Sports Pharmacology: Treating Pain and Inflammation

Case studies and solutions

Ankle Sprain

- You are treating a 21 y/o college athlete in the training room that you have just diagnosed with a grade 2 ankle sprain. She is a soccer player, and is actively going to work with your trainer to get back as soon as possible.
- You supplement her therapy with a seven day course of an NSAID to decrease inflammation.

Is inflammation a bad thing…or is it good thing?

Will adding an NSAID be helpful…or harmful?

Tennis Elbow

- You have been treating a patient with a 6 month history of tennis elbow on her dominant arm with a counterforce brace and stretching and strengthening exercises. She did not improve with an initial ten day course of an NSAID; she had two days of relief with a steroid injection

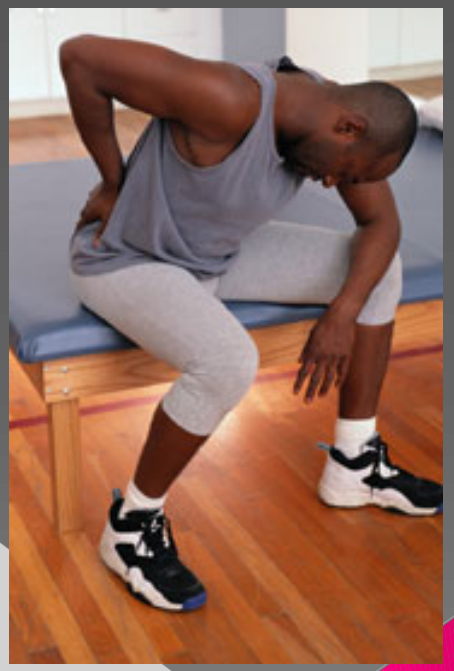
Is another course of an NSAID warranted…how about another corticosteroid injection?

Are there any alternative therapies that might help, or should you refer her to surgery?

Objectives

- Review Current Concepts on Sports-Induced Pain and Inflammation.
- Review Current Evidence and Guidance on using NSAIDs and Corticosteroids in Sports Medicine.
- Discuss New and Emerging Strategies for Sports Inflammation.

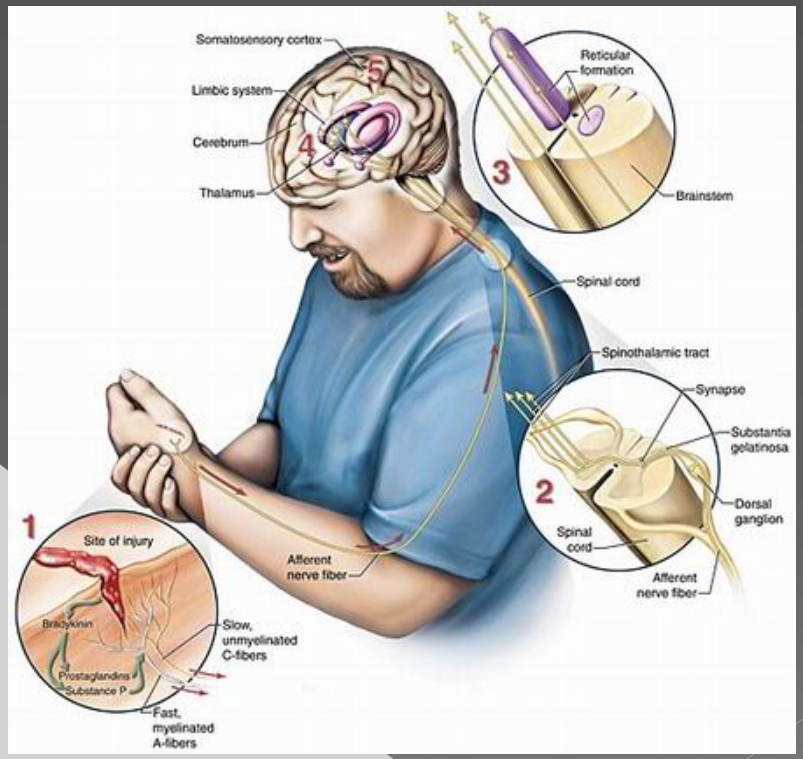
Current Concepts: Sports-Induced Pain and Inflammation



What Causes the Pain in Acute Injury?

Nociceptive Pain:

1. Peripheral Stimulation of A-Delta and C fibers;
2. In the dorsal root ganglion, synapse with second order neurons of the spinothalamic tract; pain is first modulated at this site;
3. Synapse occurs in the thalamus;
4. The brain's sensory cortex is then triggered for pain, emotion (limbic system), and a stress response (motor cortex).



Without the brain… there is no perception of Pain!

What Causes the Pain in Overuse Injuries?

