The Use of Topical Flurbiprofen Cream to Treat Plantar Fasciitis, a Randomized, Prospective Trial vs Oral NSAID Therapy

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Plantar Fasciitis

• Most common cause of plantar heel pain
• Affects up to 10% of US population
• Accounts for >600,000 patient visits annually in the US
Plantar Fasciitis

- Inflammation and pain along the plantar fascia - the tissue band that supports the arch on the bottom of the foot
- Pain is usually found on the bottom of the heel at the point where the plantar fascia attaches to the heel bone
- Becomes chronic in 5-10% of all patients
- Is not necessarily associated with a heel spur
- Over 90% resolve with conservative treatment

Plantar Fasciitis Symptoms

- Pain on standing, especially after periods of inactivity or sleep
- Pain subsides after a period of time, returns with activity after rest (post static dyskinesia)
- Pain related to footwear – can be worse in flat shoes with no support
- Radiating pain to the arch and/or toes
- In later stages, pain may persist/progress throughout the day
- Pain varies in character: dull aching, “bruised” feeling. Burning or tingling, numbness, or sharp pain, may indicate local nerve irritation
**Plantar Fasciitis Risk Factors**

- Biomechanical abnormalities
- Overly tight calf muscle
- Poor shoe choices
- Weight gain
- Barefoot walking
- Work surface

**Plantar Fasciitis Treatment - Overview**

- Mechanical – treat the cause
- Anti-inflammatory – treat the pain
- Neither done in isolation
Plantar Fasciitis Treatment

- Stretching, shoe modifications, avoid walking barefoot
- Icing and rest
- Night or resting splint
- Supplemental arch support (OTC vs. custom orthotics)
- Anti-inflammatory medication
- Steroid injections
- Physical therapy
- If conservative measures fail, surgery is an option

Other options for heel pain

- Over 90% of heel pain patients respond to initial therapies within a relatively short period of time
- For unresponsive cases, options include:
  - Minimally invasive procedures like ESWT (Extracorporeal Shock Wave Therapy)
  - Autologous Platelet Concentrate (APC) injection
  - Surgical procedures, open or endoscopic
  - Cryosurgery
  - Radiofrequency techniques
What Does Research Tell Us About Treatment?

- Approximately 80% of patients treated conservatively had complete resolution of their symptoms\(^1\)
- No evidence strongly supports the effectiveness of any treatment for plantar fasciitis
- Cochrane Review\(^2\) showed corticosteroid injections improved plantar fasciitis symptoms at one month but not at six months when compared to placebo

Research Specific to NSAIDs and Plantar Fasciitis

- Treatment protocols in most studies include ice and NSAID therapy. No studies have specifically examined their effectiveness.\(^3\)
- Although no data supports the use of NSAIDs or ice, their effectiveness in managing other musculoskeletal conditions makes them reasonable choices for adjunctive therapy\(^4\)\(^5\)
Complications of Oral NSAID Use

- High incidence events
  - GI disturbances
    - Nausea, Vomiting, Dyspepsia
  - Potential Serious Events
    - GI ulceration or bleeding
    - Hypertension
    - Cardiovascular events
    - Acute renal impairment
    - Hepatotoxicity

Oral NSAIDs - Cost of Adverse Events

- In 1983, it cost an estimated $8.6 billion to treat arthritis in the USA
- It cost an additional $3.9 billion to treating gastrointestinal side effects of NSAIDs for a total cost of 12.5 billion.
- Conclusion: 30% of medical costs when using oral NSAIDs can be attributed to gastrointestinal side effects.
Are Oral NSAIDs Still the Answer?

• The authors sought to determine if alternative therapies could offer equal efficacy with improved side effect profile

• With advancements in available transdermal carrier agents, topical NSAID formulations were selected

Background

• Topical anti-inflammatories\textsuperscript{7,9}:  
  - Advantages: Little to no systemic absorption, no GI upset, considered safe for renally impaired, good for patients that do not want to take more medications.
  - Disadvantages: Application can be difficult (locations and flexibility of patient), cost, variability in penetration/absorption.

• Recent study showed significantly higher concentrations of flurbiprofen in tendon, muscle and periosteal tissues when administered through a patch vs. oral, however, there was a large degree of variability between individuals.\textsuperscript{8}

• Purpose: Determine if topical anti-inflammatories can be an equally effective alternative to oral NSAIDs.
Effect of Compounded Topical Anti-Inflammatory Cream (Flurbiprofen) vs PO NSAID (Ibuprofen) in the Treatment of Plantar Fasciitis - A Pilot Study

Jeffrey Alexander, DPM
Gene Choi, DPM

Methods

• Power analysis, study designed to be a non-inferiority study
• 60 patients with unilateral plantar fasciitis were randomized into 2 groups: (40 experimental, 20 control)
  — Exclusion criteria: Previous professional treatment, suspicion of nerve involvement (+ tinels/valleix sign, tarsal tunnel syndrome), contralateral pain, h/o NSAID intolerance (GI upset, hypersensitivity), renal impairment, CV disease, cortisone injections, failure to comply.
  — Inclusion criteria: Symptomatic for > 4 weeks and not resolving.
  — Age: ranged from 29 – 79 (Avg: Experimental 55.7, Control 59.5)
• All patients instructed to reduce activity, ice (20min 3x/day), perform stretching exercises (written and visual instructions), and use standard OTC orthotics.
Methods

• Experimental group: Compounded topical anti-inflammatory medication containing: Flurbiprofen 10%, Baclofen 2% and Lidocaine 5% in a Lipoderm base with pentoxifylline 3%.
• Control group: Ibuprofen 800mg PO TID
• Record weekly pain scores using VAS
• Follow up weekly for 3 months.

