Interventional Pain Management Strategies for Seriously Ill Patients CME Module

Interventional Pain Management Strategies for Seriously Ill Patients
Course Description and Learning Objectives

Course Description: Despite advances in the understanding of pain management for seriously ill patients, pain is often undertreated or refractory to usual pharmacotherapies in this patient population. Per some estimates, 10-20% of patients with advanced cancer cannot achieve adequate pain control via cancer pain guidelines such as published by the World Health Organization. Hence, clinicians need to be aware of interventional pain management techniques when usual analgesic treatments fail. In this module, users can attain 1.0 hours of CME credit after successful completion of the following:

A. Content review of ten Fast Facts and Concepts covering the following topics:
   a. Sympathetic Nerve Blocks
   b. Intrathecal Pumps for Pain Control
   c. Epidural analgesia for seriously ill patients
   d. Radiation therapy for palliation of cancer pain (part 1 and 2)
   e. Radiopharmaceuticals for palliation of cancer pain
   f. Vertebroplasty and kyphoplasty
   g. Analgesic effects of Parental lidocaine
   h. Patient controlled analgesia
   i. Palliative Care Uses of Botulinum toxin injections
B. Score of 70% or higher on a 10 question quiz covering this content
C. Completion of a course evaluation.

Learning Objectives: After completion of this course, the learner will be able to:

1. Describe the indications, contraindications, and expected outcomes for nine interventional analgesic therapies for patients with serious illnesses.
2. List two different approaches to the use of radiation therapy as an analgesic modality.
3. Describe clinical situations when spinal analgesic approaches should be considered.

FAST FACTS AND CONCEPTS #97
BLOCKS OF THE SYMPATHETIC AXIS FOR VISCERAL PAIN

Gary M Reisfield MD and George R Wilson MD

Background   The sympathetic nervous system spans the length of the axial skeleton; most of the various plexi and ganglia are readily accessible to percutaneous interruption. In the palliative care setting, the most common indication for interrupting the sympathetic axis is to control pain arising from malignancies of the abdominal and pelvic viscera. Visceral pain is often described as constant, deep and is difficult to localize and characterize. When such a pain syndrome is recalcitrant to meticulous application of drug and behavioral therapy, or if the patient is intolerant to drug therapy, consultation should be sought to either a Pain specialist or Interventional Radiologist for consideration of neurolytic procedures. Potential advantages of a neurolytic procedure, compared to spinal and epidural anesthetic techniques (see *Fast Fact* #98), include cost savings and avoidance of hardware (e.g. catheters, tubes, pump), which can be cumbersome, are subject to malfunction, and pose an infection risk.

Types of Blocks   The following procedures have an established record of success in well-selected patients:
- *Celiac plexus block (CPB).* Used for upper abdominal pain – most commonly from pancreatic cancer. It is also appropriate for pain involving the GI tract from the distal third of the esophagus to the transverse colon, the liver and biliary tract, the adrenals, and mesentery. There have been over 14 controlled studies assessing the utility of a CPB, two of which are felt to be of high quality design. The data is fairly convincing that CPB can improve analgesia, decrease opioid consumption and decrease opioid-induced adverse effects compared with conventional analgesic treatments.
- *Superior hypogastric plexus block (SHPB).* Applicable to malignant pain of the gastrointestinal tract from the descending colon to the rectum, as well as the urogenital system. There is less robust data evaluating SHPB for visceral pain, with one study showing a decrease in pain intensity and less morphine consumption when SHPB was utilized.
- *Ganglion impar block.* Pain involving the rectum and perineum.

Procedure   For CPB, patients are positioned supine or prone, according to operator preference and patient comfort. Patients are intravenously hydrated and sedated. The skin and underlying tissues are infiltrated with local anesthesic. Neurolytic blocks are often preceded by local anesthetic blocks to assess adequacy of analgesic response before executing a neurodestructive procedure. In the palliative setting, local anesthetic blocks are often waived due to logistical and patient comfort issues. Neurolytic procedures are always performed under fluoroscopic, CT, or endoscopic ultrasound to minimize potential for damage to organs and spinal cord. Blocks are performed with ethyl alcohol (50-100%) or phenol (6-10%). Neurolytic blocks may provide several months of analgesia and may be repeated.

Complications & Side Effects   Side effects – referable to loss of sympathetic tone – include transient hypotension and increased intestinal motility leading to diarrhea. However, often the diarrhea is preferred over opioid induced constipation. Complications include needle injury to visceral, neural, and vascular structures; pain at the injection site; and failure to obtain an analgesic response. Contraindications to these procedures include bleeding diathesis and local infection.

Post-Procedural Management   Crucial to the success of sympatholysis is proper patient selection and technical skill. Sympathetic blocks are not a panacea and generally do not obviate the need for ongoing pharmacological management of residual pain. However, they can substantially improve analgesia and quality of life, and *may* allow for opioid dosage reduction. Note: attempts at post-block opioid reduction should be done with care to avoid unmasking existing nociceptive/neuropathic pain and precipitating opioid withdrawal.

