State of the art

PROLOTHERAPY
regenerative medicine

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abstract: Prolotherapy is a method of regenerative injection treatment that stimulates healing. This therapy has been in practice for decades in the treatment of musculoskeletal pain and osteoarthritis, and has evolved to include the use of platelet rich plasma (PRP) and autologous adult stem cell sources, such as bone marrow and adipose (fat) stem/stromal cells. Chronic musculoskeletal pain is the most common medical complaint in the United States, and one of the most common reasons for primary care visits. The American Academy of Orthopedic Surgeons estimates that 1 in 2 adults—126.6 million people—are affected by a musculoskeletal condition, comparable to the total percentage of Americans living with a chronic lung or heart condition, costing an estimated $213 billion in annual treatment, care and lost wages. Osteoarthritis (OA) is also a major health issue, and the most common joint disease, affecting millions of people in the United States. Typical medical recommendations for these conditions include prescription medications, which offer temporary relief but may have addiction potential or other unwanted side effects; cortisone, which sometimes helps but can have adverse effects on joints and joint tissue; hyaluronic acid joint injections, which are only temporary; physical therapy, osteopathic or chiropractic treatments, which may help, but not in every case; and of course surgery, which is not always indicated, has additional risk and may fail. In May 2016 Orthopedics Today reported a high incidence of pain 1 year after total knee replacement. Surgeons themselves are questioning whether surgery is always the best answer. A 2016 journal article compared surgery to other more conservative treatments for knee OA and concluded: “Surgery has historically been considered the final solution for treatment of knee osteoarthritis,” however, “there are increasing concerns regarding the lack of randomized controlled studies to support this opinion.” Therefore the need for a safe and effective nonsurgical treatment for musculoskeletal pain and OA is evident. Prolotherapy is low risk and has a high success rate. The newer, more biologic formulas, such as PRP and stem cell sources, allow treatment of more severe chronic as well as acute issues, while use of musculoskeletal ultrasound for diagnosis and injection guidance improves accuracy and precision.
rolotherapy has been in existence since the 1930s when Earl Gedney, DO, a general surgeon at the Philadelphia College of Osteopathic Medicine, caught his thumb in closing operating room doors, stretching and spraining it. After several months of pain and instability in that joint, he was told to just live with it and change professions. Dr. Gedney was not of the mindset to agree with this, so he started researching possible options. He knew of a common practice in those days of physician “herniologists.” These doctors treated hernias by injecting the stretched hernia connective tissue ring with an irritating solution, promoting closure of the defect. Dr. Gedney extrapolated his knowledge of nonsurgical hernia repair to the nonsurgical repair of joints, ligaments, and tendons. He concluded that ligament and tendon laxity (looseness) causes joint instability, leading to pain, and could be resolved by strengthening the joint connective tissue. Reasoning he had little to lose by being a guinea pig for this theory, he started injecting his thumb with these irritating solutions and had a dramatically successful result. Before long, he was back working as a surgeon. Excited about his result, he started on a lifelong career of research into this technique. In June 1937 he published the first known case report and journal article about the special technique, followed by a presentation at the February 1938 meeting of the Osteopathic Clinical Society of Philadelphia called *The hypermobile joint: further reports on injection method.*

A decade later another pioneer, George Hackett, MD, coined the word “prolotherapy,” short for “proliferation therapy,” for its ability to stimulate repair and proliferation of new connective tissue at joint injury sites. Dr. Hackett went on to publish the first formal textbook on the subject in 1956. The medical community eventually agreed that joint instability and ligament laxity lead to pain and osteoarthritis, and in 1972, *Lancet* wrote that joint instability is a leading contributor not only to irregular biomechanics and pain, but the subsequent development of OA. It is now well accepted that there is a significant association between joint injury, resulting joint instability, and then later OA. Prolotherapy is therefore an excellent treatment for OA because it not only addresses ligament injury and joint laxity, reducing instability and pain, but may also prevent further joint biomechanical damage and OA. Recent studies also show that all the various forms of prolotherapy have the potential to stimulate cartilage regeneration.
Prolotherapy: which conditions?