- **Currently unknown**
- **Microdialysis, Ultrasound, & Doppler**
- Microdialysis 4 dz Achilles; 4 normal:
  - No difference in prostaglandin E2
  - Significant increase in glutamate & substance P
  - Similar results in lateral epicondylitis/patellar tendon

Dr. Hakan Alfredson

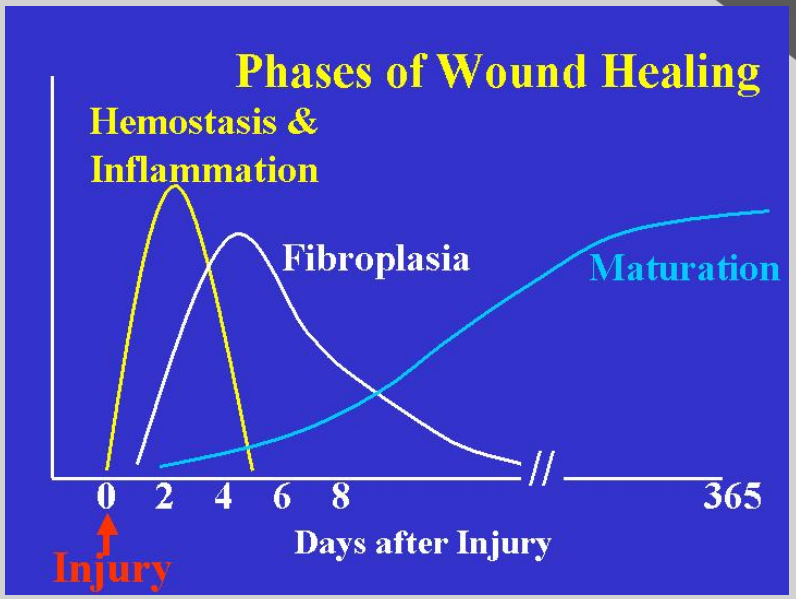
Knee Surg Sports Traumatol Arthrosc. 1999;7(6):378-81 &
Br J Sports Med. 2004 Feb;38(1)

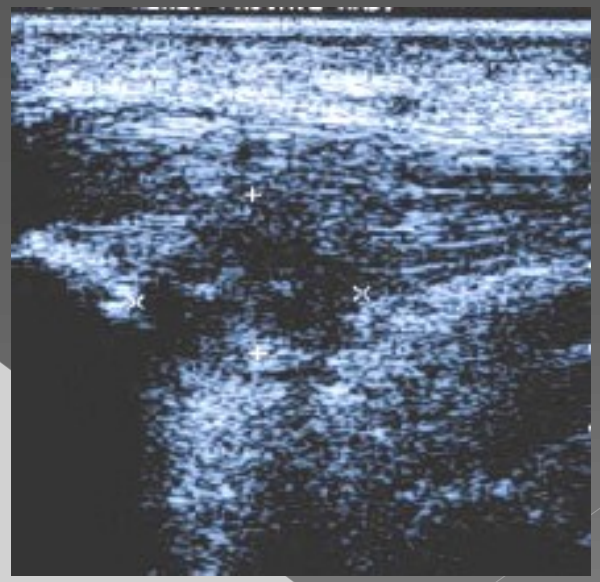
What Causes the Pain in Overuse Injuries?

- Ultrasound and color Doppler were used to evaluate patients with tennis elbow.
- In 21/22 elbows with chronic pain, but only 2/22 pain-free elbows, vascularity was demonstrated in the extensor origin.
- The patients became pain-free after a local anesthetic was injected in the area of the neo-vessels, and the patients became pain free.
- Vasculo-neural growth appears to be related to the origin of the pain in tendinopathy.

Zeisig E, Ohlberg L, Alfredson H: Extensor origin vascularity related to pain in patients with tennis elbow. Knee Surg Sports Traumatol Arthroc 2006;14(7):659-63.

Wound Healing Model





Acute Healing Model

Chronic Degeneration or Tendinopathy

Current Evidence on using NSAIDs, and Injectable Corticosteroids

NSAIDs in Sports Medicine

- One of the most widely prescribed medications in the US, with over 100 million prescriptions per year
- Prostaglandin-related and nonprostaglandin effects
- Over 50 reported studies at role of NSAIDs in Sports Medicine, with only 11 being RCT quality:
  - 8 with modest benefit vs. placebo
  - 3 with no difference with placebo
  - 0 quality trials evaluating overuse injuries

Weiler JM: Medical Modifiers of Sports Injury: The Use of NSAIDs in Sports Soft-Tissue Injury.Clinics in Sports Medicine 1992.

Anti-inflammatory Therapy in Sports Injury. The Role of Nonsteroidal Drugs and Corticosteroid Injection

Leadbetter WB: Clinics in Sports Medicine 1995 Apr;14(2):353-410.