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FAST FACT AND CONCEPT #98
INTRATHECAL DRUG THERAPY FOR PAIN

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Background   Intrathecal (IT) drug delivery can be an invaluable adjunct in the management of severe and refractory pain. While most of the evidence supporting the use of IT pain pumps in palliative care settings has been largely based on case series and consensus statements, one prospective randomized clinical trial of cancer patients with refractory pain, suggested that IT drug delivery may have better analgesia, less opioid-related side effects, and longer survival compared with oral opioids.

Candidates for IT drug therapy: Appropriate patient selection is important to optimize the safety and effectiveness of IT therapy. Candidates for IT pumps should have:
- An established diagnosis of severe chronic pain classified as neuropathic, nociceptive, or mixed;
- Pain refractory to oral analgesics or are intolerant to oral analgesics;
- Failed or are not a candidate for nonpharmacologic or surgical treatments;
- Pain that is below the neck and ideally focal in location.

Because multiple psychosocial factors can influence a patient's pain perception as well as their ability to manage a pump once implanted, a psychological evaluation should be considered for patients being evaluated for IT implantation.

Epidural vs. Intrathecal Analgesia   IT analgesia is distinguished from epidural analgesia by catheter location within the neuraxis (see *Fast Fact #85*). In the former, the catheter lies within the subarachnoid space, where small quantities of medication have direct access to spinal drug receptor sites. In the latter, larger doses of medication (necessitated by epidural fat and vascular uptake) must diffuse across the dura to reach these receptors.

There are no published guidelines on when to use the IT versus epidural route. In general, implantable IT pumps are reserved for patients with a life expectancy > 3 months. Potential disadvantages of IT relative to epidural techniques may include: lack of reprogramming/refilling capabilities near the patient's home, payor constraints, infusion volumes too great for an implantable pump, and the need for frequent patient controlled analgesia. Potential advantages of IT – relative to epidural – techniques are:
- Superior analgesia in the presence of epidural pathology (e.g. metastatic disease, radiation fibrosis, vertebral compression), widespread pain, and pain poorly responsive to high-dose epidural therapy.
- Ease of catheter placement, particularly in the presence spinal pathology.
- Fewer catheter problems such as catheter migration, fibrosis, or tip occlusion.
- Lower dose requirements may reduce side effects and lower drug costs.

Choice of System   There exists a spectrum of IT system options – from a simple, percutaneous catheter/external pump to a totally implanted system. Life expectancy, performance status, and available professional expertise may also guide which system is selected. A trial of IT analgesia may be done to assess response to therapy and proper patient selection prior to implantation of a pump. Programmable pumps are often used and can allow patients to administer bolus doses for breakthrough pain.

Drug Choice   Arner and Arner (1985) demonstrated the following relative responsiveness of pain mechanisms to intraspinal opioids: continuous somatic pain > continuous visceral > intermittent somatic > intermittent visceral > neuropathic > cutaneous (ulcers or fistulas). First line treatment for somatic pain syndromes includes a single agent opioid (most often morphine or fentanyl) or ziconotide (a selective voltage-gated calcium channel blocker with a sole FDA indication as an analgesic in IT pumps). Bupivacaine or ziconotide may be added in combination with an opioid as second line therapy. For neuropathic pain, morphine with bupivacaine or ziconotide alone is recommended. Second line therapy may include a change to hydromorphone alone or the addition of clonidine.

Complications and Side Effects Complications may occur from a) the procedure (e.g. post-spinal headache), b) medications (e.g. opioid-related respiratory depression, sedation, urinary retention, pruritis), and c) hardware (e.g. catheter kinking/disconnection/dislodgement, infection, granuloma formation at the catheter tip). Major contraindications to IT catheter placement include coagulopathy, infection at catheter insertion site, and sepsis.

Ziconotide use has been associated with increased suicidality, worsening of mood disorders, confusion, somnolence, dizziness, and new onset psychosis. Frequency of adverse effects may be attenuated by slow titration. Patients receiving ziconotide should be closely monitored for psychological side effects. Ziconotide should be avoided in patients with pre-existing psychosis.

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FAST FACTS AND CONCEPTS #85
EPIDURAL ANALGESIA

Debra Gordon RN and Mark Schroeder MD

Background   Epidural analgesia with local anesthetics, opioids, and/or alpha-agonists can provide superior regional analgesia over conventional systemic routes (IV or PO). In contrast to drugs administered systemically, drugs administered in the epidural space are extremely potent since the drug is delivered close to the site of action (opioid and alpha receptors in the spinal dorsal horn or local anesthetic blockade of nerve roots)**.** Because of this, systemic side effects such as nausea, sedation, and constipation, are minimized. In palliative care, epidural analgesia may be appropriate for patients with regional pain (e.g. pelvic pain from cervical cancer) and/or patients who do not tolerate or obtain relief from oral/parenteral drugs and non-drug therapies.

Indwelling Epidural Catheters   In patients with refractory cancer pain, anesthesiologists typically place a more durable and longer lasting epidural catheter than the epidural catheters used for childbirth. These indwelling epidural catheters, are tunneled under the skin, directed away from the spine, and covered it with clear adhesive dressing to reduce infection. Indwelling epidural catheters can remain in place for weeks to months and can be utilized in the home setting; however, longer catheter durations are associated with higher risks of serious adverse effects such as a deep epidural infection. The best estimate is that one in 35 patients with an epidural catheter in place for 74 days for cancer pain can be expected to get a deep epidural infection and 1 in 500 may die of such complications.

