INJECTIONS UNPACKED:
FORMULATIONS, FINDINGS, & FAILURES

Christina Pratt, DPM, FACFAS, FACPM

Associate Dean of Academics,

Samuel Merritt University

College of Podiatric Medicine

STUDENT TRANSATLANTIC EDUCATION PODIATRIC SURGERY

STEPS

EST. 2018

IN PARTNERSHIP WITH

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COLLABORATIVE MEDICAL CONTENT

AN EDUCATIONAL NONPROFIT

19 09

Samuel Merritt University

College of Podiatric Medicine

UNPACKING:

CORTICOSTEROIDS

HYALURONIC ACID

PLATLET-RICH PLASMA

FORMULA: CORTICOSTEROIDS

- *Per NHS:*

  Proper injection training

  Informed consent

  Sterile technique

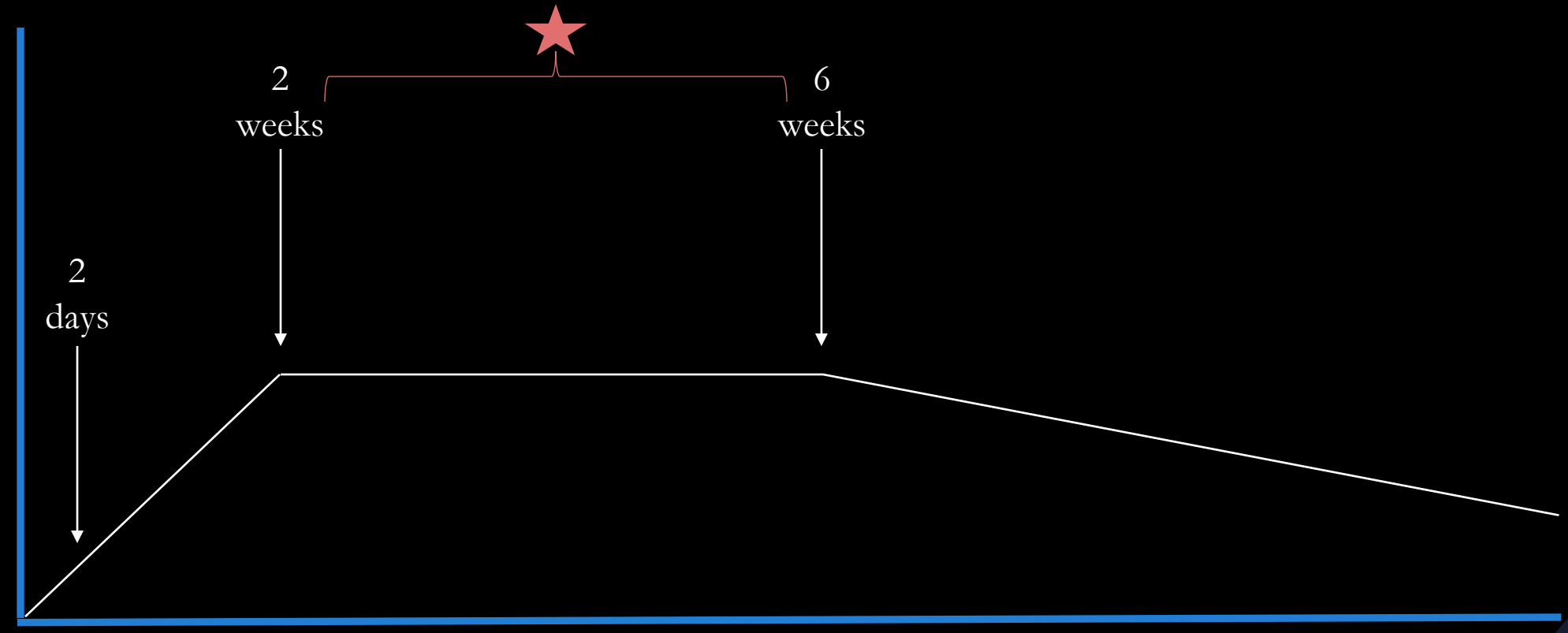
  Post-injection care

  Education of risks

Corticosteroid	Tradename(s) (Manufacturer)	Suspension/ Solution	Solubility	Notable Excipients	Approved Routes of Administration
Betamethasone acetate, betamethasone sodium phosphate	Celestone Soluspan (Merck Sharp & Dohme)	Suspension	Acetate insoluble; sodium phosphate soluble	Benzalkonium chloride (for multidose use)	Intramuscular Intra-articular Soft tissue Intralesional
Methylprednisolone acetate	Depo-Medrol (Pharmacia and Upjohn Co.)	Suspension	Insoluble	Benzyl alcohol Polyethylene glycol Polysorbate 80 (for multidose use) Or Polyethylene glycol Myristyl-gamma-picolinium-chloride (for single-dose use)	Intramuscular Intra-articular Soft tissue Intralesional
Triamncinolone acetonide	Kenalog-10 Kenalog-40 Kenalog-80 (Bristol Myers Squibb)	Suspension	Insoluble	Benzyl alcohol Polysorbate 80 (for multidose use)	Intra-articular Intralesional Intramuscular*
Methylprednisolone sodium succinate	Solu-Medrol (Pharmacia and Upjohn Co.)	Solution	Soluble	Benzyl alcohol (for multidose use) Or Preservative-free (for single-dose use)	Intravenous Intramuscular
Dexamethasone sodium phosphate	Decadron (Merck)	Solution	Freely soluble	Benzyl alcohol with or without sodium sulfite (for multidose use) Or Methylparaben Propylparaben Edetate disodium (for multidose use) Or Preservative-free (for single-dose use)	Intravenous Intramuscular (intra-articular, intralesional, soft tissue)†

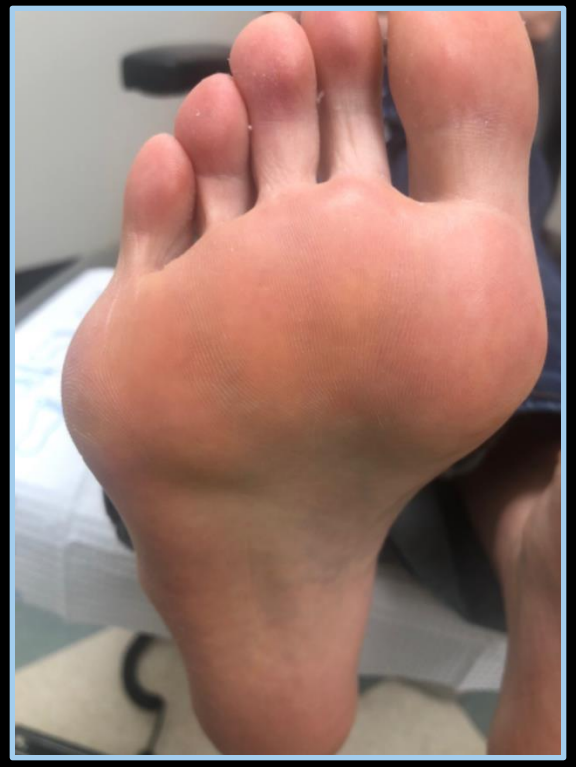
Food and Drug Administration (FDA)-approved Injectable Corticosteroids

