The transition of Acute Post-operative pain to Persistent Postoperative Pain: Is it a burden?

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Long term implications: Hyperalgesia

Taddio et al. The Lancet 1997; 349, 599 - 603.
Invasive procedures in Preterm children: Brain and cognitive development at school age

Vinall et al. Pediatrics 2014;133:412-421
chronic post surgical pain

- The pain must develop after a surgical procedure
- The pain is of at least two months duration
- Other causes for the pain have been excluded
- The possibility that the pain is from a pre-existing condition has been excluded

Macrea & Davies, 1999
prevalence persistent post surgical pain

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Amputation</td>
<td>30-50</td>
<td>50-85</td>
<td>27-30</td>
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<tr>
<td>Thoracotomy</td>
<td>30-40</td>
<td>5-65</td>
<td>52</td>
<td>16-21</td>
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<tr>
<td>Cardiac surgery</td>
<td>30-50</td>
<td>30-55</td>
<td>44</td>
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<tr>
<td>Breast surgery</td>
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<td>20-50</td>
<td>48</td>
<td>47</td>
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<td>Hip surgery</td>
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<td>12</td>
<td>28</td>
<td>12</td>
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<td>Hernia repair</td>
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<td>5-35</td>
<td>12</td>
<td>12</td>
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<td>Ceasarean section</td>
<td>10</td>
<td>6</td>
<td></td>
<td>4-10</td>
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</table>
Transition from acute to chronic Pain? Neuron centric view

From a neuron centric view to a neuron-glial view

Microglia
Astroglia

Berger JV, Knaepen L, Janssen SP, Jaken RJ, Marcus MA, Joosten EA, Deumens R. 2011 Cellular and molecular insights into neuropathy-induced hypersensitivity for mechanism-based treatment approaches

Brain Res Rev. 67(1-2):282-310
Transition from acute to chronic Pain

First stage: microglia activation

Second stage: astroglial activation

The first stage: Activation of Microglia

1. Chemokines: CCL2/CCR2
2. ATP and Purinergic receptors
3. Toll like receptors

Activated microglia and pain?

The neuropathic pain triad: neurons, immune cells and glia
Joachim Scholz & Clifford J Woolf
Transition from acute to chronic Pain

First stage: microglia activation
- ATP - P2X4 – p38MAPK
- BDNF - NMDA

onset

Second stage: astroglial activation
- IL-1B
- bFGF
- maintenance

Activated astrocytes and Pain

Astrocytes maintain the central sensitization process among other things

Autocrine loop: bFGF
CS induction: Il-1B

Regional anaesthesia to prevent chronic pain after surgery

Forest plot favoured epidural anaesthesia for the prevention of PPP outcomes at 6 months after thoracotomy with an OR of 0.33 (95% CI 0.20–0.56) and paravertebral block for breast cancer surgery with an OR of 0.37 (95% CI 0.14–0.94), respectively.

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Favours regional</th>
<th>Conventional pain control</th>
<th>OR IV, Random, 95% CI</th>
<th>OR IV, Random, 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>1.1.1 Thoracotomy (epidural analgesia)</td>
<td>Ju 2008</td>
<td>26</td>
<td>48</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Lu 2008</td>
<td>9</td>
<td>62</td>
<td>12</td>
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<tr>
<td></td>
<td>Senturk 2002</td>
<td>25</td>
<td>46</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>25</td>
<td>156</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>60</td>
<td>61</td>
<td></td>
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<tr>
<td>Heterogeneity: $\hat{\tau}^2=0.00; \chi^2=1.04$, df=2 ($P=0.59$); $\hat{\rho}=0%$</td>
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<tr>
<td>Test for overall effect: $Z=3.69$ ($P=0.0002$)</td>
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<tr>
<td>1.1.2 Breast cancer surgery (paravertebral block)</td>
<td>Ibarra 2011</td>
<td>5</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Kairaluoma 2006</td>
<td>5</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>23</td>
<td>45</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>10</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\hat{\tau}^2=0.00; \chi^2=0.27$, df=1 ($P=0.60$); $\hat{\rho}=0%$</td>
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</tr>
<tr>
<td>Test for overall effect: $Z=2.09$ ($P=0.04$)</td>
<td></td>
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</tbody>
</table>
Pharmacotherapy for the prevention of chronic pain after surgery in adults
1.Luis Enrique Chaparro¹, et al. Published Online: 24 JUL 2013

We identified 40 RCT for various pharmacological interventions including intravenous ketamine (14RCTs), oral gabapentin (10RCTs), oral pregabalin (5RCTs), non-steroidal anti-inflammatories (3RCTs), intravenous steroids (3RCTs), oral N-methyl-D-aspartate (NMDA) blockers (3RCTs), oral mexiletine(2RCTs), intravenous fentanyl (1RCT), intravenous lidocaine (1RCT), oral venlafaxine (1RCT) and inhaled nitrousoxide (1RCT). Meta-analysis suggested a modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine but not gabapentin or pregabalin. Results with ketamine should be viewed with caution since most of the included trials were small (that is<100 participants per treatment arm), which could lead to the overestimation of treatment effect.

As such therapeutic or pharmacological manipulation of the glial cells in the central nervous system, and in particular in neuropathic pain, has, despite the major pre-clinical improvements, not yet resulted into clinical applicable therapies (Basbaum et al.,(2009) Cell 139, 267-284)
Early growth response 1 (EGR1) by a 23-BP DNA decoy (AYX1)

From a neuron centric view to a neuron-glial view

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AYX1 efficacy in the CFA model

From: Mamet et al. (2014) Pain 155, 322-333
Initial demonstration AYX1 in the plantair incisional model

From: Mamet et al. (2014) Pain 155, 322-333
Is this a clinical applicable therapy?