Prolotherapy has traditionally been used for chronic injuries or pain, however it has come into use for treatment of acute injuries to stimulate faster, stronger healing. Common conditions treated\textsuperscript{19} are:

- Tendinitis/tendinosis, repetitive strain injuries, shoulder pain, rotator cuff tears
- Ligament sprains, other sports injuries
- Knee pain, meniscal tears, ligament tears
- Osteoarthritis and degenerative joint/disc disease
- Low back pain, sacroiliac joint pain/instability, sciatica
- Neck pain, whiplash, headache
- Elbow pain, golfer’s and tennis elbow
- Ankle and foot pain, plantar fasciitis
- Wrist and finger pain, thumb and finger OA
- High hamstring tendinopathy, iliopsoas tendinopathy
- Hip pain, iliotibial band syndrome, hip OA (as long as it’s not end stage)
- Temporomandibular joint dysfunction
- Hypermobility
- Other musculoskeletal pain

Types of prolotherapy

There are 3 general formula types in prolotherapy: traditional (dextrose), platelet-rich plasma (PRP) and biocellular, also known as stem cell prolotherapy, which uses autologous stem cell sources, i.e., typically bone marrow or adipose (fat) stromal tissue.

Traditional prolotherapy

Traditional, also referred to as dextrose prolotherapy, uses hypertonic (10\% to 15\%) dextrose as its main proliferating formula. Hypertonic dextrose creates an osmotic irritation which then promotes positive inflammation and healing.\textsuperscript{16} At its core, this treatment could be thought of as “tricking” the body to repair old injuries by activating a new healing cascade, raising growth factor levels and effectiveness.\textsuperscript{17} In a recent publication with pre- and posttesting and biopsies, dextrose prolotherapy was also shown effective in cartilage regeneration.\textsuperscript{12} There is a large volume of medical research including double blinded and placebo controlled studies, showing the effectiveness and safety of dextrose prolotherapy, including a recently published review.\textsuperscript{18}

Platelet-rich plasma prolotherapy

PRP has been used in prolotherapy for over 10 years. Many people have heard the term as a treatment for musculoskeletal and sports injuries, but do not realize it is a form of prolotherapy. Studies support the use of PRP for tendinopathy,\textsuperscript{15} chronic tendon and muscle injury,\textsuperscript{20} joint degeneration,\textsuperscript{21} and OA, including a study showing PRP to be more effective than hyaluronic acid for knee\textsuperscript{22} and hip OA.\textsuperscript{23} It is believed that PRP can also modulate action on articular cartilage lubrication and regeneration.\textsuperscript{13} There is a huge interest by orthopedic medicine physicians in PRP, with many, many journal publications and studies, as well as a recent textbook on its use in musculoskeletal medicine.\textsuperscript{24} There are also some interesting observations, including a case report of calcific tendonitis in a rotator cuff, treated with PRP. Results showed not only excellent resolution of symptoms and pain, but also X-ray evidence that calcium deposits previously present in the tendon were gone when followed up 1 year later.\textsuperscript{25}

Biocellular (stem cell) prolotherapy

Biocellular (stem cell or stem/stromal cell) prolotherapy is so named because it uses adult stem cell sources as the prolotherapy treatment formula. Biocellular prolotherapy is used when a more aggressive healing process is needed or desired. In the early 1990s, adult stem cells, specifically mesenchymal stem cells (MSCs), were discovered to have an active role in connective tissue repair after injury.\textsuperscript{24,27} MSCs are partially differentiated cells capable of continuing down the lineage to ligament, tendon, or cartilage cells.\textsuperscript{28} It is also believed that these cells work by changing the tissue and joint microenvironment more favorably towards healing.\textsuperscript{29} [See Figure 1 at goo.gl/gyujf.) An individual is born with these adult stem cells, they are found throughout the body, multiply to replenish dying cells and regenerate damaged tissues. The 2 main storage reservoirs of MSCs in the human body are bone marrow and adipose (fat) tissue, and both of these can be used as stem cell sources in prolotherapy. Adipose is an interesting tissue because it contains 500 to 2000 times as many MSCs as bone marrow. Adipose also retains its regenerative abilities much longer as a person ages than bone marrow does,\textsuperscript{30} as well as being easier to harvest, making adipose an ideal stem cell source, especially for older patients.\textsuperscript{31,32} The first protocol for adipose derived biocellular prolotherapy was published in 2011...
in *Journal of Prolotherapy*. Another advantage of adipose, observed specifically when treating knees, is its potential to replenish the knee infrapatellar fat pad. This fat pad not only provides a cushion, but also contains potent MSCs and MSC precursors. It has been speculated that depletion of this fat pad plays a prominent role in the initiation and progression of OA in the knee. Many cases of adipose derived biocellular prolotherapy have been done since 2011 and show objective ultrasound evidence demonstrating infrapatellar fat pad improvement that correlates with reduction of patients' pain and improved function. Biocellular prolotherapy has also been used successfully in cases of tendon injury and for acute sports injuries where faster healing is desired along with the possibility of reduced scar tissue formation. [See Figures 2, 3, and 4 at goo.gl/8gu05B.]

