Risk and Prevention of Persistent Neuropathic Post-Surgical and Post-Trauma Pain

Chris Pasero, MS, RN-BC, FAAN
El Dorado Hills, California

Persistent Post-trauma Pain

- 18.7% of patients in pain clinics have pain related to trauma (Crombie et al, 1998)
- Pain present 5-7 years after pelvic fracture or major extremity injury (Castillo et al, 2006; Mkandawire et al, 2002)
- PTSD (Bryant et al, 1999; Duckworth, Iezzi, 2006) and depression (Castillo et al, 2006; Von Korff et al, 2005) common

Persistent Post-trauma Pain

(Rivara et al, 2008)
- Multicenter (69) prospective cohort study of 3047 patients 12 months after major traumatic injury
- 62.7% reported pain related to injury
- 59.3% of these had multiple pain sites (mean 2.2); average severity 4.5 (1 site) and 8.5 (6 sites)
- Unaffected by sex; more common in younger than older individuals
Persistent Post-surgical Pain
(Wildgaard et al, 2009)

- Incidence is highly variable and comparisons difficult because there is no consensus on when and what to report:
  - Intensity of a certain level is reached
  - Pain requires regular analgesia
  - Pain beyond a certain period of time

Persistent Post-surgical Pain

- Criteria established (Macrae, 2008):
  - Pain developed after surgery
  - Pain is of at least 2 months duration
  - Other causes have been excluded
- Pain that lasts for 3 to 6 months after surgery (Kehlet et al, 2006)
- Hard to prevent and treat and often is associated with disability and poor quality of life (Katz, Cohen, 2004)

Epidemiology
(Kehlet et al, 2006; Macrae, 2008; Visser, 2006)

- ~ 20% of patients in pain clinics
- Incidence varies with surgical procedure

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Incidence</th>
<th>Severe disability</th>
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<tbody>
<tr>
<td>Amputation</td>
<td>30-85%</td>
<td>5-10%</td>
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<tr>
<td>Thoracotomy</td>
<td>5-67%</td>
<td>10%</td>
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<tr>
<td>Inguinal hernia</td>
<td>10-63%</td>
<td>2-4%</td>
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<tr>
<td>Breast surgery</td>
<td>11-57%</td>
<td>5-10%</td>
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<tr>
<td>CABG</td>
<td>30-50%</td>
<td>5-10%</td>
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<tr>
<td>C-section</td>
<td>10-12%</td>
<td>4%</td>
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Predictors (Risk Factors)
(Perkins & Kehlet, 2000; Visser, 2006)

• #1: Surgeries with significant nerve or tissue injury, e.g., thoracotomy, cardiac, amputation, inguinal hernia, breast, limb
  – Lower incidence with minimally invasive thoracoscopy than lateral thoracotomy (Landreneau, 1994); however, this is influenced by the degree of intercostal nerve injury (Wildgaard et al, 2009)
• Females more than males (Caumo et al, 2002; Gotoda et al, 2001; Katz et al, 2005)

Other Predictors

• Moderate-to-severe pre and/or early postop pain (Brandsborg et al, 2007; 2009; Franneby et al, 2006; Gerbershagen et al, 2009; Hanley et al, 2007; Jensen et al, 1985; Nikolajsen et al, 1997; Poobalan et al, 2001)
• Greater early postop analgesic needs (Taillefer et al, 2006; Tasmuth et al, 1997)

Other Predictors

• Higher BMI (Bruce et al, 2003; Massaron et al, 2007, 2008; Smith et al, 1999)
• Higher incidence of postop complications (Franneby et al, 2006)
• Reoperation (Poobalan et al, 2001)
• Genetic factors; predisposed conditions (Macrae, 2008; Wildgaard et al, 2009)
Preop Responses as Predictors

- Response to preop experimental pain stimuli (Granot et al, 2003; Werner et al, 2004) and to ice water test (Bisgaard et al, 2001) predicted severity of early but not late postop pain.
- Preop catastrophizing score correlated with severity of early but not late postop pain (Bisgaard et al, 2005).

