

Ken Hargreaves - Successful Management of Acute Pain

Today's patients are under the impression that only classic methods of pain control apply to endodontics. We now have "molecular approaches" that offer us different methods of pain control.

Careful reading of the literature gives us the best information but we need to recognize that it has levels of reliability. (Highest to lowest)

1. Systematic Review - the Highest level - a review of randomized control trials – a review of many (dozens or even hundreds) of studies to come up with the best evidence for clinical recommendations
2. Randomized Control Studies – a Single Double Blind Randomized study where both patient and clinician don't know which drug is being given
3. Cohort Studies – fairly large retrospective studies
4. Case Control and Case Series Studies
5. Expert Opinion or Case reports or Lit reviews

Through the internet you can now get the latest and best information on Analgesic Efficacy. This is called available at the "Oxford League of Analgesic Efficiency".

See <http://www.jr2.ox.ac.uk/bandolier/booth/painpag/Acutrev/Analgesics/lftab.html> for the latest table.

The NNT value in the table represents "Number Needed to Treat" and is a way statisticians compare efficacy of drugs in studies. The closer the number is to "1" the more effective the drug is an analgesic. E.g. / Ibuprofen 800 mg has NNT of 1.6 and is the best drug to treat inflammatory related pain. For example - The table shows that NSAIDs are much better for treating inflammation related pain than narcotics such as Morphine. For endo related pain – where Prostaglandins play an important role – Ibuprofen is much better. Hargreaves recommends using the internet to make EDUCATED choices for your patients by using the latest information. Palm Pilot users can use Epocrates <http://www2.epocrates.com/> to regularly update their information (Epocrates Rx is a free download)

Post Endodontic Pain

Odontalgia is the most common form of Orofacial pain (12% of population) Lipton et al JASA 124:115:1993

Incidence of Post endo Pain

- Seltzer & Bender 1961 - 40 % of 698 patients had at least some post of pain
- Georgopoulou et al IEJ 19:309, 1996 – 43% of 245 pts had pain after instrumentation -> 21% slight 22% moderate

Hargreaves emphasizes: that means ~ 60% of patients have minimal or NO pain after treatment. For these you may wish to Rx 200 mg Ibuprofen or Acetaminophen 650 mg q 4-6h. Most importantly the low dosages have FEW SIDE EFFECTS.

But 1 in 4 or 1 in 5 patients will experience moderate to severe pain after treatment.

Can we predict Patients More Likely to Experience Pain after a procedure?

(From Hutter and Hargreaves – Pathways of the Pulp- 12,000 patients examined in literature review)

Most significant Predictors (in decreasing order)

1. Preoperative hyperalgesia (pain or + to percussion) 100% of studies reported this
2. Sex - 38% of studies reported this
3. 1 Step NSRCT showed less pain - 33% of studies reported this
4. Apical Periodontitis 31% of studies reported this
5. Necrotic Pulp 25% of studies reported this

SO – the best predictor is the presence of preoperative pain or mechanical allodynia (sensitivity to percussion or chewing).

Torabinejad et al JOE 2002 (Only a Placebo administered post op – double blind) found that:

1. Preop pain is a good predictor of post op pain.
2. On average pain is maximal in first 24-48 hrs – therefore we don't need to give pain meds for more than a few days post op – with proper clean and shape of the canal.

Polycarpou et al IEJ 39: 160:200

175 Post endo patients surveyed 12-59 mos. 85 % NSRCT 15 % SRCT

Overall incidence of post endo pain 12% in patients whose treatment was judged successful

They then analyzed the factors predicting persistent post endo pain in these patients:

1. Preop persistent pain for 3 months or more prior to treatment
2. Previous chronic pain
3. Interappointment pain
4. preop pain from tooth
5. preop tenderness to percussion
6. history of previous painful treatment in Orofacial region

Central Sensitization” disorder and Pain

In the pain research community Pain is recognized of as a disease in its own right. Patients with chronic pain have a brain dysfunction that predisposes them to chronic pain conditions. This “Central Sensitization” disorder predisposes them to an exaggerated pain response. They may be more responsive to noxious input due to this disorder. Experimental data shows that patients with TMD, Fibromyalgia or Whiplash injury all responded more to injection of hypertonic saline into muscle. Peak pain, Pain duration and total pain are elevated.