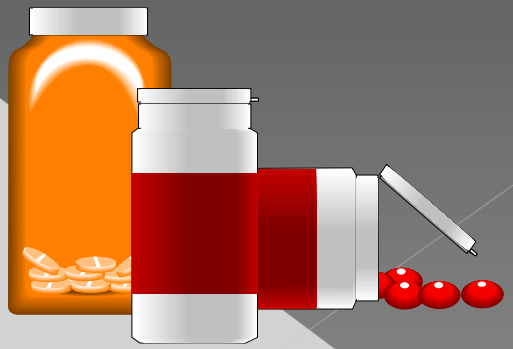
To quote the great Oriole baseball pitcher, Jim Palmer:

"Cortisone is a Miracle Drug…

…for a week"

NSAIDs in Sports Medicine

- tion: remains to be determined if NSAIDS and corticosteroids change the natural history of overuse injuries.
- : undetermined role in management of overuse injuries.



Almekinders LC: Etiology, diagnosis, and treatment of tendonitis: an analysis of the literature. Medicine and Science in Sports and Exercise, 1998.

What do we mean by the term "Inflammation"? A contemporary Basic Science Update for Sports Medicine

"As surprising as it may seem, there has not been an abundance of high quality, adequately powered randomized studies to provide the clinician with strong evidence about the role of (NSAIDs and corticosteroids) in common conditions."

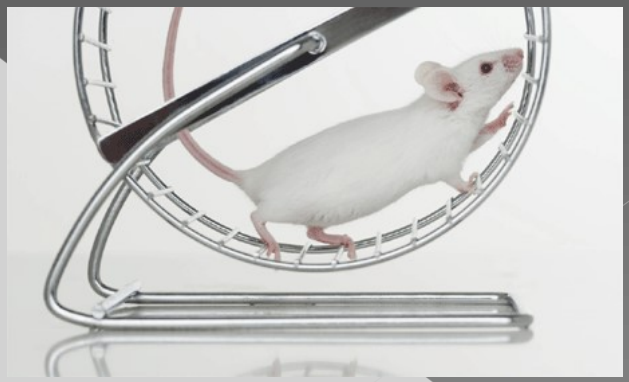
Scott A, Khan KM, Cook JL, Durino v: British Journal of Sports Medicine 2004;38:372-380.

Nonsteroidal Anti-Inflammatory Drugs and Acetaminophen in the Treatment of Acute Muscle Injury

Rahusen FT, Weinhold PS, Almekinders LC. American Journal of Sports Medicine 2004 Dec;32(8):1856-9.

Acute Muscle Injury

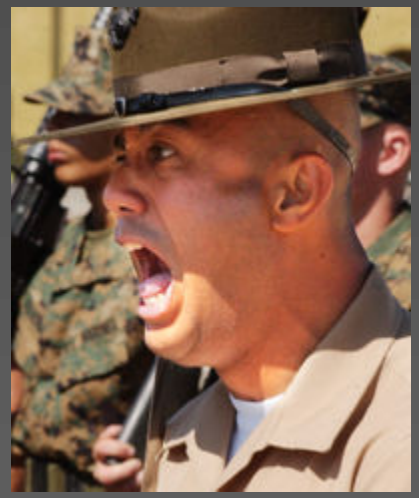
- Controlled animal study: nonpenetrating injury of anterior tibialis was created in mice. Four treatment groups:
  - Placebo
  - Rofecoxib at the time of injury
  - Rofecoxib 24 hrs before injury
  - Acetaminophen at the time of injury
- At 2,5,7 days after injury, muscle and contralateral muscle were evaluated for wet weight, gait, and histology.



Acute Muscle Injury

- Results:
  - Group 1 (PL) had more gait disturbance, and wet weight change than the other groups at day 2 ($P<0.05$)
  - Histology, wet weights and gait were comparable at all other times.
- Conclusion:
  - Similar effects with rofecoxib and acetaminophen; lack of wet weight difference suggests lack of anti-inflammatory effect.
  - Routine use of NSAIDs need to be evaluated.

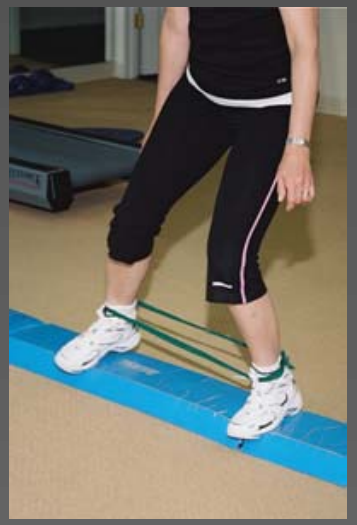
A Randomized Controlled Trial of Piroxicam in the Management of Acute Ankle Sprain in Australian Regular Army Recruits. The Kapooka Ankle Sprain Study.



Slatyer MA, Hensley MJ, Lopert R. American Journal of Sports Medicine 1997 Jul-Aug;25(4):544-53.

Kapooka Ankle Sprain Trial

- Methods: Recruits in Australia with an ankle sprain (Grade 1 and 2) were randomized to usual care with placebo (180) or piroxicam (184) 40 mg for two days, then 20 mg for 5 days.
  - Could use tylenol for pain
  - All subjects had physical therapy
- VAS, ROM, Function, Return-to-Duty, Utilization of rescue Tylenol were assessed at days 3, 7, and 14, as well as at 3 and 6 months.