Medications   The epidural solution typically contains a local anesthetic such as bupivacaine along with an opioid such as fentanyl and morphine. Clonidine is sometimes utilized when neuropathic pain is present. If the patient is getting a low dose of the anesthetic, lower leg movement and function is often preserved; at higher doses, however, patients may lose ambulation. Drugs administered epidurally are distributed by three main pathways:
- Diffusion through the dura into the CSF, then to the spinal cord or nerve roots.
- Vascular uptake by the vessels in the epidural space into systemic circulation.
- Uptake by the fat in the epidural space; creating a drug depot from which the drug can eventually enter the CSF or the systemic circulation.

Patient Controlled Epidural Analgesia (PCEA)   Epidural analgesia can be administered by intermittent boluses (by a clinician or by patient controlled epidural analgesia using an appropriate pump); continuous infusion; or a combination of both. PCEA is used to supplement a basal rate, to allow a patient to manage breakthrough pain in order to meet their individual analgesic requirements. Like IV PCA, PCEA can provide more timely pain relief, more control for the patient, and convenience for both the patient and nurse to reduce the time required to obtain and administer required supplemental boluses. Unlike IV PCA, the lockout interval of PCEA varies widely based on the lipid solubility of the opioid administered, from 10 minutes with fentanyl to 60-90 minutes when morphine is used. If local anesthetic is used, the lockout interval should be at least 15 minutes to allow for peak effect of the supplemental local anesthetic dose.

Management   Due to the proximity of drug delivery to its site of action, frequent assessment of pain relief, side effects, and signs or symptoms of technical complications (catheter dislodgement, epidural hematoma or abscess, pump malfunction, etc.) are necessary. This should be done every hour for the first 24 hours, then every 4 hours.   Assess and document on the pain management flowsheet:

- Patient's pain rating using patient-specific pain scale (e.g. 0-10), both at rest and with activity.
- Level of sedation & respiratory rate, *preferably by the same nurse during each shift.*
- Side effects: pruritis, nausea, urinary retention, orthostatic hypotension, motor block.
- Sign of catheter insertion site infection or epidural abscess such as back pain, tenderness, erythema, swelling, drainage, fever, malaise, neck stiffness, progressive numbness, or motor

block.
- Changes in sensory/motor function that may indicate an epidural hematoma including unexplained back pain, leg pain, bowel or bladder dysfunction, motor block.

This *Fast Fact* was adapted with permission from the University of Wisconsin Hospital & Clinics, Madison, WI Pain Patient Care Team '*Pain Management Fast Facts – 5 Minute Inservice*' series**.**

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FAST FACTS AND CONCEPTS #66
RADIATION FOR PALLIATION—PART 1

Carolyn Rutter MD, Candice Johnstone MD and David E Weissman MD

Background   Radiation therapy (XRT) is used with palliative intent to improve quality of life by improving function and/or diminishing symptoms – most commonly pain, bleeding, or pressure on vital structures. This *Fast Fact* describes the physiology and methods of delivering radiation therapy; *Fast Fact* #66 discusses common indications for and outcomes of palliative XRT.

How it works   XRT is the use of ionizing radiation to damage a cell's DNA. This can happen to a DNA molecule itself via a direct effect of the radiation (this is less common), or indirectly via an oxygen compound (OH, HOOH) which reacts with a DNA molecule (this pathway is more common). Damage only occurs in cells within the *radiation field*—the area through which the radiation beam passes. Both malignant and normal cells within the field are affected. Malignant cells are less efficient at repairing DNA damage and are, therefore, more likely to die. The goal is to design a radiation field that includes all of the tumor cells while excluding as much normal tissue as possible.

Types of radiation therapy   XRT can be delivered 1) from outside the body as *external beam radiation* (EBRT*)*, 2) from within the body by placement of a radiation source near the cancer (*brachytherapy*), or 3) as a radio-pharmaceutical given by mouth (e.g. iodine-131) or by intravenous injection (e.g. Strontium[89]).

Fractionation   In EBRT patients typically receive one fraction per day, but other schedules are sometimes used (e.g. *hyperfractionation*, or at least 2 doses per day).   *Fractionation* takes advantage of the different rates at which malignant and non-malignant cells repair damage caused by XRT; it gives normal tissues an opportunity to recover while continually reducing the tumor cell population.

Dosing   Radiation doses are described in units called *Gray* (Gy) or *centiGray* (cGy): 1 Gy = 100 cGy. Note**:** in the older literature, the term *rad* was used: 1 rad = 1 cGy. A *radiation prescription* includes the site being treated, beam orientation and number (e.g. two beams, AP and PA), beam type (photons or electrons) and energy (in Volts), dose per fraction (typical daily doses for palliative EBR range from 150-400 cGy), number of fractions per day, and total dose. A *radiation boost* is an extra dose of radiation, given during the last treatments, to a smaller field within the original field. The total administered dose is based on a balance between giving enough radiation to control the tumor while respecting normal tissue tolerance to minimize the risk of late side effects. Different tissues have different radiation tolerances; liver and kidney can only tolerate a small total radiation dose (< 2400 cGy), whereas bone and peripheral nerves can tolerate much larger total doses (>5000 cGy).