This means that patients who have chronic pain – pose a HIGHER risk to suffer MORE pain for a LONGER period post operatively when compared to other “normal” patients.

The best way to use this to recognize the chronic pain patient and to talk to them about the procedure – emphasizing that they are at a greater risk of pain NOT because of anything that you as a clinician will do – BUT as a result of their condition. This may mean that if you have an apparently successful case that has been healing and the patient has persistent pain – it may not require retreatment – it may be due to the fact that the patient is a chronic pain patient who is at risk for perceiving greater pain. This is firmly founded on biology.

The 3D Strategy for Treating Endo pain

1. Diagnosis
2. Definitive Dental Treatment
3. Drugs

1. **Diagnosis** – In order to successfully treat pain you need to establish its etiology (Hargreaves uses the Cardiac referred pain as an example of pain of non-dental origin)

He then goes through the typical Clinical assessment during Diagnosis:

- Review medical and dental history
- Pain – intensity, duration, location etc.
- Extraoral Exam – facial asymmetry, lymphadenopathy etc.
- Intraoral exam – pulp tests, palpation, percussion, fractures, trismus, sinus tracts, caries, faulty restorations etc. **REPRODUCING CHIEF COMPLAINT IS CRITICAL**
- Evaluate and correlate radiography

Common Features of Odontogenic Pain

- A. Etiologic factors present – i.e. / a reason for the problem -caries, leaky restoration, trauma, recent restoration etc.
- B. Chief complaint can be reproduced in the chair
- C. Pain reduced by Local Anesthesia
- D. Unilateral Pain
- E. Pain qualities: dull, aching, throbbing. These are typical “unmyelinated C fiber” since they mediate the perceptions of dull pain. Bright, sharp, stabbing, pricking pain (typical of dentinal hypersensitivity as an example) are mediated by “myelinated A fibers” – a totally differently perceived pain. The words used by patients can help you with this. Trigeminal Neuralgia is another sharp electric pain coming from myelinated fibers that is different in quality than the inflammatory related dull pain of pulpal origin.
- F. Pain is localized
- G. Thermal allodynia (Sensitivity to temperature)
- H. Mechanical allodynia (Sensitivity to percussion/chewing)

NON ODONTOGENIC PAIN – many forms

Musculoskeletal – Myofascial & TMD

Neuropathic – Trigeminal Neuralgia, (Tic Doloureux) Atypical Odontalgia (Phantom Pain)

Neurovascular – Migraine (females) Cluster Headache (Males)

Inflammatory Conditions – Sinusitis

Systemic Disorders- Cardiac Pain, Herpes virus infections, Tumors

Psychogenic – Somatoform Pain

Hargreaves shows case of Osteoblastoma in 67 year old male with pain of several years duration (in the area tooth #7). Keys to diagnosis were present of Periradicular lesion that could be “moved” when angulating films AND presence of + pulp test. Both were inconsistent with an endodontic etiology. Endo treatment was not effective. Biopsy showed Osteoblastoma

2. Definitive Dental Treatment

A. Pulpotomy & Pulpectomy – Differences in Effect

The pulpotomy procedure is actually an “axotomy”. The neurons in the pulp chamber are removed. All the receptors that detect inflammatory mediators are now gone, so literally, the patient does not have a functional nerve terminus.

The pulpectomy procedure has an analgesic effect by a completely different mechanism. In the case of a non-vital tooth, the pain is coming from neurons that innervate the PDL.

These neurons are stimulated by 2 things:

1. Bacteria or antigens that activate immune cells releasing bradykinins, PG and IL-1 that stimulate pain fibers.
2. It has recently been found that pain neurons have their own receptors that can directly detect bacteria by themselves.

Cleaning and shaping procedures remove bacteria and antigen sources that would otherwise stimulate the PDL. The mechanism for pain release between pulpotomy and pulpectomy are fundamentally different. The patient doesn't care which one you do – BOTH are effective in the appropriate situation.

