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This is an summary of prolotherapy research that is considered high quality, grade I to II level. (This will be explained shortly.)



The slides will be explained as we proceed through. The first topic will be to define treatments so we know what research applies to each treatment.



The bulk of research so far is focused on the on the areas in red that you see on the slide. These two areas are biologic repair injection and prolotherapy.

Note that perineural injection was introduced as neural prolotherapy or NPT for short. However, it is uncertain at this time if perineural injections causes proliferation so a more generic term such as perineural injection is preferred. Note that in Australia and New Zealand the term perineural injection therapy (PIT is becoming more commonly used). This may be the term that will become most widely accepted.

Def: Biologic and Biologic Repair Injection (BRI)

- **Biologic**: A preparation that is synthesized from living organisms or their products and used medically as a diagnostic, preventive, or therapeutic agent. <u>www.thefreedictionary/biologic</u>
- B.R.I.: Injection of biologics to repair connective tissue.
 - Mechanism proposed is by stimulation of a repair cascade
 - Various methods are utilized. IE: Whole blood, PRP, stem cells.
 - Emphasis is on <u>direct regenerative/proliferative effects</u> on connective tissue.

BRI (Biologic Repair Injection) is the "Injection of biologics to repair connective tissue". A "biologic" is something from a living organism. For purposes of BRI in humans, and to avoid rejection, the biologic is from the person themselves. Sometimes is it as simple as withdrawing blood and injecting it into another part of the body. There are other biologics that are removed and modified before re-injection. An example of this is drawing blood, spinning it in a centrifuge to separate blood cells from plasma, and re-injecting the plasma with concentrated platelets (platelet rich plasma) into an area of the body that needs repair. Stem cells are also biologics and can be taken from bone marrow or fat cells of patients, modified in special ways, and re-injected.

Connective tissue includes ligament, tendon, and cartilage. The primary emphasis of BRI is direct repair of "connecting tissues". These include primarily ligaments (bone to bone connections), tendons (muscle to bone connections) and cartilage (the covering layer over joints). The repair process, once begun, takes months for full completion after any single treatment, although sometimes the healing cycles are overlapped in an attempt to speed up the effect.

Def: Prolotherapy

 Prolotherapy: Injection to repair connective tissue (Not including biologics)

Prolotherapy is "Injection to repair connective tissue." (Identical purpose to biologic repair injection but, by definition, without use of biologics.) Thus, solutions used for prolotherapy do not contain anything from the person being injected. The most common solution is dextrose and others in common use that are added to dextrose include diluted sodium morrhuate (a salt of morrhuic acid which is more inflammatory than dextrose), and diluted phenol (a six carbon atom solution which is also more inflammatory and is also called carbolic acid). The dilution is usually 9 to 1 for sodium morrhuate and 99 to 1 for phenol.



Dextrose is the best understood of solutions used for proliferant injection.

It works in 4 basic ways. The first three directly stimulate repair. The last is a nerve effect which does not directly stimulate repair but indirectly does. This effect is covered in the nerve section of this talk.

Concept: Time Frame Of Pain and Functional Benefit Effects Research: Ex Dextrose

- Nerve Calming: 5 -20 seconds 2 days
- Dextrose Noninflammatory Effect on GFs: 20 min – 10 days (Pain relief reason unclear)
- Hyperosmolar/irritative or Needling Effect: 20 min -10 days (Pain relief reason unclear)
- Tissue Maturation Over time: 10 days 3 months (Repair with less insufficiency related pain stimulation)

If you are going to research, whatever you are studying may have several effects whether you are trying to measure either pain or functional changes as a result of the treatment.

Because our muscles are inhibited by nerves that are not functioning right, pain improvements also cause improvements in both pain and function.

The speed of nerve calming effect explains why patients often feel better immediately, especially if a technique is used that does not create immediate inflammation is gentler. The downregulation effect on nerves begins in 5-20 seconds and lasts up to 2 days.

When perineural injection is done alone, the effect typically lasts 4-48 hours, and after several treatments lasting benefit is usually noted.

However, there are overlapping effects from deeper injection that can continuing improvement in some subjects/patients. Growth factors DNA activity changes occur within 20 minutes as a result of dextrose exposure and changes are likely as fast with inflammatory proliferant injection.

Thus, the conclusions of a study and data gathered may vary a great deal, depending on the time of information gathering. IE: The epidural dextrose study. (Results to be available shortly with immediate effects on nerve calming studied by immediate follow-up data gathering to 48 hours)



Restoration of function in soft tissue is accomplished by altering the balance of growth factors (GF) and disrepair factors (DF). A growth factor is a complex protein (polypeptide) that changes the function of our DNA. This is much like a key being placed in a lock that turns on the "engine" of the cell almost instantaneously. These GFs are produced in our own cells and dextrose, in as little as 0.5% concentrations stimulations production GFs.

GFs that Dextrose Elevates							
	P D G F	Τ G F	E G F	b F G F	l G F	C T G F	
Lig/Tend Healing	X	X	Χ	X	X	X	
Cartilage Healing	Х	X		X	X		
Dextrose Effect	1	t	t	1	1	t	

This slide lists some of the key GFs that stimulate repair in ligament/tendon (Lig/Tend) and cartilage. The effect of dextrose exposure on these GF levels is shown in red. Dextrose also has effects on complex proteins that nerves produce (neuropeptides = nerve proteins) that are discussed elsewhere and are also quite important and the subject of research at this time.

Murphy et al ¹ found that elevation of glucose from 0.1% (a normal extracellular level) to 0.45% (level found in diabetics intermittently) results in production of as many as 15 different proteins, including key growth factors for soft tissue (IE connective tissue growth factor (CTGF) and transforming growth factor beta (TGF β). These effects occur within 20 minutes of cellular exposure to 0.45% Dextrose. Figure 7 shows growth factor elevations that result from elevation of dextrose level to 0.45%.²

1. Murphy M, Godson C, Cannon S, Kato S, Mackenzie HS, Martin F, Brady HR: Suppression subtractive hybridization identifies high glucose levels as a stimulus for expression of connective tissue growth factor and other genes in human mesangial cells. J Biol Chem 1999;274(9):5830-5834.

2. Reeves KD, Topol GA, Fullerton BD: Evidence-based regenerative injection therapy (prolotherapy) in sports medicine. In Seidenberg PH, Beutler PI. (Eds): The Sports Medicine Resource Manual, Philadelphia, Saunders (Elsevier), 2008, pp 611-619.



How GFs work is illustrated in a simple way in the figures above. The figure to the left shows a gene for healing covered by other DNA. When the GF attaches to its receptor on the cell surface it leads to an immediate change in the DNA structure, exposing key genes for healing.

Dextrose Levels > 10% Stimulate the Inflammatory Cascade

- Osmotic effect → Cells shrink → Stress with leakage of lipids → temporary inflammation
- Other concentrated solutions have similar effect but dextrose has several ways it works other than just osmotic

Simple osmosis, taught in biology, is the principle of water flowing from a low to high concentration. When a cell is surrounded by a high concentration, it loses water and shrinks. (crenates). The can stress the cell and cause it to release lipids form the cell membranes or to produce GFs as a reaction to a preceived threat. This creates a temporary inflammation.

This is identical to how we normally heal but tissues around the cell have not been stretched or damaged so the healing can proceed favorably without having to undue real damage such as that of an actual injury. Without this process we could not heal even from a simple cut.

The key is temporary inflammation. Chronic inflammation is not good. Temporary inflammation is. This is similar to the fact that acute dextrose elevation around a cell stimulate healing but chronic dextrose elevation, such as in diabetics, does not stimulate healthy changes.

The Needle Itself Stimulates Repair

- Cell membrane disruption → Lipid release
- Small blood vessel disruption → Bleeding with platelet and blood effects
- Reason why prolotherapy studies with injection control have been dismissed despite good results. These are injection, not placebo, controlled studies.

Nerve Calming Effect of Dextrose

When dextrose injection if given, immediate improvement is often noted.

This is a cross over effect on nerves which is described in the next slides.

Immediate improvement must mean that nerves in the areas of injection are affected favorably, and that the same solution that repairs ligament or tendon must also do something favorable for nerves. This is not prolotherapy. It is called perineural injection therapy and will be described in the next slides.

Why Does Healing Take Time?

- Growth of new tissue to line up along the weakened rope to strengthen it.
- Dehydration and tightening of the loose rope.
- Together these make and tissue more capable of normal activity and take several months, perhaps as much as a year.
- This is why short studies with limited followup are not good ways to study prolotherapy effects.

Def: Perineural Subcutaneous Injection (PSI)

- Subcutaneous near-nerve injection to restore function to peptidergic sensory nerves.
 - Mechanism proposed is by downregulation of the TRPV1 receptor. Initial research just completed is suggestive of this.
 - Injectants for this include primarily dextrose of mannitol currently but other solutions may be utilized as discoveries occur)
 - Emphasis is on a <u>direct, primarily immediate,</u> <u>effect</u> on peptidergic nerves.

PSI, by definition, is injection under the skin (subcutaneous) of solutions to restore function to nerves that cause pain. There are several types of sensory (sensation carrying) nerves that are capable of transmitting pain. Only certain sensory nerves are able to produce proteins. They are called "peptidergic" nerves, since peptide is another name for protein and ergic means "producing". These special nerves are found in virtually all parts of the body and they produce either healthy or damaging proteins. There is a control on the surface of the cell that determines whether the nerve produces healthy or damaging proteins. That control is called a "receptor". The receptor has been called the capsaicin (red-pepper) receptor because it is the same receptor that senses red pepper on the tongue. It has been given a more specific name and is now called the TRPV1 receptor. It is only found on the surface of protein-producing (peptidergic) nerve cells.

If the TRPV1 receptor is calm the nerves produce healthy proteins. If the TRPV1 receptor is overactive (also called up-regulated) it will produce damaging proteins. These damaging proteins include pain-producing proteins such as substance P and degeneration-producing proteins such CGRP (calcitonin gene related peptide) and NO (nitric oxide). There is a law (Hilton's Law) that says that sensory nerves that supply the skin over a joint also supply that joint and ligaments and tendons around that joint. Thus when these nerves are producing damaging proteins, they can travel into nearby joints, ligaments and tendons, causing pain and damage. Sensory nerves can conduct signals and transport proteins both directions so that anywhere along the "tree" of that nerve can be affected by proteins that that part of the nerve produces.

The primary way that perineural injection is thought to work is by calming (down-regulating) the TRPV1 receptor on the surface of the nerve cell.

Def: PDI (Perineural Deep Injection) (Hydrodissection)

- Stretching a deeper sensory or combined sensory/ motor nerve under guidance.
 - Mechanism proposed is by <u>untethering/restoration of</u> <u>normal motion</u> to a peripheral nerve.
 - If <u>dextrose</u> is utilized (Dextrose hydrodissection), an additional mechanism is <u>restoration of nerve function</u> by a direct effect of dextrose.
 - If <u>lidocaine</u> is utilized (Lidocaine hydrodissection), an additional mechanism is <u>nerve block</u>
 - If <u>steroid</u> is utilized (Steroid hydrodissection), an additional mechanism <u>is a local effect on arachadonic</u> <u>acid inflammation pathway.</u>

PDI (Perineural Deep Injection) is stretching of a deeper nerve under guidance. Our muscles are surrounded by thin but strong layers of tissue that are a bit like "Saran" wrap. These tissue layers are called fascia. They also separate our body into layers (Fascial layers). Sensory nerves have to penetrate these layers and can sometimes get trapped or irritated when they do so. Animal studies have shown that, when a nerve is touched all around, even without squeezing it, that nerve can become very irritable and swell, making it even harder for it to fit through the small holes in the fascia. When a injection of a solution is given around a nerve, the liquid and pull apart (dissect) the layers of fascia, freeing the nerve. The solutions used for injection always have some water in them, and the term commonly used for stretching apart by fluid injection is "hydrodissection" (hydro means water). Several solutions can be used. The effective of dextrose appears to be by calming the TRPV1 receptor. If anesthetic is used it would be a nerve block, as lidocaine actually stops nerve transmission for a period of time. If steroid is used, the injection will have a direct anti-inflammatory effect. For purposes of study discussion we will focus on the purpose of restoring nerve function since anesthetic and steroid effects generally are helpful only briefly, and seldom curative in effect.



The irritability of nerves when they are compressed, or even just surrounded and touched, has been known for nearly three decades. This is picture from a study by Bennett in which a piece of plastic was placed about a nerve, in this case the sciatic nerve of a rat. The nerve on both sides of the plastic swells up and becomes irritable. It is this same effect that is thought to happen in fascia. The same type of swelling is seen in neuromas of the feet in humans.

The reference for this, by permission, is:

Bennett GJ, Xie YK. A peripheral Mononeuropathy in rat that produces disorders of pain sensation like those seen in man. Pain 1988;33:1685-1690.

Prolotherapy and Perineural Injections are Complementary

- Perineural injection helps nerves produce proteins that encourage repair.
- Deeper injection with prolotherapy helps calm nerves in the area where repair is stimulated which can help nerves function better elsewhere.

The goal of prolotherapy is repair of connective tissue and the goal of perineural injection is to restore normal function in nerve. These two treatments have a complementary effect because:

- Through perineural injection nerves begin producing healthy instead of damaging proteins, which can favorably affect deeper structures, making it easier for them to heal.
- When deeper structures are injected in prolotherapy, nerves in those structures calm, helping other nerves in the nerve tree to begin functioning more normally, further reducing the levels of painful protein production by the nerves.

Def: Caudal Dextrose Injection

- Guided or unguided injection of dextrose into the caudal epidural space.
- Mechanism is proposed to be partly a hydrodissection effect and a direct nerve effect of dextrose, but this has not been determined.

There is a sac of fluid outside the spinal-cord-containing (dural) sac. It is called the epidural space. Steroids are commonly injected there. Dextrose is now under investigation as an alternative for epidural injection, with very favorable initial responses. Completion of the first study is anticipated within the next year. This is by a modified short needle approach very low in the back over the lower part of the sacrum bone using a thin needle at a depth of only about 1 inch.

Definition: PTA (Perineural Topical Application)

- Application of lotion to restore normal function in pain producing sensory nerves.
- Mechanism is proposed to be via downregulation of the TRPV1 receptor, but this has not been determined.
- Penetrating agents or other methods of delivery or solutions may be utilized. IE: Ultrasound Delivery of Transdermal Dextrose/Vitamin D

Yet another method of treatment being used more is the application of dextrose directly on the skin in the form of a cream. Dextrose is a small molecule, and, with the help of oil or other "penetrators" in cream, is thought to be able to penetrate the skin. Since dextrose affects nerves favorably by injection, if it can penetrate the skin, topical dextrose can affect nerves favorably. Other applicants are under investigation.

Sections of Talk Levels of Evidence

Next we will consider levels of evidence in research

U.S. Preventative Service Task Force Basic Classification of Evidence

- Level I: Well designed RCT (s) with clinical and statistically significant evidence.
- Level II: Well designed:
 - II-1 Controlled trials without randomization. Controlled treatment comparison studies.
 - II-2 Cohort (delayed Rx) studies from more than one center.
 - II-3 Uncontrolled trial with dramatic result. Uncontrolled trial with blindable objective outcome measure.
- Level III. Substantially flawed RCTs or other controlled studies. Single well designed cohort or case control study.

The highest level of evidence is a randomized controlled trial. (A RCT). This is a level I study. Depending on the size of the study, successful data capture, design quality, and other characteristics, subratings such as Ia or Ib may be given.