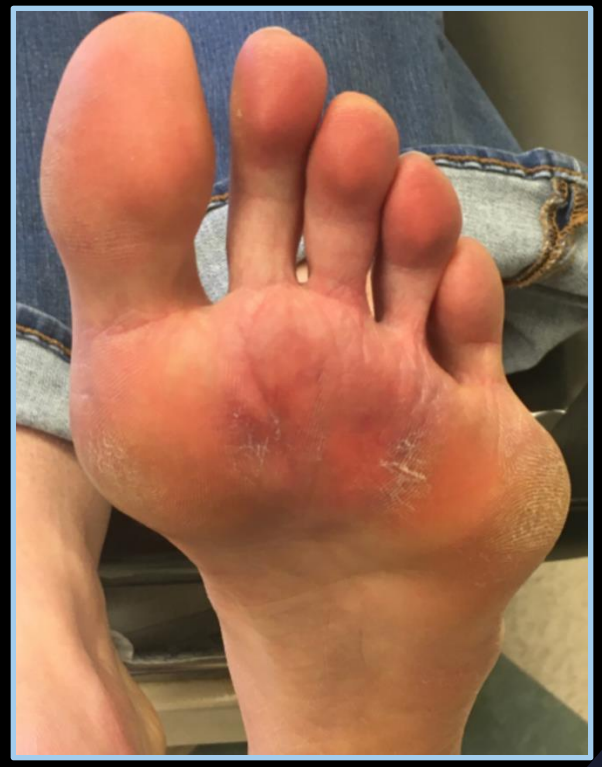
FORMULA: CORTICOSTEROIDS



FORMULA: CORTICOSTEROIDS

- **RISKS:**
  - Steroid Flare
  - Tissue Damage (fat pad atrophy)
  - Chondrotoxicity
  - Tendon/ligament rupture
  - Immunosuppression





FORMULA: CORTICOSTEROIDS

- **With which local anesthetic?** **Lidocaine**

  ropivicaine HCL / bupivacaine HCL / lidocaine HCL

  mixed with

  triamcinolone acetonide / dexamethasone sodium phosphate / betamethasone sodium phosphate

Lidocaine mixed with corticosteroids did not precipitate.

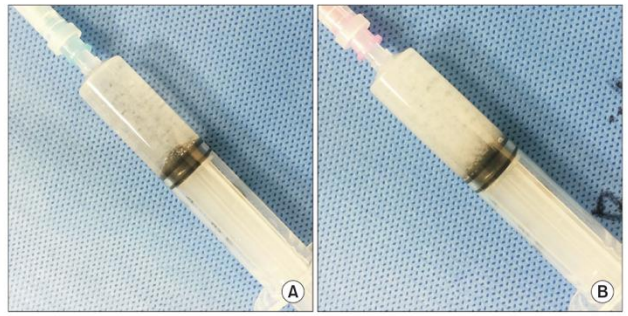


Fig. 1. Precipitation is observed as a cloudy appearance, when some local anesthetics are mixed with betamethasone sodium phosphate solution. (A) Ropivacaine-HCl+betamethasone sodium phosphate. (B) Bupivacaine-HCl +betamethasone sodium phosphate.

Original Article

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arm Annals of Rehabilitation Medicine

Crystallization of Local Anesthetics When Mixed With Corticosteroid Solutions

Hyeoncheol Hwang, MD, Jihong Park, MD, Won Kyung Lee, MD, Woo Hyung Lee, MD, Ja-Ho Leigh, MD, Jin Joo Lee, BS, Sun G. Chung, MD, PhD, Chaiyoung Lim, MD, Sang Jun Park, MD, Keewon Kim, MD, MS

Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea

Objective To evaluate at which pH level various local anesthetics precipitate, and to confirm which combination of corticosteroid and local anesthetic crystallizes.

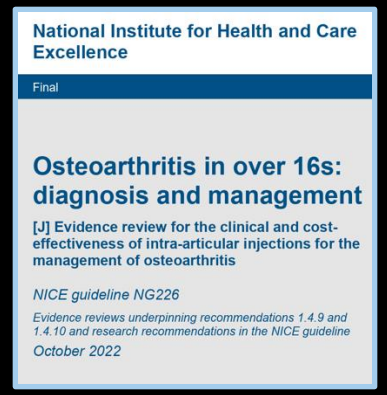
Methods Each of ropivacaine-HCl, bupivacaine-HCl, and lidocaine-HCl was mixed with 4 different concentrations of NaOH solutions. Also, each of the three local anesthetics was mixed with the same volume of 3 corticosteroid solutions (triamcinolone acetonide, dexamethasone sodium phosphate, and betamethasone sodium phosphate). Precipitation of the local anesthetics (or not) was observed, by the naked eye and by microscope. The pH of each solution and the size of the precipitated crystal were measured.

Results Alkalinized with NaOH to a certain value of pH, local anesthetics precipitated (ropivacaine pH 6.9, bupivacaine pH 7.7, and lidocaine pH 12.9). Precipitation was observed as a cloudy appearance by the naked eye and as the aggregation of small particles (<10 μm) by microscope. The amount of particles and aggregation increased with increased pH. Mixed with betamethasone sodium phosphate, ropivacaine was precipitated in the form of numerous large crystals (>300 μm, pH 7.5). Ropivacaine with dexamethasone sodium phosphate also precipitated, but it was only observable by microscope (a few crystals of 10–100 μm, pH 7.0). Bupivacaine with betamethasone sodium phosphate formed precipitates of non-aggregated smaller particles (<10 μm, pH 7.7). Lidocaine mixed with corticosteroids did not precipitate.

Conclusion Ropivacaine and bupivacaine can precipitate by alkalinization at a physiological pH, and therefore also produce crystals at a physiological pH when they are mixed with betamethasone sodium phosphate. Thus, the potential risk should be noted for their use in interventions, such as epidural steroid injections.

Keywords Crystallization, Local anesthetics, Corticosteroid, Alkalinization, Precipitation

FORMULA: CORTICOSTEROIDS
FOR: OSTEOARTHRITIS


National Institute for Health and Care Excellence

Final

Osteoarthritis in over 16s: diagnosis and management

[J] Evidence review for the clinical and cost-effectiveness of intra-articular injections for the management of osteoarthritis

NICE guideline NG226

Evidence reviews underpinning recommendations 1.4.9 and 1.4.10 and research recommendations in the NICE guideline

October 2022

- *Per NICE (NG226):*

  Symptom management, *not* long term, *not* a fix of cause

  If other therapies (NSAIDs, exercise, etc) have failed to yield improvement

  Anticipate 2-10 weeks of symptom improvement (weeks – not months, not years)

  Need further research in foot/ankle for any longer-term benefits (knee/hip well studied)

  Infection risk is low, but not 0%

  US-guidance can improve accuracy

  Patient-initiated follow up

Management of osteoarthritis

Explain that:
- osteoarthritis is diagnosed clinically and usually does not need imaging to confirm diagnosis
- management is guided by symptoms and physical function
- the core treatments are therapeutic exercise and weight management, alongside information and support.

Exercise

- For all people with osteoarthritis, offer therapeutic exercise tailored to their needs (for example, local muscle strengthening, general aerobic fitness).
- Consider supervised therapeutic exercise sessions.
- Advise people it may initially cause pain or discomfort but long-term adherence to an exercise plan will benefit the joints, reduce pain and improve function.
- Consider combining therapeutic exercise with an education programme or behaviour change approaches in a structured treatment package.

Weight management

For people who are living with overweight or obesity:
- advise them that weight loss will improve quality of life and physical function, and reduce pain
- support them to choose a weight loss goal
- explain that any weight loss is likely to be beneficial, but losing 10% is likely to be better than 5%.

For guidance and information on weight management, including interventions for weight loss, see NICE's topic page on obesity.

Information and support

- Tailor information to the person's individual needs and ensure it is in an accessible format.
- Advise where people can find further information on:
  - the condition and information that challenges common misconceptions
  - specific types of exercise
  - managing their symptoms
  - how to access additional information and support
  - benefits and limitations of treatment.

Manual therapy
Only consider for hip and knee osteoarthritis and alongside therapeutic exercise.

Devices
Consider walking aids for lower limb osteoarthritis.

Do not offer:
- acupuncture or dry needling
- electrotherapy treatments
- insoles, braces, tape, splints or supports routinely.

Pharmacological management

If needed, use:
- alongside non-pharmacological treatments and to support therapeutic exercise
- the lowest effective dose for the shortest possible time.

Review with the person whether to continue treatment. Base frequency of reviews on clinical need.

- Offer a topical non-steroidal anti-inflammatory drug (NSAID) for knee osteoarthritis.
- Consider a topical NSAID for other osteoarthritis-affected joints.