Predictors: Amputation

- Preoperative pain in extremity (Hanley et al, 2007; Krane, Heller, 1995)
- Presence of acute and/or chronic stump pain (Nikolajsen et al, 1997)
- High early postop pain intensity (Hanley et al, 2007)
- Psychosocial factors (Hanley et al, 2004; Lame et al, 2005; Sperber et al, 2008)
- Neurotoxic chemotherapy (Smith, Thompson, 1995)

Predictors: Thoracotomy

- Extent of intercostal nerve dysfunction (Benedetti et al, 1997;1998; Wildgaard et al, 2009)
- Extent of acute postop pain and analgesia
  - Higher if EA started postop (Obata, 1999)
  - Higher if high postop pain intensity after EA discontinued (Gottschalk, Ochroch, 2008)
  - Higher with IV PCA than with preop thoracic EA (Senturk et al, 2002)
Risk Factors: Breast Surgery

- Immediate axillary radiation (Keramopoulos et al, 1993)
- Preop pain (Kroner et al, 1989)
- Extent of postop pain and number of analgesic doses (Tasmuth et al, 1997)
- Possibly preop anxiety and depression (Tasmuth et al, 1996)

Predictors: Inguinal Hernia

- Preop pain (Poobalan et al, 2001)
- Intensity of continued postop pain at 1 and 4 weeks (Callesen et al, 1999)
- Recurrent repair (Callesen et al, 1999)
- Use of heavy-weight mesh for repair (Massaron et al, 2007, 2008)
- Risk higher in younger than older adults (Aasvang, Kehlet, 2005; Massaron et al, 2007, 2008; Pooblan et al, 2003)

Etiology

(Kehlet et al, 2006; Macrae, 2008)

- Major nerves “trespass” the surgical field of most surgical procedures; damage to these nerves is a prerequisite for the establishment of persistent pain.
- After surgery/trauma: Nociceptive, inflammatory, and neuropathic pain processes persist in absence of peripheral stimuli.
Neuroplasticity

- Neuronal reorganization (re-mapping) and new connections between neurons
- No simple continuum from acute (reversible, inflammatory) to persistent (changes in hardware) pain
  - Peripheral sensitization leads to reduced threshold and increased excitability
  - Central sensitization amplifies signals; constitutes abnormal perceptual response to normal sensory input and spreads sensitivity beyond peripheral injury site

Punctuate Mechanical Hyperalgesia
(Brennan, Kehlet, 2005)

- Area of the body that encompasses uninjured tissue surrounding the site of tissue injury (incision, trauma)
- Thought to represent a measurement of central sensitization and so, plasticity
- Not typically measured in the clinical setting but may be more in the future

Pathophysiology Identified in Patient Subsets

- Inguinal mesh hernia repair, mastectomy: Continuous inflammatory response (Jung et al, 2003; Mikkelsen et al, 2004)
- Thoracotomy: Extensive nerve damage → sensory threshold changes and somatosensory evoked responses to electrical stimulation correlate with pain intensity (Benedeti et al, 1998)
Phantom Pain

- Neuromatrix Theory (Melzack, 1990): Matrix in the CNS for the perception of a body part; exists even when the body part does not
- Remapping (fooling the brain): Intact limb mirror therapy (Hanling et al, 2010); virtual limb therapy (Gaggioli et al, 2010)
- Inconsistency in therapeutic response indicates multiple etiologies (Kehlet, Perkins, 2000; Sherman et al, 1984)

Nociception: “Normal” Pain Transmission

Etiology: Research Needed
(Kehlet et al, 2006; Mikkelsen et al, 2004)

- Factors other than nerve damage are likely involved in most syndromes.
- Many questions unanswered:
  - Why such variation in pain descriptions?
  - Why such inconsistency in response to treatment?
  - How do comorbidities affect syndromes?
Prevention
(Kehlet et al, 2006; Macrae, 2001; 2008)
- Surgical technique: Minimally invasive whenever possible; careful dissection
- Suppression of pain at time of surgery or trauma is not enough
- Preventive and aggressive multimodal analgesia; more research needed
  - Adequate afferent blockade
  - NSAIDs and opioids for inflammatory pain
  - Ketamine, local anesthetics, anticonvulsants

