Current Status of Dextrose Prolotherapy Research

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Past Clinical Assistant/Associate Professor (1986-2015)
University of Kansas Dept. PM&R, Kansas City Kansas
Definition of Prolotherapy

Injection of non-biologic solutions to repair/ proliferate soft tissue. (and decrease pain).

This is in contrast to injection of biologic solutions from living tissue such as platelet rich plasma or stem cells.
2015-2016: Prolotherapy Related Research and Training Advances

• Key basic science research on mechanism of dextrose prolotherapy.

• Acceleration in publication of randomized controlled trials (RCTs) for dextrose prolotherapy and favorable systematic reviews

• Marked increase in customary/required training in prolotherapy at residency and fellowship level.
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Basic Science Research Advances 2015-2016: Dextrose injection causes:

- **Ligament growth without inflammation (10% dextrose)**
  Dextrose 10% thickened the transverse carpal ligament in rabbits without inflammation, compressed the median nerve and produced carpal tunnel syndrome. (A reliable animal model for research developed at the Orthopedic Research Lab of Mayo Clinic) Oh et al 2008, Yoshii et al 2009, 2011, 2014.

- **Cartilage growth without inflammation (12.5% dextrose diluted in synovial fluid)**
  Double arthroscopy study showed chondrogenesis of a combination of type I and type II cartilage after intraarticular injection in cartilage denuded knees. Topol et al 2016

- **A direct pain reduction effect. (5% dextrose)**
  Caudal epidural injection of 5% dextrose resulted in prompt pain reduction in chronic back and buttock or leg pain of diverse causes. Maniquis-Smigel et al 2017
Ligament Growth Without Inflammation: A carpal tunnel syndrome animal model

- A study by Oh and colleagues\textsuperscript{1} demonstrated noninflammatory (no neutrophil invasion at 1 week, 2 weeks, 4 weeks, or 8 weeks) collagen bundle thickening at 8 weeks in the transverse carpal ligament rabbit equivalent after a single injection of 0.05 mL of 10\% dextrose into the carpal tunnel equivalent (subsynovial space) through a small incision with a 30-gauge needle.

- This initial study was followed by 3 randomized, masked, 2-arm studies by Yoshii et al that compared 10\% dextrose versus normal saline. One\textsuperscript{2}, two\textsuperscript{3} or four\textsuperscript{4} injections, given at weekly intervals, were evaluated in successive studies with findings measured at 12 weeks, 12 weeks, and 16 weeks, respectively, after the first dextrose injection. Energy absorption and load to failure of the subsynovial connective tissue (SSCT) were measured using a standardized approach.

The 3 studies demonstrated consistent and significant increases in tensile load to rupture (Fig. 1),

![Bar chart showing tensile load to rupture of the SSCT, comparing forepaws of each rabbit, with randomized injection of either 0.1 mL of 10% dextrose or 0.1 mL of NS on 1, 2, or 4 occasions. a = P<.05.](image)

Tensile load to rupture of the SSCT, comparing forepaws of each rabbit, with randomized injection of either 0.1 mL of 10% dextrose or 0.1 mL of NS on 1, 2, or 4 occasions. a = P<.05.

From Reeves KD, Sit RWS, Rabago D. Dextrose Prolotherapy: A narrative review of basic science and clinical research, and best treatment recommendations. Phys Med Rehabil Clin N Am; 2016; 27(4); 783-823; DOI 10.1016/j.pmr.2016.06.001
Total energy absorption to rupture of the SSCT, comparing forepaws of each rabbit with randomized injection of either 0.1 mL of 10% dextrose or 0.1 mL of NS on 1, 2, or 4 occasions. a = P<.05.

and thickening of the SSCT, presented in Fig. 3 graphically

Thickness of the SSCT in millimeters, comparing forepaws of each rabbit with randomized injection of either 0.1 mL of 10% dextrose or 0.1 mL of NS on 1, 2, or 4 occasions. a = P<.05.