Consider an oral NSAID if topical medicines are ineffective or unsuitable and offer a gastroprotective treatment alongside.

Do not offer:
- paracetamol or weak opioids routinely, unless:
  - used infrequently for short-term pain relief
  - all other treatments are ineffective or unsuitable
- glucosamine
- strong opioids
- intra-articular hyaluronan injections.

Consider intra-articular corticosteroid injections for short-term relief when other pharmacological treatments are ineffective or unsuitable or to support therapeutic exercise.

Referral for joint replacement

Consider referring people with hip, knee or shoulder osteoarthritis for joint replacement if:
- joint symptoms are substantially impacting their quality of life **and**
- non-surgical management is ineffective or unsuitable.

Do not exclude people from referral for joint replacement because of age, sex or gender, smoking, comorbidities, or overweight or obesity.

This is a summary of the recommendations on managing osteoarthritis in NICE's guideline on osteoarthritis in over 16s: diagnosis and management

NICE National Institute for Health and Care Excellence

FORMULA: CORTICOSTEROIDS
FOR: OSTEOARTHRITIS FOOT/ANKLE

Rheumatology Advances in Practice, 2025, **9(2)**, rkaf030
https://doi.org/10.1093/rap/rkaf030
Advance access publication 11 March 2025
Systematic Review and Meta-Analysis

British Society for Rheumatology
RHEUMATOLOGY ADVANCES IN PRACTICE
OXFORD

Clinical science

Intra-articular corticosteroid injections for the treatment of people with foot and ankle osteoarthritis: a systematic review

Katherine Jones [1,*], Julie Bruce [1,2], Thomas L. Lewis [1,3], Ciaran N. Nolan [4], Shannon E. Munteanu [5], Hylton B. Menz [5], Michael R. Backhouse [1,2]

[1]Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Warwick, UK
[2]University Hospitals Coventry and Warwick, NHS Trust, Coventry, UK
[3]Department of Orthopaedics, Kings College Hospital NHS Foundation Trust, London, UK
[4]Trauma and Orthopaedics, Queen Elizabeth Hospital Birmingham NHS Trust, Birmingham, UK
[5]Department of Physiotherapy, Podiatry, Prosthetics and Orthotics, School of Allied Health, Human Services and Sport, La Trobe University, Melbourne, Australia

*Correspondence to: Katherine Jones, Warwick Clinical Trials Unit, Warwick Medical School, University of Warwick, Gibbet Hill CV4 7AL, UK. E-mail: katherine.h.jones@warwick.ac.uk

- Database review of RCTs

  1711 citations → 2 RCTs / 57 patients

- Focused outcomes (pain, function, QOL, safety, cost)
- 1st MPJ OA pain/function @ 8wk – No difference vs prolotherapy with 1 injection
- PTOA of STJ pain/function – Significant improvement with 3 steroid injections *combined with HA*
- Conclusion: Insufficient evidence

FORMULA: **CORTICOSTEROIDS**

The Journal of Foot & Ankle Surgery 59 (2020) 1019–1031

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

ACFAS Clinical Consensus Statement

Consensus Statement of the American College of Foot and Ankle Surgeons: Diagnosis and Treatment of Ankle Arthritis

Naohiro Shibuya, DPM, MS, FACFAS[1], Jeffery E. McAlister, DPM, FACFAS[2], Mark A. Prissel, DPM, FACFAS[3], Jason A. Piraino, DPM, MS, FACFAS[4], Robert M. Joseph, DPM, PhD, FACFAS[5], Michael H. Theodoulou, DPM, FACFAS[6], Daniel C. Jupiter, PhD[7]

[1] *Professor, College of Medicine, Texas A&M University, Temple, TX*
[2] *Podiatrist, Arcadia Orthopedics and Sports Medicine, Phoenix, AZ*
[3] *Faculty, Advanced Foot and Ankle Reconstruction Fellowship Program, Orthopedic Foot and Ankle Center, Worthington, OH*
[4] *Associate Professor, Department of Orthopaedic Surgery and Rehabilitation, University of Florida Health, Gainesville, FL*
[5] *Chairman, Department of Podiatric Medicine & Radiology, Dr. William M. Scholl College of Podiatric Medicine at Rosalind Franklin University, North Chicago, IL*
[6] *Chief, Division of Podiatric Surgery, Cambridge Health Alliance, Instructor of Surgery, Harvard Medical School, Cambridge, MA*
[7] *Associate Professor, Department of Preventive Medicine and Community, Department of Orthopaedic Surgery and Rehabilitation, University of Texas Medical Branch, Galveston, TX*

Ankle Arthritis (2020)

The Journal of Foot & Ankle Surgery ■■ (2017) ■■–■■

Contents lists available at ScienceDirect

The Journal of Foot & Ankle Surgery

journal homepage: www.jfas.org

ACFAS Clinical Consensus Statement

American College of Foot and Ankle Surgeons Clinical Consensus Statement: Diagnosis and Treatment of Adult Acquired Infracalcaneal Heel Pain

Harry P. Schneider, DPM [1,2,3], John Baca, DPM [4], Brian Carpenter, DPM [5,6], Paul Dayton, DPM [7,8], Adam E. Fleischer, DPM, MPH [9,10], Brett D. Sachs, DPM [11,12]

[1] *Chairperson, Heel Pain Clinical Consensus Statement, Chicago, IL*
[2] *Assistant Professor of Surgery, Harvard Medical School, Cambridge, MA*
[3] *Residency Program Director, Cambridge Health Alliance, Cambridge, MA*
[4] *Private Practice, Dallas Podiatry Works, Dallas, TX*
[5] *Professor, Department of Orthopedics, The University of North Texas Health Science Center, Fort Worth, TX*
[6] *Private Practice, Paradise, TX*
[7] *Assistant Professor, College of Podiatric Medicine and Surgery, Des Moines, IA*
[8] *Residency Program Director, UnityPoint Health, Fort Dodge, IA*
[9] *Associate Professor, Dr. William M. Scholl College of Podiatric Medicine at Rosalind Franklin University of Medicine and Science, North Chicago, IL*
[10] *Director of Research, Weil Foot and Ankle Institute, Chicago, IL*
[11] *Private Practice, Rocky Mountain Foot & Ankle Center, Wheat Ridge, CO*
[12] *Faculty, Highlands-Presbyterian/St. Luke's Podiatric Medicine and Surgery Residency Program, Denver, CO*

Plantar Fasciitis (2017)

FORMULA: CORTICOSTEROIDS
FOR: OSTEOARTHRITIS FOOT/ANKLE

- *Per ACFAS CCS on Ankle Arthritis:*

  Little to no benefit beyond 12 weeks

  1st injection likely the most efficacious one

  Primary recommendation is triamcinolone, also methylprednisolone

  Response at 2 months predictor for sustained response at 1 year (Ward et al, JFAS 2008)

  Inflammatory markers (+ANA) have less response

  Consider benefit as diagnostic injection

> The panel reached consensus that the statement: "Intra-articular steroidal injection is a viable option for treatment of ankle arthritis," was appropriate.

ACFAS 2020

FORMULA: CORTICOSTEROIDS
FOR: OSTEOARTHRITIS FOOT/ANKLE

- 1708 patients over 16 years, AJ or STJ
- Adverse risk event within 90 days = **5.8%**
  - *Post-injection flare 75%*
  - *Skin reaction 25%*
  - *No infections*
- US-guidance did not affect risk of adverse event

Comparative Study > Foot Ankle Int. 2019 Jun;40(6):622-628.
doi: 10.1177/1071100719835759. Epub 2019 Mar 13.