**Who is an appropriate patient for prolotherapy?**

In the Hackett prolotherapy textbook first published in 1956 with 4 subsequent editions, the question of who was appropriate as a candidate for prolotherapy treatment was addressed. This book states that a patient should have:

1. **An appropriate medical problem**
2. **A desire for improvement**
3. **No underlying medical condition that would significantly interfere with healing**
4. **A willingness to report progress**
5. **A willingness to receive painful injections in an effort to recover from injury**

These criteria are still true today. It is important for the patient to understand this is a process of healing, and that the treated area is being stimulated to heal so will often feel worse initially before it feels better. There is also an “ebb and flow” — a “4 steps forward, 2 steps back” phenomenon — which occurs during the interval after treatment. This is especially true with PRP or biocellular prolotherapy because these are more aggressive formulas, stimulate deeper healing, and are often more uncomfortable than dextrose prolotherapy. The most important common denominator between patients who are successful is patience and an understanding of the treatment process.

**When to use which type of prolotherapy and how long does it take?**

As a physician doing prolotherapy for 20 years, it is my practice to start with the least aggressive formula that I believe will get the job done. In some cases that is dextrose or PRP, and in other cases biocellular (stem/stromal cell) is the most practical starting point, depending on the patient’s presentation and injuries. Patient preference is also important as the doctor-patient relationship is a partnership, and, once the patient understands the process, his/her input is important in this determination. Each patient is evaluated individually, and recovery may be faster in some cases than others. An average number of traditional or PRP prolotherapy treatments is 4 to 6, spaced 4 to 6 weeks apart. An average number of treatments for biocellular prolotherapy is 1 to 2, spaced 6 to 9 months apart. In some cases a patient may start with one form of prolotherapy, and then advance to a more aggressive form if results level off. See the treatment course algorithm (Figure) of where to start, when to switch, and how long the process typically takes.

**Use of diagnostic musculoskeletal ultrasound**

Ultrasound as a tool in diagnosis and treatment for musculoskeletal medicine has been gaining popularity in recent years. The ability to immediately correlate the exact spot where a patient is having pain to an image can result in a faster and better diagnosis. While MRI has its place, ultrasound may show more detail than MRI for certain locations, multiple joints can easily (and inexpensively) be scanned including contralateral joints, and every patient can get an ultrasound, even those with metal implants. Dynamic (movement) imaging can also be accomplished, to correctly estimate the extent of damage of a ligament or tendon tear. MRI falls short here as scans are done with the patient motionless, and some connective tissue tears do not show up unless the joint is mobilized. The use of ultrasound can also be valuable as a “GPS” while injecting difficult locations. And serial ultrasounds over a treatment course can help to show progress and build patient confidence. Musculoskeletal ultrasound is fast becoming the standard of care in physical medicine and rehabilitation physician training programs. Better machines are being produced, and just like when computers came down in size and price, very sophisticated, high quality ultrasound machines are now available that are portable and affordable. Some have high end features, such as color tissue elastography (also called sonoelastography), which measure the stiffness or softness of tissue. This feature, previously only available on expensive ultrasound machines, is now being offered on smaller, more portable devices, such as the Konica Minolta Sonimage HS1 system. Tissue elastography, which has been used for years in other applications, is new to musculoskeletal medicine. This technology can potentially allow the practitioner to determine tears that were undetectable with standard black and white imaging, where a diagnosis would otherwise not be possible. [See Figure 5 at goo.gl/8gu05B.] While there is a learning curve in beginning to use ultrasound, it is well worth the effort as any tool which can help the pain practitioner better diagnose and resolve a patient’s pain origin is invaluable.
Figure. Typical prolotherapy treatment algorithm.

