RUSH UNIVERSITY

RUSH MEDICAL COLLEGE • COLLEGE OF NURSING • COLLEGE OF HEALTH SCIENCES • THE GRADUATE COLLEGE

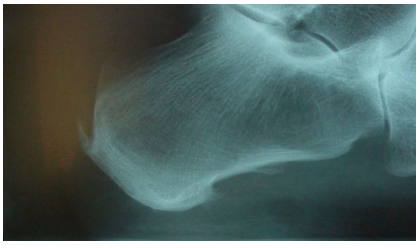
The Use of Topical Flurbiprofen Cream to Treat Plantar Fasciitis, a Randomized, Prospective Trial vs Oral NSAID Therapy

Jeffery Alexander, DPM FACFAS
Rush University Medical Center
Chicago, IL

Plantar Fasciitis

RUSH UNIVERSITY

- 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

RUSH UNIVERSITY

- 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

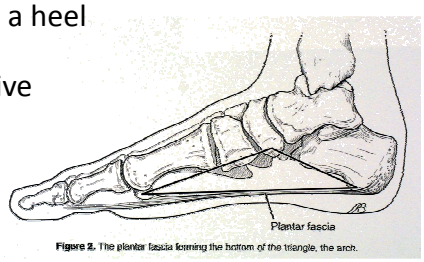


Figure 2. The plantar fascia forming the bottom of the triangle, the arch.

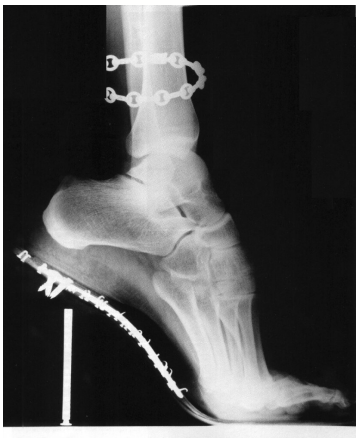
Plantar Fasciitis Symptoms

RUSH UNIVERSITY

- 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

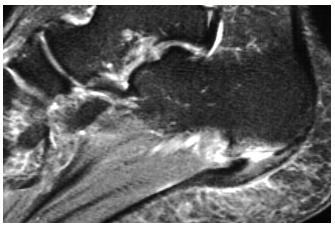
RUSH UNIVERSITY



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

Plantar Fasciitis Treatment- Overview

RUSH UNIVERSITY



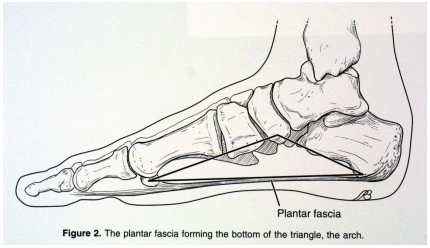


Figure 2. The plantar fascia forming the bottom of the triangle, the arch.

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

Plantar Fasciitis Treatment

RUSH UNIVERSITY

- 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

RUSH UNIVERSITY

- 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?

RUSH UNIVERSITY

- 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

RUSH UNIVERSITY

- 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

RUSH UNIVERSITY

- 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

RUSH UNIVERSITY

- 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?

RUSH UNIVERSITY

- 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

RUSH UNIVERSITY

- Topical anti-inflammatories[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.[8]
- Purpose: Determine if topical anti-inflammatories can be an equally effective alternative to oral NSAIDs.