The next level of study, which can be powerful, particularly if more than one study is published in a given area, is level II. This can include studies in which some patients are treated immediately and others delayed (delayed treatment study). It also includes studies comparing a treatment that is being studied with one that is already known to have benefit to see how the new treatment compares with the old treatment. In addition, trials in which consecutive (one after another) patients are enrolled can reach level II if they have a dramatic result or if they have an important result that is measurable objectively. (For example, an X-ray).



Using the grading method we talked about, lets look at what evidence we have thus far for dextrose use in prolotherapy and perineural injection. (Only 1 article for the latter; see Achilles tendon study by Dr. Lyftogt) We need to remember that we can have a lot of evidence for something, enough that it is clearly not experimental, but still not force change to occur in insurance coverage. We will see that is the case.

When Will Prolotherapy Be Covered by Insurance?

- When doctors start using it routinely to avoid accusations of malpractice.
- When Insurers are forced to cover it due to fear of lawsuit. (Except government insurance which may not be sue-able.)
- When enough largely self-funded studies accumulate

Prolotherapy has been studied the most of techniques mentioned today. It is often asked "When is prolotherapy going to be covered by insurance". The short answer is that, because studies are largely self funded with no pharmaceutical company financial support, it will take a while for enough research to build up. Another issue is that there has been considerable "political" resistance to prolotherapy. This had made it apparent that the only way to get prolotherapy covered by insurance is to "force it" by having so much evidence that it becomes quite unethical not to offer prolotherapy. When that occurs, insurers will be forced to cover certain types of prolotherapy will not be "overall approved". Instead it will approved area by area and condition by condition as evidence accumulates to force that.



Note that U.S. guidelines indicate that doctors have an ethical obligation to mention treatments to patients that have level I or II evidence and minimal risk, if they know about them. Multiple reviews have been published showing that prolotherapy is as safe as any other injection technique. I.E. Rabago D, Slattengren A, Zgierska A. Prolotherapy in Primary Care Practice. Prim Care. 2010 March ; 37(1): 65–80. The following slides make it clear the there is level I or II evidence for prolotherapy in treatment of several different conditions.

Although Further Research is Needed, Prolotherapy is NOT Experimental

- It is taught as an acceptable method procedure by one or more approved post graduate programs for the healing arts? (Univ Wisconsin, specialty college in AOA), and
- It is based upon sufficient learned publications supporting the safety and efficacy? (Level II or higher in multiple areas)

For a treatment to not be considered experimental it needs to meet two basic criteria. Prolotherapy meets these criteria easily. It is taught by approved post graduate programs and there is level II or higher research in multiple areas.

Summary of Published Prolotherapy Research

 Dextrose Prolotherapy has 4 areas of level I evidence (Knee OA, OSD, Finger OA, and Lateral Epicondylosis, and 5 additional areas of level II evidence (SI joint pain, Low Back Pain, Achilles Tendinosis, Groin Pain, and ACL laxity.

This slide lists 4 areas of level I evidence and 5 additional areas of level II evidence for prolotherapy using dextrose. Thus, according to the U.S. Preventative Services Task Force, doctors should be discussing this treatment. The following slides will describe that evidence.



There are certain characteristics that very high quality studies have. This is quite a challenge for largely non funded studies. In order to do so the methods need to be quite simple whenever possible to improve affordability. A look at this list on the right reveals some obvious characteristics such as a study being good size (which usually means 20 or more in each group). The outcome of a study needs to not only be significant according to statistics, but also must be significant in terms of its amount of benefit to the patients. (IE: Did it make a big difference for the patient's quality of life?) A good study needs to follow patients long enough to be sure the benefit will hold and that "capture" of data needs to be good so that one is sure that selective data was not gathered. Studies also use measures of improvement that are called measurement tools. Some are better than others and it is preferable to use a well accepted measurement tool. Several keys often not considered include simplicity and minimal discomfort or "invasiveness" so that primary physicians will want to do the technique. (Practical P.C. [practical for primary care use])

If a good quality study can be repeated that is ideal and should force change depending on the amount of "resistance to change" there is.



This is a summary of level I evidence on use of dextrose prolotherapy.

Areas of Level II Evidence

- Tennis Elbow: Dextrose or sodium morrhate are more effecive than delayed treatment.
- SI Joint: Dextrose injection is more effective than steroid injection in treating chronic SI joint pain.
- Chronic Low Back Pain: Both dextrose and saline injection result in sustainable and significant improvements in pain and disability in chronic low back pain patients.
- Compared to a well studied and effective treatment (ELE) of Achilles tendinosis: Both dextrose PSI and combination treatment result in faster improvement in symptoms but no significant different in eventual outcome.
- Dextrose injection in groin pain results in higher full sport return than any therapy study and as much as expensive surgical options.
- Dextrose injection in knee osteoarthritis results in substantial long term functional improvement. (Twice the MCID)
- Dextrose intraarticular injection reduces pain, swelling and ACL laxity by objective machine measure progressively to 36 months in knee OA patients with KT-1000 documented ACL laxity.
- Dextrose injection in Hypoechoic regions in Achilles tendinosis results in impressive pain
 reduction accompanied by objective changes in <u>non blinded</u> ultrasound measurements.

This is a summary of level II evidence on use of dextrose prolotherapy.

RCT: Signif. Diff.	I	Thumb OA 2014, Knee OA 2013, Knee OA 2012 , OSD 2011.		
RCT: Signif Diff. Small	I	Finger OA 2000, Lat Elbow 2008		
RCT: Signif Diff. Design Limits	I	Knee OA 2000		
RCT: Signif Diff. Rx Compar.	П	Ster vs Dex SI		
RCT: Signif Diff. Delay vs Immed	Ш	Lat Elbow 2013		
RCT: Non Sig. Diff. Active control	П	Back Pain 2003, Achilles Tendinosis 2009.(PSI)		
Controlled (NonRand): Sig. Diff	Ш			
Delayed Rx (NonRand): Sig Diff	Ш			
Consecutive: Marked Change	II	Groin Pain 2008, Knee OA 2012 Single Arm		
Consecutive: Objective Measure	Ш	ACL 2003, Achilles Tendinosis 2010		
RCT/Consecutive Patient: Trends seen but size issues	ш	Multiple		

This is a table that shows the current dextrose prolotherapy studies completed and the level of evidence that they represent.

Thumb (TMC) OA 2014 Dextrose vs Steroid

 Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a doubleblind randomized clinical trial. J Orthop Sci 2014 Aug 27. [Epub ahead of print]

Jahangiri et al performed a well designed clinical trial comparing the use of steroid injection versus injection of dextrose for arthritis of the most commonly affected joint of the thumb. (The base of the thumb, also called the carpometacarpal joint.)



The requirements for this study were age 40 or more, pain three months or more, pain at least 3 on a 0 to 9 pain scale for pain with movement, and X-ray evidence of mild to moderate arthritis.

96 subjects passed screening and agreed to participate and, of these, 60 were selected randomly and assigned with 30 in each of two groups.

All were 40 years old or older.

Prior steroid injection accepted but more than 3 months before anywhere and not more than 6 months before if TMC.

Patients taking NSAIDs at time of study were excluded.

This may have favored those who would not have responded as well to steroidl

The worst thumb was chosen for treatment.

The clinical assessor and patient were blinded.

Dextrose solution was 10% concentration with 1% lidocaine.

The steroid group received saline only (no lidocaine) for first two injections and lidocaine in steroid for the third injection.

This had the potential to affect blinding if there was a difference in analgesia but, typically, injection of a joint results in analgesia. There was not test given on success of blinding but each group improved significantly which likely helped with masking, and, actually the saline group did better initially.

Hand function measure was via Health Assessment Questionnaire Disability Index (HAQ-DI) for eating, gripping and dressing, with the total of all three measures added together. Lateral pinch measured in pounds by a hydraulic pinch gauge, and pain with movement of the joint was measured by a 100 mm VAS from 0 (no pain) to 9 (worst pain).
The HAQ-DI is a widely used measurement tool. Those portions pertinent to the thumb were asked.

The dextrose was administered as 1 ml volume divided between intra an extrarticular. It is unclear if the saline was and the steroid was injected intraarticularly only.

This was a military study. (Army Univ Medical Sciences)



The statistical analysis description was well done.

Mean age participants 63.6 years.

73% were female.

In more than half the most affected hand was non dominant.

There were no differences in the groups BEFORE treatment except in pinch force, with the dextrose group worse at onset. (9.6 vs 11.6). (Table 1 in article)

As noted above, at the 6 month period the group treatment with 10% dextrose injection statistically significantly better pain and function improvements. The pinch improvement improvements did not reach significance between the two gruops.

It is important to note that the dextrose concentration of 10% does not have an inflammatory mechanism, similar to the RCT by Reeves et al in 2000, and again indicating that the mechanism of benefit from dextrose injection is not primarily, or only, but inflammation.

REC	
Good Size	Moderate Size
Sig Clinically	Both Pain and Functional Measures
Sig Statistically	Both Pain and Functional Measures
Adequate F-UP	6 Months is a bit short
Data Capture	10% or less dropout.
Accepted Tool	Reasonable choices.
Simple	Yes
Inexpensive	Yes
Min invasive	Yes
Grade	1

This study was well designed and moderate in size. Follow up was a bit short at 6 months and data capture was good.

Grade of the study is I and is the second successful RCT on treatment of finger arthritis with dextrose.

Knee OA 2013 (Dextrose vs Saline vs In-Home Exercise

 Rabago D, Patterson JJ, Mundt M, Kijowski R, Grettie J, Segal NA, Zgierska A Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. Ann Fam Med. 2013 May-Jun;11(3):229-37.

One level I study considered was published in the Annals of Family Medicine in 2013. This was a well designed randomized controlled study double blinded between dextrose injection and saline injection and also with a random assignment to in-home exercise. There is a free PDF of the whole article at http://www.annfammed.org/content/11/3/229.full?sid=cf599129-aa40-4ec3-8776-4ef8b83034fe

Here is a news article on the paper which is easy reading

http://www.medicaldaily.com/articles/15890/20130524/sugar-water-injections-knee-painarthritic-knees-prolotherapy.htm

Here is the abstract: (The following two slides will summarize)

PURPOSE Knee osteoarthritis is a common, debilitating chronic disease. Prolotherapy is an injection therapy for chronic musculoskeletal pain. We conducted a 3-arm, blinded (injector, assessor, injection group participants), randomized controlled trial to assess the efficacy of prolotherapy for knee osteoarthritis. METHODS Ninety adults with at least 3 months of painful knee osteoarthritis were randomized to blinded injection (dextrose prolotherapy or saline) or at-home exercise. Extra- and intra-articular injections were done at 1, 5, and 9 weeks with asneeded additional treatments at weeks 13 and 17. Exercise participants received an exercise manual and in-person instruction. Outcome measures included a composite score on the Western Ontario McMaster University Osteoarthritis Index (WOMAC; 100 points); knee pain scale (KPS; individual knee), post-procedure opioid medication use, and participant satisfaction. Intention-to-treat analysis using analysis of variance was used. RESULTS No baseline differences existed between groups. All groups reported improved composite WOMAC scores compared

with baseline status (P <.01) at 52 weeks. Adjusted for sex, age, and body mass index, WOMAC scores for patients receiving dextrose prolotherapy improved more (P <.05) at 52 weeks than did scores for patients receiving saline and exercise (score change: 15.3 ± 3.5 vs 7.6 ± 3.4 , and 8.2 ± 3.3 points, respectively) and exceeded the WOMAC-based minimal clinically important difference. Individual knee pain scores also improved more in the prolotherapy group (P = .05). Use of prescribed postprocedure opioid medication resulted in rapid diminution of injection-related pain. Satisfaction with prolotherapy was high. There were no adverse events. CONCLUSIONS Prolotherapy resulted in clinically meaningful sustained improvement of pain, function, and stiffness scores for knee osteoarthritis compared with blinded saline injections and at-home exercises.



Subject were randomly assigned to either at-home exercise or blinded injection of either dextrose prolotherapy or saline injeciton. Injections were both extra and intraarticular. Next Subjects either received dextrose injection or a home based program exercise program. Those that received injection were given the option of receiving a single pain pill prior to injection. Then they were injected with either dextrose or saline in a method described in the next slide. Injections were given 3 times at weekly intervals than then as needed with relative rest for 2-3 days afterwards. Those assigned randomly to home-based exercise were given a manual with 10 exercises, which were demonstrated in person. They then were contacted intemittently for encouragement and to answer questions about the exercises. Monthly mail in logs were utilized through the first 6 months to encourage and document compliance further. Subjects were informed that this was standard of care treatment and that they would likely be candidates for a follow-up study that would involve dextrose injection to further encourage compliance with exercises.

Those that received dextrose injection received 6 5 ml of 25% dextrose in the knee via a kneebent approach without ultrasound guidance and 15% dextrose into collateral ligaments in each side. This was given every 4 weeks up to 4 treatments)

The primary measuring tool was the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) which has a 24 items with 5 points each. Five items are for pain, 2 are for stiffness and 17 are function related.

A Knee pain scale was also used.

For simplicity we will consider the WOMAC results, since the results from the two main scales parallel each other.



This study involved much more injections at one time than the previous single injection study earlier. This is a depiction of areas of injection. This would be expected to address more mechanical structures of importance outside the knee and potentially nerve structures as well since many of the injections were of superficial structures which would be the equivalent of perineural subsutaneous injection. Overall, this study involved contact with deep structure with intention of repair and would be considered prolotherapy.



This graph shows changes over 1 year in the well-accepted WOMAC score. The improvement in the dextrose group was 24%, and the improvement in excess of 15 exceeds the level that clearly indicates a clinically significant improvement (MCID = minimal clinically important difference). The solid black line represents the results in knees treated with dextrose. The dash line is the saline group result and the dotted line is the exercise group result.

Note that exercise is the standard of care. However the standard of care is not necessarily effective care. This study suggests that dextrose prolotherapy may improve upon standard care of knee osteoarthritis for certain patients. This is not a large study but reinforces results in other studies to be summarized below.

usual care, so what this means is that



This graph shows changes over 1 year in the pain subscale of the WOMAC. The important thing to notice is that pain improvements were clearly diverging in the dextrose treated subjects even after only 1 treatment. It is also important to notice that the improvement was measured at 5 weeks which is too early for useful repair to occur. This suggests that there is an effect of dextrose other than repair. This would likely be an effect via decreasing nerve sensitivity in the region. (See information on perineural injection seen above)

REC	2013 Knee OA Crossover (Rabago et al)
Good Size	Moderate to somewhat small size
Sig Clinically	Yes.
Sig Statistically	Yes.
Adequate F-UP	Yes
Data Capture	Yes
Accepted Tool	Excellent tool choice
Simple	No. Multiple area of injection.
Inexpensive	Yes in materials. Moderate in terms of time
Min invasive	Yes in terms of surgery. Moderate in # injections
Grade	la-

This is a summary of the strengths of this study, with size somewhat small, and complexity of injection amount the only observed limitations. The key is that this and the following study both indicate that dextrose injection is better than standard of care exercise. This study suggests another mechanism of dextrose other than repair alone, given speed of improvement in pain. However, as there were still significant numbers of partial responders, it also suggests that not all pain sources in the knee were treated by this method.

Knee OA 2012 (Dextrose vs Exercise Crossover) • Dumais R, Benoit C, Dumais A, Babin L,

Bordage R, de Arcos C, Allard J, Bélanger M. Effect of Regenerative Injection Therapy on Function and Pain in Patients with Knee Osteoarthritis: A Randomized Crossover Study. Pain Med. 2012; 13(8):990-999.

The next level I study considered was published in the Journal of Pain Medicine and had a clear design of randomization, with randomized exercise control and a crossover design. There is no free pdf.

