Regenerative Injections for Musculoskeletal Disorders: Separating Evidence vs. Promotion Regarding Platelet-Rich Plasma and Stem Cell Injections

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**Introduction**

Musculoskeletal disorders (MSDs) are key contributors to the burden of pain, lost productivity, and disability worldwide, including workers’ compensation in the U.S. MSDs can occur for a number of work or non-work reasons, including aging, sports injuries, or overuse injuries. Many of the chronic and degenerative MSDs causing symptoms and activity limitations may be associated with prolonged recovery, persistent complaints or recurrence. There are few effective treatments to repair the effects of most chronic and degenerative MSDs, and many patients report slow or incomplete response to care.

For these reasons, researchers and clinicians have been exploring the potential for regenerative injections to offer non-surgical treatment that can potentially repair damaged ligaments, tendons, and joint surfaces affected by arthritis. This field, at times referred to as orthobiologics, holds promise. However, as with many emerging medical treatments, there is need to separate current evidence from uncertainty. While there are a number of “regenerative” injections including prolotherapy, the focus of this newsletter is on Platelet-Rich Plasma (PRP) and stem cell injections.
Rationale

A significant number of work-related MSDs are due to soft tissue conditions including tendon and ligament disorders. While many patients are diagnosed with "tendinitis" or "tendonitis" suggesting an inflammatory condition, in reality these conditions are commonly the result of a degenerative condition referred to as "tendinosis" or "tendinopathy." Some patients who experience ligament injuries recover over time. However, other ligamentous injuries, such as anterior cruciate ligament (ACL) tears, have limited blood supply and, thus, do not heal. The articular cartilage that lines joint surfaces, such as knee and hip, is similarly subject to damage from factors such as age, injury, or overuse resulting in degenerative arthritis that is associated with limited repair and recovery mechanisms.

PRP and stem cell injections have become popular recently in hopes they promote repair and recovery of these tissues. When tissue is damaged, for example when a person sprains their lateral ankle ligaments and recovery occurs over several weeks, healing involves a cycle of processes.

- **Phase One** where platelets aggregate to insure clot formation in addition to releasing a number of chemicals that act as growth factors to help attract inflammatory blood cells to the area.
- **Phase Two** involves cell proliferation with removal of debris and growth of new blood vessels and extracellular matrix that serves as the base for collagen tissue deposition (a protein component of connective tissues).
- **Phase Three** with production of sufficient collagen to repair the damaged area with scar tissue and remodeling to maximally increase the strength of the repaired tissue.

When the natural wound-healing process works well as described above, the patient in this example with the sprained ankle, would experience initial pain and swelling followed by gradual resolution of symptoms, improved swelling, and increased strength and stability.

However, in other cases, recovery may not occur due to:

- limited blood supply
- slow cell turnover
- injury factors
- age
- medical comorbidities including smoking, vascular disease, diabetes, and weight

Examples include tennis elbow (lateral epicondylitis) or Achilles tendinopathy with persistent symptoms and limited function. These conditions may have prolonged symptoms and a lack of consensus on the types of treatments that are effective. In addition, surgical treatment may not result in satisfactory outcomes for some patients. The goal of using regenerative injections is to inject the damaged area with concentrated cellular material that can improve the natural healing processes for these tissues.
Patients considering treatment with PRP or stem cell injection should understand:

- the nature of the proposed treatment (including type of injection)
- harvesting issues
- limits of literature
- reported benefits vs. risks
- alternative interventions
- potential contraindications
- injection protocols
- post-injection recommendations

Some of these issues are briefly discussed below.

**Types of Injections**

There are a number of types of injections that have been used in an effort to enhance musculoskeletal repair mechanisms including:

- autologous blood
- autologous conditioned serum
- stem cell
- PRP

Autologous blood uses the patient’s own blood, which has a lower concentration of platelets and growth factors than PRP.

Autologous conditioned serum is produced using the serum obtained after centrifuging and manipulating the patient’s own blood, which has a lower concentration of platelets than PRP.

Stem cells are cells that can differentiate into other types of cells that divide and repair tissue as described above. Adult stem cells can be derived from adipose tissue (fat), bone marrow, or blood. Adipose tissue is often used involving aspiration of material and addition of agents to extract material for centrifuging, followed by addition of autologous plasma to eventually produce the stem cell concentrate for injection.

The most commonly used injection is PRP. In this procedure, the patient undergoes a standard blood draw. An agent is often added to prevent clotting and depending upon the commercial system, other activation agents may be added. The whole blood is repeatedly spun in a centrifuge resulting in separation into several layers that have higher concentrations of different blood components:

- plasma
- a buffy coat with platelets and white blood cells
- a layer of red blood cells

The platelet rich layer is then maintained in a sterile environment until used on the patient.
There is a lack of consensus in many areas involving the preparation of PRP and stem cell injection materials. For example, there is a lack of evidence regarding:

- the optimal agents to add for anticoagulation and activation
- benefits of different preparation kits
- ideal number and techniques for centrifuging and deriving material for injection
- recommendations for volume
- concentration of cells to inject to improve outcomes

**MSDs Conditions and Evidence**

PRP or stem cell injections are being used to treat a variety of MSDs including:

- tendon, muscle and ligament injuries
- degenerative arthritis
- disc disease
- neuropathic pain, as an adjunct to surgical repair

However, there are a number of methodologic problems involved in many of these studies resulting in unclear evidence of efficacy for most of these conditions. In addition to the methodologic flaws in several studies, other stem cell trials have been criticized for bias from businesses with financial interests using strategies including:

- direct to consumer advertising
- promoting unapproved stem cell interventions
- using “pay to participate”

Also, most lack FDA clearance or institutional review board approval.¹

A recent analysis of use of stem cell therapy for knee osteoarthritis found gaps in reported benefits comparing claims by centers offering treatment and published evidence of efficacy.² Furthermore, FDA approval for use of PRP or stem cell injection in current practice is very limited and most of the commonly utilized procedures are being performed “off label.”³

The current recommendations supporting PRP injections by the Official Disability Guidelines (ODG) Treatment in Work Comp involve the following disorders:

- **Elbow lateral epicondylitis**: Patients with severe and recalcitrant lateral elbow pain and functional limitations who fail a twelve month trial of conservative care including physical therapy, home exercise therapy, or bracing. A single injection is supported in this case in an effort to avoid surgical release. Ultrasound guidance is generally not required for this injection.

