonates and infants in intensive care develop profound degrees of tolerance to opioids and a variety of sedative-hypnotics.
• The optimal management of tolerance and withdrawal in neonates has not been established.
• Long term consequences of opioids in neonates are not well understood.
Opioid-induced hyperalgesia: everything hurts more.
How do you treat this problem?

- Optimize non-opioid analgesics.
- Micro-dose naloxone infusions – effective for prevention, unclear for treatment
- Consider switching among opioids.
- Consider drugs with anti-hyperalgesic, anti-tolerance actions:
  - NMDA antagonists (methadone, ketamine)
  - Anticonvulsants, antidepressants
  - Clonidine
  - NSAIDs
Opioid Dose Escalation Among Children With Advanced Cancer

Collins, Grier, Kinney, Berde

• 199 children with metastatic cancer
• Analyzed opioid use, problems, use of extraordinary / technologic interventions.
• 18 extreme cases: opioid dosing increased > 100-fold.
For a small number of patients with life-shortening illness, they have two choices: either be asleep or have severe pain.
Fatigue/Somnolence/Mental Clouding/Sleep Disturbance

• As we treat pain more effectively, fatigue and somnolence become more common and more associated with impaired quality of life.

Wolfe et al.  J Clin Oncology
2008  26:1717-23.

Ullrich et al. J Pain Symptom Management
Stimulants for Treatment of Fatigue/Somnolence/Mental Clouding/

• In adults, stimulants have an extensive track record of RCTs
  (Bruera et al, Breitbart et al, multiple studies)

• Pediatric case series
  Yee and Berde
  J. Pain & Symptom Management
  1994 9: 122-5
Stimulants for opioid-induced sedation: an N of 1 paradigm for pediatric palliative care trials.

Ullrich, Berde, Wolfe, Hinds, Guyatt, et al, in progress

- Clinical trials are difficult in pediatric palliative care.
- Small numbers, diverse patients.
- How do you keep a child in a placebo group in a parallel design?
- How is there individual benefit if the blinding is not broken before the child dies?
N of 1 Trials - Guyatt et al
Decisions for individuals as well as groups.

- **Individual decisions**: N & 1 trials
- **Group** randomized-controlled, double-blind 3-phase **crossover clinical trial**
- 2 statisticians, 2 types of data management
Questions Regarding Palliative Sedation:

1. Is administration of sedatives closer to assisted suicide than administration of opioids?
   Truog, Berde, Mitchell, Grier NEJM 1992

2. Is application of the doctrine of double-effect more problematic with regard to terminal sedation compared to use of opioid infusions?
   Quill, Dresser, & Brock NEJM 1997
Sedation in End-of-Life Care

- Use only in extraordinary circumstances
- Continue opioids along with sedatives
- Principle of double-effect – Brock and Quill
- NEJM – problems and inconsistencies
- Pediatric case series
  
  Truog, Berde, Mitchell, Grier
  
Sedation in End-of-Life Care: Choice of Drugs and Approaches

- Sedation is a continuum.
- Style matters.
- Benzodiazepines, barbiturates, propofol, ketamine, nitrous oxide, neuroleptics….
- Is awakening ever intended?
- Ketamine as an analgesic infusion in conscious subjects.
Choice among sedatives

- Benzodiazepines show wide variability in effect and dose-response.
- Do you call it anesthesia?
- In our hospital, pentobarbital is a ward drug, propofol is an anesthesia/ICU drug.
- Can it be done on regular wards?
- Compatibilities with other infusions
- What can be given subcutaneously versus IV?
Considerations prior to institution of invasive methods of analgesia

• Consider nature of child’s pain and suffering
  – Procedures don’t fix emotional/psychic/spiritual suffering
  – Specific therapies may be preferable, e.g. chemo, XRT, steroids, surgery, pleurocentesis....
  – Consider the expected natural course of disease

• Location of the Pain Generators
  – Localized vs. diffuse pain
  – Head and neck vs. lower body
  – Anatomic access to tissue compartments, e.g. spinal, epidural, pre-vertebral
Considerations (cont.)