Adverse Events and Their Risk Factors Following Intra-articular Corticosteroid Injections of the Ankle or Subtalar Joint

Sophia E Anderson [1], Bart Lubberts [1], Anne D Strong [1], Daniel Guss [2], A Holly Johnson [3], Christopher W DiGiovanni [2]

FORMULA: CORTICOSTEROIDS

- RISK: **Post-injection flare (5%)**

  Within 24-48 hr, increase in pain/inflammation

  Literature shows increase proportional with corticosteroid concentration

  Acetates (insoluble, crystallization) much more likely to cause flare

  Treatment: Self-limiting, rest, ice, elevation, NSAID

FORMULA: CORTICOSTEROIDS
FOR: PLANTAR FASCIITIS

Consensus Statement: The panel reached consensus that the statement "Corticosteroid injections are safe and effective in the treatment of plantar fasciitis" was appropriate.

ACFAS 2017

- *Appreciate phases:*

Acute = week 0-6

Subacute = week 6 – 12

Chronic = week 12+ and on

Refractory = no improvement 6+ months

FORMULA: CORTICOSTEROIDS
FOR: PLANTAR FASCIITIS

- *Per ACFAS CCS on Heel Pain:*

  Expected benefit is 4 weeks, beyond this is minimal

  Not “disease-modifying”

  US-guidance for anatomic precision, but not required

  Recommend 2-3 injections within 12 month period (1 injection q 4 months)

  No symptomatic improvement - No further injections

FORMULA: CORTICOSTEROIDS

IN SUMMARY…

- Literature does not support using as primary therapy, rather should be supportive to other therapies (exercise, orthotics)
- Expect weeks (not months) of symptom improvement and do not continue to inject with no reported improvement
- Must appreciate physiology of both corticosteroids and local anesthetics
- Higer doses do not prolong benefit, Use lowest effective dose and limit frequency

MOST COMMON: Triamcinolone acetonide 20-40mg/mL + Lidocaine 1%

FORMULA: HYALURONIC ACID

- HA is viscoelastic (viscous *and* elastic) – plump hydrated skin, absorbing load of joints, supporting movement of joints
- "Viscosupplementation" expanding in foot/ankle because of high success in knee, yet decades later (US approval in 1997) we are without large RCTs foot/ankle specific
- Multiple smaller studies support HA injections for ankle OA

Witeveen et al, Foot Ankle Surg 2010

Chang et al, Arch Phys Med Rehabil 2013

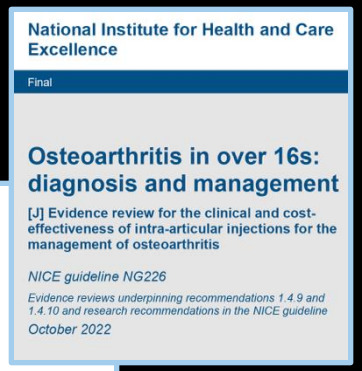
Hernandez et al, Orthop Traumatol Surg Res 2013

Henrotin et al, Semin Arthritis Rheum 2015

Murphy et al, JFAS 2017

FORMULA: HYALURONIC ACID
FOR: OSTEOARTHRITIS

- *Per NICE (NG226):*


National Institute for Health and Care Excellence

Final

Osteoarthritis in over 16s: diagnosis and management

[J] Evidence review for the clinical and cost-effectiveness of intra-articular injections for the management of osteoarthritis

NICE guideline NG226

Evidence reviews underpinning recommendations 1.4.9 and 1.4.10 and research recommendations in the NICE guideline

October 2022

Intra-articular injections

1.4.9 Do not offer intra-articular hyaluronan injections to manage osteoarthritis.

1.4.10 Consider intra-articular corticosteroid injections when other pharmacological treatments are ineffective or unsuitable, or to support therapeutic exercise. Explain to the person that these only provide short-term relief (2 to 10 weeks).

Why the committee made the recommendations

There was no evidence showing that hyaluronan injections improved quality of life or physical function, or reduced pain, in people with knee or hip osteoarthritis. Evidence showed a potential harm for hip osteoarthritis. Limited evidence for other osteoarthritis-affected joints showed inconsistent benefits and some potential harms. Based on their expert opinion, the committee agreed that these results were generalisable to other forms of osteoarthritis and that hyaluronan injections should not be offered.

National Institute for Health and Care Excellence

Final

Osteoarthritis in over 16s: diagnosis and management

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October 2022

Table 50: UK costs of intraarticular injections

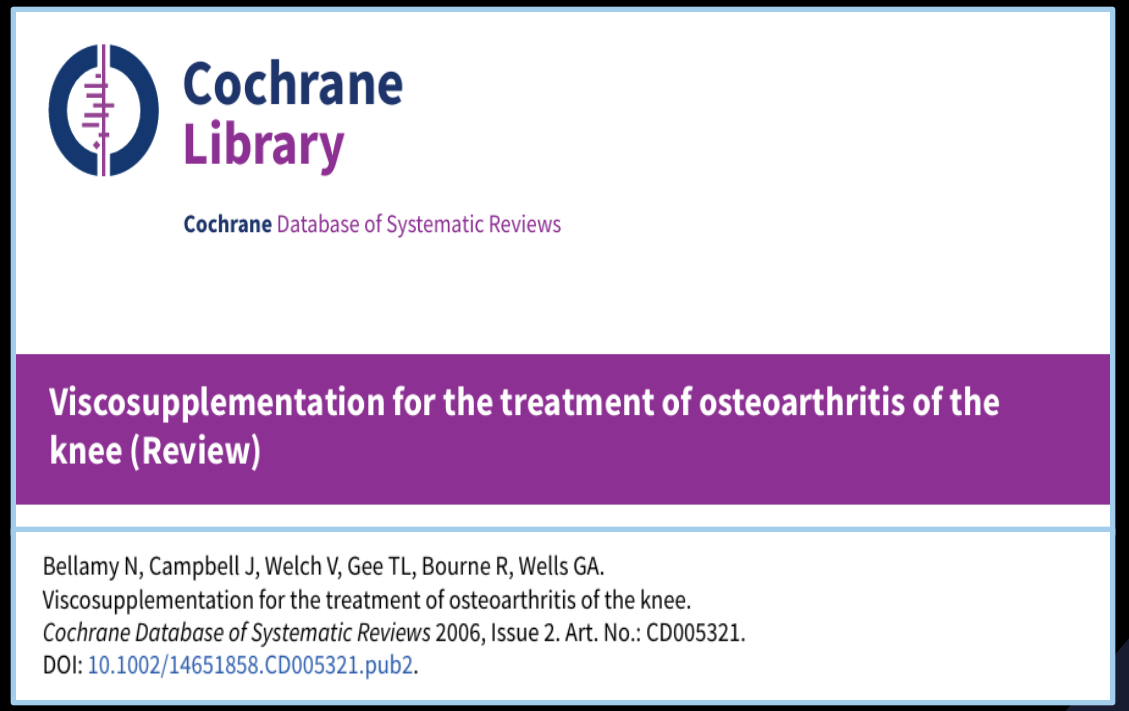
Drug	Product description	Cost	No. of injections	Total cost
Corticosteroid injections				
Prednisolone (Deltastab®)	25mg/1ml suspension	£6.87	1	£6.87
Methylprednisolone with lidocaine	10mg/1ml suspension	£3.94	1	£3.94
	40mg/1ml suspension	£3.89	1	£3.89
	20mg/2ml suspension	£7.06	1	£7.06
	80mg/2ml suspension	£7.01	1	£7.01
Triamcinolone hexacetonide	20mg/1ml suspension	£12.00	1	£12.00
Methylprednisolone (Depo-Medrone®)	40mg/1ml	£3.40	1	£3.40
	80mg/2ml	£6.14	1	£6.14
Triamcinolone acetoride				
(Adcortyl®)	10mg/1ml	£0.89	1	£0.89
(Kenalog®)	40mg/1ml	£1.49	1	£1.49
Dexamethasone	3.3mg/1ml	£2.32	1	£2.32
Hydrocortisone (Hydrocortistab®)	100mg/1ml	£2.12	1	£2.12
Hyaluronans				
Durolane®	Box containing 1 pre-fillled 3ml syringe	£199.17	1	£199.17
Euflexxa®	Box containing 3 pre-filled 2ml syringes (1 treatment)	£195.00	3	£195.00
Fermathron®	Box containing 1 pre-filled 20mg/2ml syringe	£39.00	3	£117.00
Orthovisc®	Box containing 1 pre-filled 2ml syringe	£65.00	3	£195.00
Ostenil®	Box containing 1 pre-filled 20mg/2ml syringe	£34.23	3	£102.69
Ostenil Plus®	Box containing 1 pre-filled 40mg/2ml syringe	£80.65	3	£241.95
RenehaVis®	Box containing 1 pre-filled dual chambered 1.4ml syringe	£112.00	3	£336.00
Syplasyn®	Box containing 1 pre-filled 20mg/2ml syringe	£35.50	3	£106.50
Synocrom®	Box containing 1 pre-filled 20mg/2ml syringe	£30.00	3	£90.00
Synocrom Mini	Box containing 1 pre-filled 10mg/1ml syringe	£22.50	1	£22.50
Synolis	Box containing 3 pre-filled 2ml syringes (1 treatment)	£205.00	3	£205.00
Synvisc (Hylan G-F20)	Box containing 3 pre-filled 2ml syringes (1 treatment)	£205.00	3	£205.00
Synvisc ONE (Hylan G-F20)	Box containing 1 pre-filled 6ml syringe	£205.00	1	£205.00