*RS Ulrich, 1984*
View through a window may influence recovery from surgery, Science 224:4220-421.

Patients with window view on nature
(Enriched Environment)

Patients with window facing a brick building wall
(Restricted Housing)

shorter hospital stay
use of less analgesic
less complain to the staff

Yes, enriched (healing) housing is a clinical applicable therapy and affects the neuron-glia interaction
RQ: Is it possible to modulate such a complex glial-neuron interaction as noted during the transition from acute to chronic pain without using pharmacological interventions?

Answer: Yes, it seems that housing does change the complex glial-neuron interaction and interferes with the transition from acute to chronic pain.
Modulation of the glia-neuron interaction: non-pharmacological?

$T = 0$:

injection of 2mg of carrageenan in the right knee of the rat

Reduction in the duration of pain

Modulation of the glia-neuron interaction: non-pharmacological?

\[ T=0: \]

injection of 2mg of carrageenan in the right knee of the rat

Restricted environment

Enriched environment

GFAP Intensity at DPO21

ipsi > contra

ipsi = contra

EE balances GFAP density between the ipsi- and contralateral sides
predictors of persistent post surgical pain

- **Study 1:**
  1490 hospitalized patients, various surgical procedures
  6 months follow-up

- **Study 2:**
  1000 day surgery patients, various surgical procedures
  12 months follow-up

- **Study 3:**
  500 patients with hysterectomy
  3 & 6 months follow-up
Somatic and Psychologic Predictors of Long-term Unfavorable Outcome After Surgical Intervention

Madelon L. Peters, PhD,* Micha Sommer, MD,† Janneke M. de Rijke, PhD,† Fons Kessels, MD, MSc,‡ Erik Heineman, MD, PhD,§ Jacob Patijn, MD, PhD,† Marco A. E. Marcus, MD, PhD,† Maarten van Kleef, MD, PhD,‡ and Johan W. S. Vlaeyen, PhD*

Outcome: increased pain at follow-up

Predictors:

surgery-related & clinical
- demographics: sex, age, education
- pre-operative pain, ASA grade
- duration of surgery
- type of operation: minor, intermediate, major
- anatomical site
- type of anesthesia (general, locoregional, both)

psychological
- surgical fear
- pain catastrophizing
- optimism
- self-efficacy

main predictors:

<table>
<thead>
<tr>
<th>Study 1</th>
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<tbody>
<tr>
<td>More extensive operation</td>
</tr>
<tr>
<td>Duration of surgery</td>
</tr>
<tr>
<td>Pre-operative pain</td>
</tr>
<tr>
<td>Acute Pain Intensity</td>
</tr>
<tr>
<td>Surgical Fear</td>
</tr>
<tr>
<td>Catastrophizing</td>
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<tr>
<td>Optimism</td>
</tr>
</tbody>
</table>
Preoperative Anxiety and Catastrophizing
A Systematic Review and Meta-analysis of the Association With Chronic Postsurgical Pain

Maurice Theunissen, MSc,* Madelon L. Peters, PhD,† Julie Bruce, PhD,‡ Hans-Fritz Gramke, MD, PhD,* and Marco A. Marcus, MD, PhD*

29 studies included: 16 positive association
13 no association
0 negative association

pooled OR: 2.1
(95% CI: 1.5 – 3.0)
N=14
consistent predictors

- type of procedure
- younger age
- pre-operative pain
- high levels of acute pain
- psychological factors (anxiety, negative cognitions & expectations)
- (genetic factors)
- (pain sensitivity / pain modulation capacity (QST, CPM))
Development of a risk index for the prediction of chronic post-surgical pain

A. Althaus¹, A. Hinrichs-Rocker¹, R. Chapman², O. Arráñz Becker³, R. Lefering¹, C. Simanski⁴, F. Weber⁵, K.-H. Moser⁶, R. Joppich⁷, S. Trojan⁷, N. Gutzeit¹, E. Neugebauer¹

- pre-operative pain in the operating field
- other chronic pre-operative pain
- post-surgical acute pain
- capacity overload
- comorbid stress symptoms
Are Psychological Predictors of Chronic Postsurgical Pain Dependent on the Surgical Model? A Comparison of Total Knee Arthroplasty and Breast Surgery for Cancer

Anne Masselin-Dubois, *, † Nadine Attal, *, †, ‡ Dominique Fletcher, *, †, ‡, § Christian Jayr, † Aline Albi, † Jacques Fermanian, ‡ Didier Bouhassira, *, †, ‡ and Sophie Baudic *, †, ‡

- TKA n=89; breast: n=100
- PPSP: average pain at 3 months ≥ 3 (0-10 scale)
- Neuropathic pain: DN4 at 3 months ≥ 3 (0-7 scale)

Predictors PPSP:
- older age
- acute post-operative pain (day 2)
- state anxiety & catastrophizing
Post-operatieve pijn: een up-date

Acute Pain Service

Ready et al. 1988
Maier et al 1994

< 20 %

of all patients should experience severe pain after 1997

< 5 % by 2002

Audit Commission (UK), London 1997
Working together
A definition what is quality. An agreement how to work together and all should have the same passion to reach that goal.