• Availability of expertise among anesthesiologists or neurosurgeons or other specialists
  – Expertise with post-op regional anesthesia is not sufficient
  – Adult expertise doesn’t translate well
  – Ongoing involvement and co-management is required

• Availability of expertise among parents, nurses, home-care companies
  – Nursing assessments
  – Pharmacy resources
  – Distance from health care providers
  – Night and weekend coverage
Adult Literature on Interventions for Cancer Pain

• One randomized clinical trial comparing implantable drug delivery system to comprehensive medical management for refractory cancer pain

• 72 studies total but most are retrospective case series and prospective cohort studies
  – Cochrane Review 2008
• n = 202, multicenter RCT, 1999-2001

• Results at one month
  – Pain reduction (VAS)
    • ↓ 39.1% for CMM, ↓ 51.5% for IDDS (p=0.055)
  – Composite toxicity (CTC)
    • ↓ 17.1% for CMM, ↓ 50.3% for IDDS (p=0.004)
  – Side effects (CTC)
    • Fatigue and depressed level of consciousness significantly less with IDDS than CMM (p < 0.05)
    • Impotence and pruritis worsened with CMM
Estimated 6-Month Survival

- Because IDDS group experienced a larger average reduction in toxicity score, data suggest that improved mortality in the IDDS group may be partially explained by effects of intrathecal pain therapy.
Regional Anesthesia for Pediatric Advanced Cancer

- **Case reports**

- **Case Series**
  - Meignier et al. 1992 (n = 5)
  - Anghelescu et al, Pediatric Anesthesia 2010 (n = 10)
  - Carullo et al, ISPPP Abstracts 2010, manuscript under review (n = 16: 11 implanted ports for cancer, 5 implanted pumps for neurodegenerative disorders)
Our initial case series:
Regional analgesia in pediatric terminal malignancy.

- N = 11, study period June 1986 – April 1994
  - Represented approximately 3% of children dying of malignancy over the study period
- Epidural and subarachnoid infusions via tunneled catheters
  - 4 patients with epidural infusions
  - 2 patients with subarachnoid infusions
  - 3 patients with epidural infusions replaced by subarachnoid infusions
  - 1 patient – intermittent caudal morphine
  - 1 patient – thoracic epidural infusion followed by celiac plexus block
- Duration of infusions – 3 days to 7 weeks
Indications

• Severe systemic side effects of systemic opioids limiting dose escalation and effective analgesia

• Opioid resistance and severe neuropathic pain secondary to involvement of spinal nerve roots, large peripheral nerve, or spinal cord compression by tumor

• Analgesia for thoracocentesis (i.e. malignant pleural effusions, instillation of intrapleural chemotherapy)
Adequacy of analgesia

• Analgesia satisfactory in all cases after regional anesthesia was instituted and remained satisfactory throughout the treatment course.
• Essentially all cases required local anesthetics in addition to opioids.
• Intrathecal route preferred.
Choice of Approach

- Percutaneous catheters
- Tunneled catheters
- Implanted ports
- Implanted pumps
- Epidural versus subarachnoid (intrathecal, spinal) location
Implantable Epidural/Intrathecal Port with Polyurethane Catheter

- Portal
- 20 G Catheter
- loss of resistance syringe
- tunneling tool
- 0.2 micron add-on filter
- 24 ga PORT-A-CATH® needle
- 16 G Tuohy needle
- 2 syringes.
Children with cancer generally require inclusion of local anesthetics in the mixture. Due to the low potency of local anesthetics, this precludes implanted pumps and instead leads us to favor implanted ports with external infusion pumps.
Ports Vs. Pumps

- Pumps (e.g. Medtronic pumps) are preferable for longer term use with hydrophilic, very high spinal potency drugs (e.g. baclofen, clonidine, hydromorphone), and are generally used for neurodegenerative disorders and refractory spasticity.
Ports Vs. Pumps: Body Size Considerations