Kapooka Ankle Sprain Trial

- Results: Piroxicam vs. Placebo
  - Lost training days: 2.74 vs. 8.75 P<.001
  - Improved VAS, function and ankle endurance at all time points.
  - Nausea 6.8% vs. 0.3% P<.005
- However:
  - Increased ankle instability by anterior drawer testing at days 3, 7, and 14.
  - Lesser swelling found at 7 and 14 days in the placebo group.
  - Increased ROM in the placebo group.

Overall, balance is in favor of utilization of NSAIDs.

The Efficacy of Paracetamol in the Treatment of Ankle Sprains in Comparison with Dicolfenac Sodium

Kayli C, Agus H, Surer L, Turgut A:
Saudi Medical Journal 2007
Dec;28(12):1836-9.

Ankle Sprains

- Prospective double blind study of 100 patients with first or second degree ankle sprain.
- Randomized to diclofenac 150 mg/day or paracetamol 1500 mg/day for five days.
- VAS pain scales were comparable at day of onset as well as week six ($p>0.05$); however, accelerated decrease in pain with paracetamol at visits at 2 days and 10 days ($p<0.05$).
- Similar improvement in ankle ROM as well as GI adverse events.
- Conclusion: Both effective in short term treatment of ankle sprain.

What about Evidenced Base Abstracts?

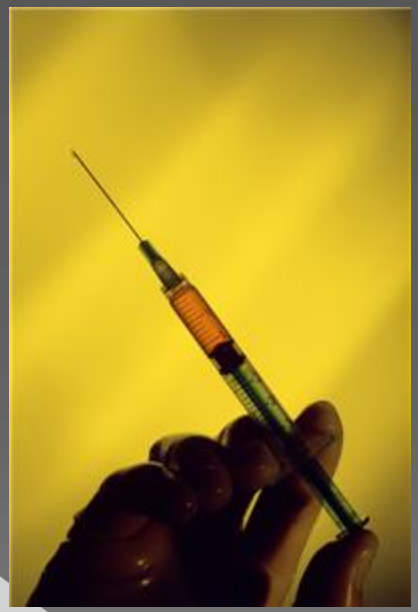
- Ankle Sprain
  - Controlled trials of nonsteroidal anti-inflammatory drugs (NSAIDs; e.g., piroxicam [Feldene], celecoxib [Celebrex], naproxen [Naprosyn]) in patients with ankle sprain showed that, compared with placebo, NSAIDs were associated with improved pain control and function, decreased swelling, and more rapid return to activity. (Evidence Rating B)

Ivins D: Acute Ankle Sprain: An Update American Family Physician Physician 2006;74:1714-20, 1723-4, 1725-6.

What about Evidenced Base Abstracts?

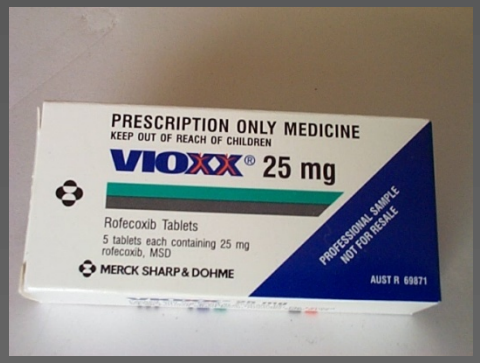
- Tennis Elbow:
  - NSAIDs and Corticosteroid Injections:
    - There is some support for the use of topical NSAIDs to relieve lateral elbow pain at least in the short term. There remains insufficient evidence to recommend or discourage the use of oral NSAID, although it appears injection may be more effective than oral NSAID in the short term. A direct comparison between topical and oral NSAID has not been made and so no conclusions can be drawn regarding the best method of administration.
  - Surgery:
    - At this time there are no published controlled trials of surgery for lateral elbow pain. Without a control group, it is not possible to draw any conclusions about the value