Here is the abstract: (The following two slides will summarize)

OBJECTIVE:

We assessed the effectiveness of regenerative injection therapy (RIT) to relieve pain and restore function in patients with knee osteoarthritis.

DESIGN:

Crossover study where participants were randomly assigned to receive exercise therapy for 32 weeks in combination with RIT on weeks 0, 4, 8, and 12 or RIT on weeks 20, 24, 28, and 32. **PATIENTS:**

Thirty-six patients with chronic knee osteoarthritis.

INTERVENTIONS:

RIT, which is made up of injections of 1 cc of 15% dextrose 0.6% lidocaine in the collateral ligaments and a 5 cc injection of 20% dextrose 0.5% lidocaine inside the knee joint.

OUTCOME MEASURES:

The primary outcome was the Western Ontario and McMaster Universities Osteoarthritis Index of severity of osteoarthrosis symptoms (WOMAC) score (range: 0-96).

RESULTS:

Following 16 weeks of follow-up, the participants assigned to RIT presented a significant reduction of their osteoarthritis symptoms (mean \pm standard deviation: -21.8 \pm 12.5, P < 0.001). WOMAC scores in this group did not change further during the last 16 weeks of follow-up, when

the participants received exercise therapy only (-1.2 \pm 10.7, P = 0.65). WOMAC scores in the first 16 weeks did not change significantly among the participants receiving exercise therapy only during this period (-6.1 \pm 13.9, P=0.11). There was a significant decrease in this groups' WOMAC scores during the last 16 weeks when the participants received RIT (-9.3 \pm 11.4, P=0.006). After 36 weeks, WOMAC scores improved in both groups by 47.3% and 36.2%. The improvement attributable to RIT alone corresponds to a 11.9-point (or 29.5%) decrease in WOMAC scores. **CONCLUSIONS:**

The use of RIT is associated with a marked reduction in symptoms, which was sustained for over 24 weeks



Subjects either received dextrose injection or a home based program exercise program. Those that received dextrose injection received 5 ml of 25% dextrose in the knee via a kneebent approach without ultrasound guidance and 15% dextrose into collateral ligaments in each side. This was given every 4 weeks up to 4 treatments)

Those assigned randomly to a home based exercise program received four strengthening exercises: (Isometric quads, leg extension exercises with quadriceps roll, straight leg raise, and sitting end range knee extension; three sets of 10 reps daily) This was via instruction by a senior physiotherapist, who reviewed exercises every 4 weeks. The same physical therapist was used throughout the study.

- The primary measuring tool was the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index)w which has a 24 items with 5 points each. Five items are for pain, 2 are for stiffness and 17 are function related.
- A Brief Pain Inventory (Short Form) was also used, as well as other secondary measures.
- Everyone stayed in their groups for 12 weeks (4 dextrose injections). They then were crossed over to start the other treatment at 20 weeks.



The WOMAC score dropped quickly (improved) in those receiving dextrose, and held improvement during the crossover into exercise.

The exercise group improved minimally and then improved rapidly after dextrose injection began such that differences between the groups became much less after three injections of dextrose.

	16 week Between Group Difference (P value)	36 week Difference	Overall Crossover Design Test
WOMAC total	.002	.046	<.001
WOMAC pain	.01	.28	.02
WOMAC stiffness	.02	.01	.002
WOMAC function	.0044	.06	.001

This is the significance of differences on the major measure (WOMAC). The second column shows that most measures were no longer significantly different after each group had the opportunity to receive dextrose. The third column takes into account the information from both portions of the crossover, showing clearly significant differences between the treatments.

Data Collection Weaknesses

- Group one: 1 dropped out from injection group due to no benefit and 2 due to complete benefit. 18/21 analyzed.
- Group two: 3 did not participate once assigned to exercise group, 2 were lost to follow-up and 1 had pain after injections and dropped out. (18/24 analyzed)
- Overall these are unlikely to have affected conclusions or significance other than by reducing power in analysis.

There was some weakness in capture of data but these should not have affected outcome or conclusions significantly

REC	2012 Knee OA Crossover (Dumais et al)
Good Size	Moderate Size
Sig Clinically	Very much so.
Sig Statistically	Yes, unequivocally.
Adequate F-UP	Limited
Data Capture	Limited
Accepted Tool	Excellent tool choice
Simple	Yes
Inexpensive	Yes
Min invasive	Yes
Grade	Ib (Single study)

This is a summary of the strengths of this study, with size somewhat small, limited time of followup to less than 1 year and some limitation of data capture. Since exercise has clearly been shown to be beneficial in knee osteoarthritis, and prolotherapy with dextrose was clinically significantly better than exercise, this is a strong support for prolotherapy.

This treatment would be practical for primary care doctors to perform since it involved injection inside the knee and over the collateral ligaments on each side.

Osgood-Schlatter Disease

Topol GA, Podesta LA, Reeves KD, Raya MF, Fullerton BD, Yeh H. Hyperosmolar Dextrose Injection for Recalcitrant Osgood-Schlatter Disease. Pediatrics 2011;128(5):e1121e1128.

The next study was published in the best journal in Pediatrics in late 2011 and was also a level I randomized controlled study. This is an open access study, so is available on line without charge.

A full PDF is available by going to the following internet site: http://pediatrics.aappublications.org/content/128/5/e1121.long



There are 3 images on this slide. The top image is a model of the kneecap, the middle image is an ultrasound of the same area in a normal person and the lower image is an ultrasound of a patient with Osgood Schlatter Disease (OSD).

The kneecap is shown on the top image. The middle image shows the end of the kneecap only. The kneecap connects with the patellar tendon, which is shown on all three images at the arrow positions. If you look closely you will see that the tendon in the bottom image is darker in areas and thicker which will represent swelling and edema in the tendon.

The right arrow points are positioned over the lower leg bone (tibia) where the patellar tendon attaches. The bump on the tibia where the tendon attaches is called the tibial tuberosity. In this middle section the bump on the tibia is smooth. In the lower section the bump on the tibia is fragmented on ultrasound image, which occurs to varying degrees in OSD.



This is a larger image of the subject with OSD. The yellow lines represent the direction of tiny needle injections used in the study. Ultrasound was not used for injection in this study, but is used here just to show the anatomy and to illustrate that injections were shallow, only a little more than 1 centimeter in depth. This ultrasound image is included to show the direction of the small (allergy size) needles that were used in the study, and the shallow depth, which is only a little more than 1 centimeter for the deepest injection.



Here are those same areas of injection shown on the ultrasound, but from a straight on view of the knee.



The frequency of this condition is seen by the fact that the primary investigator visited rugby clubs and simply asked who had knee pain, examined to diagnose Osgood Schlatter Disease (OSD) and offered treatments. Nearly 10 percent met criteria for symptomatic OSD and more than 80% of these were willing to join the study. Subjects were randomized to usual care, which is helpful for OSD, so this is a treatment comparison study. Injection alone has been found to have benefit in previous studies, and, in this study injection with lidocaine was added as an arm to compare with dextrose. Noted is that the subjects often had both legs affected and thus more then 20 knees were treated in each group. The results were significant, however, just considering one knee per subject for analysis.

Subjects were given injections of lidocaine or dextrose/lidocaine monthly X 3 or usual care, and were blinded to what they were injected with. After 3 months they were all offered dextrose so that data to 1 year could be gathered for longer term outcome data gathering.



A sports measurement scale was used which clearly shows when complete resolution of symptoms occurs (no stiffness or soreness), since some athletes do not realize that stiffness is not normal.

The spread of scores from stiff (1) to altered sport (4) to altered sleep (7) is shown. The key was alteration of sport and that was the requirement for admission into the study.





This graph shows changes over 12 months in the NPPS score. The solid black line represents the results in knees treated with dextrose. The solid blue line is lidocaine and the blue and then black line depicts results in knees that were treated with lidocaine and then received dextrose. The knees receiving dextrose rapidly dropped in levels of pain and functional limits .





This graph is similar but shows results comparing usual care to dextrose. The differences between dextrose and usual care were even more.

OSD: Significance of Differences Between Groups. ANOVA and two "Post Hoc" Tests				
		ANOVA	Tukey	
	Dextrose vs Exercise	<.00001	<.00001	
	Dextrose vs LIdocaine	.004	.017	
	Lidocaine vs Exercise	.024	.046	

When there are more than two groups that are being compared, errors can occur. These are compensated for by what is called a 'Post Hoc Multiple Comparison Tests. The most accurate is probably the Tukey.

Prolotherapy study results comparing dextrose to other injection have sometimes not shown a significant difference and have been ignored. This study clearly shows that lidocaine injection is not a placebo control and could easily confound results from studies only comparing two forms of injection. The inclusion of a usual care group helps illustrate the beneficial effect of injection alone, although dextrose injection was superior to lidocaine injection.



Less than 1% of articles reviewed in major journals by a research organization called "Essential Evicence Plus" are chosen to be reviewed.

This review of the article was by a PhD from Tufts University who rates the article in the I range (Ib-), clearly indicating that dextrose injection is effective in youths with OSD. Note that the only error here is the statement about scarring with higher concentration dextrose, which has never been shown to occur. Because OSD has changes in both cartilage and tendon, these results are consistent with potential benefit for both cartilage and tendon.

OS	D 2011 Strengths/Weaknesses	
Key Features	RCT: Osgood Schlatter Study 2011	
Good Size	Moderate Size	
Sig Clinically	Very much so.	
Sig Statistically	Yes, unequivocally.	
Adequate F-UP	2 years, more than enough.	
Data Capture	Perfect	
Accepted Tool	NPPS not well studied and no MCID.	
Simple	Yes	
Inexpensive	Yes	
Min invasive	Yes but any injection difficult in this age group.	
Practical PC	Several injections may be excessive.	
Grade	Ib (Single study)	

This study meets the criteria to change the way medicine is performed mostly but the measurement tool was not the most accepted version. (Although it showed dramatic improvements in both pain and function and has been used in other studies.) More importantly, despite use of a small needle, pediatricians may be resultant to use injection to treat and pain condition in adolescents. The small needle injection, however, was tolerated very well in the clinical study.

Thumb (TMC) OA 2014 Dextrose vs Steroid

 Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a doubleblind randomized clinical trial. J Orthop Sci 2014 Aug 27. [Epub ahead of print]

Jahangiri et al performed a well designed clinical trial comparing the use of steroid injection versus injection of dextrose for arthritis of the most commonly affected joint of the thumb. (The base of the thumb, also called the carpometacarpal joint.



The requirements for this study were age 40 or more, pain three months or more, pain at least 3 on a 0 to 9 pain scale for pain with movement, and X-ray evidence of mild to moderate arthritis.

96 subjects passed screening and agreed to participate and, of these, 60 were selected randomly and assigned with 30 in each of two groups.

All were 40 years old or older.

Prior steroid injection accepted but more than 3 months before anywhere and not more than 6 months before if TMC.

Patients taking NSAIDs at time of study were excluded.

This may have favored those who would not have responded as well to steroidl

The worst thumb was chosen for treatment.

The clinical assessor and patient were blinded.

Dextrose solution was 10% concentration with 1% lidocaine.

The steroid group received saline only (no lidocaine) for first two injections and lidocaine in steroid for the third injection.

This had the potential to affect blinding if there was a difference in analgesia but, typically, injection of a joint results in analgesia. There was not test given on success of blinding but each group improved significantly which likely helped with masking, and, actually the saline group did better initially.

Hand function measure was via Health Assessment Questionnaire Disability Index (HAQ-DI) for eating, gripping and dressing, with the total of all three measures added together. Lateral pinch measured in pounds by a hydraulic pinch gauge, and pain with movement of the joint was measured by a 100 mm VAS from 0 (no pain) to 9 (worst pain).

The HAQ-DI is a widely used measurement tool. Those portions pertinent to the thumb were asked.

The dextrose was administered as 1 ml volume divided between intra an extrarticular. It is unclear if the saline was and the steroid was injected intraarticularly only.

This was a military study. (Army Univ Medical Sciences)





There was a well-described statistic analysis section. Mean age of participants was 63.6 years. 73% were female. There were no differences between groups overall in in any variable except pinch, with the dextrose group worse at onset. (9.6 vs 11.6). (Table 1 in article)

The results at 6 months are shown here. Clinical significance of pain improvement was seen in both groups exceeding twice the MCID for pain improvement, but the dextorse group improved significantly more. Pinch force improvements were not significantly different. Functional improvement on the HAQ-DI (Hand assessment questionnaire- Disability Index) improved significantly more in the dextrose group.

This was a randomized controlled trial with subjects and the clinical assessor blinded as to the treatment received.

The authors in the full article conclude that both methods improve pain and function and there is no important difference between dextrose and steroid use regarding costs. However, side effects of steroid use and apparent benefit of dextrose suggests that dextrose injection if a better treatment than steroid injection. However, further research with a large sample size is needed to compare possible complications of LC vs DX injections in the management of OA.

Here is the abstract:

Purpose: To compare the advantages of prolotherapy in the treatment of first carpometacarpal osteoarthritis(OA) with those of corticosteroid local injection in the short and long term. **Methods:** We performed a randomized controlled trial from March 2010 to March 2011 in an outpatient clinic at a university hospital. Sixty participants (60 hands) with OA

of the first carpometacarpal joint were assigned equally to two groups. For the corticosteroid group, after 2 monthly saline placebo injections, a single dose of 40 mg methyl-prednisolone acetate (0.5ml) mixed with 0.5 ml of 2% lidocaine was injected. For the dextrose (DX) group, 0.5 ml of 20% DX was mixed with 0.5 ml of 2%lido-

caine and the injection was repeated monthly for 3 months. Pain intensity, hand function and the strength of lateral pinch grip were measured at the baseline and at 1, 2, and 6 months after the treatment.

Results: Mean age(STD) was 63.6 (9.7) years, and mean(STD) visual analog scale (VAS) was 6(2). The two groups were comparable at 2 months, but significantly different at 1 month, with better results for corticosteroid, and at 6 months with apparently more favorable outcome for DX mean difference (95%CI) in VAS = 1.1 (0.2,

2.0), p = 0.02]. After 6 months of treatment, both DX and corticosteroid injection increased functional level, but DX seemed to be more effective [mean difference(95%CI) in total function score = 1.0 (0.2,1.8), p = 0.01].

Discussion: For the long term, DX seems to be more advantageous, while the two treatments were comparable in the short term. Because of the satisfactory pain relief and restoring of function, we would prefer DX prolotherapy for the treatment of patients with OA. Level of evidence: Therapeutic studies – investigating the results of treatment; level I.

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REC	
Good Size	Moderate Size
Sig Clinically	Both Pain and Functional Measures
Sig Statistically	Both Pain and Functional Measures
Adequate F-UP	6 Months is a bit short
Data Capture	10% or less dropout.
Accepted Tool	Reasonable choices.
Simple	Yes
Inexpensive	Yes
Min invasive	Yes
Grade	1

This is a summary of the strengths of this study, with size somewhat small, and complexity of injection amount the only observed limitations. The key is that this and the following study both indicate that dextrose injection is better than standard of care exercise. This study suggests another mechanism of dextrose other than repair alone, given speed of improvement in pain. However, as there were still significant numbers of partial responders, it also suggests that not all pain sources in the thumb were treated by this method.

Finger OA 2000

 Reeves KD, Hassanein K: Randomized prospective placebocontrolled double-blind study of dextrose prolotherapy for osteoarthritic thumbs and fingers (DIP, PIP and trapeziometacarpal Joints) : Evidence of clinical efficacy. Jnl Alt Compl Med 2000;6(4):311-320.