Data

• Patients’ weekly pain scores were rated using the visual analog pain scale (VAS) on initial visit and subsequent weekly follow up visits.
  • Experimental group:
    – Avg: 4.3667 point decrease in pain. (σ: 1.846)
    – Avg: 65.3% (0.6526) relief in pain (σ: 0.1945)
  • Control group:
    – Avg: 3.6 point decrease in pain. (σ: 0.5477)
    – Avg: 60.9% (0.6086) relief in pain (σ: 0.1132)
• Reported adverse events
  – Topical: Texture complaints (2/40)
  – Oral: GI Upset (4/20)
### Statistics

#### F-test: % Change in VAS
- \( P = 0.30559 \)
  - **Accept \( H_0 \): No significant difference between oral vs. topical.**

#### F-test: Mean differences in VAS
- \( P = 0.03052 \)
  - **Reject \( H_0 \): Topical significantly better relief than oral.**

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#### Analysis of Variance (One-Way) CI=95%

**Using Mean differences**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Sample size</th>
<th>Sum</th>
<th>Mean</th>
<th>Variance</th>
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<tr>
<td>Control</td>
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**ANOVA**

<table>
<thead>
<tr>
<th>Source of Variation</th>
<th>SS</th>
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<th>MS</th>
<th>F</th>
<th>p-level</th>
<th>F crit</th>
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<td>2.20417</td>
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<td>48.93333</td>
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<td>Total</td>
<td>51.1375</td>
<td>19</td>
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**ANOVA: Mean differences in VAS**
- \( P = 0.37977 \)
  - **Accept \( H_0 \): No significant difference between oral vs. topical.**

**ANOVA: % Change in VAS**
- \( P = 0.64041 \)
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#### F-Test Two-Sample for Variances (CI=95%)

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<td>Standard Deviation</td>
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**Using % differences**

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<td>Mean</td>
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### Statistics

#### T-test: Mean differences in VAS
- $P = 0.16975$
- Accept $H_0$: No significant difference between oral vs. topical.

#### T-test: % Change in VAS
- $P = 0.54811$
- Accept $H_0$: No significant difference between oral vs. topical.

#### Results

- Topical compounded anti-inflammatory cream with flurbiprofen is **NON INFERIOR** to oral NSAIDs in treating plantar fasciitis.
- Adverse Events:
  - Topical Cream: 5% (2/40) complained that the cream was “sticky” (1/40) or “gritty” (1/40), but both of these patients continued to use it because of the efficacy
  - Oral NSAID: 20% (4/20) with GI Upset, but none of these patients discontinued therapy
Where Does the NSAID Go? 6

**Oral vs. Topical NSAID**

- Comparison of Median Maximum Concentrations, cMax, of NSAID in Joint Tissue after Topical and Oral Administration
- NSAID is Maximized in Cartilage and Minimized in Plasma After Topical Application

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**What about Flurbiprofen and Plantar Fasciitis?**

**Better penetration into soft tissues in topical formulations than oral** 8

<table>
<thead>
<tr>
<th>Tendon</th>
<th>Periosteum</th>
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<tr>
<td>Oral 7%</td>
<td>Oral 9%</td>
</tr>
<tr>
<td>Topical 160%</td>
<td>Topical 65%</td>
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<table>
<thead>
<tr>
<th>Muscle</th>
<th>Bone</th>
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<tbody>
<tr>
<td>Oral 3%</td>
<td>Oral 4%</td>
</tr>
<tr>
<td>Topical 77%</td>
<td>Topical 11%</td>
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Advantages of Topicals

**Improved Safety Profile**
- Avoids GI 1st pass metabolism
  - Traditionally 25% GI side effects using PO NSAIDs
- Most topical components do not reach systemic levels
  - Finch et al (2009)- Ketamine levels were below detectable limits
  - ME Lynch et al (2003)- Blood levels showed no significant absorption of Amitriptyline or Ketamine
  - No specific absorption of either agent after 7 days of treatment
  - 15% of topical NSAIDs is thought to be absorbed systemically

**Discussion**
- Limitations:
  - Small sample size, unable to appreciate safety advantages of topical formulations.
  - Limited follow up.
- Future research: Blinded prospective study comparing the topical compound cream with a placebo cream.
References


Referenced


• 8 Kai S, Kondo E, Kawaguchi Y, et al. *Flurbiprofen concentration in soft tissue is higher after topical application than after oral administration.* British J Clinical Pharm. 2012. 75:3;799-804.

• 9 Pandey MS, Belgamwar VS, Surana SJ. *Topical delivery of flurbiprofen from pluronic lecithin organogel.* Indian J Pharm Sci. 2009. 71;87-90.

• 10 Dexter F, Chestnut DH. *Analysis of statistical tests to compare visual analog scale measurements among groups.* Anesthesiology. 1995. 82:896-902.