Current Guidance on using NSAIDs, and Injectable Corticosteroids



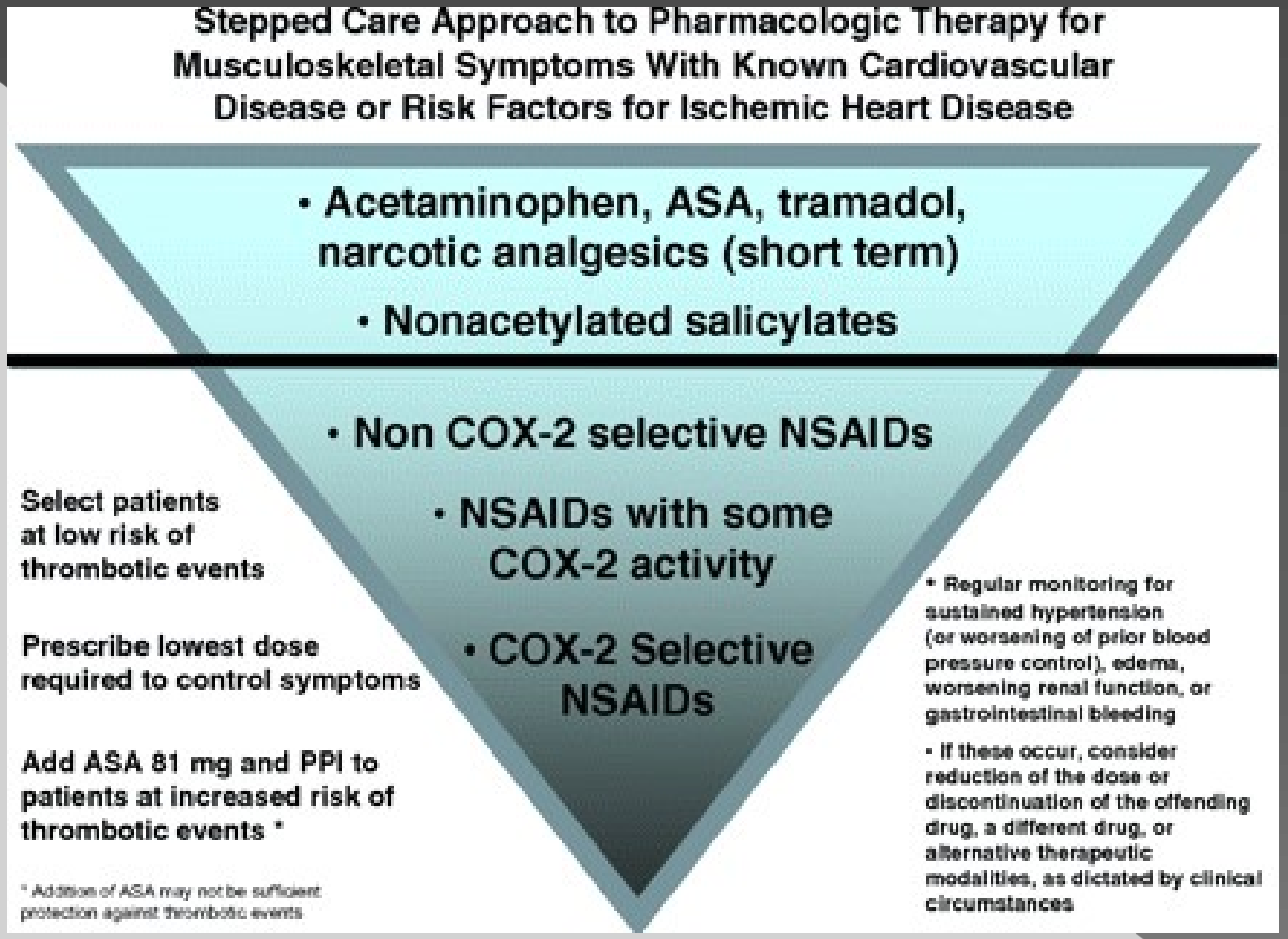
New FDA Recommendations

- April 6, 2005
  - The three COX2 agents are associated with an increased risk of serious adverse CV events c/w placebo.
  - Data from large clinical trials do not demonstrate a significant increased CV risk of the COX2 agents over the non-selective NSAIDs.
  - The COX2 agents reduce the incidence of GI ulcers visualized at endoscopy.
  - Box warning label for all prescription NSAIDs including increased risk of CV events.



Use of Nonsteroidal Anti-inflammatory Drugs An Update for Clinicians: A Scientific Statement From the American Heart Association

Elliott M. Antman, MD; Joel S. Bennett, MD; Alan Daugherty, et al: Circulation. 2007;115:1634-1642.



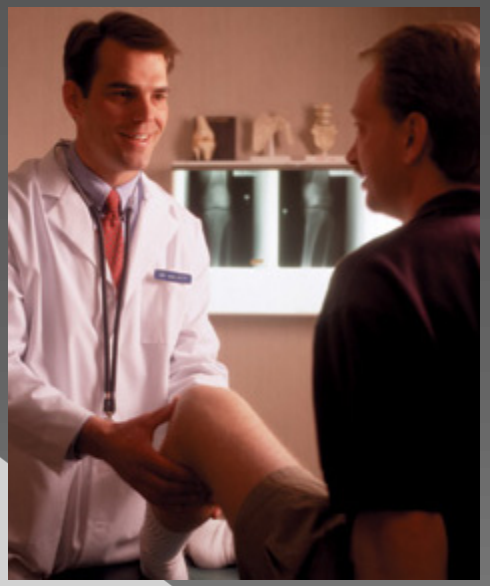
Utilize NSAIDs at the lowest dose and for as short as possible.

Practical Management: Nonsteroidal Anti-inflammatory Drug Use in Athletic Injuries

Mehallo CJ, Drezner JA, Bytomski JR: Clinical Journal of sports Medicine 2006;16:170-174.