Corticosteroid Injection
Average cost 1 injection
= **£ 4.76**

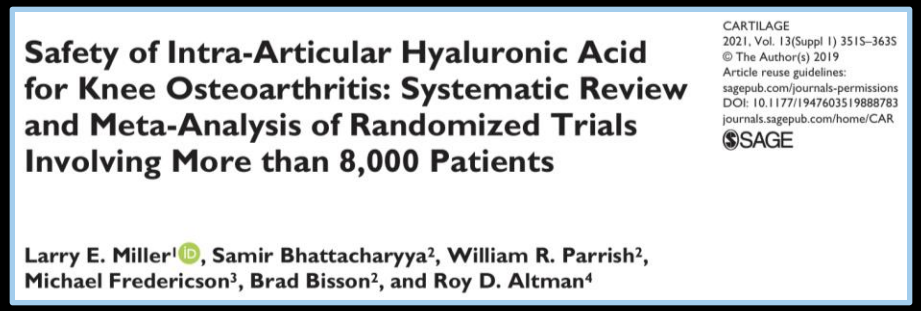
HA Injection
Average cost 1 injection
= **£ 82.68**

FORMULA: HYALURONIC ACID
FOR: OSTEOARTHRITIS (KNEE)

- Cochrane review of 76 RCTs, with f/u through 1.5 years
- Significantly better than placebos
- Longer efficacy than corticosteroids
- Fewer adverse events
- At 5 - 13 weeks post-injection, greatest improvement in pain/function



FORMULA: HYALURONIC ACID
FOR: OSTEOARTHRITIS (KNEE)


Safety of Intra-Articular Hyaluronic Acid for Knee Osteoarthritis: Systematic Review and Meta-Analysis of Randomized Trials Involving More than 8,000 Patients

CARTILAGE
2021, Vol. 13(Suppl 1) 351S–363S
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DOI: 10.1177/1947603519888783
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Larry E. Miller[1], Samir Bhattacharyya[2], William R. Parrish[2], Michael Fredericson[3], Brad Bisson[2], and Roy D. Altman[4]

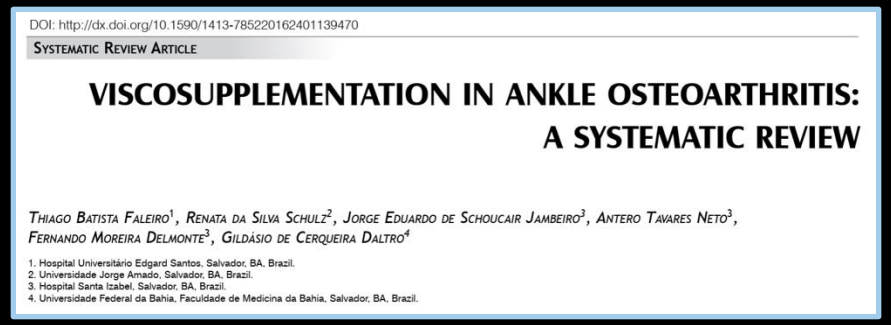
- 2021 study of 35 RCTs (8078 patients) for knee OA
- HA injections in knee vs placebo (saline)
- No difference in overall adverse events at 6 months f/u

  Local events (injection site pain, swelling, effusion - subsided within 2 to 3 days):

  HA = 14.5% Saline 11.7%

- Safe, effective and recommended in OA

FORMULA: HYALURONIC ACID
FOR: OSTEOARTHRITIS (ANKLE)



DOI: http://dx.doi.org/10.1590/1413-785220162401139470

SYSTEMATIC REVIEW ARTICLE

VISCOSUPPLEMENTATION IN ANKLE OSTEOARTHRITIS: A SYSTEMATIC REVIEW

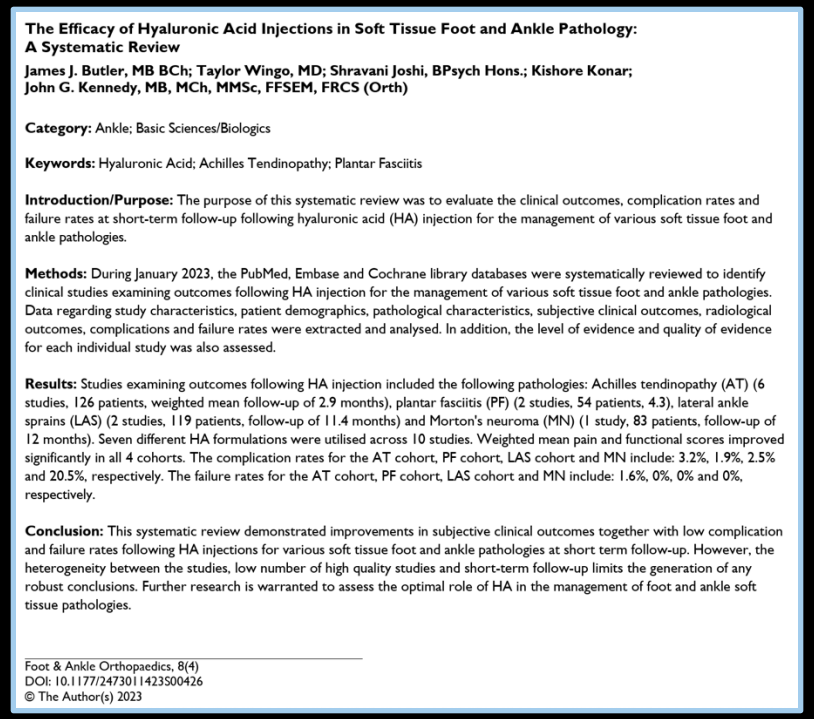
THIAGO BATISTA FALEIRO[1], RENATA DA SILVA SCHULZ[2], JORGE EDUARDO DE SCHOUCAIR JAMBEIRO[3], ANTERO TAVARES NETO[3], FERNANDO MOREIRA DELMONTE[3], GILDÁSIO DE CERQUEIRA DALTRO[4]

1. Hospital Universitário Edgard Santos, Salvador, BA, Brazil.
2. Universidade Jorge Amado, Salvador, BA, Brazil.
3. Hospital Santa Izabel, Salvador, BA, Brazil.
4. Universidade Federal da Bahia, Faculdade de Medicina da Bahia, Salvador, BA, Brazil.