From Reeves KD, Sit RWS, Rabago D. Dextrose Prolotherapy: A narrative review of basic science and clinical research, and best treatment recommendations. Phys Med Rehabil Clin N Am; 2016; 27(4); 783-823; DOI 10.1016/j.pmr.2016.06.001
Representative biopsy showing difference in thickness of the SSCT in a dextrose injected (A) and saline-injected (B) rabbit forepaw after 4 weekly injections. The main map for A and B includes an outlined area shown below as a magnified inset map. FDP, flexor digitorum profundus; FDS, flexor digitorum superficialis. The arrow depicts the thickness of the subsynovial connective tissue (SSCT).

From Reeves KD, Sit RWS, Rabago D. Dextrose Prolotherapy: A narrative review of basic science and clinical research, and best treatment recommendations. Phys Med Rehabil Clin N Am; 2016; 27(4); 783-823; DOI 10.1016/j.pmr.2016.06.001
Chondrogenesis with 12.5% dextrose injection.

- Stage IV knee OA → pre treatment arthroscopy → Six monthly injections of IA dextrose X6 with ultrasound guidance → post treatment arthroscopy + biopsy with histopathology → Blind comparison readings by 3 arthroscopists.
- 6 participants with denuded areas in medial compartment cartilage.
- Methylene blue (MB) staining for cartilage
- Blind comparison of 9 areas on each medial condyle with indication of which arthroscopy showed more cartilage or neither.

Each video arthroscopy followed a set order of movement through 9 sections (A-I) of the medial condyle. Figure A shows the left knee medial condyle) and figure B shows how markers for each area were placed on the video.

Figure A

Figure B

Topol et al 2016
Blinded Reading Method 2 of 2

- Computer randomization of each video to either “Arthroscopy A” or “Arthroscopy B”.
- Both videos loaded onto timeline of video editing program.
- Three orthopedic surgeons with 14, 16, and 20 years of experience performing knee arthroscopies volunteered to be outside reviewers.
- Reviewers made 54 responses (comparing 9 zones in 6 participants).
- Question was: “Comparing arthroscopy A with arthroscopy B, which zone has the appearance of additional cartilage growth, A, B, or N (neither)?”

Topol et al 2016
Blinded Reading Results

• In 19 of 54 zones evaluated (35%), all 3 readers agreed that the posttreatment zone showed cartilage growth compared with the pretreatment zone. Figure A shows the zones of the medial condyle for orientation, and Figure B shows the number of zones for which all 3 reviewers agreed on growth. For example, all reviewers rated zone I as showing more growth in 3 of the 6 participants.

• In 35 of 54 zones assessed, the 3 readers did not all agree.

Figure A

Figure B

Topol et al 2016
Photography and Immunohistology of Biopsy Areas

- New areas of cartilage were seen. See examples A-C.
- Photography confirmed biopsy locations.
- Immunohistologic typing showed a combination of fibrocartilage (Type I) hyaline like (Type 2

*Topol et al 2016*
Neither MB nor Normal Saline are Chondrogenic

- MB has history of substantial use in early arthroscopy to highlight areas of cells (specifically cartilage cells) prior to the development of advanced optics. There is no evidence of chondrogenicity of MB.
- **There is evidence for chondrotoxicity of MB**, reflected by discomfort in injected knees for up to 2 weeks after arthroscopy and corroborated by a study demonstrating chondrotoxicity of MB ink. (Getgood et al 2011)
- Saline flush studies or arthroscopic surgery accompanied by saline flush have no evidence of chondrogenesis. (Thorlund et al 2015)
- Conclusion is that **only the dextrose component of treatment can be considered the active agent** in chondrogenicity.

Direct pain reduction with 5% dextrose injection

• D5W versus saline injection in caudal epidural space in participants with low back pain along with buttock or leg pain. (35 participants with spinal stenosis, lumbar radiculopathy, nonspecific low back pain, failed low back surgery or peripheral neuropathy).

• One masked injection, followed by measurement of pain in 15 min, 2, 4, 48 hours and 2 weeks.

A prompt and significant analgesia effect of epidural dextrose was seen in contrast to epidural saline at 15 minutes, 2, 4 and 48 hours.