Practical Management: Nonsteroidal Anti-inflammatory Drug Use in Athletic Injuries

- NSAIDs should be avoided in fractures and stress fractures at risk for non-union.
- A short course of NSAIDs in ligament injury (3-7 days) is likely beneficial.
- A short course of NSAIDs in muscle injury (3-7 days) is likely beneficial.
- The use of NSAIDs in chronic tendon injury is useful for analgesia, but should not be expected to accelerate healing.



Pain Medications in the Locker Room: To Dispense or Not

Smith BJ, Collina SJ: Current Sports Medicine Reports 2007;6:367-370.

Pain Medications in the Locker Room: To Dispense or Not

- High quality pain control and sports injury studies are lacking.
- If medications are utilized, they should be administered at the lowest dose for as short a duration as possible.

New and Emerging Strategies for Sports Inflammation and Pain

Topical Nitric Oxide

- Inhibition of nitric oxide has been shown to reduce collagen content, contraction, and synthesis by wound fibroblasts in vitro.
- In animal studies, nitric oxide synthase inhibition resulted in a reduction in the cross sectional area and load to failure of healing tendons.
- Topical glyceryl trinitrate has been used for over 100 years as a therapy for angina pectoris; a pro-drug of nitrous oxide.

Topical Nitric Oxide Application of Chronic Extensor Tendinosis at the Elbow

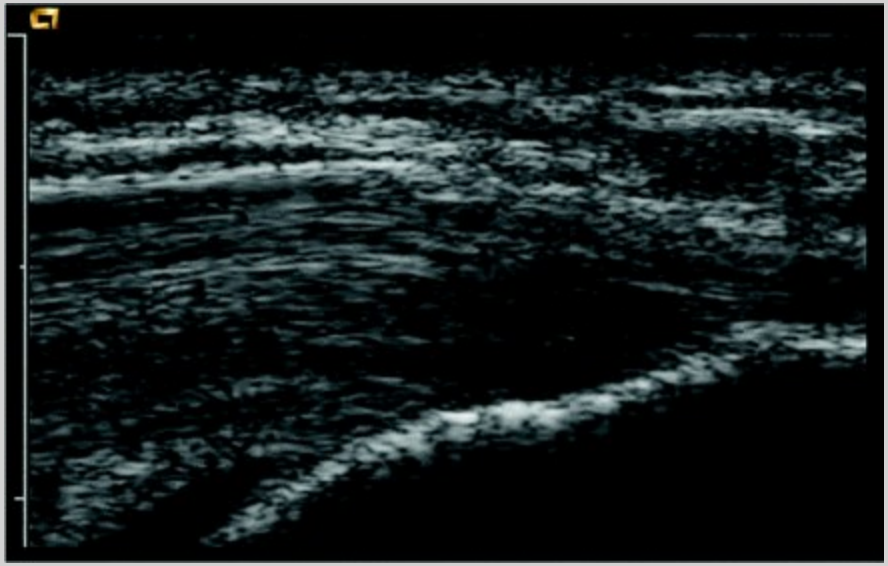
A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial

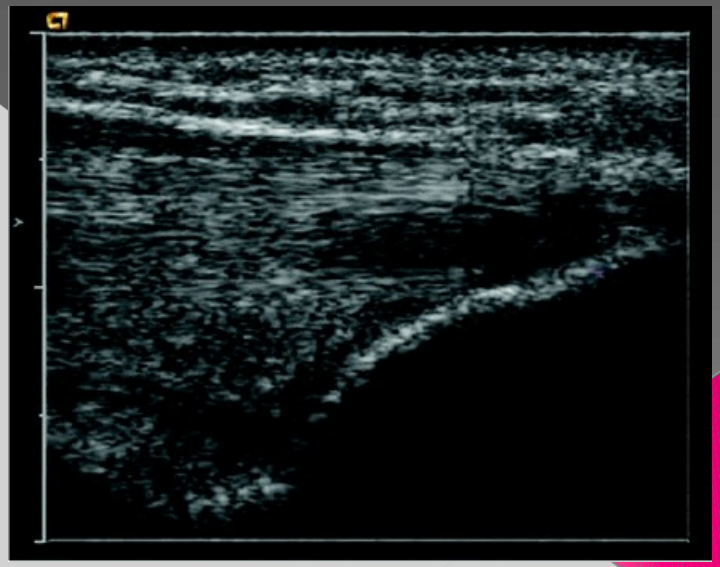
Paolini JA, Appleyard RC, Nelson J, Murrell GA: The American Journal of Sports Medicine 2006; 31(6): 915-920.

Topical Nitric Oxide

- 86 recruited subjects: one half received one quarter patch Nitrodur 5mg/24hr; one half placebo.
- Ongoing rehabilitation program.
- 81% of patients treated with nitro were asymptomatic with ADLs at 6 months; 60% of the placebo group. P=.005.
- Headache in 63% of patients with nitro; 57% of placebo; no significant difference.