- 2016 systematic review of 5 RCTs for ankle OA
- Overall improvement in functional outcome scores, at times statistically significant
- HA injection vs. exercise therapy in one study, equivalent improvement at 12 months (Karatosun 2008)
- One study showed better outcomes with 3 injection series vs single injection (Witteveen 2010)

Authors	Year of publication	Place of study	Intervention	Number of patients
Cohen et al.[20]	2008	Canada	HA x Saline	30
Salk et al.[17]	2006	USA	HA x Saline	20
DeGroot et al.[19]	2012	USA	HA x Saline	64
Karatosun et al.[22]	2008	Turkey	HA x Physical therapy	30
Witteveen et al.[21]	2010	The Netherlands	4 HA regimens	26

FORMULA: HYALURONIC ACID
FOR: SOFT TISSUE FOOT/ANKLE



The Efficacy of Hyaluronic Acid Injections in Soft Tissue Foot and Ankle Pathology: A Systematic Review

James J. Butler, MB BCh; Taylor Wingo, MD; Shravani Joshi, BPsych Hons.; Kishore Konar; John G. Kennedy, MB, MCh, MMSc, FFSEM, FRCS (Orth)

Category: Ankle; Basic Sciences/Biologics

Keywords: Hyaluronic Acid; Achilles Tendinopathy; Plantar Fasciitis

Introduction/Purpose: The purpose of this systematic review was to evaluate the clinical outcomes, complication rates and failure rates at short-term follow-up following hyaluronic acid (HA) injection for the management of various soft tissue foot and ankle pathologies.

Methods: During January 2023, the PubMed, Embase and Cochrane library databases were systematically reviewed to identify clinical studies examining outcomes following HA injection for the management of various soft tissue foot and ankle pathologies. Data regarding study characteristics, patient demographics, pathological characteristics, subjective clinical outcomes, radiological outcomes, complications and failure rates were extracted and analysed. In addition, the level of evidence and quality of evidence for each individual study was also assessed.

Results: Studies examining outcomes following HA injection included the following pathologies: Achilles tendinopathy (AT) (6 studies, 126 patients, weighted mean follow-up of 2.9 months), plantar fasciitis (PF) (2 studies, 54 patients, 4.3), lateral ankle sprains (LAS) (2 studies, 119 patients, follow-up of 11.4 months) and Morton's neuroma (MN) (1 study, 83 patients, follow-up of 12 months). Seven different HA formulations were utilised across 10 studies. Weighted mean pain and functional scores improved significantly in all 4 cohorts. The complication rates for the AT cohort, PF cohort, LAS cohort and MN include: 3.2%, 1.9%, 2.5% and 20.5%, respectively. The failure rates for the AT cohort, PF cohort, LAS cohort and MN include: 1.6%, 0%, 0% and 0%, respectively.

Conclusion: This systematic review demonstrated improvements in subjective clinical outcomes together with low complication and failure rates following HA injections for various soft tissue foot and ankle pathologies at short term follow-up. However, the heterogeneity between the studies, low number of high quality studies and short-term follow-up limits the generation of any robust conclusions. Further research is warranted to assess the optimal role of HA in the management of foot and ankle soft tissue pathologies.

Foot & Ankle Orthopaedics, 8(4)
DOI: 10.1177/24730114231S00426

- 2023 AOFAS Annual Meeting
  1. Achilles tendinopathy (6 studies)
  2. Plantar fasciitis (2 studies)
  3. Lateral ankle insufficiency (2 studies)
  4. Morton’s neuroma (1 study)
- Low complications (highest for Morton’s neuroma) and failure rates 0% aside from Achilles cases (1.6%)
- Pain/function score improvement statistically significant across all four pathologies

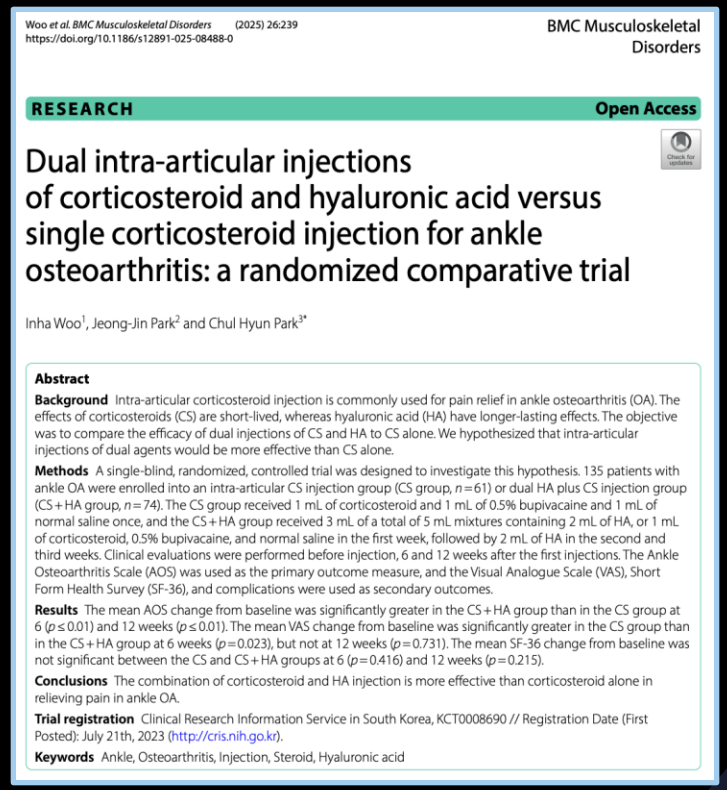
FORMULA: HYALURONIC ACID
FOR: OSTEOARTHRITIS ANKLE

- Recent March 2025 RCT of 135 patients with ankle OA
- HA + Corticosteroid

  ** 2mL HA + 1mL triamcinolone + 1mL bupivacaine + 1mL saline*

  ** 2mL HA at 1 week and 2 weeks later*
- Corticosteroid

  ** 1mL triamcinolone + 1mL bupivacaine + 1mL saline*
- HA + Corticosteroid: AOS score improvement at 6 and 12 weeks over HA alone ($p<0.01$)



Woo *et al. BMC Musculoskeletal Disorders* (2025) 26:239
https://doi.org/10.1186/s12891-025-08488-0

BMC Musculoskeletal Disorders

RESEARCH Open Access

Dual intra-articular injections of corticosteroid and hyaluronic acid versus single corticosteroid injection for ankle osteoarthritis: a randomized comparative trial

Inha Woo[1], Jeong-Jin Park[2] and Chul Hyun Park[3*]

Abstract

Background Intra-articular corticosteroid injection is commonly used for pain relief in ankle osteoarthritis (OA). The effects of corticosteroids (CS) are short-lived, whereas hyaluronic acid (HA) have longer-lasting effects. The objective was to compare the efficacy of dual injections of CS and HA to CS alone. We hypothesized that intra-articular injections of dual agents would be more effective than CS alone.

Methods A single-blind, randomized, controlled trial was designed to investigate this hypothesis. 135 patients with ankle OA were enrolled into an intra-articular CS injection group (CS group, $n=61$) or dual HA plus CS injection group (CS + HA group, $n=74$). The CS group received 1 mL of corticosteroid and 1 mL of 0.5% bupivacaine and 1 mL of normal saline once, and the CS + HA group received 3 mL of a total of 5 mL mixtures containing 2 mL of HA, or 1 mL of corticosteroid, 0.5% bupivacaine, and normal saline in the first week, followed by 2 mL of HA in the second and third weeks. Clinical evaluations were performed before injection, 6 and 12 weeks after the first injections. The Ankle Osteoarthritis Scale (AOS) was used as the primary outcome measure, and the Visual Analogue Scale (VAS), Short Form Health Survey (SF-36), and complications were used as secondary outcomes.

Results The mean AOS change from baseline was significantly greater in the CS + HA group than in the CS group at 6 ($p \leq 0.01$) and 12 weeks ($p \leq 0.01$). The mean VAS change from baseline was significantly greater in the CS group than in the CS + HA group at 6 weeks ($p=0.023$), but not at 12 weeks ($p=0.731$). The mean SF-36 change from baseline was not significant between the CS and CS + HA groups at 6 ($p=0.416$) and 12 weeks ($p=0.215$).

Conclusions The combination of corticosteroid and HA injection is more effective than corticosteroid alone in relieving pain in ankle OA.