Change in 0-10 NRS Pain Scores Over 2 Weeks (± Standard Error)
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Evaluating Research and Making a Strength of Recommendation: The Steps

• Apply Bias tool to evaluate study quality.
• Assign level of evidence to individual study.
• Assign Strength of Recommendation (SOR)
Evaluating Research and Making a Strength of Recommendation: The Steps

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Two Bias Tools: PEDro vs Cochrane

http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm

<table>
<thead>
<tr>
<th>PEDro</th>
<th>Cochrane Bias Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility criteria specified</td>
<td>Random sequence generation</td>
</tr>
<tr>
<td>Random allocation</td>
<td>Allocation concealment</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Allocation concealment</td>
</tr>
<tr>
<td>Similar groups</td>
<td>Blinding of participants and personnel</td>
</tr>
<tr>
<td>Blind subjects</td>
<td>Blind assessors</td>
</tr>
<tr>
<td>Blind treaters</td>
<td></td>
</tr>
<tr>
<td>Blind assessors</td>
<td>Incomplete outcome data</td>
</tr>
<tr>
<td>Data loss &lt; 15%</td>
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</tr>
<tr>
<td>Treatments received as allocated</td>
<td></td>
</tr>
<tr>
<td>Intergroup statistical comparison</td>
<td>Selective reporting</td>
</tr>
<tr>
<td>Mean &amp; Standard Deviations</td>
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</table>
## Bias Tools: Difference = Strictness

http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm

<table>
<thead>
<tr>
<th>PEDro</th>
<th>Cochrane Bias Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>7-11 score on the modified Delphi List</strong></td>
<td>4.5-6 and no major other issues (e.g. no dissimilarity of groups and eligibility clear)</td>
</tr>
<tr>
<td>= satisfactory bias control</td>
<td>= satisfactory bias control</td>
</tr>
</tbody>
</table>
Example of application of risk of bias tool (Cochrane) ≈ 5/6


<table>
<thead>
<tr>
<th>Source</th>
<th>Sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and researchers</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data addressed</th>
<th>Selective outcome reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topol et al.\textsuperscript{64}</td>
<td>Low (A random numbers table was used for assignment)</td>
<td>Unclear (Relevant information was not reported)</td>
<td>Low (Identical control solution prepared in manner that blinded the subjects and treating/evaluating physicians)</td>
<td>Low (Outcome assessor blinded)</td>
<td>Low (No loss to follow up)</td>
<td>Unclear (No protocol was provided)</td>
</tr>
</tbody>
</table>
Evaluating Research and Making a Strength of Recommendation: The Steps

• Apply Bias tool to evaluate study quality.

• Assign level of evidence to individual study.

• Assign Strength of Recommendation (SOR)
<table>
<thead>
<tr>
<th>Level</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic reviews (with homogeneity) or randomized controlled trials</td>
</tr>
<tr>
<td>1b</td>
<td>Individual randomized controlled trials good quality</td>
</tr>
<tr>
<td>1c</td>
<td>All or non randomized controlled trial</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic reviews (with homogeneity) or cohort studies</td>
</tr>
<tr>
<td>2b</td>
<td>Individual cohort study or lower quality randomized controlled trials</td>
</tr>
<tr>
<td>2c</td>
<td>“Outcomes” research; ecological studies</td>
</tr>
<tr>
<td>3a</td>
<td>Systematic review (with homogeneity) of case-control studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual case-control study</td>
</tr>
<tr>
<td>4</td>
<td>Case series (and poor quality cohort and case-control studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit clinical appraisal, or based on physiology,</td>
</tr>
<tr>
<td></td>
<td>bench research or “first principles”</td>
</tr>
</tbody>
</table>
### Assign Levels of Evidence by Study Design
From Centre of Evidence Based Medicine, Oxford
(Not applicable designed removed for simplicity)

https://www.essentialevidenceplus.com/product/ebm_loe.cfm?show=oxford
Last accessed January 29, 2017

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td><strong>Systematic reviews</strong> (with homogeneity) of multiple RCTs</td>
</tr>
<tr>
<td>1b</td>
<td><strong>Individual</strong> randomized controlled trials moderate to good quality</td>
</tr>
<tr>
<td>2b</td>
<td>Low quality <strong>individual</strong> randomized controlled trials</td>
</tr>
<tr>
<td>4</td>
<td>Case series</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit clinical appraisal, or based on physiology, bench research or “first principles”</td>
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</table>