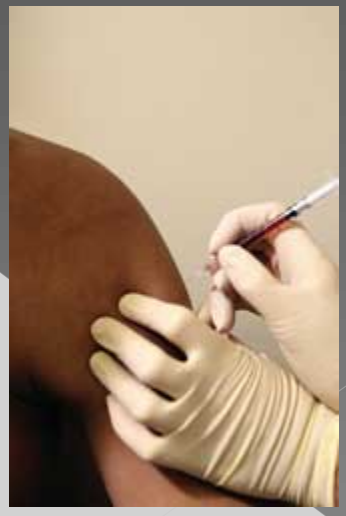
Autologous Blood and Ultrasound Guided Injections





Dry Needling and Autologous Blood

- The hypothesis behind autologous blood is that the transforming growth factor-beta and basic fibroblast growth factor carried in the blood act as humoral mediators to induce the healing cascade.
- 2ml of blood is mixed with 2ml of marcaine and injected into the painful area, after dry needling is completed.

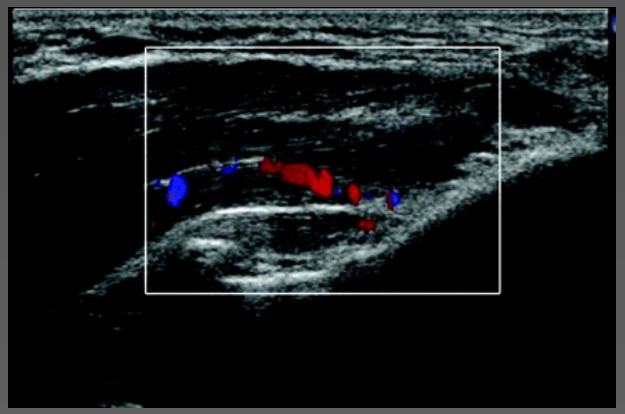


Medial Epicondylitis: Is Ultrasound Guided Autologous Blood Injection an Effective Treatment?

Suresh SP, Ali KE, Connell DA:
British Journal of Sports Medicine
2006;40:935-939.

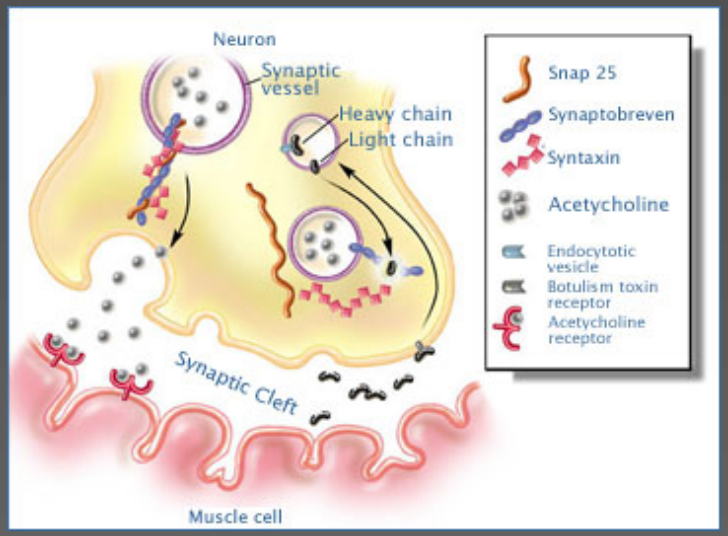
Autologous Blood

- 20 patients with symptoms over 12 months.
- Pt had needle fenestration followed by 2 autologous blood injections; assessment at 4 weeks and 10 months.
- Significant decrease in VAS (8-2), Nirschl Score (6-1) and neovascularity (6.1-3.6).



Botulinum Toxin

- Botulinum toxin A blocks the presynaptic release of acetylcholine at the motor end-plate by intracellular division of SNAP-25 (synaptosomal-asssociated protein of 25 kDa).
- This results in a palsy of skeletal muscle.



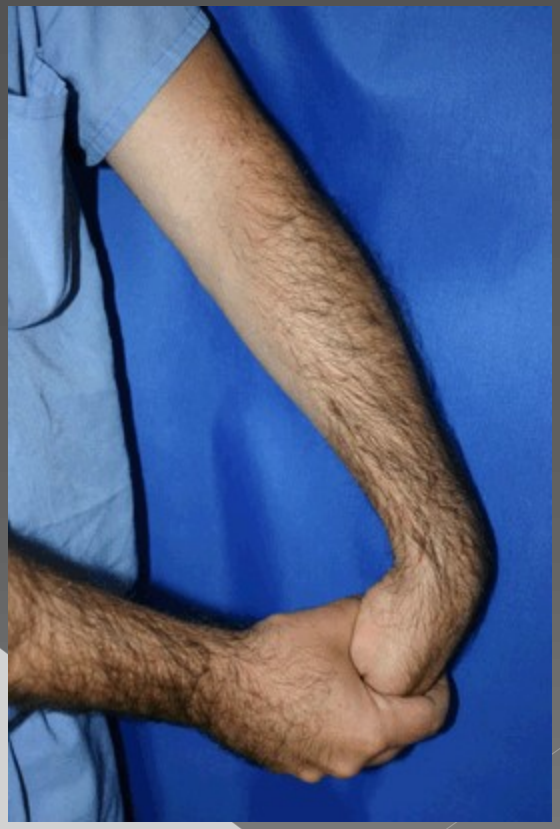
Treatment of Chronic Radial Epicondylitis with Botulinum Toxin A