Hasselgren & Reit JOE 1989 – Evaluated effectiveness of Pulpotomy on Pain. They found pulpotomy was very effective initially and over 28 days. The intracanal medicament used (Cresatin, CMCP, Eugenol ZOE, Saline or dry cotton) was irrelevant and didn't effect the results.

Hargreaves and Baumgartner- (Principles of Endo) 80% reduction in pain with pulpotomy. So, this is a good treatment for emergencies. Pulpectomy resulted in 75% reduction in selected cases. The whole point was to show that operative procedures– as an emergency procedure - COMBINED with analgesics are MUCH better in reducing patient's pain than simply medicating the patient with analgesics.

EFFECTS OF OCCLUSAL ADJUSTMENT on POST OP PAIN

Rosenberg et al JOE 1998 studied the effect of occlusal adjustment on Post op Pain. They did both “real” and “mock” (fake) post op occlusal adjustment and compared PO pain levels. With “Real” adjustments – 80% had no post op pain. In patients with “Mock” adjustment or “No” adjustment – most experienced moderate to severe PO pain. The best results were obtained in patients with preoperative pain and who were + to percussion tests preoperatively.

Important – **THE SAME PATIENTS WHO WE KNOW ARE THE MOST LIKELY TO EXPERIENCE POST OP PAIN (the ones with preop pain and/or preop percussion sensitivity) ARE ALSO THE MOST LIKELY TO BENEFIT FROM POST OP OCCLUSAL ADJUSTMENT TO BECOME PAIN FREE.**

3. DRUGS

NSAIDS & Cardiovascular Risk

Mechanisms of Action of NSAID-like Drugs (Naproxyn, Aspirin, and Ibuprofen) work by inhibiting cyclooxygenase

- Peripheral Hypothesis – Inhibition of Cyclooxygenase (at site)
- Central Hypothesis – Inhibition of Cyclooxygenase (in brain)

There are two forms of Cyclooxygenase:

Cox 1

Constitutive

Present in Stomach Kidneys Platelets

Many traditional NSAIDS preferentially

Inhibit Cox1

Cox 2

Inducible

Synthesized in inflamed tissue (IL-1, TNF-alpha, LPS)

Cox2 inhibitors should have fewer GI and renal side effects

Biopsies from dental pulp show high levels of expression of Cox2 (Nakanishi et al) so we would expect that Cox2 inhibitors would work well. Vioxx was found to be an effective pain reliever for pulpal pain BUT NO BETTER THAN IBUPROFEN. Vioxx was withdrawn from market in Sept. 2004 due to cardiovascular risks. Vioxx (Rofecoxib)

inhibitors have been shown to increase the levels of enzymes that cause prothrombic events that are associated with heart attack and stroke. One study showed that a one day administration of Vioxx (for third molar extraction) caused a 16x (!!) increased level of Tissue Plasminogen Activator (TPA) of oral tissue as measured via punch biopsy. TPA levels are associated with cardiac and stroke risk. It doesn't take 6 months or 6 weeks – you can see it after immediate administration. The FDA now says that long term Vioxx use is PROTHROMBIC.

Is this a “Class” effect or “drug” effect? I.e. / is this drug specific or does it apply to all NSAIDS? This is an important question that we must answer – considering how we depend on these drugs for pain relief.

The British Medical Journal “the Lancet” concluded that Rofecoxib (Vioxx):

- o Does have adverse cardiovascular effects
- o Effects are dose related
- o Manifest themselves in early months of use
- o The effect could have been predicted 3 years before

Hargreaves went on to show many studies that showed Vioxx increased risk of heart attack and stroke very early during use.

Celebrex vs. Vioxx

Some studies show it is less risky but others show it also has some risk, albeit less.

Aspirin and Ibuprofen re Cardiac Protection (Anti-platelet Effects)

Many of our patients are taking small dosages of aspirin for its cardio-protective effects. Studies have shown that if they take the Aspirin first, then Ibuprofen – they have all the benefits of the aspirin. BUT if they take the Ibuprofen first and then the Aspirin second, the Ibuprofen BLOCKS the cardio-protective effects of aspirin. SO, in your patients taking “baby Aspirin” – you DO NOT want to medicate them with Ibuprofen. You should use acetaminophen instead. Many patients also DO NOT mention taking this low dose aspirin on their medical history and Hargreaves now makes a point of SPECIFICALLY asking his patients about this, since it will influence his decision of meds.