• Lo-profile ports can be positioned over the lower chest even in 2 – 4 year old children.
• Medtronic pumps are much larger than the ports, and are too large for the abdomen of children < 30 kg.
• Medtronic pumps require a 14-gauge Tuohy needle for dural entry. The Smiths Medical Port II port kit uses a 16-gauge Tuohy needle.
• The size of the Medtronic needle and catheter may be prohibitive for infants and toddlers.
Advantages of Spinal (Intrathecal) Infusions

• More flexible and reliable for pain anywhere below mid thoracic
• Avoids limiting systemic accumulation of local anesthetics, as seen with epidural
• Avoids local anesthetic tolerance/tachyphylaxis
• Lower incidence of catheter occlusion
Advantages of Spinal Infusions

- Can provide profound analgesia even with movement-related pain for dermatomes below the clavicles.
- Can help maintain alertness, if that is desired.
- Can permit boluses as well as infusion.
Disadvantages of Spinal Infusions

- Potential for CSF leak
- Meningitis
- More difficult to target for upper body pain
Disadvantages of Spinal Infusions, Particularly with Local Anesthetics

• Occasionally, the level fluctuates.
• Spinal block at abdominal levels can be scary.
• Non-anesthesiologists are unfamiliar with spinal-induced autonomic blockade, or treatment of hypotension with ephedrine and other vasoconstrictors.
Advantages of Epidural Infusions

- Avoids potential for CSF leak
- Can target for upper body pain
Disadvantages of Epidural Infusions

• Effectiveness in long term use can be limited by ceiling on local anesthetic dosing and tolerance/tachyphylaxis

• Epidural fibrosis with long-term use (e.g. > 2-4 months)
Recent intrathecal port and pump experience
Carullo, Weldon, Berde, 2010, ISPP abstracts, manuscript under review

- Retrospective chart review
- N = 16 (11 ports, 5 pumps)
- Study population – patients under age 18 years at diagnosis with pain secondary to terminal malignancy who underwent intrathecal port implantation
- Study period – 2000-2011
- Outcomes: safety, adequacy of analgesia, side effects with intrathecal infusions of bupivicaine + opioid + other additives (i.e. clonidine, ketamine)
Technical aspects - 1

• General endotracheal anesthesia
• Lateral position, wide draping, antibiotics, real-time fluoroscopy
• Pain physician at the back, general surgeon at the front.
• Cephalad advancement of catheters to the dorsal horn levels, not the root levels most important to the patient’s pain.
Level of Catheter Tip

- Pelvic and leg tumor
  T11-12
- Abdominal tumor
  T6-9
- Thoracic tumor
  T4-6

Level is based on avoidance of side-effects and targeting near root entry zones.
Dermatomal Levels vs. Dorsal Horn Levels
Technical aspects - 2

• Implanted ports from the start, rather than temporary catheters.
• Preference for subarachnoid route in most cases – more versatile, less susceptible to local anesthetic tachyphylaxis, less problem with fibrosis over time. Easier to screen for infection by withdrawal of CSF.
Disadvantages of Spinal Infusions

• It’s a technologic, labor-intensive approach.
• Expertise not readily translated from adult pain specialists or pediatric anesthesiologists who work mostly in the OR.
• Things can go wrong, e.g. infection, CSF leak, disconnection, drug delivery problems.
• Still need a systemic route for meds for terminal dyspnea/terminal distress.
Complications

- Limiting local anesthetic dosing particularly with epidural infusions which can reach upper limit of safety for systemic toxicity
- Decreased motor and bladder function (tumor progression vs. opioid infusion)
- PDPH
- Respiratory depression
- Infection (immunologically suppressed patient population)
Nerve-Destructive Procedures: Advantages

• “Permanent”
• Avoids need to be hooked up to a pump
• Most useful in locations where there is no protective sensation (especially visceral blocks) or where somatic functions are already lost.
• Somatic neurodestructive blocks are now used more in the developing world than in the developed world.
Nerve-Destructive Procedures: Disadvantages

• “Permanent”

• Most children and adolescents keep “two views” (curable/ not curable; short life span/ longer life span) and don’t want to think about having any irreversible deficits.