Simulation   Prior to the first treatment, patients undergo *simulation*, where the exact location of the field is mapped. Permanent or temporary marks are placed on the skin to help ensure that the treatment field can be reproduced in the same location at every treatment. Various types of immobilization ranging from standard pads, head cups to customizable devices are utilized depending on the clinical situation.

Delivering EBRT   If the radiation prescription calls for daily fractions, patients come to the radiation therapy department once a day, five days a week. While most XRT regimens for curative intent often last 5-7 weeks, most palliative XRT regimens can be condensed to a shorter range of one day (e.g. to relieve pain from bone metastases) to three weeks. Treatments are delivered inside a shielded, enclosed room. A radiation therapist operates the radiation machine (typically a linear accelerator) from outside the room while watching the patient on a camera. Each daily treatment takes only a few minutes and is painless.

Toxicity   At least once a week patients see the radiation oncologist to evaluate response and assess/treat toxicity. Toxicity depends upon the area being treated and, except for fatigue, is limited to tissues within that field. Early/acute toxicities occur during or shortly after treatment and resolve within one to two months (e.g. oral mucositis during oral radiation). Late toxicities occur months to years after treatment (e.g. coronary artery disease following chest radiation). Early toxicity is related to inflammation and death of rapidly dividing cells (such as in the skin or gastrointestinal tract), while late effects result

from vascular changes and cell death of slowly dividing cells. Radiation oncologists have a host of medications, salves, and mouth rinses to help alleviate acute toxicities (see *Fast Facts* #121, 130, 185).

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FAST FACTS AND CONCEPTS #67
RADIATION FOR PALLIATION – PART 2, 2 ND EDITION

Carolyn Rutter MD and David E Weissman MD

Background Fast Fact #66 discussed the physiology and methods of delivering radiation therapy (XRT). This Fast Fact reviews the common indications for and outcomes of palliative XRT.

Decision Making The most important decision when considering palliative XRT is to assess the balance between anticipated functional/symptomatic benefit versus time spent receiving therapy and acute toxicities. It is vital to review 1) the estimated prognosis, 2) current and anticipated best functional status outcome, 3) expected toxicities, and 4) treatment burden—time spent coming to XRT site, time off work for family, and cost.

Bone Metastases External beam therapy achieves pain relief in over 75% of patients with healing and reossification occurring in 65-85% of lytic lesions in non-fractured bone. Pain relief may begin within the first few treatments and peaks by 4 weeks following XRT completion. A standard radiation prescription in the US is 300 cGy x 10 fractions. However, data exist to support a single large fraction (800 cGy x 1) for extremity lesions, especially in patients with expected survival < 3 months. Surgical fixation prior to XRT is indicated for large lesions, when >50% of the cortex is replaced by tumor, or when fracture has occurred in a weight-bearing bone.

Radionuclide therapy with Strontium 89 or Samarium 153 is indicated for multiple sites of painful bone metastases (typically breast or prostate cancer). Peak analgesic effect occurs 3-6 weeks following treatment. Side effects are hematological with decreased blood counts in 10-30% of patients. Worsening of pain (a 'pain flare') may occur following administration and prior to pain relief. Radionuclide therapy can be combined with external beam radiation and can be given more than once.

Epidural Metastases and Spinal Cord Compression External beam radiation is the primary definitive treatment for epidural metastases with or without spinal cord compression, in conjunction with a short-course of steroids. The standard US prescription is 300 cGy x 10 fractions, although shorter courses can be used if needed (e.g. 400 cGy x 5). Results of treatment are directly related to the neurological status at the time treatment starts. Ambulatory patients at the start of treatment generally remain ambulatory, while non-ambulatory patients are unlikely to have return of weight-bearing function. Indications for surgery include no tissue diagnosis, spinal instability, bone fragments causing cord damage and progression during/after XRT.

Brain Metastases Whole-brain external beam radiation or – for small lesions – stereotactic radiosurgery (e.g. 'Gamma Knife'), can relieve symptoms and prolong survival. The standard US prescription is 300 cGy x 10 fractions; although shorter courses can be used (e.g. 400 cGy x 5). Surgery is indicated for good prognosis patients with a single accessible lesion or for refractory neurological symptoms (e.g. seizures).

Other Indications The following are all appropriate for consideration of palliative radiation:

- Obstruction: vascular (superior vena cava syndrome), esophagus, airway, rectum, biliary tract
- Pain: adrenal metastases causingflank pain, tumors causing nerve impingement
- Bleeding: stomach, esophagus, head/neck cancer, bladder, cervix
- Ulceration/fungation

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FAST FACTS AND CONCEPTS #116
RADIOPHARMACEUTICALS FOR PAINFUL OSSEOUS METASTASES
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Introduction   This *Fast* Fact reviews bone-seeking radiopharmaceuticals (radionuclides), which occupy a valuable niche in the palliation of painful bone metastases. See *Fast Facts* #66 and 67 for a general discussion of palliative radiation.

