Best of Pediatric Pain Research

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Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial

Naveen Poonai MD, Gina Bhullar BSc, Kangrui Lin MD, Adam Papini MD, David Mainprize BSc, Jocelyn Howard MD, John Teefy BSc, Michelle Bale BSc, Cindy Langford RN, Rodrick Lim MD, Larry Stitt MSc, Michael J. Rieder MD PhD, Samina Ali MD

- **Poonai N, Bhullar G, Lin K, et al. Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial. CMAJ 2014; 186(18): 1358-63.**

- **http://www.ncbi.nlm.nih.gov/pubmed/25349008**

Objectives & Methods

- **Objective**
  - Determine whether morphine administered orally has superior efficacy to ibuprofen in fracture-related pain
- **Methods**
  - Parallel group, randomized, blinded design
  - Children presented to ED with uncomplicated extremity fracture: either morphine (0.5 mg/kg orally) or ibuprofen (10 mg/kg) for 24 hours after discharge
  - Primary outcome: change in pain score using Faces Pain Scale - Revised (FPS-R) -pain scores immediately before and 30 minutes after receiving each dose

Results: Efficacy

Table 2: Mean pre–post differences in pain scores* between groups†

Dose	Oral morphine		Ibuprofen		Between-group difference (95% CI)	*p* value‡
	No. of participants	Pre–post difference, mean ± SD	No. of participants	Pre–post difference, mean ± SD		
1	66	1.5 ± 1.2	68	1.3 ± 1.0	0.2 (–0.2 to 0.6)	0.3
2	55	1.3 ± 1.3	54	1.3 ± 0.9	0.0 (–0.4 to 0.4)	0.9
3	41	1.3 ± 1.4	48	1.4 ± 1.1	–0.1 (–0.7 to 0.4)	0.6
4	34	1.5 ± 1.4	36	1.1 ± 1.2	0.4 (–0.2 to 1.1)	0.2

Note: SD = standard deviation, CI = confidence interval.
*Determined using the Faces Pain Scale — Revised.
†Reflects the number of participants taking the dose of each medication at the corresponding time interval.
‡Unpaired *t* test.

- n=66 (morphine), n=68 (ibuprofen) [- plus PRN Q6h dose 2-4]
- Both morphine and ibuprofen: reduction in pain scores
- No significant differences in change in pain scores between morphine and ibuprofen between groups at any of 4 time points

Results

Table 3: Proportion of participants with adverse effects between groups

Adverse effect*	Patient group, no. (%)		p value†
	Morphine n = 66	Ibuprofen n = 68	
Any	37 (56.1)	21 (30.9)	< 0.01
Nausea	18 (27.3)	4 (5.9)	< 0.01
Vomiting	8 (12.1)	2 (2.9)	0.04
Drowsiness	23 (34.8)	14 (20.6)	0.07
Dizziness	8 (12.1)	6 (8.8)	0.5
Constipation	4 (6.1)	1 (1.5)	0.2
Other‡	8 (12.1)	3 (4.4)	0.1

*Some patients had more than 1 adverse effect.
†Pearson χ^2 test.
‡Includes headache, abdominal pain, irritability and hyperactivity.

- Participants in morphine group had significantly more adverse effects than those in ibuprofen group (specifically nausea, vomiting, and drowsiness)

Limitations

- Q6h administration of PRN morphine: Duration of action shorter
- Broad inclusion criteria may have added substantial between-subject variability, thereby decreasing power
- Study not powered to detect between-group differences in adverse effects, analgesia for breakthrough pain or pain between reduced and non-reduced fractures
- Study underpowered to detect rare adverse effects

Interpretation

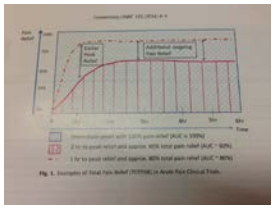
- No significant difference in analgesic efficacy between orally administered morphine and ibuprofen
- However, morphine was associated with significantly greater number of adverse effects
- Results suggest that ibuprofen remains safe and effective for outpatient pain management in children with uncomplicated fractures

Citius, Altius, Fortius…?

- **Moore, R.A., Derry S, Straube S, Ireson-Paine J, Wiffen PJ: Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. Pain, 2014. 155(1): p. 14-21.**
- http://www.ncbi.nlm.nih.gov/pubmed/23969325
- Systematic review of the kinetics of oral ibuprofen (30 studies, 1015 subjects)

Citius, Altius, Fortius…?