A Double-Blind, Placebo-Controlled, Randomized Multicenter Study

Placzek R, Drescher W, Deuretzbacher, Hempfing A, Meiss L: The Journal of Bone and Joint Surgery 2007. Volume 89 A (2): 255-260.

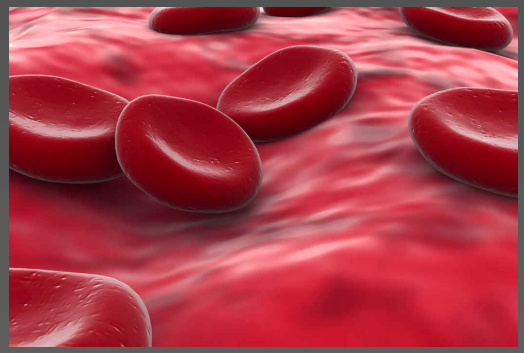
Botulinum Toxin A

- Methods: Prospective, double-blind, placebo controlled trial.
  - 130 patients randomized to two injections 3 to 4cm distal to the lateral epicondyle
  - Average age 47; duration of symptoms 9 months.
  - Global assessment,VAS, wrist, grip and third finger extension strength, assessed from 2 to 18 weeks.
- Results:
  - VAS ($p < 0.05\%$), Global Assessment ($p<0.05$) at 2,6,12,18 weeks.
  - No significant differences in wrist strength between groups, however, third finger strength was diminished, which persisted until week 18.
  - No impairment in work in either group.



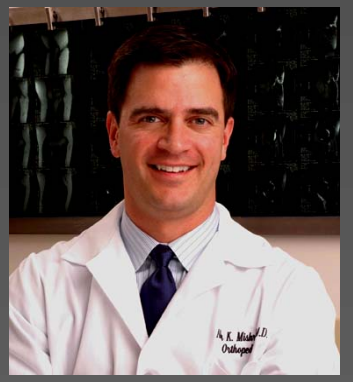
Platelet Rich Plasma (PRP)

- Platelet Rich Plasma
  - More concentrated amount of platelets than blood (539%).
  - Powerful Growth Factors:
    - Platelet derived growth factor;
    - Transforming growth factor beta;
    - Epidermal growth factor.
  - Process: (30 minutes)
    - 55 ml whole blood is drawn, then centrifuged to produce 5ml of PRP (GPS system);
    - Buffered to physiologic pH using Na-bicarbonate 8.4%;
    - 2ml used for injection.
  - Injection technique:
    - 22 gauge with 5 tendon penetrations;
    - Initial analgesia with acetaminophen or hydrocodone.



Platelet Rich Plasma

- Mishra et al: Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. The American Journal of Sports Medicine 2006, Vol 34 (11): 1174-1778.
  - 140 patients initially screened.
  - 15 PRP treated (Duration 15 m, Age 48, VAS 80); 5 control patients (Duration 12 m, Age 42, VAS 86).
  - 8 Week Follow-up
    - PRP 60% improved; CON 16%.
  - Final Follow-up (Mean 25 months)
    - PRP 93% improved with VAS less than 10.
    - 3/5 CON withdrew.
  - Of note: not blinded or placebo controlled; no observed complications.



Summary

- The evidence to support the use of NSAIDs in sports medicine in acute and overuse injuries is…
  - Limited;
  - Subject to debate;
  - And requires further study.
- Current recommendations:
  - Treatment should be individualized and if used, administered for as short as possible, with recognition that most treatment is focused on analgesia.
- The future may well be in the area of promoting growth factors.

Ankle Sprain

- You are treating a 21 y/o college athlete in the training room that you have just diagnosed with a grade 2 ankle sprain. She is a soccer player, and is actively going to work with your trainer to get back as soon as possible. You supplement her therapy with a seven day course of an NSAID to decrease

Is inflammation a bad thing…or is it good thing?

Will adding an NSAID be helpful…or harmful?

Tennis Elbow

- You have been treating a patient with a 6 month history of tennis elbow on her dominant arm with a counterforce brace and stretching and strengthening exercises. She did not improve with an initial ten day course of an NSAID; she had two days of relief with a steroid injection.

Is another course of an NSAID warranted…how about another corticosteroid injection?

Are there any alternative therapies that might help, or should you refer her to surgery?

New Sports Medicine Dogma

- Make the Diagnosis
- Treat the Pain
- Control the Inflammation
- Expedite Return to Function

Promote Inflammation?