Isotopes and Physiology   Many isotopes available in this country – ^{89}Sr (strontium-89), ^{153}Sm (samarium-153), and ^{32}P (phosphorus-32) – work by binding with high affinity to hydroxyapatite in regions of rapid bone turnover near osteoblastic metastases, delivering therapeutic doses of localized beta radiation, with a tissue penetration measured in millimeters.
The precise mechanism of analgesia is unknown but is probably not dependent solely on cell kill. Rather, analgesia may also be a function of inhibition of lymphocyte-associated cytokines or alterations in osteoclast and/or osteoblast activity. Radium-223 is a newer isotope which is a targeted alpha emitter with more selective binding to areas of increased bone turnover in bone metastases. It thereby leads to highly localized cytotoxic effects.

Benefits   The benefits of many of the radiopharmaceuticals have been limited to pain relief and delay of skeletal events. Analgesia may begin within 3-7 days, but more typically begins within one to two weeks after administration. Analgesia will last from two to six months; treatment may be repeated. Symptom improvement is noted in 60-80% of patients, with complete analgesia in 20-30% of responders. Only radium-223 has shown a survival benefit compared with placebo in select patients. Patients with castration-resistant metastatic prostate cancer lived 3 months longer. In addition, radium-223 appears to be associated with less myelosuppression and adverse events.

Procedure   The radiopharmaceutical is delivered in the outpatient setting by a single IV injection or for radium-223, six injections given at 4 week intervals. Administration requires no special monitoring.

Patient selection   Patients with multiple painful bone metastases, demonstrated by bone scan and/or plain X-ray, corresponding to site(s) of pain and an expected survival of >12 weeks are appropriate for radiopharmaceutical therapy. For patients with castration-resistant prostate cancer and bone-predominant disease, radium-223 should be strongly considered. Evidence supporting efficacy in prostate and breast cancer is substantial; data for other tumor types are limited.

Contraindications
- Preexisting myelosuppression (e.g. WBC <3.0K and Platelets <60-100K).
- Oncological urgencies/emergencies in which radiopharmaceuticals will be of no benefit (e.g. actual or impending spinal cord compression or pathologic fracture).
- Renal insufficiency (relative contraindication).
- Evidence of disseminated intravascular coagulation (relative contraindication).
- Pregnancy

Adverse effects
- Marrow suppression: Reversible, moderate neutropenia and thrombocytopenia – manifested by approximately 30-70% drop in leukocyte and platelet counts – is a predictable side effect. Depending on the specific agent this begins two to four weeks following administration, with a nadir between weeks four to six. Bone marrow recovery occurs by weeks eight to twelve.
- Pain flare: Increasing pain occurs in 10-20% of patients, usually within the first week of administration. It is transient and may be predictive of a good therapeutic response.

Comparative Data   There is little data comparing agents. However, the International Atomic Energy Agency sponsored a randomized, single-blind study comparing a single doses of oral ^{32}P (12 mCi) and intravenous ^{89}Sr (4 mCi). There were no significant differences in onset/duration/degree of analgesia or functional improvement. Hematologic 32P was associated with significantly more thrombocytopenia.

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Because ^{32}P is also known to have a long half-life and be incorporated into marrow cells, it is rarely used in the US.

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FAST FACTS AND CONCEPTS #202
VERTEBROPLASTY AND KYPHOPLASTY FOR VERTEBRAL COMPRESSION FRACTURES
Marcin Chwistek MD and Rohtesh Mehta MD

Background   Vertebral compression fractures (VCFs) occur in up to 20% of patients above the age of 50, mostly due to osteoporosis. Malignant VCFs are the result of osteolytic lesions from multiple myeloma or metastatic carcinoma and occur in up to 30% of patients with bone metastases. VCFs can cause significant acute and long-term pain, can compromise pulmonary function, and impair activities of daily living. Vertebroplasty (VP) and balloon Kyphoplasty (BKP) are minimally invasive surgical techniques used for treatment of both osteoporotic and malignant VCFs.

Technique   VP involves percutaneous injection of cement (polymethylmethacrylate - PMMA) into a fractured vertebral body. BKP involves inserting an inflatable balloon in the vertebral body first – to attempt to elevate the vertebral end plates – with subsequent insertion of PMMA. Both are outpatient procedures, done under conscious sedation and local anesthesia, with fluoroscopic guidance. Some clinicians will augment multiple levels at once.

Patient Selection   Careful correlation of a patient's symptoms with the level of the fracture is important, as not all fractures are painful, and alternative causes of pain need to be considered. Patients with painful acute or chronic VCFs (only after neurological compromise has been ruled out) are appropriate for interventional consideration, although outcomes are slightly better in the acute setting. BKP is substantially more expensive than VP. Some practitioners empirically favor BKP in case of significant kyphosis (deformity more than 20°) or when VP is difficult due to posterior vertebral cortex involvement, which makes cement extravasation more likely. VP, on the other hand, is favored when insertion of balloon device is technically difficult due to severe vertebral collapse (> 65% reduction in vertebral height) or if the fracture is more than 3 months old, in which case elevation of the endplate is unlikely.