Trial registration Clinical Research Information Service in South Korea, KCT0008690 // Registration Date (First Posted): July 21th, 2023 (http://cris.nih.go.kr).

Keywords Ankle, Osteoarthritis, Injection, Steroid, Hyaluronic acid

FORMULA: HYALURONIC ACID
FOR: OSTEOARTHRITIS ANKLE

- **1 Injection Formulation for Ankle OA**
  - High molecular weight HA (ex: MonoVisc)
  - Inject 3-6mL total volume
  - Repeat in 6-12 months with positive response

- **3 Injection Formulation for Ankle OA**
  - Medium molecular weight HA (ex: Hyalgan)
  - Inject 1-2mL total volume q week for 3 weeks
  - Repeat series in 6-12 months with positive response

FORMULA: HYALURONIC ACID

IN SUMMARY…

- Overall, data remains limited on foot/ankle specific pathologies
- Evidence that HA injections for ankle OA are useful and safe
- No direct proven superiority over other conservative therapies
- HA injections for soft tissue pathologies are showing promise
- All of the above played against high cost

FORMULA: **PRP**

Clarification: *PRP not currently within scope of podiatry practice in UK*

RCPod position statement

8 June 2023

The RCPod position is that there are no appropriate circumstances that enable podiatrists to prepare and inject PRP. We base this statement on Medicines and Healthcare products Regulatory Agency (MHRA) guidance which is drawn from the legislation and regulation governing medicines and healthcare products.

Regardless of how the PRP is manufactured, the MHRA believes podiatrists will be using PRP in clinical practice based on actual or implied claims that PRP is used with the intention of reducing pain and/or promoting healing. Due to the mechanism by which PRP is claimed to achieve these outcomes, the claims are 'medicinal claims' and therefore the use of PRP by podiatrists in clinical practice will come under the remit of Human Medicines Legislation (HMR).

PRP and its use as a medicinal product is subject to needing a marketing authorisation and a manufacturing licence. Podiatrists are not exempt from these requirements.

As such, podiatrists cannot provide PRP to patients and cessation guidance issued on Thursday 8 June 2023 still stands. This practice must stop immediately.

FORMULA: PRP

- Better for degenerative pathologies rather than inflammatory pathologies
- Slower to see benefit (most efficacious around week 6-12)

- *Are there "bad patients" for PRP?*

  Anemias, thrombocytopenia, current anti-coagulation use
  Immunosuppression
  Auto-immune diseases (RA)
  Inflammatory states
  Smoker

FORMULA: PRP
FOR: PLANTAR FASCIITIS

- BEST USE CASE = subacute fasciosis or early chronic cases without significant thickening >6mm
- Active degeneration of fascia
- Not for tears

Consensus Statement: The panel reached consensus that the statement "Other injection techniques (e.g., amniotic tissue, platelet-rich plasma, botulinum toxin, needling, and prolotherapy) are safe and effective in the treatment of plantar fasciitis" was uncertain—neither appropriate nor inappropriate.

Although other injection techniques are emerging for the treatment of plantar fasciitis, they have been supported only by low-quality studies consisting of case series, retrospective comparative studies, or small trials, lacking long-term follow-up data. Rather than speculate on the value of these injection therapies, the panel thought that further investigation is needed to assess how these will compare with the more conventional treatment protocols.

ACFAS 2017

Acute = week 0-6

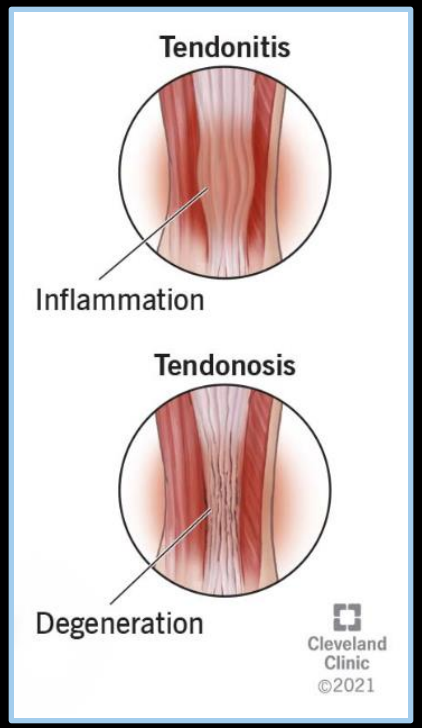
→ *Subacute = week 6 – 12*

Chronic = week 12+ and on

Refractory = no improvement 6+ months

FORMULA: PRP
FOR: ACHILLES TENDINOPATHY

- BEST USE CASE = Non-insertional, non-calcific tendinopathy
- Mid-substance degeneration
- Not for tears
- With 2-3 months of eccentric PT

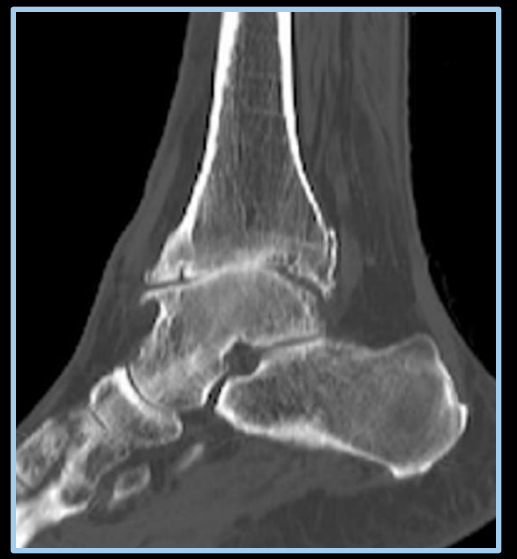


FORMULA: PRP
FOR: OTHER TENDINOPATHY

- Peroneal tendinitis, Posterior tibial tendinitis
- BEST USE CASE = Mild - Moderate degeneration of tendon without tear (ex: Stage 1 PTTD)
- Should not have significant mechanical instability (ex: severe cavus)
- Once structural failure happens, little to no benefit

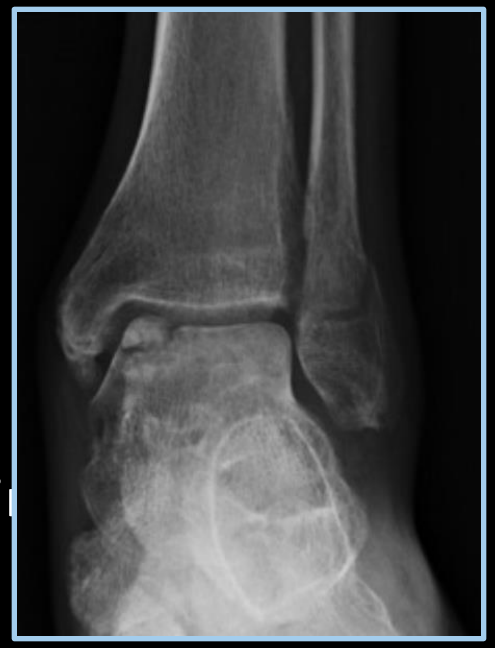
FORMULA: PRP
FOR: OSTEOARTHRITIS ANKLE

- BEST USE CASE = Mild - Moderate OA, not end stage
- Minimal synovitis/inflammation
- Younger patient – more cartilage metabolism
- Structural failure/joint collapse is “too far gone”



FORMULA: PRP
FOR: OSTEOCHONDRAL LESIONS (OLT)

- BEST USE CASE = Small lesions, done intra-operative
- Microfracture / Arthroscopy adjunctive treatment
- Surrounding cartilage is stable
- Younger patient – more cartilage metabolism
- After bone marrow is stimulated, PRP can enhance heali



FORMULA: PRP

IN SUMMARY…

- Not a fix everything solution in any condition
- Benefits shown to be very dependent on patient and pathology and severity
- Best outcomes appreciated in degenerative conditions of bone, cartilage, soft tissue
- Expect more post-injection pain/local symptoms, compared to steroid or HA
- Expect a longer delay to potential benefit

Injections unpacked:

Consider them as **part of the solution**,

not the whole answer to treatment.