- Typically, RCTs with effective blinding are rated as 1b but the degree of quality rating and size of study relate to whether it is rated at 1b- versus 1b. If an RCT has major flaws, however, it may be downgraded to 2b in its rating.
Jan 6, 2012
Dextrose injection effective for Osgood-Schlatter disease

• **Bottom line**: An injection of a solution of 12.5% dextrose and 1% lidocaine is an effective treatment of Osgood-Schlatter disease (OSD) symptoms in young athletes. The mechanism of action is not clear. *(LOE = 1b-)*


• **Reviewer**: Allen F. Shaughnessy, PharmD, MMedEd
Professor of Family Medicine
Tufts University
Boston, MA
Bottom line: Dextrose prolotherapy appears to be more effective in decreasing pain and stiffness and improving function in patients with knee degenerative joint disease (DJD) than saline injections and home exercise. (LOE = 1b)


Reviewer: Henry C. Barry, MD, MS
Professor
Michigan State University
East Lansing, MI
Evaluating Research and Making a Strength of Recommendation: The Steps

- Apply Bias tool to evaluate study quality.
- Assign level of evidence to individual study.
- Assign Strength of Recommendation (SOR)
Determine Strength of Recommendation
(For use of a treatment in a given condition)


• Comments: “In March 2002, the Agency for Healthcare Research and Quality (AHRQ) published a report that summarized the state-of-the-art in methods of rating the strength of evidence. The authors of the AHRQ report proposed that any system for grading the strength of evidence should consider three key elements:”

• “Quality is the extent to which the identified studies minimize the opportunity for bias and is synonymous with the concept of validity.” = The bias assessments we have described.

• Quantity = Number of studies and number of subjects included.

• Consistency = How similar findings are between different studies on the same topic.
# Strength of Recommendation Levels

<table>
<thead>
<tr>
<th></th>
<th>Recommendation based on consistent and good-quality patient-oriented evidence.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Recommendation based on inconsistent or limited-quality patient-oriented evidence.</td>
</tr>
<tr>
<td>B</td>
<td>Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, treatment, prevention or screening</td>
</tr>
</tbody>
</table>

**Consistent:** Most studies found similar or at least coherent conclusions (coherence means that differences are explainable).

**Inconsistent:** Considerable variation among study findings and lack of coherence.
**Strength of Recommendation Determination**

Modified from table 2 Ebell et al

1. Is the recommendation based on patient-oriented evidence (ie., an improvement in morbidity, mortality, symptoms, quality of life, or cost?)
   - Yes (Y)
   - No (N)
   - Strength of Recommendation = C

2. Is the recommendation based on opinion, bench research, a consensus guideline, usual practice, clinical experience, a case series study, or a substantially flawed single randomized controlled trial?
   - Yes (Y)
   - No (N)
   - Strength of Recommendation = C

3. Is the recommendation based on one small-to-medium-size randomized controlled trial of moderate to good quality or a systematic review with inconsistent findings between studies?
   - Yes (Y)
   - No (N)
   - Strength of Recommendation = B

4. Is the recommendation based on consistent findings from at least two good-quality randomized controlled trials or a systematic review/meta-analysis of same.
   - Yes (Y)
   - No (N)
   - Strength of Recommendation = A
2015-2016: Years of Systematic Reviews
   Both General and Specific


# Progression in number of areas with a SOR grade of B or more as RCT evidence increases

<table>
<thead>
<tr>
<th>Indication</th>
<th>Sanderson 2015</th>
<th>Covey 2015</th>
<th>Hauser 2016</th>
<th>Reeves 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achilles tendinopathy</td>
<td>B</td>
<td>A</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Plantar fasciopathy</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Osgood-Schlatter</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>A-B</td>
</tr>
<tr>
<td>Knee Osteoarthritis</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Epicondylitis</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Rotator Cuff Tendinopathy</td>
<td></td>
<td></td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Finger Osteoarthritis</td>
<td></td>
<td></td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Myofascial pain</td>
<td></td>
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<td>B</td>
<td></td>
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<tr>
<td>Sacroiliac pain</td>
<td></td>
<td></td>
<td></td>
<td>B</td>
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Customary/Required Training in Dextrose Prolotherapy: Examples

• 37 residency or fellowship programs that include training in neuromusculoskeletal medicine (NMM). (IE: Integrated family practice/NMM, Internal medicine/NM or osteopathic manual medicine (OMM)/NMM.