Treatment algorithm

Evaluation:
- patient history, physical exam,
- review of previous studies,
- musculoskeletal ultrasound in
  office to confirm diagnosis

Determine if candidate for
dextrose, PRP, or
stem cell prolotherapy

Discuss options

If excess degeneration,
severe tendinosis,
muscle tear,
or if patient
prefers PRP over
dextrose prolotherapy,
and if no
contraindications

PRP prolotherapy
× 2 treatments,
interval 4–6 weeks

If average case

Dextrose prolotherapy
× 2 treatments, interval 3–4 weeks

Re-evaluate

If no substantial
improvement or
if results
have plateaued

If doing well,
continue treatment

Dextrose prolotherapy
× 2–4 treatments,
interval 3–4 weeks

Should be completed and
90% – 100% improved. If not, re-evaluate,
consider PRP prolotherapy
or biocellular (stem cell)
prolotherapy

Re-evaluate

If doing well,
continue re-evaluating
every treatment

Usual course
4–6 treatments
should be completed and
90% – 100% improved

If no substantial
improvement or
if results
have plateaued

Biocellular (stem cell) prolotherapy
(note: may also start here as
indicated by severity
of problem or patient preference)
× 1–2 treatments,
6–12 months apart

PRP prolotherapy
if needed at recheck visits
× 1–2 treatments

Should be completed and
90% – 100% improved

*Based on a combination of
objective and subjective measures,
such as pain reduction, better
stability, increased function, and
improved on orthopedic testing and
ultrasound imaging.
[Prolotherapy] could be thought of as ‘tricking’ the body to repair old injuries by activating a new healing cascade, raising growth factor levels and effectiveness.

Conclusion
Musculoskeletal pain and osteoarthritis are common complaints and can be a challenge for the treating physician. Traditional medical treatment options may not be straightforward, and may be only temporary, ineffective, or high risk. Osteoarthritis has been shown to develop after connective tissue injury, which leads to biomechanical change and ultimately degeneration and pain. Traditional dextrose prolotherapy, PRP prolotherapy, and biocellular (stem cell or stem/stromal cell) prolotherapy are low risk procedures with a high success rate. These procedures are regenerative in nature and work by stimulating repair of joints, ligaments, tendons, muscle and cartilage. An added benefit is that when joints are stabilized, biomechanical joint injury and further OA may be prevented. Different types of prolotherapy are appropriate for different situations and conditions, and the choice of which form of prolotherapy to use is arrived at after a thorough evaluation, diagnostic musculoskeletal ultrasound and/or other imaging, discussion with the patient, and a working diagnosis as to what is causing his/her pain. While prolotherapy regenerative medicine is the wave of the future, now encompassing platelet and stem cell biotechnology, its origins are from the past and based on a very simple premise that the body can be stimulated to heal, reducing or eliminating pain.

References


FIGURE 1: The Mesenchymal Stem Cell (MSC)

- **Multipotent Differentiation**
- **Mesenchymal Stem Cell**
  - (abbreviated “MSC”)
  - Derived from Mesoderm

**Excretes cytokines/growth factors; Changes tissue microenvironment more favorably towards healing**

FIGURE 2: Infrapatellar Fat Pad before/after Adipose-Derived Biocellular Prolotherapy

**BEFORE:** Note fat pad extensive hypoechoic regions and disorganized fibers consistent with inflammation.

**6 months LATER:** Improved texture with more echos and organization, less inflammation; even patella tendon looks better. Patient also reports substantial improvement and pain reduction.

From: Alderman, Donna D., research pending publication
FIGURE 3: Achilles Tendon Tear before/after treatment with Biocellular Regenerative Therapy (Autologous Regenerative Matrix).


FIGURE 4: Abdominal Rectus Muscle Tear treated by Adipose-Derived Tissue SVF + High Density Platelet-Rich Plasma (Biocellular Regenerative Matrix)

FIGURE 5: Color tissue sonoelastogram showing occult muscle tear causing pain in 20 year runner.

Side by side comparison of B mode (black and white) and color sonoelastogram of gastrocnemius. Note the red area which shows “soft” tissue, site of occult tear. Patient received PRP prolotherapy to that area and pain resolved.

From: Alderman, Donna D. research, publication pending