Relative contraindications include the presence of any neurologic damage related to the fracture, fractures with a burst component (where bone fragments extend into the spinal canal), systemic or local infection, uncorrected hypercoagulable state, and severe cardiopulmonary disease.

Complications

- Cement Extravasation is more common in VP (up to 40%, depending on the series) than in BKP (up to 13%). Cement leaks are rarely symptomatic.
- Pulmonary or neurologic emboli can occur from displaced bone marrow in <1% of cases.
- Infectious complications such as pyogenic spondylitis and osteomyelitis are very rare.

Outcomes   Multiple randomized, unblinded, controlled trials have shown VP/BKP to provide better analgesia than medical management alone. RCTs have shown efficacy in pain and functional improvement for both BP and BKP vs non-surgical management in patients with osteoporotic (10, 11) and cancer-induced VCFs (12). In some of these studies the improvements lasted up to 12 months. **However**, two blinded, randomized, sham-procedure controlled trials showed the efficacy of VP to be similar to controls who received a sham procedure for osteoporotic VCFs (8,9). The injection of a local anaesthetic into the periosteum may explain this finding. Of note, these studies were criticized for patient selection, low pain scores, insufficient amount of cement used and other methodological issues. **Pain reduction** occurs in 67-100% of cases with VP and in BKP; often more than a 5 point drop (on a 0-10 scale) in the immediate postoperative period, along with significant decrease in analgesic use at 1 month. Pain relief seems to be better in patients with osteoporotic VCFs as compared to those with malignant fractures. BKP is reported to contribute to better long-term pain control (more than 2 years) than VP (73% vs. 41%, respectively); however, these data are not from a head-to-head comparison. Both BKP and VP may lead to partial vertebral height restoration in selected patients, along with reductions in depression, anxiety, drowsiness, and fatigue (13).

Summary   VP and BKP are effective analgesic interventions for painful VCFs in many patients, including cancer patients, and can be particularly helpful for patients who poorly tolerate opioids and other analgesics. Although understanding of the precise mechanism of action and precise indications are still evolving, these minimally invasive procedures should be considered as a part of a multidisciplinary approach to patients with painful VCFs. The choice of the vertebral augmentation procedure for a patient with either benign or malignant VCF is still largely guided by the experience of the practitioner performing the procedure. Patients taking opioids should be evaluated carefully after VP or BKP, as they may need dose reductions.

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FAST FACTS AND CONCEPTS #180
PARENTERAL LIDOCAINE FOR NEUROPATHIC PAIN

Jay Thomas MD, PhD

Background   In recent years reports have described the use of parenteral lidocaine for neuropathic pain. This *Fast Fact* reviews the use of parenteral lidocaine for neuropathic pain.

Mechanism   Lidocaine is a local anesthetic that is a nonselective sodium channel blocker. Animal and human studies demonstrate that injured nerves develop abnormal, spontaneously active sodium channels at sites of nerve injury, along damaged nerves, and at the dorsal root ganglia of damaged nerves. Lidocaine can suppress this ectopic, spontaneous firing of aberrant sodium channels at concentrations that do not affect normal nerve or cardiac conduction and thereby modulate neuropathic pain (1).

Clinical Trial Data
- Small controlled studies have shown effective relief of neuropathic pain associated with spinal cord injury, diabetic neuropathy, central pain syndrome, chronic regional pain syndrome, and post-herpetic neuralgia with the use of parenteral lidocaine in adults (2-6).
- A meta-analysis concluded that systemic lidocaine is superior to placebo for neuropathic pain, is as effective as other adjuvant analgesics, and is well tolerated in adults (7).
- Two small controlled trials in cancer pain found no benefit of systemic lidocaine (8,9). However, other case reports and one retrospective study support its use (10).
- One trial indicated that an analgesic response to lidocaine is a predictor of a response to mexiletene, an oral congener of lidocaine (11). In practice, the validity of this finding has been questioned and a high rate of side effects (predominantly gastrointestinal) from mexiletene have limited its use.

Dosing   Multiple regimens have been described.
- Typically a bolus dose between 1-5 mg/kg is administered intravenously over 15 to 60 minutes depending on the dose.
- A retrospective analysis suggested that a flat-rate trial dose of 500 mg IV over 30 minutes was effective in managing neuropathic pain in adults; however it was associated with a high prevalence of iatrogenic lightheadedness (12).
- Time to analgesia from the bolus dose has been reported to be between 1-45 minutes (13).
- If patients respond to initial bolus, ongoing IV or subcutaneous infusions can be provided over days to months depending on response.
- Serum lidocaine levels should be followed at steady state (t½ ~100 minutes, so 3-5 half-lives for steady state ~5-8 hrs) and intermittently afterwards as clinically indicated. A target level of 2-5 mg/liter is based on dose-response studies and avoidance of side effects as below (13).