- Ibuprofen salts: fast-acting formulations Moore, R.A., et al., Faster, higher, stronger? Evidence for formulation and efficacy for ibuprofen in acute pain. Pain, 2014. 155(1): p. 14-21.
  - produced significantly better analgesia over 6h, fewer re-medications than standard formulations
  - 200-mg fast-acting ibuprofen (NNT 2.1; 95% confidence interval 1.9-2.4) was as effective as 400 mg standard ibuprofen (NNT 2.4; 95% CI 2.2-2.5), with faster onset of analgesia.
- More rapid absorption, faster initial pain reduction, good overall analgesia in more patients at the same dose, and probably longer-lasting analgesia, but with no higher rate of patients reporting adverse events.
- However, earlier onset preferred in other pain condition, such as chronic nociceptive or neuropathic pain? Peloso, P.M., Faster, higher, stronger: to the gold medal podium? Pain, 2014. 155(1): p. 4-5.



THE EFFECT OF TREATMENT EXPECTATION ON DRUG EFFICACY: IMAGING THE ANALGESIC BENEFIT OF THE OPIOID REMIFENTANIL

Sci Transl Med 16 February 2011:
Vol. 3 no. 70 pp. 70ra14
DOI:10.1126/scitranslmed.3001244

- **Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011 Feb 16;3(70):70ra14.**

- **http://www.ncbi.nlm.nih.gov/pubmed/21325618**

Opioid Analgesia = Self-fulfilling Prophecy?

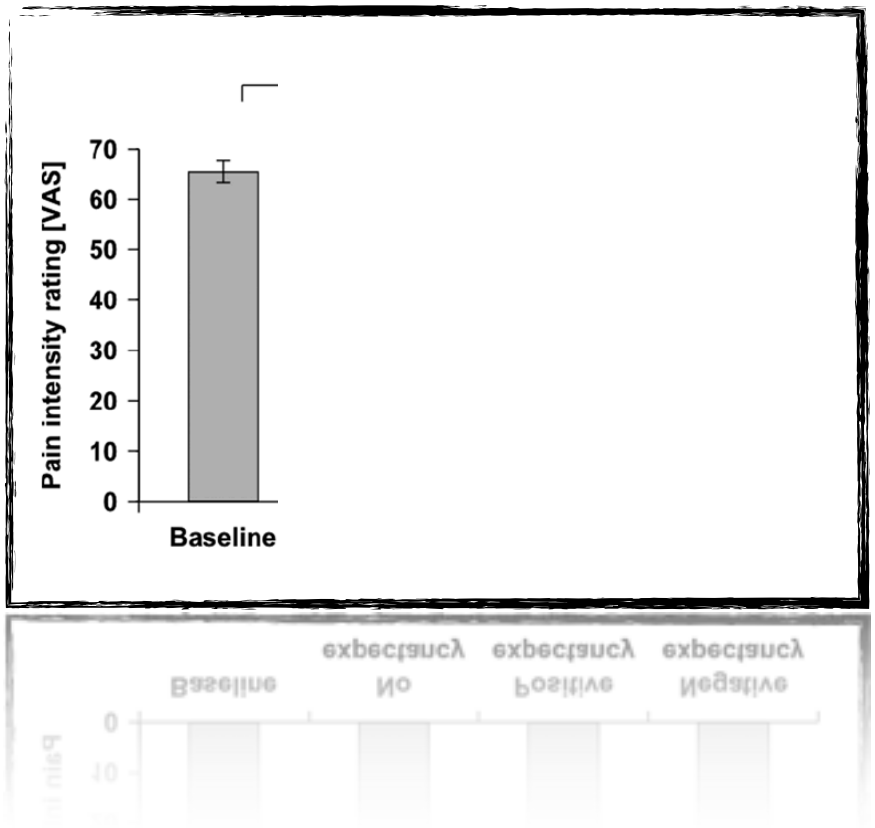
- Expectation of the success of a pain treatment can markedly influence its effectiveness Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011 Feb 16;3(70):70ra14.

- 22 healthy adults were exposed to pain-provoking heat and also given the opioid remifentanil

- Authors informed subjects the drug would (1) have no effect, (2) diminish the sensation of pain, or (3) make the pain worse