The next study was the first randomized control trial on use of dextrose prolotherapy in finger osteoarthritis.

To view a full PDF go to the following site: http://drreeves.com/sites/default/files/Finger%20Arthritis%20Study.pdf




The dextrose group was favored in improvement of pain with grip, finger movement, and at reset. However, the difference in movement pain was the most impressive, reaching statistical significance with 42% versus 15% improvement. (A P value of < 0.5 is significant) This means that this result would occur by chance only 1/20 times.



The result on flexibility of the fingers is shown here. Those injected with dextrose improved by 8 degrees in range of motion and those injected with lidocaine lost more than 8 degrees of range of motion. After 6 months those joints injected with lidocaine received dextrose injection and range of motion improved similarly to the dextrose treated joints.

Finger OA 2000 Strengths/Weaknesses	
Key Features	REC: Finger OA Dextrose Inj. (2000 JACM)
Good Size	Small size
Sig Clinically	Yes. Difference exceeded MCID of 2.
Sig Statistically	Yes, for grip pain and ROM despite small size.
Adequate F-UP	6 months blind and 1 year total.
Data Capture	Good. Only medical dropout to 6 months.
Accepted Tool	VAS Pain but no functional hand measure.
Simple	Yes
Inexpensive	Yes
Min invasive	Yes, but method used was uncomfortable.
Practical PC	Injections not tolerated enough for P.C. use
Grade	Ib- (Small RCT)

Finger injection into the joint is uncomfortable even with a tiny needle and limit use of this method, along with resistance to prolotherapy in general. However, there are new methods of injection, which appear to be equally effective and minimally uncomfortable. This was a small study and used pain and range rather than a standard arthritis scale. However, it showed that injection with dextrose was clearly beneficial and more so than lidocaine injection in patients with symptomatic hand osteoarthritis.

The ideal treatment for finger arthritis would not involve injection at all. Note that studies on use of cream application for arthritis are in formulation at this time.

Extensor Tendinosis

 Scarpone M, Rabago DP, Zgierska A, Arbogast G, Snell E: The efficacy of prolotherapy for lateral epicondylosis: a pilot study. Clin J Sport Med 2008;18(3):248-5

This study was published in the Clinical Journal of Sports Medicine and was on "tennis elbow", also called "extensor tendinitis" or "extensor tendinosis". Tennis elbow is more accurately termed a tendinosis because the primary change is degenerative, not inflammatory. That explains why anti-inflammatory (i.e. steroid) injections typically improve pain only temporarily and less so when repeated.

For a full PDF equivalent view go to: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2751593/





The 2 month data (red) showed no significant difference between groups but by 4 months the differences between groups reached statistical significance with a reduction in pain of 90% in those subjects receiving dextrose + sodium morrhuate versus saline.

This illustrates again the importance of adequate follow-up to distinguish between temporary effects of steroid and longer terms effects of proliferant injection.



The ability to lift up something at the wrist (while palm is down), also called extensor strength, showed a substantial difference between groups favoring the dextrose/sodium morrhuate group.

Key Features	RCT: Lat Epi Dex/NaMorr (2008 CJSM)
Good Size	Small size
big Clinically	Yes. Very impressive difference
ig Statistically	Yes, for pain/ext stren. Note for grip.
Adequate F-UP	1 yr phone but results not documented.
Data Capture	Good. Only medical dropout to 6 months.
Accepted Tool	VAS Pain but no functional hand measure.
imple	Yes
nexpensive	Yes
Vin invasive	Moderate. NaMorr pain with injection.
ractical PC	NaMorr use will not encourage P.C. use
Grade	Ib- (Small RCT + Blinding ?)

The weaknesses of the tennis study are related to its size and the use of a more inflammatory agent (sodium morrhuate) along with dextrose, which primary doctors may be more reluctant to use. Nevertheless, results were impressive in this randomized controlled trial.

Knee OA Intraarticular RCT 2000

 Reeves KD, Hassanein K. Randomized Prospective Double-Blind Placebo-Controlled Study of Dextrose Prolotherapy for Knee Osteoarthritis With or Without ACL laxity. Alt Ther Hlth Med 2000;6(2):68-80

The next randomized control trial was on knee arthritis. It was the first randomized control trial of prolotherapy in knee arthritis and was published in the journal Alternative Therapies in Health and Medicine. It involved a simple injection in the knee and no other pain sources about the knee were treated. Thus this method may have left untreated several pain sources, but is easily repeated due to its simplicity.

For a pdf of the article go to:

http://www.drreeves.com/sites/default/files/Knee%20Arthritis%20Study.pdf



These were subjects with advanced knee arthritis and all candidates for knee replacement.

All TKA Candidates and Many Bone on Bone

- No significant differences overall between groups.
- Dextrose group tended to be more severe. More dextrose knees were stage IV (25 versus 15 knees by skier's view.

Although these subjects due to pain and stage of arthritis were candidates fore knee replacement, the group receiving dextrose had more knees that were void of cartilage on a skier's view, (more accurate determination of lack of cartilage than a standing view), and buckling episodes appeared to be more in the dextrose group, (the lidocaine group had very little buckling at study onset). However, these differences did not reach statistical significance.

Multivariate Results: Knee OA: Single Intraarticular

 Multivariate analysis of paired observations between 0 and 6 months for pain, swelling, buckling episodes, and knee flexion range revealed significantly more benefit from the dextrose injection (P=.015)

Overall the group receiving dextrose did better statistically between 0 and 6 months. Because multivariate analysis was significant we are able to look at individual areas of differences in the variables.



The 6 months result for walking pain favored the dextrose group, but not significantly. Subjective swelling in the knee however, improved 44% in the dextrose group versus 18% in the lidocaine group.

Also notable is that the dextrose group, when followed to one year, continued their pattern of improvement with further improvement in pain, swelling, and buckling. These patient were treated as needed after the first 6 months.



The improvement in range of motion was highly significant in favor of the group receiving dextrose. Buckling episodes improved 67% in the dextrose group and the change could not be determined accurately in the lidocaine group since they were not buckling to begin with.

A substantial improvement in knee flexibility and a reduction in buckling tendency are both important because research indicates that buckling tendency and loss of knee flexibility are two common indications for knee replacement.

Yakhdani HR, Bafghi HA, Meijer OG, Bruijn SM, van den Dikkenberg N, Stibbe AB, van Royen BJ, van Dieën JH. Stability and variability of knee kinematics during gait in knee osteoarthritis before and after replacement surgery. Clin Biomech 2010; 25(3):230-6.

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Knee OA 2000 Strengths Weakneses		
Key Features	RCT: Single Inj. OA Change (2000 ATHM)	
Good Size	Yes	
Sig Clinically	Yes. Pain, ROM, buckling progressively better.	
Sig Statistically	Swelling and range but not pain to 6 months.	
Adequate F-UP	Good follow up to 1 year.	
Data Capture	Good.	
Accepted Tool	VAS Pain and gonio. range but no WOMAC	
Simple	Yes	
Inexpensive	Yes	
Min invasive	Yes, low volume single injection method.	
Practical PC	Quite practical for primary care.	
Grade	II-1 Suspect L-BA was not a placebo control.	

The knee study did not show statistically significant improvement in all variables but was a large sized randomized control trial showing significant improvement in several key areas of knee performance. The study is flawed and not quite level I due to no use of no well accepted functional tools.

It is also important to note that results may have been reduced by use of a needle a bit too short to injection through the fat pad. (1-1/4 inch needle was used and the fat pad can be more thick than that) However, it is a simple, reproducible and minimally invasive method, and led to progressive benefit with intermittent use to one year in this group with advanced arthritis.

The fact that both groups improved in pain does not negate the fact that range and stiffness improved much more in the dextrose group. Lack of a non injection group is a limitation, as the non dextrose group may have been an active treatment via a hypoosmolar or other effect

Note that knee buckling and pain are the two biggest reasons for knee replacement, and dextrose affected both in a progressive manner.

This study showed that that even a single injection method using non-inflammatory dextrose resulted in clinical benefit.

Steroid vs Dextrose SI Injection

 Kim WM, Lee HG, Won Jeong C, Kim CM, Yoon MH. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. J Altern Complement Med Dec 2010, 16(12) p1285-90.

A randomized controlled study of the use of prolotherapy on the SI joint compared dextrose to steroid injection. As a treatment comparison trial it was blinded and randomized and would be a high level II study.

A full pdf is available at the following internet site:

http://harborfm.pbworks.com/w/file/fetch/63256359/prolotherapy%20for%20SI%20jt%20pain.pdf

Here is the abstract:

Kim WM; Lee HG; Won Jeong C; Kim CM; Yoon MH. ARTICLE TITLE: A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain [In Process Citation] ARTICLE SOURCE: J Altern Complement Med (United States), Dec 2010, 16(12) p1285-90

AUTHOR'S ADDRESS: Department of Anesthesiology and Pain Medicine, Chonnam National University Hospital, Gwang-Ju, Korea.

ABSTRACT: Abstract Objectives: Controversy exists regarding the efficacy of ligament prolotherapy in alleviating sacroiliac joint pain. The inconsistent success rates reported in previous studies may be attributed to variability in patient selection and techniques between studies. It was hypothesized that intra-articular prolotherapy for patients with a positive response to diagnostic block may mitigate the drawbacks of ligament prolotherapy. The purpose of this study was to evaluate the efficacy and long-term effectiveness of intra-articular

prolotherapy in relieving sacroiliac joint pain, compared with intra-articular steroid injection. Design: This was a prospective, randomized, controlled trial. Settings/location: The study was conducted at an outpatient pain medicine clinic at Chonnam National University Hospital in Gwang-ju, Korea. Subjects: The study included patients with sacroiliac joint pain, confirmed by (ven)50% improvement in response to local anesthetic block, lasting 3 months or longer, and who failed medical treatment. Interventions: The treatment involved intra-articular dextrose water prolotherapy or triamcinolone acetonide injection using fluoroscopic guidance, with a biweekly schedule and maximum of three injections. Outcome measures: Pain and disability scores were assessed at baseline, 2 weeks, and monthly after completion of treatment. Results: The numbers of recruited patients were 23 and 25 for the prolotherapy and steroid groups, respectively. The pain and disability scores were significantly improved from baseline in both groups at the 2-week follow-up, with no significant difference between them. The cumulative incidence of (yen)50% pain relief at 15 months was 58.7% (95% confidence interval [CI] 37.9%-79.5%) in the prolotherapy group and 10.2% (95% CI 6.7%-27.1%) in the steroid group, as determined by Kaplan-Meier analysis; there was a statistically significant difference between the groups (log-rank pv <v0.005). Conclusions: Intra-articular prolotherapy provided significant relief of sacroiliac joint pain, and its effects lasted longer than those of steroid injections. Further studies are needed to confirm the safety of the procedure and to validate an appropriate injection protocol.



It is not easy to determine if pain is coming from the sacroiliac joint. In order to be more confident that their patients did have pain from the SI joint, the authors used X-ray guidance to inject anesthetic into the joint. If the patient's pain improved 50% or more then it was considered that they had pain in large part from the SI joint. The pain also had to be chronic so it would not likely go away on its own. (More than 3 months)

Subjects were then randomized to receive steroid injection (trimcinolone) or 25% dextrose injection, also under X-Ray guidance, into the SI joint. 2.5 ml of either solution was injected.

The data "capture" was good with minimal patient dropout, 1 in each group, and follow up was for a total of 15 months.



Quick improvement was seen in each group in both measures of pain and disability, as this two week data shows. Pain improved by 3/4 in each group and disability measures by 2/3.

It is important to note that the speed of improvement cannot be due to repair of the SI ligament, as that takes several months. This speed of improvement indicates a nerve mechanism.

Steroid treats inflammation that is prostaglandin based. Dextrose injection treats inflammation that is nerve based. They are two different pathways.



The long term data is shown in this slide. The authors considered "substantial benefit" to be more than a 50% level of pain relief and the percentage of patients that maintained that level of pain relief was followed. Although the 2 week data looked good for both groups, later data showed highly significant differences between groups. The number of subjects with more than 50% pain relief in the steroid-injection group was only 10% at 15 months compared to nearly 60% in the dextrose group. This suggests a longer term effect of dextrose on the tissue, and that process is thought to involve repair as described earlier. Thus is takes several months for it to be observed.

SI 2010 Strengths/Weaknesses		
Key Features	RCT:SI Steroid vs Dextrose: JACM 2010	
Good Size	Moderate Size	
Sig Clinically	Very much so.	
Sig Statistically	Yes, unequivocally.	
Adequate F-UP	15 months	
Data Capture	Very good	
Accepted Tool	Yes ODI and	
Simple	Yes	
Inexpensive	No. Requires Fluoro. But single injection	
Min invasive	Moderate. But limited by specificity.	
Practical PC	Fluoro removes it from this possibility	
Grade	Ib (Single study, peer review limits in JACM)	

If one considers the sacroilaic (SI) joint study, it rates high in all elements except it is not truly inexpensive, requiring X-ray guidance. Due to the use of the special X-ray (fluoroscopy) it will not be practical for primary doctors to use which will limit spread of this technique.

Dex vs Dex/NaM vs Wait and See Results to 16 weeks

- Both prolotherapy groups did better than the wait and see group. P < .05
- IE: (16 week): PRTEE Improved 18.7 in Dex, 17.5 in Dex/NaM and 9.3 In wait and see groups. (P < .05). Grip strength better in Dex than both (P < .05)
- These improvement exceed the MCID and further improvements were noted to 32 weeks, although wait and see groups were not followed after 16 weeks.

Results: The improvements in both prolotherapy groups was significantly better than in the wait and see control group at 4, 8 and 16 weeks. (P < .05) The differences were clinically important. For example, the Patient Rated Tennis Elbow Evaluation has been evaluated for what is a clinically important difference. A 7 point improvement (22%) is a little better an a 11 point improvement (37%) is much better.

In this study at 16 weeks the dextrose group improved 18.7 points, the dextrose/sodium morrhuate group improved 17.5 points, and the wait and see group improved 9.3 points. Grip was better in the dextrose group than in both other groups.

The reference for MCID was:

https://uhra.herts.ac.uk/dspace/bitstream/2299/6682/1/Measuring_PRTEE_clinically_Importan t_Change_submission_revised.pdf Thesis on : Measuring clinically Important Change with the Patient-rated Tennis Elbow Evaluation (PRTEE) Short title: Measuring change with the PRTEE

Extensor Tendinosis

 Rabago D, Lee KS, Ryan M, Chourasia AO, Sesto ME, Zgierska A, Kijowski R, Grettie J, Wilson J, Miller D. Hypertonic dextrose and morrhuate sodium injection (prolotherapy) for lateral epicondylosis (tennis elbow): results of a single-blind, pilot-level, randomized controlled trial. Am J Phys Med Rehabil. 2013 Jul;92(7):587-96. doi: 10.1097/PHM.0b013e31827d695f.

This study was published in the American Journal of Physical Medicine and rehabilitation.

This article is an article under NIH public access.

Paste http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3700532/ into you browser to see it in its entirely



2 subjects dropped form the dextrose group. 1 for unrelated medical urgency and 1 due to advice of a specialist. 1 stopped from the dextrose/morrhute group due to medical urgency and 1 from the wait and see group due to deciding against participation after starting.

Randomization was to three groups. One group received proliferant injection with dextrose 10.7% and sodium morrhute 0.7% on 3 occasions (@ 0, 4 and 8 weeks). A second group received 20% dextrose at the same interval. The third group received no treatment for the first 16 weeks.