In other studies patients having had a previous heart attack and taking Ibu + ASA had an increased risk vs. those taking ASA alone. So, IF a patient with a history of heart attack is under your care and they have a second heart attack after you prescribed IBU (and they were already on ASA) – then you may be at legal risk unless you can defend your choice of medications. Acetaminophen or acetaminophen with an opiate is probably a better choice in that situation.

New drug **Combunox** – Ibuprofen 400 mg + Oxycodone 5 mg

Until recently there was no published research to indicate that this medication works. Hargreaves suggests you use PubMed on the internet www.pubmed.org to search for info when any new drug is released. For example : In an older study that he found comparing Ibu with Ibu + 2.5 mg Oxycodone, Ibu + 5 mg Oxycodone & Ibu + 10 mg Oxycodone – there was NO DIFFERENCE from IBU w/o Oxycodone . BUT side effects of 10 mg Oxycodone ARE significant and there seems to be no benefit in adding this medication to Ibu. SO there seems to be minimal benefit in RX of this drug, although it may be heavily publicized.

Pharmacogenetics

In the near future, we will be tailoring drug regimens not only to symptoms but to the individual's genetic predisposition.

E.g. #1 Red Heads

Anecdotal clinical reports suggested that red headed patients are more difficult to anesthetize. (the mutated MC1R (melanocortin) receptor gene causes the red hair). A recent study of General Anesthesia showed that red headed patients required significantly more anesthesia. Another paper (Kessler - in preparation) using Lidocaine/pulp tests showed similar results. For this patient you may wish to change anesthetics or use more aggressive pain medication.

E.g. #2 Influence of Patient Sex

Mu opiate receptor - activated by Oxycodone, codeine, morphine

Delta Opiate Receptor – no drugs currently available to activate this

Kappa Opiate Receptor - activated by Pentazocine (Talwin)

Early studies (1960s) of Pentazocine showed it to not be much better than placebo. However, once the genes were cloned – in females the Kappa Opiate receptors were found to be higher. The original 60s studies were done on MEN. When the studies were repeated with both sexes using Pentazocine, females got up to 5x the analgesia

(depending on the day of their menstrual cycle) when compared to men. So the effectiveness of medications can also be sex/DNA specific.

Hargreaves is now doing genotyping his patients to determine which drugs may be effective. The cost of Genotyping patients is becoming affordable and likely will be important in the future.

What does NOT work for Post Op pain?

1. Antibiotics

Walton and Chiappinelli (JOE '97)

80 patients – Dx of Necrosis with chronic apical periodontitis – all patients had C&S (+/- obturation)

Patients given:

- o PenVk – 69% reported PO pain
- o Placebo – 79% reported PO pain
- o No Tx – 70% reported PO pain

THEREFORE – AB has NO measurable EFFECT.

Results: Ab had no effect

Fouad Rivera and Walton (OOO)

30 patients - Dx of Necrosis with AAA - all patients had C&S with CaOH medicament

Patients given 600 mg Ibu q6h x 1 d then prn and either:

- o Prophylactic Pen Vk (1 g at appt 500 mg 6h)
- o Placebo

Result: Pain measured at 6, 12, 24, 48 and 72 hrs po. NO DIFFERENCES among groups for pain OR swelling

All groups had reduction in symptoms - THEREFORE AB has NO measurable EFFECT.