• As tumor spreads, sources of pain extend beyond the area of the nerves originally blocked.
Home and Hospice Care: Management Challenges for Spinal Infusions

- This approach is foreign to many palliative care clinicians.
- Working with hospice and infusion company pharmacies.
- How do you do Make-a-Wish trips?
- How do you get on airplanes?
Drug Selection for Spinal Infusions for Pediatric Advanced Cancer

- Balance between analgesia and side-effects.
- Combined local anesthetic-additive infusions always needed
- Our preference has trended towards: ropivacaine, hydromorphone, ketamine

[note: ketamine is not preservative-free in the U.S. and is not approved for this route in the U.S., and this to be recommended for extraordinary situations in palliative care only.]
Case #1

A 14 Year old boy from St. Louis presents with severe radiating buttocks and leg pain and inability to sit, stand or lie flat. He has a large intrapelvic malignant nerve sheath tumor arising from his sciatic nerve.
History

• Neurofibromatosis Type 1
• Rhabdomyosarcoma of the bladder and prostate, successfully treated with surgery, chemo, age 3; left with urinary diversion.
• Left leg pain and mass, 2006, presumed to be neurofibroma.
• Chemo from July 2007 – January 2008, no response to traditional agents plus Gleevec
History

- Feb. 2008  Increasing pain, despite escalating regimen including methadone, oxycodone, gabapentin/pregabalin, oxcarbazepine, duloxetine (Cymbalta), prednisone.
- Sedated at rest, but unable to tolerate movement or positioning.
History

- 2\textsuperscript{nd} opinion at St. Jude’s – recommended either no surgical treatment or radical hemipelvectomy.
- 3\textsuperscript{rd} opinion at Children’s and DFCI seen by Oncology, Radiation Oncology, General Surgery, and Orthopedic Surgery services.
History

- Recommended pre-op XRT for 1 month, followed by “internal hemi-pelvectomy” with sciatic nerve section.
- Problem: at his home hospital in St. Louis, there are no regular facilities for sedation or anesthesia for XRT.
- He can’t lie flat or lie still.
Pre-operative Treatment Plan - 1

• March 1, 2008 went to the OR for placement of intrathecal port.
• Begun on a spinal infusion of bupivacaine and fentanyl.
• Became more comfortable, alert, able to move around, sleep, get up.
Subsequent course

• Very comfortable with low dose spinal infusion
• bupivacaine 0.1% with fentanyl 5 mcg/ml
• patient controlled spinal analgesia: basal rate 0.6 ml/hr, bolus 0.7 ml, lockout 20 min
• Ambulating on day 2 – develops spinal headache, resolves with fluoro-guided epidural blood patch.
• Returns to St. Louis for 1 month of chemo and XRT
Surgical Resection
March 31, 2008

• Surgery: debulking of tumor resection of large portions of ilium and ischium, femoral head “floating in the breeze”.

• Complete sectioning of the sciatic nerve, leaving the left leg weak and numb from the knee downwards.
Postop Course

- Post-op, surgical pain was well-managed.
- As we tapered spinal infusion, he felt “phantom pain”
- Good analgesia and alertness with intrathecal ropivacaine-hydromorphone-ketamine (roughly 0.6 mg/hr).
- Pathology showed a different tumor, an angiosarcoma, at the margins of resected tissues.
Subsequent Course - 1

• 4/08 returned to St. Louis, underwent rehab, more chemo, more XRT, angiogenesis inhibitor regimen.
• Continued good analgesia with intrathecal infusion, alert, went on family vacations.
• 4/08 – 9/08 Multiple attempts to taper off spinal infusion - movement-related pain as well as phantom pain.
Subsequent Course - 2