The primary measurement tool was the Patient-Rated Tennis Elbow Evaluation (100 points) at 4, 8, and 16 wks (all groups) and at 32 wks (Just the groups receiving injection treatment). It has five items for pain and ten for function< It has good reliability and sensitivity to change, and scores range from 0 (no pain or disability) to 100 (extreme pain or disability). The minimal clinical important difference for PRTEE is 11 points or 37% improvement.

Secondary measure were pain free grip strength, MRI 0-3 grading from no tendinopathy to full thickness tear, ultrasound measures to be reported in a separate article, and a 5 point satisfactory rating with 5 = vary satisfied.

Ultrasound guidance was used for prolotherapy.



A significant difference was noted between each of the prolotherapy groups and the wait and see group, at one or more points for both dextrose and dextrose/sodium morrhuate but not at every point in time. Each group continued to increase but data to 32 weeks was not available for comparison The prolotherapy groups each achieved MCID easily and the wait and see group did not.

The PRTEE score for both prolotherapy groups substantially exceeded minimal clinical important difference on the PRTEE, whereas that of the wait-and-see control group participants did not. Each prolotherapy group continued improving through 32 weeks and data would have been helpful to compare with control, but was not available. However, by 32 weeks each group had improved 57% (dextrose) and 75% (dextrose/mannnitol) in the PRTEE score, quite clinically remarkable. The ordinal difference between each prolotherapy group and the control group was not significant at each point in time, given the magnitude of the difference that appeared to be a limitation of the size of the study.

Grip strength improved in the dextrose group significantly more in the dextrose group than either of the other groups at 16 weeks.



This is the data in graphic form. Compared to the MCID of 11 or 37% the Dextrose group improved by 45% at 16 weeks and 57% by 32 weeks. The Dextrose/Sodium morrhuate group improved by 54% at 16 weeks and 75% by 32 weeks.

The participants receiving PrT-DM reported more severe and persistent injection related pain taking up to 3 wks to resolve.

Key Features	
Good Size	Small size
Sig Clinically	Yes. Substantial changes in primary measure.
Sig Statistically	Borderline, a function of small group size .
Adequate F-UP	Only 16 weeks follow-up of non-blinded control.
Data Capture	Good. Only medical dropout to 6 months.
Accepted Tool	Well accepted tool.
Simple	Yes. Did use ultrasound guidance for injection.
Inexpensive	Yes
Min invasive	Yes. Sodium morrhuate more uncomfortable.
Practical PC	Yes, although used Ultrasound guidance.
Grade	II Small, non-blinded control with short duration fup.

A very useful pilot study. The use of a wait and see control group was very helpful although follow-up to 16 weeks was too short to take advantage of the control group comparison further. Both dextrose and sodium morrhuate were clearly effective in improving function considerably on a well accepted tool.

BACK PAIN 2003

 Yelland MJ, Glasziou PP, Bogduk N, Schluter PJ, McKernon M: Prolotherapy injections, saline injections, and exercises for chronic lowback pain: A randomized trial. Spine 2003;29(1):9-16.

The only blind and randomized study of back pain studying a single intervention was published in the journal Spine.

For a PDF of this article go to: http://www.cebp.nl/media/m1107.pdf



110 patients consented to participate in the study, and they were assigned to either 20% dextrose in .2% lidocaine or to normal saline. It is very important to notice that the injection method was limited to only 5 injections on each side, which would not be considered a comprehensive approach.

However this study was excellent in terms of data capture to 1 year and had good data capture to 2 years.





The important thing to notice about this slide is the strong evidence of ability to improve pain and functional limitations and to hold benefit to a 2 year point of follow-up which would be comparable or better than long term follow-up data post back surgery.

Back Pain 2003 Strengths/Weaknesses		
Key Features	RCT: 20% Glu vs Saline 2003 Spine	
Good Size	Yes	
Sig Clinically	Yes. Substantial disab impr to 2 years. Su	
Sig Statistically	No.	
Adequate F-UP	Good follow up to 2 year.	
Data Capture	Good.	
Accepted Tool	VAS Pain and Roland Morris	
Simple	Method simple but likely incomplete	
Inexpensive	No. 6 injections at 2 weeks a lot of time/etc.	
Min invasive	Limited injections each session	
Practical PC	Impractical treatment frequency for P.C.	
Grade	II-1 No real control arm.	

The improvement in functional limits and pain in both groups indicated that both treatments methods were beneficial. However this study is dismissed by those that overlook the substantial improvement over 2 years. Instead, they focus on thinking that saline injection is a placebo and that dextrose is not better than placebo treatment.

This study reminds us how important it is to have a usual care treatment group so that the result of the study are not dismissed.

Achilles Tendonosis

 Yelland MJ, Sweeting KR, Lyftogt JA, Ng SK, Scuffham PA, Evans KA.
Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. Br J
Sports Med (England), Apr 2011, 45(5) p421-8.

The 2009 Achilles Tendon study published in the British Journal of Sports Medicine and compared usual care with dextrose injection. This was not typical prolotherapy as neither the Achilles tendon nor its attachment were injected directly. This treatment was likely a cross between regular prolotherapy and PSI (Perineural Subcutaneous Injection). The injection frequency (weekly) is that more typically seen with PSI

No free PDF is available. Here is the abstract:

<u>Br J Sports Med.</u> 2011 Apr;45(5):421-8. doi: 10.1136/bjsm.2009.057968. Epub 2009 Jun 22. **Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial.**

Yelland MJ, Sweeting KR, Lyftogt JA, Ng SK, Scuffham PA, Evans KA.

Source

Griffith University, Logan and Gold Coast, Australia. m.yelland@griffith.edu.au

Abstract

OBJECTIVE:

To compare the effectiveness and cost-effectiveness of eccentric loading exercises (ELE) with prolotherapy injections used singly and in combination for painful Achilles tendinosis. **DESIGN:**

A single-blinded randomised clinical trial. The primary outcome measure was the VISA-A questionnaire with a minimum clinically important change (MCIC) of 20 points. **SETTING:**

Five Australian primary care centres. **PARTICIPANTS:**

43 patients with painful mid-portion Achilles tendinosis commenced and 40 completed treatment protocols.

INTERVENTIONS:

Participants were randomised to a 12-week program of ELE (n=15), or prolotherapy injections of hypertonic glucose with lignocaine alongside the affected tendon (n=14) or combined treatment (n=14).

MAIN OUTCOME MEASUREMENTS:

VISA-A, pain, stiffness and limitation of activity scores; treatment costs.

RESULTS:

At 12 months, proportions achieving the MCIC for VISA-A were 73% for ELE, 79% for prolotherapy and 86% for combined treatment. Mean (95% CI) increases in VISA-A scores at 12 months were 23.7 (15.6 to 31.9) for ELE, 27.5 (12.8 to 42.2) for prolotherapy and 41.1 (29.3 to 52.9) for combined treatment. At 6 weeks and 12 months, these increases were significantly less for ELE than for combined treatment.

TRIAL REGISTRATION NUMBER:

ACTRN: 12606000179538.



This study was of patients with Achilles Tendinosis affecting the mid substance of the Achilles rather than its insertion. The mid substance patients are those who have a bump on the Achilles where it is abnormally large. (It accumulates fluid and swells in the area it is affected. It is important to be aware that eccentric lengthening exercises are clearly helpful, with several studies showing that eccentric lengthening is a helpful and thus "active" treatment. Thus there was not placebo group here. Instead this study design compared one beneficial treatment (ELE) to another that is being studied (Dextrose injection). One group received both treatments at the same time.




This study was of patients with Achilles Tendinosis affecting the mid substance of the Achilles rather than insertional. These are the patients with a bump on the Achilles where it is abnormally large. It is important to be aware that eccentric lengthening exercises are clearly helpful so that usual care is actually effective. Therefore, one again that there was not a true placebo group. Rather this study design compared one beneficial treatment (ELE) to another that is being studied (Dextrose injection), and to both together.



An improvement of more than 20 on the VISA-A scale is clinically significant. Both ELE and Improvement in the main functional scale, the VISA-A scale was significantly faster in those receiving dextrose injection or both treatments but the overall amount of increase in VISA-A scale was similar enough in all groups not to reach statistical significance.



There was a trend to more improvement in pain and stiffness in the group receiving peritendinous injection of dextrose. However this was not statistically significant. Given the magnitude of difference, however, this suggests that the study size was likely too small. Funds to repeat the study in a larger version have not been available.



There was a trend to more improvement in pain and stiffness in the group receiving peritendinous injection of dextrose. However this was not statistically significant. Given the magnitude of difference, however, this suggests that the study size was likely too small. Funds to repeat the study in a larger version have not been available.

Achilles Tendinosis 2009 Strengths/Weaknesses		
Key Features	RCT: ELE vs LT vs BOTH 2009 BJSM	
Good Size	Small	
Sig Clinically	VISA-A clearly shows signif change in all groups	
Sig Statistically	No.	
Adequate F-UP	Good follow up to 1 year.	
Data Capture	Good.	
Accepted Tool	VISA-A and pain/stiffness/activ. limitation	
Simple	Simple but less than optimum for LyT	
Inexpensive	More cost effective for combined treatment.	
Min invasive	Compared to pain of ELE, LyT likely less	
Practical PC	Treatment frequency an issue for P.C.	
Grade	II-1 No real control arm.	

This study showed that subcutaneous injection performed equally to known effective physical therapy for Achilles tendinosis and that both did better. It was too small to show much else.

Groin Pain Study

• Topol GA, Reeves KD. Regenerative injection of elite athletes with career-altering chronic groin pain who fail conservative treatment: a consecutive case series. Am J Phys Med Rehabil. 2008;87(11):890-902.

This groin pain study was not randomized but was consecutive patient, good size, with very little dropout, long follow-up, and clearly treated athletes who had failed usual care and who had no alternatives but surgery.

No free PDF is available. Here is the abstract

<u>Am J Phys Med Rehabil.</u> 2008 Nov;87(11):890-902. doi: 10.1097/PHM.0b013e31818377b6. Regenerative injection of elite athletes with career-altering chronic groin pain who fail conservative treatment: a consecutive case series.

Topol GA, Reeves KD.

Source

Physical Medicine and Rehabilitation Service, Jaime Slullitel Rosario Orthopedic and Trauma Institute, Argentina.

Abstract

OBJECTIVE:

To obtain multisport and long-term outcome data from the use of regenerative injection therapy on career-threatened athletes.

DESIGN:

Consecutive enrollment of elite performance-limited athletes with chronic groin/abdominal pain who failed a conservative treatment trial. The treatment consisted of monthly injections of 12.5% dextrose in 0.5% lidocaine in abdominal and adductor attachments on the pubis. Injection of the nociceptive source was confirmed by repetition of resistive testing 5 mins after injection.

RESULTS:

Seventy-five athletes were enrolled. Seventy-two athletes (39 rugby, 29 soccer, and 4 other) completed the minimum two-treatment protocol. Their data revealed a mean groin pain history of 11 (3-60) mos. Average number of treatments received was 3 (1-6). Individual paired t tests for Visual Analog Scale (VAS) of pain with sport (VAS Pain) and Nirschl pain phase scale measured at 0 and an average of 26 (6-73) mos indicated VAS Pain improvement of 82% (P < 10) and Nirschl pain phase scale improvement of 78% (P < 10). Six athletes did not improve following regenerative injection therapy treatment, and the remaining 66 returned to unrestricted sport. Return to unrestricted sport occurred in an average of 3 (1-5) mos. **CONCLUSIONS:**

Athletes returned to full elite-level performance in a timely and sustainable manner after regenerative injection therapy using dextrose.



75 were enrolled and only 3 were disqualified due to receiving other treatment prior to completion of a 2 treatment trial. The keys to this study were the exam specificity, achieving in two ways. First, reproduction of exact pain by either squeezing legs together or doing a partial setup. Second, complete relief of pain with those same maneuvers after injection to further confirm diagnosis and confirm completeness of injection.



NPPS: Nirschl Pain Phase Scale

- 0: No pain or stiffness
- 1: STIFF/SORE after sport
- 2: Stiff/sore before and after sport
- 3: Pain during sport
- **4. SPORT ALTERED**
- 5. Painful self care.
- 6. Self care interference.

7. SLEEP ALTERED

A sports measurement scale was used which clearly shows when complete resolution of symptoms occurs (no stiffness or soreness), since some athletes do not realize that stiffness is not normal.

The spread of scores from stiff (1) to altered sport (4) to altered sleep (7) is shown. The key was alteration of sport and that was the requirement for admission into the study.



All participants were required to have at least altered sport (phase 4). Thus initial levels of the sports scale (NPS) averaged more than 4.

With a mean of 3 injections, the 6 month follow-up is shown in the middle bars. Follow-up to mean of 26 months showed the results were sustained with additional treatment in only three athletes in these vigorous elite level athletes. (Predominantly rugby athletes)



An examination of function scores before (blue) and after (red) treatment showed that 72/72 athletes were sport impaired by their pain pre treatment and only 6/72 were sport impaired by pain after treatments.

Sli	de	1	0	7
Sli	de	1	0	7

G	Groin Pain Rx Options			
Туре	Verrall (Therapy)	Topol (Dextrose)	VanVeen (Surgery)	
Size	27	72	55	
Subjects	All comers	All comers	Abdominal Involvement	
Previous Rx Failure	Not required	Required	Not documented	
Pain Duration	5(2-11 mo)	11(3-60 mo)	>3 mo	
Full Sport	74% (12-18 mo)	92% by 3 mo	91% by 3 mo	
Full Level Play	Not confirmed	92% by 3 mo	92% by 3 mo	
Follow-up	2 years	26(6-73 mo)	2 yrs	

Comparing outcome in this study to the best therapy outcome study available and the best surgical outcome study available showed clearly superior results in speed and percentage return to full sport in the dextrose and surgically treated patients and no clear difference, other than an expected marked difference in costs, between dextrose injection and surgery. The references for the studies compared are: Verrall GM, Slavotinek JP, Fon GT, Barnes PG: Outcome

verrail Givi, Slavolinek JP, Fon GT, Barnes PG. O

of conservative management of athletic

chronic groin injury diagnosed as pubic bone stress

injury. Am J Sports Med 2007;35:467-74

van Veen RN, de Baat P, Heijboer MP, et al.: Successful endoscopic treatment of chronic groin pain in athletes. *Surg Endosc 2007;21:189–93*

Groin Pain 2008: Strengths/Weaknesses		
Key Features	CP: Groin Pain Study: AJPM&R 2008	
Good Size	Yes	
Sig Clinically	Yes. Very impressive difference	
Sig Statistically	No control.	
Adequate F-UP	Exceptional. Mean 26 (6-73 mo)	
Data Capture	Exceptional. 100% data capture.	
Accepted Tool	NPPS not well studied, but specific for sport	
Simple	Yes	
Inexpensive	Yes	
Min invasive	Small needle injection min-mod invasive	
Practical PC	Technique not for beginners	
Grade	II-3 (CP study with exceptional results)	

The groin pain study by its good size, dramatic outcome, excellent data capture and long-term follow-up is easily a level II study.

Knee OA 2012: Single Arm Dextrose

 Rabago D, Zgierska A, Fortney L, Kijowski R, Mundt M, Ryan M, Grettie J, Patterson JJ. Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single-arm uncontrolled study with 1-year follow-up. J Altern Complement Med. 2012 Apr;18(4):408-14.

This knee study on dextrose injection was published in 2012.

No free PDF is available. Here is the abstract:

Altern Complement Med. 2012 Apr;18(4):408-14. doi: 10.1089/acm.2011.0030.

Hypertonic dextrose injections (prolotherapy) for knee osteoarthritis: results of a single-arm uncontrolled study with 1-year follow-up.