14

RUSH UNIVERSITY

Effect of Compounded Topical Anti-Inflammatory Cream (Flurbiprofen) vs PO NSAID (Ibuprofen) in the Treatment of Plantar Fasciitis- A Pilot Study

Jeffey Alexander, DPM
Gene Choi, DPM

Methods

RUSH UNIVERSITY

- 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

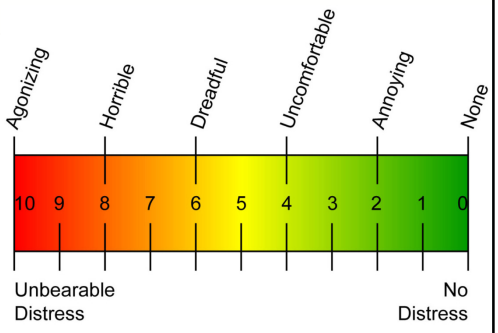
RUSH UNIVERSITY

- 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

RUSH UNIVERSITY

- 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

RUSH UNIVERSITY

F-Test Two-Sample for Variances (CI=95%)

Descriptive Statistics: Using Mean differences

VAR	Control	Experimental	
Sample size	20	40	
Mean	3.6	4.36667	
Variance	0.3	3.40952	
Standard Deviation	0.54772	1.84649	
Mean Standard Error	0.24495	0.47676	
Summary			
F	11.36508	F Critical value (5%)	5.87335
p-level 1-tailed	0.01526	**p-level 2-tailed**	**0.03052**
H0 (5%)?	***rejected***		

F-Test Two-Sample for Variances (CI=95%)

Descriptive Statistics: Using % differences

VAR	Control	Experimental	
Sample size	20	40	
Mean	0.60857	0.65264	
Variance	0.01282	0.03781	
Standard Deviation	0.11321	0.19446	
Mean Standard Error	0.05063	0.05021	
Summary			
F	2.95047	F Critical value (5%)	5.87335
p-level 1-tailed	0.1528	**p-level 2-tailed**	**0.30559**
H0 (5%)?	***accepted***		

F-test: % Change in VAS

- P = 0.30559
- Accept H_o: **No significant difference between oral vs. topical.**

F-test: Mean differences in VAS

- P = 0.03052
- **Reject** H_o: Topical significantly better relief than oral.

19

Statistics

RUSH UNIVERSITY

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

Using Mean differences

Summary

Groups	Sample size	Sum	Mean	Variance
Experimental	40	65.5	4.36667	3.40952
Control	20	18.	3.6	0.3

ANOVA

Source of Variation	SS	df	MS	F	p-level	F crit
Between Groups	2.20417	1	2.20417	0.8108	**0.37977**	4.41387
Within Groups	48.93333	18	2.71852			
Total	51.1375	19				

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

Summary

Groups	Sample size	Sum	Mean	Variance
Experimental	40	9.78958	0.65264	0.03781
Control	20	3.04286	0.60857	0.01282

ANOVA

Source of Variation	SS	df	MS	F	p-level	F crit
Between Groups	0.00728	1	0.00728	0.22574	**0.64041**	4.41387
Within Groups	0.58066	18	0.03226			
Total	0.58795	19				

- ANOVA: Mean differences in VAS
  - P = 0.37977
  - Accept H_o: **No significant difference between oral vs. topical.**
- ANOVA: % Change in VAS
  - P = 0.64041
  - Accept H_o: **No significant difference between oral vs. topical.**

20

Statistics

RUSH UNIVERSITY

Comparing Means [t-test assuming unequal variances (heteroscedastic)]

Descriptive Statistics: Using Mean differences

VAR	Sample size	Mean	Variance
	40	4.36667	3.40952
	20	3.6	0.3

Summary

Degrees Of Freedom	18	Hypothesized Mean Difference	0.E+0
Test Statistics	1.43033	Pooled Variance	2.71852
Two-tailed distribution			
p-level	**0.16975**	**t Critical Value (5%)**	**2.10092**
One-tailed distribution			
p-level	0.08488	t Critical Value (5%)	1.73406
Paqurova criterion			
Test Statistics	1.43033	p-level	0.83023
Ratio of variances parameter	0.79116	Critical Value (5%)	0.06359

Comparing Means [t-test assuming unequal variances (heteroscedastic)]