Micro-fragmented Adipose Tissue Injection Therapy for Treatment of Ankle Osteoarthritis: A Systematic Review & Meta-Analysis

Diana Kvach BS[1], Dorsa Javaheri BS[1], Melissa Jaballas BS[1], Alize Koolen BS[1], Christina Pratt DPM FACFAS[2]

[1] Student, Samuel Merritt University College of Podiatric Medicine, Oakland, CA
[2] Asst Professor, Samuel Merritt University College of Podiatric Medicine, Oakland, CA

Samuel Merritt University
College of Podiatric Medicine

Statement of Purpose

This systematic review evaluates the efficacy of micro-fragmented adipose tissue (MFAT) injections for reducing pain associated with ankle osteoarthritis (OA), while aiming to engage the podiatric community and address the gap in research compared to it's established use in OA of the knee.

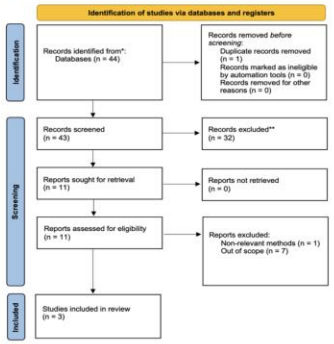
Introduction

Osteoarthritis is a debilitating and painful condition characterized by degeneration of articular surfaces, cartilage destruction, and inflammation. Unlike other lower extremity joints, etiology is often post-traumatic, with prevalence higher in younger age groups[1]. Thus, minimally invasive treatment options are preferred to maintain activity and delay joint replacement or fusion[2]. MFAT injection is a minimally invasive therapy that has been shown to induce vascular stabilization and inhibit several macrophage inflammatory pathways[3]. MFAT therapy is being increasingly utilized and has been shown to reduce pain and improve function in patients with knee OA[4].

Methodology

Following the PRISMA guidelines and PICO model, a systematic review was conducted. Studies published up to 2024 were screened from Cochrane, PubMed, and Google Scholar, using the search terms: 'micro-fragmented', 'adipose tissue', 'fat tissue', 'injection', 'intra-articular', and 'ankle osteoarthritis'. Two authors carried out study selection and four reviewers assessed bias using the Risk of Bias in Non-randomized Studies of Interventions tool. Preoperative and postoperative Visual Analog Scores (VAS) were extracted to generate forest plots for given follow-up periods. Data analysis was conducted in R Studio via a 'metafor package', implementing a random effects model to find standardized mean differences (SMD) and I² statistics for heterogeneity.

Figure 1: *Study Selection*



Results

The literature search yielded 43 potentially relevant articles upon initial screening. 40 studies were excluded as they were either not clinical in nature, did not include treatment of ankle OA, were out of scope, or did not meet inclusion criteria. Therefore, only 3 studies, with a combined population size of 63 patients that underwent MFAT, were included in the analysis (Figure 1). All studies were non-randomized and either prospective or retrospective in nature. Risk of bias was serious for one of the studies and moderate for all others (Figure 2)[5,6,7].

All studies evaluated VAS scores following autologous MFAT transfer from the lower abdomen or flank areas. Initial VAS scores varied between approximately 5 to 8 (Table 1). Follow up was done at 6, 12, and 24 months postoperatively, with the exception of Shimozono et al. who only reported two postoperative time points for 11 patients, at 6 months and at an average final follow-up of 16.1 months.

All studies reported significant pain reduction at 6 months, with an overall mean difference of 3.3017 (95% CI: [2.9384; 3.6650]).

Figure 2: *Risk of Bias Analysis*

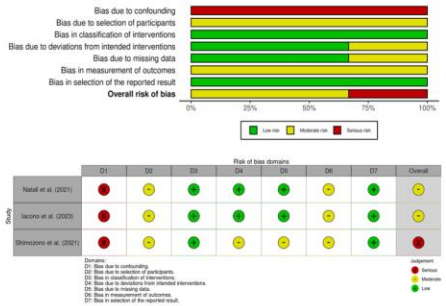


Table 1: *Average VAS Scores*

	N	Preoperative VAS	6 months VAS	12 months VAS	24 months VAS
Natali et al. (2021)	31	7.03 ± 0.95	3.61 ± 0.92	3.26 ± 0.63	4.35 ± 1.25
Iacono et al. (2023)	21	6.9 ± 1.0	3.7 ± 1.1	3.6 ± 0.9	3.1 ± 0.6
Shimozono et al. (2021)	11	6.6 ± 1.5	3.9 ± 1.9	4.5 ± 2.5	

The z-value of 17.81 and p-value of < 0.0001 indicate that this result is statistically significant, suggesting that the treatment has a substantial effect on improving pain (Figure 3).

At 12 months, the decrease in VAS was sustained with a SMD of 3.4252 (95% CI: [2.8562; 3.9942], z-value of 11.80, p-value of < 0.0001). Given the average final follow-up time of Shimozono et al., the authors compared this data to the 12-month follow-up in the other two studies, a decision that must be considered when noting Shimozono et al.'s smallest reduction in VAS from preoperative visit to 12 months (Figure 4).

At 24 months, Iacono et al. and Natali et al. continued to show a decrease in VAS with a SMD of 3.7865 (95% CI: [3.4162; 4.1568], z-value of 20.04, p-value of < 0.0001) (Figure 5).

All studies depicted statistically significant decreases in VAS at every follow-up when compared to preoperative scores. Heterogeneity was within none to moderate range, suggesting some variability in effects across the studies but overall instills confidence that the treatment is reliable.

Figure 3: *VAS initial vs 6 months*

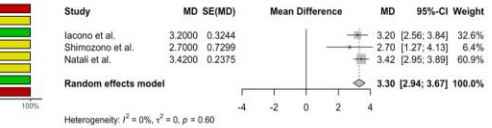


Figure 4: *VAS initial vs 12 months*

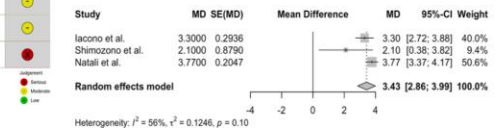
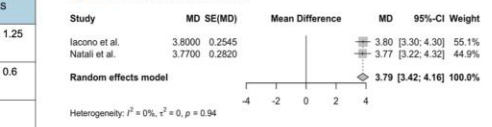


Figure 5: *VAS initial vs 24 months*



Analysis & Discussion

The reduction in VAS scores across all given time points (up to 2 years) demonstrates that MFAT is safe and effective in the management of ankle osteoarthritis. These results reflect the well-established findings of effectiveness of adipose tissue-based therapies in treatment of knee OA[8]. In addition, past research has also shown that this treatment modality offers anti-inflammatory and tissue regenerative properties through the stromal and mesenchymal stem cell composition of micro-fragmented adipose tissue[9,10]. MFAT therapy therefore has the advantage of being regenerative rather than solely palliative when compared to current standard treatments (corticosteroid, arthrodesis, etc.). However, the evidence supporting MFAT remains limited compared to more established interventions, including other biologics.

The limitations of this analysis include small population size, with only 3 studies and 63 total patients that underwent MFAT; the study findings cannot be generalized. Additionally, the prospective and retrospective design of these studies further limit the conclusions that can be drawn. To confirm MFAT's efficacy, future research should prioritize randomized controlled trials with placebo or control groups. Finally, the risk of bias assessed by the reviewers was deemed moderate to high for all included studies, which should be considered when applying their findings.

Conclusion

MFAT therapy effectively reduces pain in ankle OA patients for up to two years. Future research should focus on randomized controlled trials comparing this treatment modality against current standards and other biologics to provide higher-quality evidence.

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STEPS STUDENT TRANSATLANTIC EDUCATION PODIATRIC SURGERY EST 2018

THANK YOU

Christina Pratt, DPM, FACFAS, FACPM

Associate Dean of Academics,

Samuel Merritt University College of Podiatric Medicine