Rabago D, Zgierska A, Fortney L, Kijowski R, Mundt M, Ryan M, Grettie J, Patterson JJ.

Source

Department of Family Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI 53715, USA. David.rabago@fammed.wisc.edu

Abstract

OBJECTIVE:

The objective of this study was to determine whether prolotherapy, an injection-based complementary treatment for chronic musculoskeletal conditions, improves pain, stiffness, and function in adults with symptomatic knee osteoarthritis (KOA) compared to baseline status.

DESIGN:

This was a prospective, uncontrolled study with 1-year follow-up.

SETTING:

The study was conducted in an outpatient setting.

PARTICIPANTS:

Adults with at least 3 months of symptomatic KOA, recruited from clinical and community settings, participated in the study.

INTERVENTIONS:

Participants received extra-articular injections of 15% dextrose and intra-articular prolotherapy injections of 25% dextrose at 1, 5, and 9 weeks, with as-needed treatments at weeks 13 and 17. **OUTCOME MEASURES:**

Primary outcome measure was the validated Western Ontario McMaster University Osteoarthritis Index (WOMAC). Secondary outcome measure was the validated Knee Pain Scale (KPS). Tertiary outcome measure was procedure-related pain severity and participant satisfaction.

RESULTS:

Thirty-six (36) participants (60 ± 8.7 years old, 21 female) with moderate-to-severe KOA received an average of 4.3 ± 0.7 prolotherapy injection sessions over a 17-week treatment period and reported progressively improved scores during the 52-week study on WOMAC and KPS measures. Participants reported overall WOMAC score improvement 4 weeks after the first injection session (7.6 ± 2.4 points, 17.2%), and continued to improve through the 52-week follow-up (15.9 ± 2.5 points, p<0.001, 36.1%). KPS scores improved in both injected (p<0.001) and uninjected knees (p<0.05). Prescribed low-dose opioid analgesia effectively treated procedure-related pain. Satisfaction was high and there were no adverse events. Female gender, age 46-65 years old, and body-mass index of 25 kg/m(2) or less were associated with greater improvement on the WOMAC instrument.

CONCLUSIONS:

In adults with moderate to severe KOA, dextrose prolotherapy may result in safe, significant, sustained improvement of knee pain, function, and stiffness scores. Randomized multidisciplinary effectiveness trials including evaluation of potential disease modification are warranted to further assess the effects of prolotherapy for KOA.





The method here was the same as that of the randomized controlled study described earlier. This is a depiction of areas of injection. This would be expected to address more mechanical structures of importance outside the knee and potentially nerve structures as well since many of the injections were of superficial structures which would be the equivalent of perineural subsutaneous injection. Overall, this study involved contact with deep structure with intention of repair and would be considered prolotherapy.

Knee OA 2012 Single Arm Results

- WOMAC change 17.2% at first 4 week follow-up. (1 injection) and 36% at 52 week follow-up. (Average 4.3 injections)
- Note MCID (Minimal Clinically Important Difference) for total WOMAC in Knee OA approximates 16.

The benefits in both pain and functional improvements were substantial in this study. For example by 4 weeks improvements already exceeded the minimal clinically important difference (MCID) for patients with knee arthritis and, by 1 year more than doubled that improvement with a mean number of injections of 4.3

Knee OA 2012 Single Arm: Strengths/Weaknesses		
Key Features	Knee OA 2012	
Good Size	Yes – 36 subjects	
Sig Clinically	Twice MCID difference.	
Sig Statistically	No control.	
Adequate F-UP	Good follow-up to 1 year.	
Data Capture	Excellent data capture	
Accepted Tool	WOMAC and KPS	
Simple	Yes	
Inexpensive	Yes	
Min invasive	Multiple injections about the knee	
Practical PC	Technique not for beginners	
Grade	II-3 (CP study with exceptional results)	

Given the degree of improvement, excellent data capture and follow-up to 1 year, this would be level II-3 study. However the technique involvement multiple injections in a method clearly not for beginners. (Not easily imitatable)

ACL Study

 Reeves KD, Hassanein K. Long-term effects of dextrose prolotherapy for anterior cruciate ligament laxity. Altern Ther Health Med, May-Jun 2003, 9(3) p58-62.

A study on the subjects with damage of the anterior cruciate ligament (ACL) of the knee was published in 2003

For a PDF of this study go to: http://drreeves.com/sites/default/files/ACL%20Laxity%20Study.pdf



18 patients were enrolled, with 2 dropouts before a year for reasons not connected with the treatment.

Several very important features of this study are worth mentioning.

- These were older subjects who did not want surgery. Most had arthritis of the knee as well and most would quality for knee replacement.
- The treatment only involved injection of the knee. It did not require any special training in trying to directly inject the ligament (or what was left of it)
- The KT-1000 (joint looseness measuring device) is objective and well-studied. It will successfully demonstrate changes in looseness of the knee. However was objective and was performed in a blinded manner in that the performer did not know which knee was affected. However, the KT-1000 can not determine if the ACL ligament is completely torn and a number of the 16 subjects may have had completely torn ACL ligaments.
- Both knees were treated in those who had pain in both knees since some subjects were enrolled in a knee osteoarthritis study as well, and, if both knees were tightened, the ability to tell a difference with treatment could have been prevented

Despite the challenges of a simple single injection method, advanced arthritis in many, potential complete tears in the ACL, treating both knees instead of just one in these patients who also had arthritis, of the 16 subjects who received full treatment (minimum of 3 injections at 2 month intervals), 9 were no longer loose by 1 year.



Improvements in pain and looseness (as measured by machine) were progressive over 36 months. Note these patients were receiving as needed injection with dextrose due to the presence of osteoarthritis related pain as well.

Key Features	CP: ACL Laxity Alt Ther Health Med 2003
Good Size	Small size
Sig Clinically	Yes, and progressive over time.
Sig Statistically	No group to compare with.
Adequate F-UP	36 months
Data Capture	Fair to Good. 14/18 to 3 years (Medical in 2)
Accepted Tool	KT-1000 well studied but no MRI available
Simple	Yes
Inexpensive	Yes
Min invasive	Yes. Single injection.
Practical PC	Yes. Likely to pick this up if repeated.
Grade	II-C

This study was small, and although level II due to the use of objective measure, should be repeated in a larger size and with MRI confirmation of whether the ACL ligament was still intact at the start of the study.

Achilles Study (Ryan): 2010

 Ryan M, Wong A, Taunton J. Favorable outcomes after sonographically guided intratendinous injection of hyperosmolar dextrose for chronic insertional and midportion achilles tendinosis. Am J Roentgenol. 2010 Apr;194(4):1047-53.

An Achilles tendon study that was also level II due to objective measures, and used 25% dextrose for injection, in consecutive subjects with pre and post ultrasound examinations, was published in the American Journal of Roentgenology.

For a PDF of this study go to: http://www.ajronline.org/doi/pdf/10.2214/AJR.09.3255



99 subjects were enrolled and 25% dextrose was injected in areas of observed abnormality in the Achilles tendon. An average of 5 injection sessions were given. 4 month follow-up was 100% and long-term follow-up was fair to good.



The % improvement in pain increased from 4 months to more than 1 year indicated clearly sustainable improvement.



The tendon changes were rated in severity before (blue) and after (red) treatment. The severity of changes decreased from 0 to 4 months. The long term data follow-up was for pain only.

Ultrasound Data

Midportion Tendinosis: Size of hypoechoic region (mm2 ± SD) $81.60 \pm 108.7 \rightarrow 52.1 \pm 87.1$ (P < .05) Insertional Tendinosis Intratendinous tear size (mm ± SD) $5.3 \pm 4.5 \rightarrow 1.6 \pm 2.8a$ (P < .05)

Changes were significant by ultrasound, although it should be noted that the measure, although objective, was not measured in a blind fashion.

Key Features	CP: Achilles Tendon Am J Roent 2010	
Good Size	Yes	
Sig Clinically	Yes, and progressive over time.	
Sig Statistically	No group to compare with.	
Adequate F-UP	12+ months	
Data Capture	Excellent to 4 months. Fair to good to 1> 1 year.	
Accepted Tool	Pain measure only but with ultrasound use.	
Simple	Yes	
Inexpensive	No, with guidance for every injection .	
Min invasive	Multiple injections	
Practical PC	Too much technology and injection for P.C.	
Grade	II-C	

This was a good size study with an objective measure. However the amount of injection , (a median of 5 treatments) and need for ultrasound guidance will preclude its use by primary care doctors.

Plantar Fasciosis Study: Dextrose vs PRP

• Kim E, Lee JH. Autologous platelet-rich plasma versus dextrose prolotherapy for the treatment of chronic recalcitrant plantar fasciitis. PMR. 2014;6(2):152-158.

A 2014 publication by Kim et al from Seoul, Korea, was a single blind (subject blinded) comparison of dextrose versus PRP injection in the plantar fascia of those with chronic plantar fasciosis.

Plantar Fasciosis Study Method

- Twenty one patients with chronic plantar fasciosis with more than 4 mm thickness of plantar fascia.
- Injection at time 0 and 2 weeks with 2 ml of PRP or 15% dextrose/lidocaine.
- Outcome measures: Foot Functional Index pain, disability and activity limitation subscales.
- Data collected at 0, 2 and 6 months.

The method is clear. Two injections of each at 2 week intervals. It is notable that this is shorter than the usual healing interval of 6 to 8 weeks.



Note there were errors in calculations of percentage for foot functional index, pain and disability. Given the numbers provided, the percentage improvements are as summarized as above. The values above are correct.

On the foot function index improvement with standard deviation in parentheses for Dextrose group was from 132.5(31.1) to 97.7(52.5) = 26% and for the PRP group was from 151.5(37.9) to 81.6(55.3) = 46%. The article stated 15.1% and 30.4%

Pain subcategory improvement: 56.5(14.0) to 41.14(21.4) = 27% for dextrose and 60.4(14.7) to 33.7(23.4) = 44% for PRP. The article stated 17.1% and 29.7%

Disability subscale improvement: 53.1(15.7) to 40.3(21.8) = 24% dextrose and 55.8(19.5) to 31.9(22.4) = 43% PRP.

Note 1 dropped out of the PRP group, which can make a difference in the outcome AND the groups were small, which explains why the outcomes are not significantly different although they appear to be trending in favor of PRP. Note PRP is more expensive and this study does not address cost effectiveness.

Key Features	RTCP: Plantar Fasciosis PMR 2014	
Good Size	Small	
Sig Clinically	Yes in both groups.	
Sig Statistically	No control group.	
Adequate F-UP	6 months.	
Data Capture	Good to 6 months.	
Accepted Tool	Yes (HAQ) (Hand Assessment Questionnaire)	
Simple	Yes	
Inexpensive	Moderate, with ultrasound guidance and PRP.	
Min invasive	Two injection sessions.	
Practical PC	Moderate technology.	
Grade	11	

This was randomized and blinded treatment comparison study of those with pain duration mean of 2.8 years. The results in both groups were significant clinically. Both were active groups and the results were not significantly different from each other. Follow up was somewhat short at 6 months.

Data capture was good, but with 1 dropout in a small study, not excellent.

Given that this was a treatment comparison study, and small, although blinded, it would be a level II study



Here are some studies related to PRP injection, not comparing it with dextrose prolotherapy. Lttle information is available to compare to dextrose to platelet rich plasma because of cost factors and no interest in companies to support such a comparison. That will come with time. For now, a few articles are of particular importance.

PRP vs Dextrose: Small Study on Plantar Fasciosis

 Kim E, Lee JH. Autologous plateletrich plasma versus dextrose prolotherapy for the treatment of chronic recalcitrant plantar fasciitis. PMR 2014; 6(2):152-8. doi: 10.1016/j.pmrj.2013.07.003. Epub 2013 Jul 19.
Improving Study Quality PRP

- PRP vs Shock Wave Jumper's Knee Randomized (Success)
- PRP vs Steroid vs Saline Lat Epicondy RCT blinded (Design Issues)
- PRP vs Saline RCT Knee OA blinded (Success)
- PRP vs HA in Knee OA (Mixed Success) But Systemic GF effect issue

PRP vs Shock Wave for Jumper's Knee • Vetrano M, Castorina A, Vulpiani MC, Baldini R, Pavan A, Ferretti A. Platelet-Rich Plasma Versus Focused Shock Waves in the Treatment of Jumper's Knee in Athletes. Am J Sports Med. 2013 Feb 13.

This study in the American Journal of Sport's Medicine was a level I (Randomized but not blinded trial) comparing PRP to focused shock waves. (Blinded study was not approved by the human subject committee)

The PDF is not available on line but here is the abstract and the following slides were formed from a review of the original article.

Background: Tendinopathies represent a serious challenge for orthopaedic surgeons involved in treatment of athletes.

Purpose: To compare the effectiveness and safety of platelet-rich plasma (PRP) injections and focused extracorporeal shock wave therapy (ESWT) in athletes with jumper's knee. Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: Forty-six consecutive athletes with jumper's knee were selected for this study and randomized into 2 treatment groups: 2 autologous PRP injections over 2 weeks under ultrasound guidance (PRP group; n = 23), and 3 sessions of focused extracorporeal shock wave therapy (2.400 impulses at 0.17-0.25 mJ/mm2 per session) (ESWT group; n = 23). The outcome measures were Victorian Institute of Sports Assessment–Patella (VISA-P) questionnaire, pain visual analog scale (VAS), and modified Blazina scale. A reviewer who was blinded as to the group allocation of participants performed outcome assessments before treatment and at 2, 6, and 12 months after treatment. Nonparametric tests were used for within-group Friedman/Wilcoxon test) and between-group (Kruskal-Wallis/Fisher test) testing, and the significance level was set at .05. Results: The 2 groups were homogeneous in terms of age, sex, level of sports participation, and pretreatment clinical status.

Patients in both groups showed statistically significant improvement of symptoms at all followup assessments. The VISA-P, VAS, and modified Blazina scale scores showed no significant differences between groups at 2-month follow-up (P = .635, .360, and .339, respectively). The PRP group showed significantly better improvement than the ESWT group in VISA-P, VAS scores at 6- and 12-month follow-up, and modified Blazina scale score at 12-month follow-up (P\.05 for all). Conclusion: Therapeutic injections of PRP lead to better midterm clinical results compared with focused ESWT in the treatment of jumper's knee in athletes. Keywords: jumper's knee; platelet-rich plasma; extracorporeal shock wave therapy; tendinopathy/therapy



The criteria used for inclusion in the study were an established diagnosis of chronic jumper's knee at the insertion of the patellar tendon at the lower pole of the patella for at least 6 months before treatment and failure of nonoperative management.

No anesthetic was used as other studies have suggested that this decreases efficacy of both PRP (plantar fascia study) and ESWT. (Activates C fibers to release neuropeptides, blocked by anesthetic)

Participants were all athletes, elite or non-elite, 18-50 years of age. PRP GROUP

PRP Type: The PRP was obtained by a single centrifugation of whole blood to isolate platelets using MyCells Autologous Platelet Preparation System (Kaylight Ltd, Ramat-Hasharon, Israel). From 10 ml draw. \rightarrow 6-7 ml plasma with 3-5 times platelet concentration. Leukocyte and RBC count not listed. Mario Vetrano was emailed for this with no reply.

Color doppler guidance was used for injection. One injection site. (location not stated). Multiple aliquots used for total of 2 ml. No anesthetic was included. 2 rest for 15 minutes without moving leg and a moderate compression bandage was applied. 2 Full loading + normal ADL.