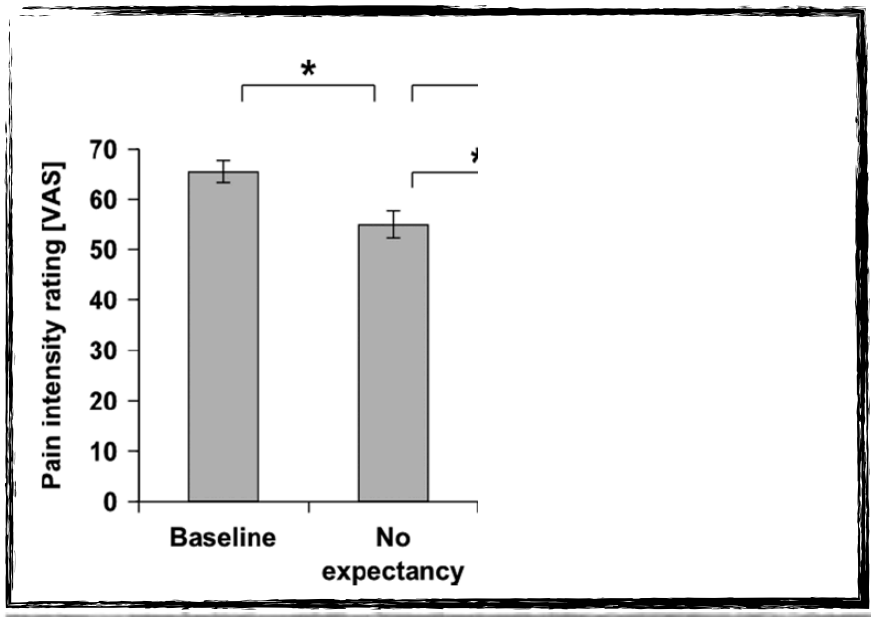
Opioid Analgesia = Self-fulfilling Prophecy?

- Saline (Placebo)



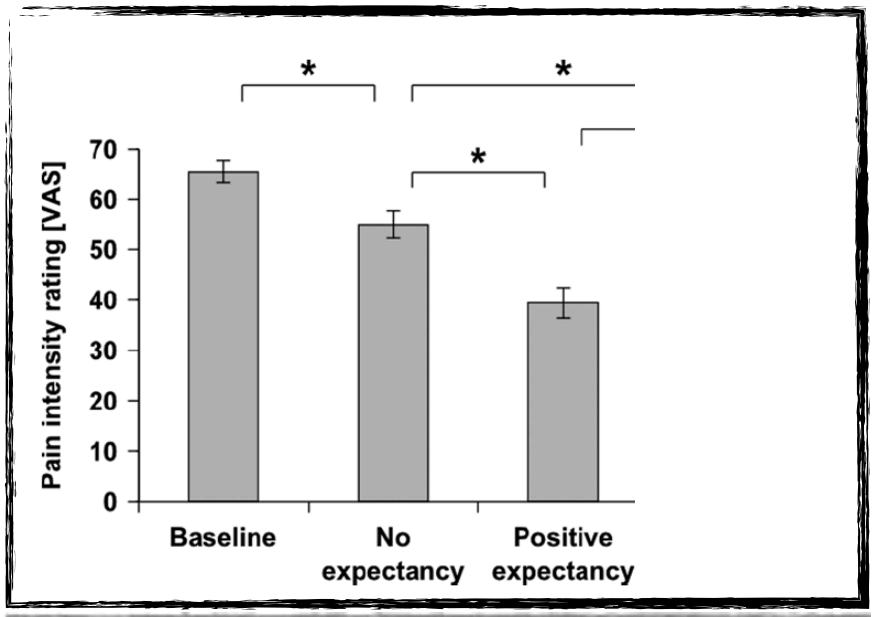
Opioid Analgesia = Self-fulfilling Prophecy?

- Remifentanil infusion started (unknown to subject)



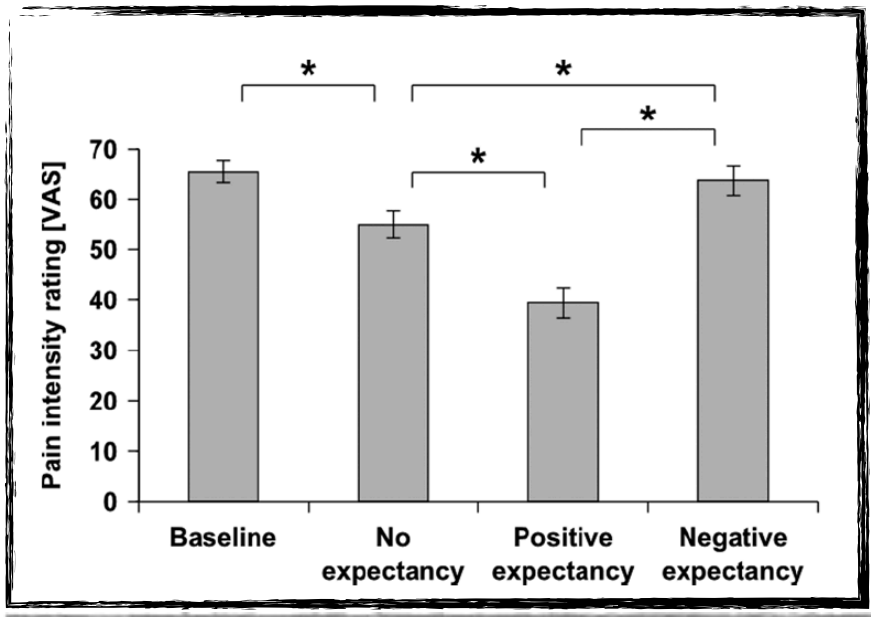
Opioid Analgesia = Self-fulfilling Prophecy?