- 10/08 Increased back pain and right leg pain.
- Imaging showed tumor at L4, narrowed spinal canal. To the OR for spinal decompression, posterior instrumentation.
- Catheter cut during surgery, spliced.
- Some leakage of CSF through the wound.
- Continued analgesia with spinal infusion.
Subsequent Course - 3

- Thanksgiving day – playing quarterback from wheelchair in family touch football game.
- Felt his port erode through the skin.
- 11/08 port removed.
- Increased pain, treated with increased IV opioids and IV ketamine infusion, short period of deep sedation.
- Brief improvement with a fluoro-guided caudal-to-lumbar epidural steroid injection.
Subsequent Course - 4

- 12/08 increasing low back pain and right leg pain
- PET scan - ? Small lung lesions, not visible on CXR
- 1/08 Progressive paraparesis.
- MRI showed large tumor around L4.
- Decision to stop chemotherapy.
- At home, getting XRT, consideration of cyberknife
- Severe pain with movement, some sedation.
- Continued with IV PCA and IV ketamine, multiple adjuvants.
Subsequent Course - 5

• 1/08 Replacement of intrathecal port
• Resumed infusion of ropivacaine, hydromorphone and ketamine, continued systemic analgesics
• XRT, cyberknife
• Going on trips with family, part-time attendance at school.
• Episodic escalation of pain treated with escalation of spinal hydromorphone and ketamine, maintaining constant spinal ropivacaine.
Case #2  Refractory Localized Pain in the Arm, Shoulder and Upper Back

- 17 year old male with metastatic sarcoma, mass effect to the apex of the lung and extending through the chest wall.
- Unable to abduct shoulder for 1 month
- Shooting pain down the arm, shooting pain in upper back.
- Poor movement-related pain relief from systemic opioids, adjuvants.
- What is the neuroanatomy of his pain?
Pancoast’s syndrome

In this case, apparent involvement of both brachial plexus and intercostal nerve afferents.
Combined Local Approach:
High thoracic epidural (tip at T3) and
Supraclavicular brachial plexus catheter
Cases #3 and #4
Refractory Upper Abdominal Pain and Retching

• 17 year old with small blue round cell desmoplastic tumor originally in the pelvis, with large hepatic mass compressing the duodenum.

• 14 year old with a mitochondrial disorder with peripheral and spinal neurodegeneration, cachexia, abdominal pain, dysmotility, and refractory retching.
Celiac Plexus Blockade

- Upper abdominal visceral malignancy, especially pancreatic cancer
- No numbness or weakness is felt.
- May cause diarrhea or orthostatic hypotension, generally improves after first week.
- May also improve appetite and reduce nausea from pancreatic cancer.
Treatment of children with refractory spasticity and distress associated neurodegenerative disorders using implanted intrathecal baclofen pumps

- Metachromatic leukodystrophy (3)
- Infantile ascending heredity spastic paralysis (2)
- Various white matter disorders….
- Spinocerebellar ataxia, Friedrich’s ataxia
Case #5

• A cognitively intact 12 year old girl with infantile hereditary ascending spastic paralysis, and neurogenic scoliosis.
• Refractory pain due to lumbar plexopathy, spasticity and arachnoiditis following scoliosis repair.
• Extensive medication trials.
• Currently comfortable with a Medtronic pump using an intrathecal mixture of baclofen, bupivacaine, and hydromorphone.
Conclusions

• Much of how we approach refractory pain is extrapolated from adults.

• Some of the differences in management between children and adults relate to biology (e.g. consequences of neuroplasticity), to different diseases and prognoses, and to specific developmental issues in coping with severe illness.
Conclusions

• More research is needed on all aspects of management of pain, distress and suffering in pediatrics, but especially for children with neurologic disorders.

• In deciding among approaches to pain management, primary considerations related to quality of life and to adhering to patients’ and parents’ goals and wishes.