Henry, Reader and Beck JOE

41 patients with pulpal necrosis, AP, spontaneous pain (~ 70% moderate)

After NSRCT, randomly given:

- o Pen 500 mg q6h x 7d
- o Placebo
- o All given Ibu 400 or T3

Results: Pain – No difference, Swelling – No difference, Percussion pain – No difference, # of analgesic tablets taken – No difference

Effect on incidence of flare ups

Pickenpaugh, Reader et al

70 patients with asymptomatic pulpal necrosis & AP. Tx: NSRCT- randomly given:

- o Amoxicillin 3g 1 hr before appt
- o Placebo 3g 1 hr before appt
- o All given Ibu 400 or T3

Results: ~10% developed moderate- severe pain@48-72 hrs

- o Amox -> 4 flare ups
- o Placebo -> 3 flare ups

Prophylactic antibiotics had **NO EFFECT** on incidence of flare ups

We should use them **ONLY to control the systemic spread of infection**

Flexible Pain Control		
	<u>ASA- Like Drugs Indicated</u> <u>(Patients who Can take ASA-like</u> <u>Drugs)</u>	<u>ASA- Like Drugs CONTRA Indicated</u> <u>(Patients who Can NOT take ASA-like</u> <u>Drugs)</u>
<u>Mild Pain</u>	<u>Ibu 200 mg</u>	<u>APAP 600 – 1000 mg</u>
<u>Moderate Pain</u>	<u>NSAID – Minimally</u> <u>Effective Dose</u>	<u>APAP 600 – 1000 mg</u> <u>With equivalent of Codeine 60 mg</u>
	<u>NSAID Plus APAP</u> <u>Or NSAID Plus APAP/Cod.</u>	
<u>Severe Pain</u>	<u>NSAID – Max Dose and</u> <u>APAP/Oxycodone 10 mg</u> <u>Combination</u>	<u>Acetaminophen 1000 mg with equivalent</u> <u>of Oxycodone 10 mg</u>

We now have recognized that we can add Acetaminophen to Ibuprofen and get substantially greater analgesia than either drug alone AND avoids the side effects of Opiates.

Studies supporting this:

- Cooper et al (Compendium) Ibu 200 mg + APAP 650 (combined) was better than either alone.
 - Brevik et al (OOO) 3rd molar pain model using NSAID 100 mg Diclofenac (equivalent to 800 mg Ibu). The study showed greater analgesia when combined with APAP. Adding Codeine to the mix didn't improve pain management appreciably but DID risk greater side effects. SO the APAP/NSAID combination worked well.
- Mehnick (2004 IEJ) Endo pain patients tested. Placebo, Ibu 600 mg and Ibu 600 Mg and APAP 1 gm. **The combination of Ibu and APAP resulted in significantly greater pain reduction.**

Chronic Pain and Central Sensitization

Chronic pain can be considered a disease in its own right. One of the major triggers for this central form of pain called "Central Sensitization" is a barrage of impulses from the periphery. The classic example is phantom limb pain after amputation. It has been virtually cured by use of LA at the amputation site AND epidural anesthesia that effectively stops the barrage of afferent impulses, blocks the development of Central Sensitization and prevents the occurrence of chronic pain.

We now ask the question: **Can we use a similar mechanism with our patients?** Will long acting anesthetics (like Bupivacaine) have some longer term effect – even days after the injection? Hargreaves says YES.

Studies:

Gordon et al (Pain 70:209) **Pre-Emptive Analgesia**

– Patients under General Anes. Having mandibular 3rd molar extractions. One group received mandibular injection with placebo, the other receives Bupivacaine 1:200 K epi. Measured Blood levels of Beta endorphins were used as a pain gauge in these unconscious patients. Placebo patients showed much higher levels than the Bupivacaine patients. 48 hr post op - the placebo patients are taking 3 x more analgesics than the Bupivacaine patients and are STILL reporting more 50% more pain. The long acting anesthetic gives benefit to patients even days later by blocking these impulses to the brain. Further studies as to the TIMING of the injection showed that this effect was best accomplished by giving the injection at the END of the appointment. Hargreaves now gives patients Marcaine at the END of the procedure – it is now the first drug in POST OP pain control. This appears to be effective for both block and infiltration anesthesia.

Jebeles et al (Int J Pedo) Tonsillectomy study in children

Double blind study of 22 patients undergoing tonsillectomy. One group got Saline infiltration, the other .25% Marcaine 1:200K epi .

Results: One injection of Bupivacaine at the time of surgery made them feel more comfortable even a week after the procedure. A test using water drinking resulted in dramatically reduced times to drink a measured amount of water – less overall pain.