- Remifentanil (subject being told "started infusion")



Opioid Analgesia = Self-fulfilling Prophecy?

- Subjects were told remifentanil was stopped (but it wasn't...)
- Are these our chronic pain patients?
- Positive treatment expectancy substantially enhanced (doubled) the analgesic benefit of remifentanil. Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011 Feb 16;3(70):70ra14.
- In contrast, negative treatment expectancy abolished remifentanil analgesia



Opioid Analgesia = Self-fulfilling Prophecy?

- Functional magnetic resonance imaging (fMRI) examined brain activity Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011 Feb 16;3(70):70ra14.

- **Thermal pain** itself causes activation of a so-called pain circuit, which encompasses numerous brain regions including somatosensory cortex, cingulate cortex, insula, thalamus, and brainstem

- **Expectation of increased pain** was accompanied by more neural activity in the hippocampus, midcingulate cortex, and medial prefrontal cortex**-- brain areas that mediate mood and anxiety--** than was observed in these regions during expectation of analgesia

Opioid Analgesia = Self-fulfilling Prophecy?

- Conversely, individuals who **expected drug to mitigate their pain** showed increases in anterior cingulate cortex and striatum, signs that **descending mechanisms of pain inhibition were engaged** Bingel U, Wanigasekera V, Wiech K, Ni Mhuircheartaigh R, Lee MC, Ploner M, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. Sci Transl Med. 2011 Feb 16;3(70):70ra14.

- **A drug with a true biological effect may appear to be ineffective to a patient conditioned to expect failure**

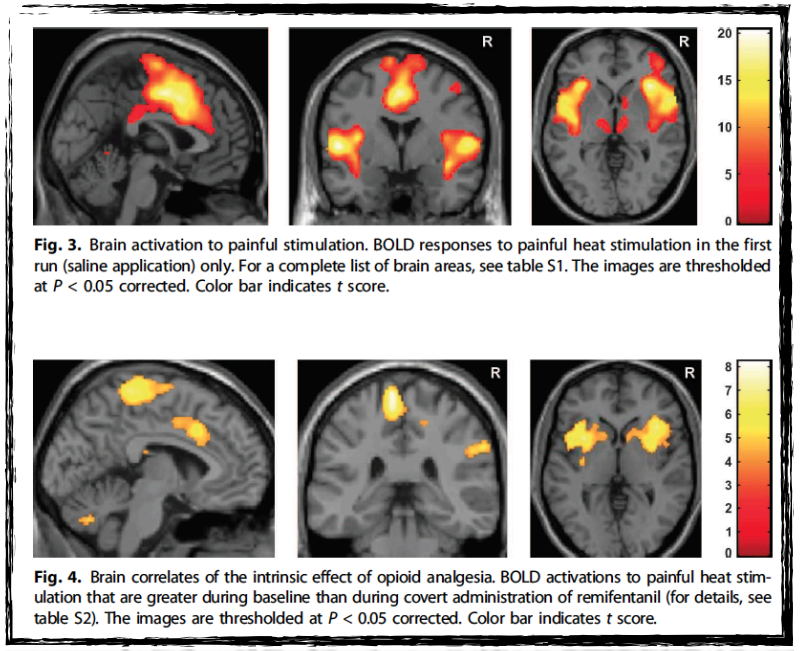


Fig. 3. Brain activation to painful stimulation. BOLD responses to painful heat stimulation in the first run (saline application) only. For a complete list of brain areas, see table S1. The images are thresholded at $P < 0.05$ corrected. Color bar indicates t score.

Fig. 4. Brain correlates of the intrinsic effect of opioid analgesia. BOLD activations to painful heat stimulation that are greater during baseline than during covert administration of remifentanil (for details, see table S2). The images are thresholded at $P < 0.05$ corrected. Color bar indicates t score.

Further Training

Education in Palliative & End-of-life Care [EPEC]: Become an EPEC-Pediatrics Trainer | Phoenix, AZ | May 4-5, 2015

8th Annual Pediatric Pain Master Class | Minneapolis, MN | June 20-26, 2015

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