ESWT GROUP 3 sessions at 24 to 48 hr intervals with 2400 impulses each and energy density of .17 to .25 mJ/mm2 depending on pain tolerance. Inline US guidance used to focus on the damaged area in the tendon.

One week after last session, stretching and muscle strengthening for 2 weeks and then water activities only if mild discomfort or pain. Then 4 weeks gradual return to training activity if min or no pain and eventual symptom limited return to sport



15 points or 27% increase in VISA P is a minimal clinically important difference in MCID for change in the VISA-P. The reference for that is: Hernandez-Sanchez S, Hidalgo MD, Gomez A. Responsiveness of the VISA-P scale for patellar tendinopathy in athletes Br J Sports Med. 2012 Sep 25.

Examination of improvements in both groups indicate that each had evidence of providing significant clinical benefit. However the PRP group improved to more than double the MCID and was significantly better than the extracorporeal shock wave therapy group.



These are pain levels using a visual analogue scale (VAS). The Minimal Clinically Important difference (MCID) and Patient Acceptable Symptom Score (PASS) has not been established fur jumper's knee.

For Rotator cuff dysfunction related pain they have and they are 1.4 for MCID and 3.0 for PASS. The reference for that is: Tashjian RZ, Deloach J, Porucznik CA, Powell AP. Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. J Shoulder Elbow Surg. 2009 Nov-Dec;18(6):927-32.

Although both groups easily achieved the MCID for pain improvement, the PRP group results clearly exceeded PASS level improvements and, again, PRP results were significantly better at 6 and 12 months.

The Blazina scale of symptomatic tendinopathy is only 4 points and thus less sensitive to change. Nevertheless the PRP group showed significantly better results at 12 month follow-up

PRP vs Steroid vs Saline in Tennis Elbow With <u>3 Month Followup</u>

 Krogh TP, Fredberg U, Stengaard-Pedersen K, Christensen R, Jensen P, Ellingsen T. Treatment of Lateral Epicondylitis With Platelet-Rich Plasma, Glucocorticoid, or Saline: A Randomized, Double-Blind, Placebo-Controlled Trial. Am J Sports Med. 2013 Jan 17. [Epub ahead of print]

PRP vs Steroid vs Saline in Tennis Elbow : Results @ 3 Months

- No significant difference between groups in PRTEE or
- Steroid was more effect at reducing tendon thickness and color doppler activity at 3 months.
- Virgin elbows may be problematic for study

Buffy Coat PRP vs Repetitive Needling in Rotator Cuff Damage

Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. Clin Rehabil. 2013 Feb;27(2):113-22. doi: 10.1177/0269215512448388. Epub 2012 Oct 3.

PDF available via medical library. Here is the abstract

Abstract

OBJECTIVE:

To compare the effects of platelet-rich plasma injection with those of dry needling on shoulder pain and function in patients with rotatorcuff disease.

DESIGN:

A single-centre, prospective, randomized, double-blinded, controlled study.

SETTING:

University rehabilitation hospital.

PARTICIPANTS:

Thirty-nine patients with a supraspinatus tendon lesion (tendinosis or a partial tear less than 1.0 cm, but not a complete tear) who met the inclusion criteria recruited between June 2010 and February 2011.

INTERVENTION:

Two dry needling procedures in the control group and two platelet-rich plasma injections in the experimental group were applied to the affected shoulder at four-week intervals using ultrasound guidance.

MEASUREMENTS:

The Shoulder Pain and Disability Index, passive range of motion of the shoulder, a physician global rating scale at the six-month follow-up, adverse effects monitoring and an ultrasound measurement were used as outcome measures.

RESULTS:

The clinical effect of the platelet-rich plasma injection was superior to the dry needling from six weeks to six months after initial injection (P < 0.05). At six months the mean Shoulder Pain and Disability Index was 17.7 ± 3.7 in the platelet-rich plasma group versus 29.5 ± 3.8 in the dry needling group (P < 0.05). No severe adverse effects were observed in either group. **CONCLUSIONS:**

Autologous platelet-rich plasma injections lead to a progressive reduction in the pain and disability when compared to dry needling. This benefit is certainly still present at six months after treatment. These findings suggest that treatment with platelet-rich plasma injections is safe and useful for rotator cuff disease.



Chronic pain in shoulder in these cases: > 6 mo

VAS > 5 required.

Pain arc or impingement.

Normal strength testing. (Minimal Neurogenic inflammation.)

Tendinosis OR < 1 cm tear

Failure of conservative therapy for 3 months

Postulated improvement of pain and inhibition as primary result. (No comment about healing.) Patients informed that both treatments should have stimulate healing to some degree. Syringes sealed with plaster. The reaction may have unblinded them but depends in part on

PRP type.

Patients blind and the evaluator was blind.

Lidocaine was used for anesthesia of the supraspinatus tendon in all subjects which MAY blunt PRP effect. (controversial but just 1 ml of .5% lidocaine.)

40-50 times dry needling in the lesion area.

Making PRP: 25 ml blood draw for all patients. Centrifugation at 1600 g to separate eryhthrocytes.

Then centrifugation at 2000 g to separate PRP from PPP. 3 ml PRP obtained, and targeted for the area of damage. Clearly much less needling.

The number of dropout was of concern. 4 (20%) of the 20 in the PRP group dropped out before 6 months. 5/19 (>25%) of the needling group dropped out by 6 months. The dropouts

occurred after the 4 week (2nd injection) period, so they had received full treatments and still failed to follow-up. Thus only 30/39 had data to evaluation which may skew results considerably. See data next slide.



Results were encouraging, however, in both groups . Data as follows:

SPADI Composite

	Time 0	3 Mo	onths	6 Months
PRP	62.3	21.1	17.7	
Dry needling		62.8	34.6	29.5

SPADI Change and (Percent)

	3 mo 6 mo	1	
PRP	41.2(66%)	44.6	(72%)
Dry Needling	28.2 (45%)		33.3 (53%)

The changes are so much more than the MDIC for SPADI that, even if an intention to treat analysis had occurred, results in both groups were clinically significant, although the differences between the groups may not have been.

Source for MDIC for SPADI is: <u>Arthritis Rheum.</u> 2009 May 15;61(5):623-32. doi: 10.1002/art.24396. **Measuring shoulder function: a systematic review of four questionnaires.** <u>Roy JS</u>, <u>MacDermid JC</u>, <u>Woodhouse LJ</u>. Two patients with partial-thickness tears (1 articular tear and 1 bursal surface tear) of the supraspinatus improved to tendinosis without tear in the platelet-rich plasma group. None did so in the

Leukocyte Filtered PRP 1-2 Rx vs Saline Injection in Knee OA

Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med. 2013 Feb;41(2):356-64. doi: 10.1177/0363546512471299. Epub 2013 Jan 8.

PDF is available via medial library. Here is the abstract.

Background: Specific growth factors have been proposed as therapeutic proteins for cartilage repair.

Hypothesis: Platelet-rich plasma (PRP) provides symptomatic relief in early osteoarthritis (OA) of the knee.

Study Design: Randomized controlled trial; Level of evidence, 1.

Methods: A total of 78 patients (156 knees) with bilateral OA were divided randomly into 3 groups. Group A (52 knees) received a single injection of PRP, group B (50 knees) received 2 injections of PRP 3 weeks apart, and group C (46 knees) received a single injection of normal saline. White blood cell (WBC)–filtered PRP with a platelet count 3 times that of baseline (PRP type 4B) was administered in all. All the groups were homogeneous and comparable in baseline characteristics. Clinical outcome was evaluated using the Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire before treatment and at 6 weeks, 3 months, and 6 months after treatment. They were also evaluated for pain by a visual analog scale, and overall satisfaction with the procedure and complications were noted.

Results: Statistically significant improvement in all WOMAC parameters was noted in groups A and B within 2 to 3 weeks and lasting until the final follow-up at 6 months, with slight worsening at the 6-month follow-up. The mean WOMAC scores (pain, stiffness, physical function, and total score) for group A at baseline were 10.18, 3.12, 36.56, and 49.86, respectively, and at final follow-up were 5.00, 2.10, 20.08, and 27.18, respectively, showing significant improvement. Similar improvement was noted in group B (mean WOMAC scores at baseline: 10.62, 3.50, 39.10, and 53.20, respectively; mean WOMAC scores at final followup:

6.18, 1.88, 22.40, and 30.48, respectively). In group C, the mean WOMAC scores deteriorated from baseline (9.04, 2.70, 33.80, and 45.54, respectively) to final follow-up (10.87, 2.76, 39.46, and 53.09, respectively). The 3 groups were compared with each other, and no improvement was noted in group C as compared with groups A and B (P\.001). There was no difference between groups A and B, and there was no influence of age, sex, weight, or body mass index on the outcome. Knees with Ahlback grade 1 fared better than those with grade 2. Mild complications such as nausea and dizziness, which were of short duration, were observed in 6 patients (22.2%) in group A and 11 patients (44%) in group B.

Conclusion: A single dose of WBC-filtered PRP in concentrations of 10 times the normal amount is as effective as 2 injections to alleviate symptoms in early knee OA. The results, however, deteriorate after 6 months. Both groups treated with PRP had better results than did the group injected with saline only.

Keywords: platelet-rich plasma; osteoarthritis



This is the only study reviewed recently that excluded both Ahlback 3 and 4 stages.

1 patient in the single PRP group had 2 knee replacements.

Statistical correction for two knees not mentioned, and that is critical.

100 ml blood drawn. Centrifuged 15 min at 1500 RPM. The PRP was then extracted through a pipette and transferred to a test tube, and a leucocyte filter (Imugard III-PL, Terumo Penpol Ltd, Thiruvananthapuram, India) was then used to filter off the leucocytes. The final PRP was assessed for platelet count and was supplied for injection in a 10-mL syringe (approximately 8 mL per knee). Mean platelet count 310,000. 1 ml CaCl was injected with each 4 ml of PRP. Ca may have therapeutic effect.

Global WOMAC was obtained.

22% in the single PRP injection and 44% in the double PRP injection had reactions to injection consisting of various things: Syncope, dizziness, headache, nausea, gastritis, sweating, and tachycardia. Note pain was not mentioned as a large issue. (low WBC product) Nevertheless saline group had none



This illustrates improvement in the composite WOMAC score at 3 and 6 months. The differences between PRP and Saline were substantial but no differences were seen between the PRP groups. The improvement in each group decreased by 6 months but still exceeded the MCID. The percentage improvement at 6 months was 45% for 1 PRP injection and 43% in 2 PRP injections.

The percent improvement in WOMAC at 3 months was $1 - 39.1/79.6 \times 100 = 1-.49 \times 100 = 51\%$ in the PRP group.

The percent improvement at 6 month was 1- 36.5/79.6 x 100 = 54%

These both imply that there is a substantial pain source not addressed by the treatment method.

PRP vs HA In Knee OA: ACP

Cerza F; Carni S; Carcangiu A; Di Vavo I; Schiavilla V; Pecora A; De Biasi G; Ciuffreda M Comparison Between Hyaluronic Acid and Platelet-Rich Plasma, Intra-articular Infiltration in the Treatment of Gonarthrosis Am J Sports Med 2012; 40(12) p2822-7.

PDF Not available on Line:

Here is the abstract. Full article review was conducted for this summary.

AUTHOR(S): AUTHOR'S ADDRESS: Alessandro Carcangiu, Orthopaedics and Traumatology Unit of P. Colombo Hospital of Velletri, Vicolo dell'Annunziatella, 50 Rome, Italy, 00142. alessandro.carcangiu@gmail.com.

ABSTRACT: BACKGROUND: Arthrosis is particularly prevalent in the knee. Infiltration treatment for gonarthrosis is among the most widely used techniques in orthopaedic practice. PURPOSE: To compare the clinical response of hyaluronic acid (HA) and platelet-rich plasma (PRP) treatment in 2 groups of patients affected by gonarthrosis. STUDY DESIGN: Randomized controlled trial; Level of evidence, 1. METHODS: A total of 120 patients affected by clinically and radiographically documented gonarthrosis were included in this study. The gonarthrosis was graded using the Kellgren-Lawrence radiographic classification scale. The 120 patients were randomized into 2 study groups in a 1:1 ratio: 60 patients received 4 intra-articular injections of PRP (specifically, autologous conditioned plasma [ACP], 5.5 mL), and 60 patients received 4 intra-articular injections of HA (20 mg/2 mL). An unblinded physician performed infiltration once a week for 4 weeks into the knee affected by clinically relevant gonarthrosis (in both groups). All patients were evaluated with the Western Ontario and McMaster (WOMAC) score before the infiltration and at 4, 12, and 24 weeks after the first injection. RESULTS: Treatment with a local injection of ACP had a significant effect shortly after the final infiltration and a continuously improving sustained effect up to 24 weeks (WOMAC score, 65.1 and 36.5 in the HA and ACP groups, respectively; P < .001), where the clinical outcomes were better compared with the results with HA. In the HA group, the worst results were obtained for grade III gonarthrosis,

whereas the clinical results obtained in the ACP group did not show any statistically significant difference in terms of the grade of gonarthrosis. The mean WOMAC scores for grade III gonarthrosis were 74.85 in the HA group and 41.20 in the ACP group (P < .001). CONCLUSION: Treatment with ACP showed a significantly better clinical outcome than did treatment with HA, with sustained lower WOMAC scores. Treatment with HA did not seem to be effective in the patients with grade III gonarthrosis.



All subjects had received physical or pharmacologic therapy. The AP X-Ray was in full extension. With bilateral knees only the worst side was considered in evaluation. If platelet count was less than 150.000, patients were excluded. I did not see exclusions listed.

Mean blood draw for ACP preparation was only 12 ml. Volume if ICP injected was not stated.

Superolateral approach for injection (93% success rate noted) No guidance.

Knees were grade II most commonly then grade I and then grade III the least.

Note activation not mentioned despite very low leukocyte levels.

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This illustrates improvement in the composite WOMAC score at 4, 12 and 24 weeks. At every point the intergroup difference of significant, and deterioration in improvement from HA was apparent by 3 months, with less than and MCID difference at 12 and 24 weeks.

The percent improvement in WOMAC at 3 months was $1 - 39.1/79.6 \times 100 = 1 - .49 \times 100 = 51\%$ in the PRP group.

The percent improvement at 6 month was 1- 36.5/79.6 x 100 = 54%

These both imply that there is a substantial pain source not addressed by the treatment method.

PRP vs HA in Knee OA: Buffy Coat PRP

- Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys Med Rehabil. 2012 May;91(5):411-7. doi: 10.1097
- 3 PRP sessions vs 3 HA sessions
- 6 month WOMAC and NRS pain signif better. PDF requested

PDF available through medical library

Here is the Abstract:

m J Phys Med Rehabil. 2012 May;91(5):411-7. doi: 10.1097/PHM.0b013e3182aab72.

Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid.

Spaková T, Rosocha J, Lacko M, Harvanová D, Gharaibeh A.

Source

Associated Tissue Bank of Faculty of Medicine UPJS, Kosice, Slovakia.

Abstract

OBJECTIVE:

This study aimed to find a simple, cost-effective, and time-efficient method for the preparation of platelet-rich plasma (PRP), so the acquired benefits will be readily available for multiple procedures in smaller outpatient clinics and to explore the safety and efficacy of the application of PRP in the treatment of degenerative lesions of articular cartilage of the knee. **DESIGN:**

DESIGN: The study w

The study was designed as a prospective, cohort study with a control group. A total of 120 patients with Grade 1, 2, or 3 osteoarthritisaccording to the Kellgren and Lawrence grading scale were enrolled in the study. One group of patients was treated using three intra-articular applications of PRP, and the second group of patients was given three injections of hyaluronic acid. Outcome measures included the Western Ontario and McMaster

Universities Osteoarthritis Index and the 11-point pain intensity Numeric Rating Scale. **RESULTS:**

On average, a 4.5-fold increase in platelet concentration was obtained in the PRP group. No severe adverse events were observed. Statistically significantly better results in the Western Ontario and McMaster Universities Osteoarthritis Index and Numeric Rating Scale scores were recorded in a group of patients who received PRP injections after a 3- and 6-mo follow-up. **CONCLUSIONS:**

Our preliminary findings support the application of autologous PRP as an effective and safe method in the treatment of the initial stages of knee osteoarthritis. Further studies are needed to confirm these results and to investigate the persistence of the beneficial effects observed.