Descriptive Statistics: Using % differences

VAR	Sample size	Mean	Variance
	40	0.65264	0.03781
	20	0.60857	0.01282

Summary

Degrees Of Freedom	12	Hypothesized Mean Difference	0.E+0
Test Statistics	0.61802	Pooled Variance	0.03226
Two-tailed distribution			
p-level	**0.54811**	**t Critical Value (5%)**	**2.17881**
One-tailed distribution			
p-level	0.27406	t Critical Value (5%)	1.78229
Paqurova criterion			
Test Statistics	0.61802	p-level	0.45089
Ratio of variances parameter	0.49584	Critical Value (5%)	0.06414

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

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

21

Results

RUSH UNIVERSITY

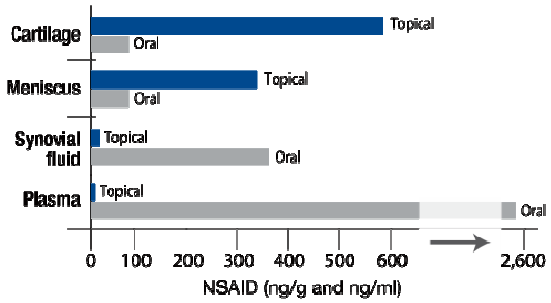
- Topical compounded anti-inflammatory cream with flurbiprofen is ***NON INFERIOR*** to oral NSAIDs in treating plantar fasciitis.
- Adverse Events:
  - Topical Cream: 5% (2/40) complained that the cream was "sticky" (1/40) or "gritty" (1/40), but both of these patients continued to use it because of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

Where Does the NSAID Go? [6]

RUSH UNIVERSITY

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 Meniscus and Minimized in Plasma After Topical Application



Rolf C, et al. Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. Rheumatology (1999); 38:564-567.

What about Flurbiprofen and Plantar Fasciitis?

RUSH UNIVERSITY

Better penetration into soft tissues in topical formulations than oral [8]

Tendon
Oral 7%
Topical 160%

Periosteum
Oral 9%
Topical 65%

Muscle
Oral 3%
Topical 77%

Bone
Oral 4%
Topical 11%

– All percents are tissue:plasma concentrations

[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.

Advantages of Topicals

RUSH UNIVERSITY

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)- Ketamime levels were below detectable limits
  - ME Lynch et al (2003)- Blood levels showed no significant absorption of Amitriptyline or Ketamime
  - No specific absorption of either agent after 7 days of treatment
  - 15% of topical NSAIDs is thought to be absorbed systemically

Discussion

RUSH UNIVERSITY

- 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

RUSH UNIVERSITY

- [1] Wolgin M, Cook C, Graham C, Mauldin D. Conservative treatment of plantar heel pain: long term follow up. *Foot Ankle Int.* 1994:15:97-102.
- [2] Crawford F, Thomson C. Interventions for treating heel pain. *Cochrane Database Syst Rev*. 2003;(3):CD000416.
- [3] Buchbinder R. Clincal Practice. Plantar Fasciitis. *New Engl J Med.* 2004;350:2159-66.
- [4] Pfeffer G, Bacchetti P, Deland J, Lewis A, Anderson R, Davis W. Comparison of custom and prefabricated orthoses in the initial treatment of proximal plantar fasciitis. *Foot Ankle Int.* 1999;20:214-21.
- [5] DiGiovanni BF, Nawoczenski DA, Lintal ME, Moore EA, Murray JC, Wilding GE, et al. Tissue-specific plantar fasciastretching exercise enhances outcomes in patients with chronic heel pain. A prospective, randomized study. *J Bone Joint Surg Am.* 2003;85-A:1270-7.
- [6] Rolf C, et al. Intra-articular absorption and distribution of ketoprofen after topical plaster application and oral intake in 100 patients undergoing knee arthroscopy. *Rheumatology* (1999); 38:564-567.

Referenced

RUSH UNIVERSITY

[7] Jorge LL, Feres CC, Teles VE. *Topical preparations for pain relief: efficacy and patient adherence.* J Pain Research. 2011. 4;11-24.

[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.