• Walter Reed Military Medical Center PM&R Training Program.

• Harvard Department of Physical Medicine and Rehabilitation, Massachusetts General Hospital and Spaulding Rehabilitation Hospital integrated Sports Medicine Fellowship
Basic Standards in NMM Training Include Prolotherapy Training

For listing of programs affected by these basic standards see:
http://files.academyofosteopathy.org/PSE/ResidencyTrainingPrograms.pdf
5.291 Recognize fractures and surgical orthopedic diseases and make appropriate referrals.

5.292 Understand principles and indications for prolotherapy.

5.293 Understand principles and indications for intraarticular injections.

5.294-5.296 Not pertinent

5.297 Perform an examination of the musculoskeletal system.

5.298 Examine for ligamentous laxity and understand use of prolotherapy.
PROCEDURE CHECK OFFS

These procedures need to be supervised to ensure competence prior to allowing the resident to perform them without supervision. If you have never been checked-off, you must complete the procedure with an attending present. Check-off’s can be done by any NMM attending.

- HVLA
- ME
- SCS
- MFR
- Trigger point injections
- Neural prolotherapy
- Knee injection
- Shoulder injection
- PRP/prolotherapy

Trigger point injections and Neural prolotherapy procedure check-offs are all to be completed and passed by October 1. No exceptions for vacation or holidays are accepted.

All other injection check-offs are due by June 1, 2017.
The following procedures are required for graduation:

- 10 joint injections
- 3 ultrasound guided joint injections
- 10 trigger point injections
- 1 PRP
- 3 Prolotherapy
“The National Capital Consortium (NCC) Physical Medicine & Rehabilitation Residency Training Program) is the sole Military training program for the specialty. The residency program is predominantly Army, but accepts all military applicants with approval for training coming from the respective branch. The program also sponsors rotations for interns and medical students interested in the practice of PM&R.”

“In outpatient clinic, residents will gain experience in injection techniques such as joint, soft-tissue, neuroma, fluoroscopic-guided, and ultrasound-guided. In addition, they will learn basic acupuncture techniques, intra-thecal baclofen programming, and EMG-guided botulinum toxin injection among others. Our clinic staff are also currently active in the regenerative medicine techniques such as platelet-rich-plasma and prolotherapy.”
Clinical and Educational Objectives

- Become proficient at diagnostic and therapeutic intra-articular, tendon sheath and bursal injections.
- Become proficient at trigger point, botox and prolotherapy injections for indicated subacute and chronic musculoskeletal diagnoses (physiatry clinic).
- Become proficient at MSK ultrasound and interventional MSK ultrasound guided procedures for joint injection, percutaneous tenotomy, and platelet rich plasma injection.
Summary:
The only reason prolotherapy would be considered experimental would be due to a lack of knowledge of current medical literature and current status of prolotherapy training.

<table>
<thead>
<tr>
<th>Experimental Treatment</th>
<th>Prolotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not taught at medical school</td>
<td>Taught at medical school on electives</td>
</tr>
<tr>
<td>Not taught in residency or fellowship training.</td>
<td>Routine or required training in many (minimum 40) residencies and fellowships across the United States</td>
</tr>
<tr>
<td>Not based on “sufficient learned publications” (SOR not higher than C in any area based on PubMed literature)</td>
<td>SOR Level A for one -twoarea. SOR level B for many areas</td>
</tr>
<tr>
<td>Risks greater than any potential benefit</td>
<td>More than 70 published studies, including studies targeting potential complications indicate prolotherapy is a low risk procedure.</td>
</tr>
</tbody>
</table>
Any Questions?