Goal to find a simple, cost effective and time efficient method for prep or PRP. 120 patients with grade 1=3 OA according to Kellgren and Lawrence grading scale. Also 4 excluded.

27 ml blood drawn in 3 tubes. Centrifuge X 1 15 min at 3200 RPM. They collect plasma plus buffy coat and then 10 min at 1500 RPM to separate leukocytes. Then plasma layer was collected and it appearss that was spun again at 1500 to prepare the PRP and PPP without leukocytes.

Not so strict on platelet count (< 100,000) exclusions.

60 minute platelet preparation time. Concentration of platelet mean was 4.5 times. Mean WBC was 23.2 (conc mean 3.6) and RBC was 3.8. (conc mean 0.6)

Mostly grade II subjects.



This illustrates improvement in the composite WOMAC score at 4, 12 and 24 weeks. At every point the intergroup difference of significant, and deterioration in improvement from HA was apparent by 3 months, with less than and MCID difference at 12 and 24 weeks.

Percent improvement at 3 months in PRP group was 73% and at 6 months was 51%

PRP vs HA in Knee OA: Buffy Coat Frozen PRP

• Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, Fornasari PM, Marcacci M. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. BMC Musculoskelet Disord. 2012 Nov 23;13:229. doi: 10.1186/1471-2474-13-229.

• 3 PRP sessions vs 3 HA sessions

PDF available Free at http://www.biomedcentral.com/1471-2474/13/229 Here is the astract

Abstract

BACKGROUND:

Platelet Rich Plasma (PRP), a blood-derived product rich in growth factors, is a promising treatment for cartilage defects but there is still a lack of clinical evidence. The aim of this study is to show, through a randomized double blind prospective trial, the efficacy of this procedure, by comparing PRP to Hyaluronic Acid (HA) injections for the treatment of knee chondropathy or osteoarthritis (OA).

METHODS:

109 patients (55 treated with HA and 54 with PRP) were treated and evaluated at 12 months of follow-up. The patients were enrolled according to the following inclusion criteria: age> 18 years, history of chronic (at least 4 months) pain or swelling of the knee and imaging findings of degenerative changes of the joint (Kellgren-Lawrence Score up to 3). A cycle of 3 weekly injections was administered blindly. All patients were prospectively evaluated before and at 2, 6, and 12 months after the treatment by: IKDC, EQ-VAS, TEGNER, and KOOS scores. Range of motion and knee circumference changes were measured over time. Adverse events and patient satisfaction were also recorded.

RESULTS:

Only minor adverse events were detected in some patients, such as mild pain and effusion after the injections, in particular in the PRP group, where a significantly higher post-injective pain reaction was observed (p=0.039). At the follow-up evaluations, both groups presented a clinical

improvement but the comparison between the two groups showed a not statistically significant difference in all scores evaluated. A trend favorable for the PRP group was only found in patients with low grade articular degeneration (Kellgren-Lawrence score up to 2). CONCLUSIONS:

Results suggest that PRP injections offer a significant clinical improvement up to one year of follow-up. However, conversely to what was shown by the current literature, for middle-aged patients with moderate signs of OA, PRP results were not better than those obtained with HA injections, and thus it should not be considered as first line treatment. More promising results are shown for its use in low grade degeneration, but they still have to be confirmed.



Technically single blind but evaulator was blinded as well.

150 ml blood draw venous for every knee with 1480 RPM X 6 min to separate erythrocytes, then 3400 rpm for 15 min to produce 20 ml with 5 analyzed and 15 frozen for 5 ml X 3 visits. This could associate with degranulation, but freeze thawing can be a method to release intracelluar GFs.

Leukocytes has 1.2 times the usual value, clearly in between. Other components not described but likely low RBC since first spin said to remove those.



More pain in the PRP patients. However intolerance of treatment only occurred in the HA group (3 subjects)

MCID = 6.7 points from previous collections of data.

Note this improvement is significant, comparable to other studies and was sustained to 1 year, longer than other studies were followed.

PRGF (Endocet) vs HA in Knee OA:

 Sánchez M, Fiz N, Azofra J, Usabiaga J, Aduriz Recalde E, Garcia Gutierrez A, Albillos J, Gárate R, Aguirre JJ, Padilla S, Orive G, Anitua E. A randomized clinical trial evaluating plasma rich in growth factors (PRGF-Endoret) versus hyaluronic acid in the short-term treatment of symptomatic knee osteoarthritis. Arthroscopy. 2012 Aug;28(8):1070-8.

Available via medical library but not free on line..

Here is the abstract:

Abstract

PURPOSE:

This multicenter, double-blind clinical trial evaluated and compared the efficacy and safety of PRGF-Endoret (BTI Biotechnology Institute, Vitoria-Gasteiz, Spain), an autologous biological therapy for regenerative purposes, versus hyaluronic acid (HA) as a short-term treatment for knee pain from osteoarthritis.

METHODS:

We randomly assigned 176 patients with symptomatic knee osteoarthritis to receive infiltrations with PRGF-Endoret or with HA (3 injections on a weekly basis). The primary outcome measure was a 50% decrease in knee pain from baseline to week 24. As secondary outcomes, we also assessed pain, stiffness, and physical function using the Western Ontario and McMaster Universities Osteoarthritis Index; the rate of response using the criteria of the Outcome Measures for Rheumatology Committee and Osteoarthritis Research Society International Standing Committee for Clinical Trials Response Criteria Initiative (OMERACT-OARSI); and safety. RESULTS:

The mean age of the patients was 59.8 years, and 52% were women. Compared with the rate of response to HA, the rate of response to PRGF-Endoret was 14.1 percentage points higher (95% confidence interval, 0.5 to 27.6; P = .044). Regarding the secondary outcome measures, the rate of response to PRGF-Endoret was higher in all cases, although no significant differences were reached. Adverse events were mild and evenly distributed between the groups.

CONCLUSIONS:

Plasma rich in growth factors showed superior short-term results when compared with HA in a randomized controlled trial, with a comparable safety profile, in alleviating symptoms of mild to moderate osteoarthritis of the knee.

LEVEL OF EVIDENCE:

Level I, randomized controlled multicenter trial.



Random assignment without blinding.

* Activation required because no WBCs

Philosophy of PRGF (Plasma Rich in Growth Factors) use is as follows by authors "Recent data support the application of platelet-rich plasma products as an effective and safe method in the treatment of the initial stages of knee OA. Some growth factors present in platelet-rich plasma products, including transforming growth factor β , platelet-derived growth factor, and insulin-like growth factor 1, contribute to the maintenance of a homeostatic balanced status between anabolism and catabolism on the articular cartilage, and others such as vascular endothelial growth factor and basic fibroblast growth factor show chondroinductive roles."

36 ml of blood drawn, spun at 580 g for 8 min and then pipetted and picked up 2 ml just above the buffy coat. Activation was done. 2 ml from each of 4 tubes for an 8 ml volume.

•Exclusions from the study were considerable.

- 7 were excluded due to taking NSAIDs.
- 9 had steroid injections or surgery against the protocol
- 7 no improvement or lost to followup.

Total of 23/176 = 13% or more than 1/8.

Only 6 months follow-up, like most of the other knee PRP vs HA studies (only Filardo et al was to 1 year)


The values were calculated from a table in the study. The authors emphasized a barely significant difference in the WOMAC pain which is incorrect to even mention in the presence of no change in the WOMAC summed score. (Not even approaching significance.)

The results are better than a single minimal clinically important difference, but not approaching double and are not different.



PRP Vs HA Study Summarization

- Cerza 2012 APC (Low WBC) 6 month 54% Impr WOMAC. WOMAC 36.5 @ 6 mo (Worse patients but no grade IV)
- Spakova 2012 Buffy Coat High WBC 6 month 51% Impr WOMAC 18.85 @ 6 mo (more grade II)
- Filardo/Kon 2012 High WBC Frozen PRP Twice MCID in both groups (For IKDC) but no differences, sustainable to 1 year. Older but still no grade IV.
- Sanchez 2012 Plasma Rich in Growth Factor 6 Month. Only sightly more than MCID for WOMAC but no differences (Incorrectly stated a subscale was different) @ 6 mo. No grade IV
- All wimply (no grade IV)
- Note in Patel 2013 Leukocyte filtered PRP vs Saline, 44% mean WOMAC improvement (about 22.5) at 6 months in PRP group. Rare grade 3 and no grade 4. (Less severe of all studies)

Spakova Notable is that the best the patients mean WOMAC achieved at 3 months was 14.35 and 18.85 at 6 months compared to best of 39.1 and 36.5 in Cerza with worse patients.

Some authors define PRP as only platelets and attribute better results to leucocyte depletion, because of the deleterious effects of proteases and reactive oxygen released from white cells; others consider them as a source of important cytokines and enzymes, that may be important also for the prevention of infections, and report that PRP significantly inhibits the growth. (Comment from Filardo article.

Another important comment from Filardo et al is the following: "There was a tendency towards better improvement (or PRP over HA) only in patients affected by earlier degrees of knee degeneration was observed, thus suggesting that the clinical application of PRP should be mainly restricted to this patient subgroup, whereas the indication of this treatment for high grade degeneration is lower. Due to the not significantly better results with respect to HA, PRP cannot be considered as the first line of treatment for knee OA and should be therefore restricted to patients who do not benefit from other conservative or injective treatments such as HA or, if used as first line treatment, it should be mainly targeted to patients affected only by early degrees of knee cartilage degeneration. " (Others have found better results but only in up to and including grade II also.

Systemic Effects on GFs with Focal PRP Injection

 Wasterlain AS, Braun HJ, Harris AH, Kim HJ, Dragoo JL. The systemic effects of platelet-rich plasma injection. Am J Sports Med. 2013 Jan;41(1):186-93. doi: 10.1177/0363546512466383. Epub 2012 Dec 4.



BIOLOGIC REPAIR INJECTION: STEM CELLS

Now we will consider some evidence of the benefit stem cells. Controlled studies are lacking. Consecutive patient studies are worth mentioning in some cases due to durability of benefit or objective follow-up measures.

Adipose Stem Cells Injection in Osteoarthritis of the Knee With Pre and Post Arthroscopy

 Jo CH, Lee YG, Shin WH, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. Stem Cells. 2014;32(5):1254-1266.

This is a level II study, although merely consecutive subject because of the objective evidence of cartilage growth by pre and post arthroscopy and merits discussion for that reason.

Method Of Adipose Stem Cell Study

- 18 subjects, grade 2 or more Kellgren-Lawrence severity on X-ray, pain 4/10 or more.
- Injection of stem cells at time 0. Arthroscopy and biopsy at time 0 and 6 months.
- A WOMAC score was obtained at 0 and 6 months, as well as a 0-10 VAS for pain, a KSS score, a blinded MRI reading was obtained and a cartilage volume measure (semiautomated segmentation method).
- Note 8 weeks of only toe touch weight bearing was utilized, Which has it own complications.

There were 9 subjects in a dosage escalation safety study. Three received 10,000,000 stem cells in 3 ml saline, three received 50,000,000 and three received 100,000,000.

Then, with safety shown, 9 additional subjects received 100,000,000 stem cells.

Fat was aspirated, and then stem cells were grown for 3 weeks to achieve cell concentrations for injection.

Follow up was at time of injection and 1,2,3 and 6 months after injection. Second look arthroscopy was performed 6 months after injection and a 2 mm punch biopsy was obtained from the center of the cartilage defect of the medial femoral condyle at first arthroscopy and from the adjacent area at second arthroscopy in those who gave consent.

WOMAC (Western Ontario and McMaster Osteoarthritis Index) was also performed at 0 and 6 months as a standardized measure of clinical improvement. Other testing at 0 and 6 months included a pain measure (visual analog score from 0 to 10), MRI general readings and volume analysis and histology with appropriate stains and cartilage typing.

Results from Adipose Stem Cell Study

- 17/18 completed follow up, 16/18 had 2nd arthroscopy.
- 6 month improvements were WOMAC (39%; 21.4 points), pain 45%, and KSS (50%).
- Size of cartilage defect improved significantly (40% in medial femur and 49% in medial tibia).
- Cartilage volume improved about 14% in the femoral condyle and 22% in the medial tibial condyle.
- Type II cartilage staining was positive in the middle and deep zones of the cartilage.

18 enrolled. 1 dropped out after firsst injection, 1 did not consent to second arthroscopy and 16/16 completed 6 months and 2nd arthroscopy.

Notable is that all had osteoarthritis of the knee of Kellgren-Lawrence grade 3 or 4.

WOMAC improvements were not seen in the low or mid range stem cell group.

In the high range stem cell group WOMAC improved from 54.2(5.2) to 32.8(6.3). Pain improved from 8.0(2.2) to 4.4(6.3). KSS score increased from 41(6.8 to 79(12.5).

Radiographic changes did not change but serial MRI examinations showed gradual regeneration with thin cartilage noted at 3 months that thickened and bacame mature with isointensity at 6 months. The cartilage defect improved in size by 40% (497mm² to 298 mm²) in the femoral condyle and by 49% in the tibial condyle(333mm² to 171mm²) although the depth of the defect did not show significant changes.

Cartilage volume improvements are noted as above.

The ICRS grade improved in the medial tibial and femoral dondyle.

Summary of Adipose Stem Cell Study

- One injection led to similar benefits to multiple dextrose injections clinically.
- Growth of cartilage was clearly shown and is likely more than a soon-to-be-submitted study on dextrose injection.
- Toe touch weight bearing is a substantial restriction which is difficult to follow and can lead to other pain issues in the elderly.
- Only 6 months follow-up
- Cost effectiveness remains to be seen.
- Nevertheless, an exciting study

Key Features	CP Obj Data: 2014 Stem Cell Journal
Good Size	Small
Sig Clinically	Yes in both groups.
Sig Statistically	No control group.
Adequate F-UP	6 months.
Data Capture	Good to 6 months.
Accepted Tool	Standard biopsy, cartilage typing, WOMAC,etc
Simple	No, but only one treatment.
Inexpensive	No.
Min invasive	No. Harvesting of stem cells required.
Practical PC	High technology.
Grade	11

Small study with significant clinical benefit and significant benefits statistically in multiple areas. Somewhat short follow up at 6 months. Data capture was good. Good tools. This was by no means a simple study as it required culture of stem cells, and of course the related expense is high.

Clearly grade II with the degree of objective data available for this consecutive patient study with good data capture.

Adipose Synovium Stem Cells in Knee OA

 Koh YG, Jo SB, Kwon OR, Suh DS, Lee SW, Park SH, Choi YJ.
Mesenchymal Stem Cell Injections Improve Symptoms of Knee
Osteoarthritis. Arthroscopy. 2013 Jan 29. pii: S0749-8063(12)01884-1.
doi: 10.1016/j.arthro.2012.11.017.
[Epub ahead of print]



The numbers of stem cells were not as high as the study on cartilage growth presented preveiously. Clinical improvements were not impressive but there was only one treatment given. Stem cells were from adipose source.