Adverse Reactions   Lidocaine has dose-related side effects that become progressively more severe at levels higher than 5 mg/liter, including myoclonus (~8 mg/l), seizures (>10 mg/l), and cardiovascular collapse (>25 mg/l) (14). Lightheadedness is the most frequently reported side effect and can occur even at levels less than 5 mg/liter (12). Although lidocaine after a myocardial infarction has been associated with a trend towards increased risk of arrhythmias, cardiac monitoring during studies of normal volunteers and patients has noted no cardiac risks at clinically appropriate levels. Lidocaine is rapidly and extensively metabolized by the liver. Metabolites are excreted by the kidney, thus adjustments may be needed in the case of liver and renal insufficiency, guided by monitoring steady state blood levels.

Pediatric Patients   The dosing and efficacy of intravenous lidocaine for pain has not been well established in pediatrics. Case reports and a retrospective analysis have described the safe and effective use of parenteral lidocaine to treat cancer related neuropathic pain, sickle cell pain, and chronic pain in children, adolescents, and young adults at a typical dose of 25-80 mcg/kg/minute (15-17).

Summary   There is weak evidence that systemic lidocaine can relieve neuropathic pain in selected patients. Definitive evidence to support its use in cancer pain (both neuropathic and opioid-refractory) awaits further prospective trials. Most practitioners, however, would not use it as a first line treatment and a pain or palliative care consult should precede its use.

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FAST FACTS AND CONCEPTS #92
PATIENT CONTROLLED ANALGESIA IN PALLIATIVE CARE

Eric Prommer MD

Introduction   Patient Controlled Analgesia (PCA) is a technique allowing patients to self-administer parenteral analgesics. The primary advantage of PCA is to shorten the interval from the time of patient-defined need to the time of actual analgesic administration. PCA is an effective, safe, and well-accepted treatment for post-operative pain, sickle cell crisis pain (as young as age 4), and cancer pain. In general, PCA will provide the same degree of analgesia compared to other delivery systems with the same or less total amount of medication.   PCA allows for more immediate relief of incident (breakthrough) pain and can provide patients with a greater sense of personal control over their pain.

Indications   The primary indication for PCA is the patient who requires parenteral analgesia (e.g. severe pain and/or oral/transdermal/rectal route not useable) and has *incident pain* or other pain patterns that are not predictable. PCA is also indicated for use as a method of rapid dose titration and dose finding in acute, severe pain. Relative contraindications include patients who a) do not have the cognitive ability to understand how to use a PCA device, or b) have an anticipated need for parenteral opioids less than 24 hours.

PCA devices   Most devices have a drug reservoir and infusion system whereby PCA administration can occur with or without a background continuous infusion.   Thus, PCA devices need the following orders: 1) PCA dose in mg or mcg ('patient initiated dose,' 'patient demand dose,' or 'bolus dose'), 2) Delay Interval ('lockout') – in minutes (period during which the patient cannot obtain additional demand medication), 3) Continuous infusion (CI) Rate in mg/hr or mcg/hr (if CI is used), and 4) Hour Limit – maximum amount of drug to be dispensed in a defined period of time. Often the one-hour limit is set to deliver 3-5 times the estimated required hourly dose. (Note: due to the need for frequent dose adjustments, the Hour Limit is often omitted in palliative care.) Most palliative care patients will need both PCA demand and CI dosing. Opioids used in PCA devices include morphine, hydromorphone, fentanyl, and methadone. IV or SQ are the most common routes of administration; PCA can also be used with epidural, intrathecal, or intraventricular opioid administration (see *Fast Facts* #28, 85, and 98).

Dosing in opioid-naïve patients   The following information is for morphine, the first-line drug of choice for most patients. Note: dosing and delay interval information will differ with other opioids.   Start dosing: PCA demand dose = 1-3 mg morphine; Delay Interval = 8-10 min. Initial CI (if any) is dependent on the clinical situation. For instance, 1 mg/hour of IV morphine is approximately equivalent to 35 mg bid of oral morphine ER. This may be excessive for opioid-naïve patients; conversely many opioid-naïve patients with severe pain will easily tolerate this, so the decision to immediately start a CI depends on clinician judgment. If not started immediately, one can initiate a CI after four hours by summing the total demand dose given over 4 hours and converting that into an hourly rate (e.g. if 16 mg is given over four hours, CI would be 4 mg/hour). A new PCA demand dose can then be calculated at 50% of the hourly CI rate (4 mg/hr ÷ 2 = 2 mg PCA demand dose, Delay Interval 8-10 min).

Dosing in non-naïve patients   Convert their current total oral/transdermal dose to a total 24-hour IV dose; divide by 24 to give the hourly CI rate in mg/hour (see *Fast Fact* #36 on dose conversions). The PCA demand dose is initially calculated at 50% of the hourly rate.

Risk of Overdose   The patient who is pushing his or her own PCA button will fall asleep before serious signs of overdose occur as long as only the patient pushes the button. Note: special care is needed for patients with sleep apnea as they will be more sensitive to opioids.