Key: Multimodal Analgesia
(Kehlet et al, 2006)
- Combinations of drugs that attack more than one pain mechanism
- Some drugs add analgesia
- Some drugs work synergistically
- Added benefit: Lower doses of each drug → fewer adverse effects

Multimodal Approach
(Fassoulaki et al, 2005)
- RCT (N = 50): Breast cancer surgery
- Placebo or oral gabapentin, EMLA to surgical area, and ropivacaine in wound
- Pain at 3 months: 44% v. 82% (placebo)
- Pain at 6 months: 30% v. 57% (placebo)
- Methodology/conclusions criticized: Did not control for other factors, e.g., chemo or radiation therapy (Kehlet, 2006).
Three Methods Compared
(Senturk et al, 2002)

• RCT (N = 69): Thoracotomy
• Groups: Pre, intra, postop thoracic EA (1); just postop TEA (2); IV PCA (3)
• Far superior early pain relief with group 1
• Incidence of pain at 6 mo: Group 3: 78%; group 2: 63%; group 1: 45%
• Highest pain severity in group 3, but no affect on daily life in any of the groups

Preventive EA
(Katz, Cohen, 2004; Katz et al, 2003)

• RCT (N = 131): Major GYN surgery
• Pre and post incision EA reduced postop morphine consumption and hyperalgesia
• Surveyed at 3 wks: Reduced pain/disability
• Surveyed at 6 months: No reduction
• May have failed to address all underlying mechanisms that initiate persistent pain

IV Ketamine and EA
(Lavand’homme et al, 2005)

• RCT (N = 85): Colon resection for neoplasm
• Combinations of IV ketamine plus IV or EA local anesthetic, clonidine, and opioid administered intraop or postop
• PMH almost completely eliminated by each preventive intervention
• 1-year residual pain: IV only (28%); EA postop only (11%); EA intra and EA and IV postop (0%)
Further Research Needed

• Spinal anesthesia
  – Survey (N =1299): 32% post hysterectomy pain; lower risk with spinal than intra or postop EA (Brandsborg et al, 2007)
• Continuous peripheral nerve block (De Cosmo et al, 2009)
• Best methods for prevention of both postsurgical and post-trauma pain

Clinical Presentation
(Kehlet et al, 2006)

• Key warning sign: Pain that persists beyond expected healing period
• Poor response to initial (traditional) treatments
• Wide range of sensory-discriminative descriptors: Aching, cramping, sharp, shooting, stabbing, tender, numb and other dyesthesias

Clinical Presentation
(Massaron et al, 2008)

• SF McGill Pain Questionnaire (N = 1311) post inguinal hernia
• 18.1% had chronic pain; severe and interfered with normal activities in 2.1%
• Descriptors:
  – 71.3% = nociceptive; 8.9% neuropathic; 19.8% nociceptive + neuropathic
  – “Tender” and “aching” most common
Treatment
(Kehlet et al, 2006; Macrae, 2001; 2008)
• Early referral to a pain specialist with access to multiple disciplines for evaluation and treatment of both pain and co-morbidities
• Avoid pigeon-holing: Treatment does not depend on type of surgery or trauma.
• Target the progression of mechanisms, not just the disturbances they produce.

Treatment
(Kehlet et al, 2006; Macrae, 2001; 2008)
• Use multimodal approach to attack multiple underlying mechanisms:
  – NSAIDs and opioids for those with persistent inflammatory pain
  – Ketamine, local anesthetics, anticonvulsants, and antidepressants for neuropathic pain
• Often multiple drug trials required

The Good News
• Persistent post-surgical and post-trauma pain have become a focus of increasing interest among clinicians and researchers (Kehlet et al)
• Several studies currently underway to identify mechanisms and best methods for prevention and treatment
• For many, pain gradually decreases over months to years
ASPMN 20th Annual Meeting

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References and Suggested Reading