Dose titration and Loading Doses   See *Fast Facts* #20 Opioid Dose Escalation, #54 Opioid Infusions in the Imminently Dying Patient, and #72 Opioid Infusion Titration Orders.
Common Sense Cautions   These dosing recommendations are rough guidelines—clinicians need to take into account pain severity, patient age, renal and pulmonary function, co-morbid illness, and other psychoactive medications. When in doubt, it is advised to use a lower CI rate (with upward dose

adjustments of the CI rate no more frequently than every 8 hours), while adjusting the PCA dose at frequent intervals (q30-60 minutes) to effectively control pain.

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FAST FACTS AND CONCEPTS #324
PALLIATIVE USES OF BOTULINUM NEUROTOXIN

April Zehm MD, Mihir Kamdar, MD

Non-cosmetic uses of botulinum neurotoxin (BoNT) have been FDA-approved for a growing number of spastic neuromuscular conditions, headaches, and secretory conditions (see *Fast Fact* #299). While supporting evidence is limited for many indications and expense can be a barrier, this *Fast Fact* will review potential BoNT uses for seriously ill patients when traditional treatment modalities have failed.

Pharmacology   BoNTs are a metabolic waste product of the bacteria *Clostridium botulinum*. In large quantities, BoNTs cause botulism, a rare but potentially lethal illness resulting from muscle paralysis. In minute quantities, the toxin can be therapeutic for overactive muscle conditions via reversible inhibition of presynaptic acetylcholine release at the neuromuscular junction. They are also known to inhibit gland secretion via parasympathetic effects. At least one of the seven antigenically different serotypes (A) may have direct analgesic effects (1).

Practical Aspects   Treatment with BoNTs involves direct, localized injection of a saline solution containing the diluted toxin at the site of intended action (intramuscular or subcutaneous). It is usually an office-based procedure. Procedural specialists often provide this service, but other clinicians could become certified after training and demonstrating proficiency, depending on individual institutional regulations. Onset of action is generally within 3-4 days. The toxins' effects can last 3-4 months for striated muscle and 6-9 months for autonomic neurons.

Specific Palliative Indications
Spasticity   Controlled studies suggest BoNTs can be particularly useful for short-lived spasmodic pain that may be difficult to target with systemic analgesics. Serotype A is FDA-approved to treat spasticity of the upper and lower extremities in adults. In children, different BoNT formulations are used off-label to treat many muscle groups; the only FDA-approved pediatric indication is cervical dystonia in patients over age 16. Available data suggests BoNT A is safe and improves function, self-worth, and parental/caregiver perception of care for cerebral palsy (CP)-related spasticity in children when used as an adjunct to traditional therapies (2). Other evidence suggests BoNTs may have a role in:
- Stroke-related spasticity and pain (3-5)
- Non-malignant chronic neck pain (6)
- Pain and spasticity in head and neck cancer patients (7-9).

Neuropathic pain syndromes   Case reports and case series suggest BoNTs may reduce neuropathic pain and reduce opioid use from post-mastectomy and post-thoracotomy pain syndromes (10-12). A randomized controlled trial (RCT) suggested that BoNT reduces pain severity and attack frequency in trigeminal neuralgia (13) and should be considered for patients who cannot tolerate other standard treatments due to toxicities. RCTs also show BoNT can improve pain scores, reduce recovery time, and decrease opioid use in post-herpetic neuralgia (14-15).

Sialorrhea   Randomized trials show BoNT injections into salivary glands are beneficial for sialorrhea from many neurologic conditions (CP, amyotrophic lateral sclerosis, Parkinson's disease, multiple system atrophy, corticobasal degeneration), with results lasting several months (16-18).

Depression   Psychotherapy and anti-depressant medications remain the mainstay of depression treatment (see *Fast Fact* #309), but BoNTs show promise in patients with limited prognoses. Single glabellar region BoNT injections show anti-depressant effects within 2 weeks and lasting 4 months, as demonstrated by several RCTs (19-21).

Other Uses   Anecdotally, BoNTs have been used for radiation proctitis pain, chronic pelvic pain, phantom

limb pain, chronic regional pain syndrome, multiple sclerosis tremors or spasticity, chronic low back pain, neurogenic bladder, diabetic neuropathy, and speech failure following laryngectomy.

Financial Issues   Cost and insurance coverage can be significant barriers. Medicare often covers BoNTs for non-cosmetic indications with a small co-payment. Private insurance coverage can be variable, leading some patients to require prior authorization and others to pay entirely out of pocket. Depending on the supplier and pharmacy, a single vial of BoNT can cost over $800, which may limit its use in hospice patients.

Risks and Limitations   The diminishing effect of BoTN over months can require repeat injections over time. Depending on injection site, patient age, and tolerance of the procedure, sedation or even general anesthesia may be required, introducing additional risks. Furthermore, there is a lack of large randomized controlled trials for many indications. Although the side effect profile is felt to be low if injected correctly, clinicians should be aware of the following potential adverse reactions, most of which occur within hours to days of the injection, and usually subside after several days (22-24):
- Anaphylaxis or botulism-like systemic reactions: most have occurred in off-label use in children; consequently, the FDA issued a black box warning for all BoNT products in 2009.
- Bruising, edema or pain at the injection site (2-3%)
- Flu-like symptoms (1.7-20%)
- Ptosis or diplopia (2-13%)
- Dry mouth, dysarthria, or dysphagia (2-10%)

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