- **Knee patellar tendinosis**: Patients with refractory knee pain and functional limitations who fail a twelve month trial of conservative care including physical therapy, home exercise therapy, and NSAIDs. A single injection is supported in this case.

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• **Knee osteoarthritis:** Patients with refractory knee pain and functional limitations with mild to moderate osteoarthritis who fail a six month trial of conservative care including physical therapy, home exercise therapy, NSAIDs, and intra-articular steroid injection. Patients under the age of 50 are more likely to obtain benefit. Patients with severe osteoarthritis have low probability of benefit and are thus not candidates for PRP injection. A single injection is supported in this case.

ODG and the American College of Occupational and Environmental Medicine (ACOEM) do not currently recommend PRP for other indications (though there is no recommendation for some indications due to limited evidence) or stem cell therapy for treatment of any work related MSDs.

**Injection Considerations and Procedure**

There are a number of potential contraindications to PRP or stem cell injection including medical conditions and injection barriers. PRP and stem cell injections may be contraindicated in patients with:

- active cancer
- immunologic disease
- bleeding disorder or anticoagulation
- active systemic infection
- allergy to agents

Pregnant women should discuss benefit vs. risk with their physicians. Patients taking antiplatelet agents, chronic aspirin or non-steroidal anti-inflammatory agents (NSAIDs), or chronic steroids are not candidates since the use of these medications suppresses the inflammatory and repair processes that are the mechanism of action. Patients who are able to temporarily cease use of these medications should avoid use for at least one week prior to PRP or stem cell administration. Injections cannot be performed if there is non-intact skin or acute infection in the affected area.

Administration of PRP or stem cell injection is performed similarly to the techniques of other joint or soft tissue injections like steroids and may utilize ultrasound guidance to improve placement of the injected material depending upon the MSD condition.

Patients should expect a temporary increase in pain and tenderness after injection due to the triggering of the inflammatory and repair process. There are conflicting recommendations regarding the use of ice applications in the first few days after injection (PRP is performed to provoke initial inflammation and swelling followed by repair mechanisms). Acetaminophen can be used for post-injection pain. Aspirin, NSAIDs, steroids, and antiplatelet agents should be avoided for up to four to six weeks after injection to avoid inhibiting the repair process. Complications occur in some patients and can include:

- bleeding
- bruising
- clot formation
- infection
- allergic reaction
- skin discoloration
- scarring or calcification
• needle complications (e.g. nerve or vascular injury)
• persistent pain

Post-injection activity, rehabilitation, and return to work protocols vary depending upon the MSD condition and provider preferences. For example, patients may require brief decrease in activity until post-injection pain or swelling decreases before resuming lifting or gripping for upper extremity disorders or weight bearing for lower extremity disorders. Physical therapy and home exercise programs also vary by condition.

Case Management Considerations
Claims examiners and case managers involved in cases where PRP or stem cell injections are proposed should bear several factors and considerations in mind. For example:
• Clarify if the proposed PRP injection for a diagnosis with guideline support for the treatment option. If so, determine if the injured worker meets guide criteria including failed conservative care for a specified duration.
• Assess if the provider has discussed alternatives, limited evidence, proposed benefits, contraindications, risks, expectations for PRP injection therapy.
• Confirm the post-injection rehabilitation plan and return to activity goal including return to work.
• Given the limited guideline supported indications at the present time, Utilization Review (UR) or Peer Review options should be utilized when permitted by jurisdictional requirements.
• Independent Medical Evaluation is an option depending upon additional considerations for causation, work-related treatment recommendations, advice regarding alternatives, injections in settings where there are no guideline recommendations, return to work, etc.

Resources
There are a number of internet sources for information on PRP injections. Many are promotional; however, the following web sites include better evidence based information and patient materials for interested individuals:

American Academy of Orthopedic Surgeons:
Platelet-Rich Plasma
Platelet-rich Plasma: The Path Forward
Stem Cell Centers On The Rise, Claim High Efficacy For Treatment Of Knee Osteoarthritis Despite Lack Of Evidence
Use of Emerging Biologic Therapies. Position Statement

WebMD:
Platelet-Rich Plasma Helps Tennis Elbow
New Achilles Tendon Treatment Falls Short of Hype
How Are Platelet-Rich Plasma Injections Used To Treat Knee Osteoarthritis?

Journal of Family Practice:
Is platelet-rich plasma right for your patient?
Conclusion

Although the field of orthobiologics and regenerative injections including PRP and stem cell injections has become more prominent due to the treatment of many athletes with soft tissue sports injuries, the promise of this field should be tempered by the limits of high quality medical evidence and guideline support outside of a few indications discussed in this newsletter. Clearly, better evidence is required from high quality randomized controlled trials to improve our understanding of best use of this treatment option.

For the present, patients are best served by having a better understanding of the limited evidence and expectations, benefits, risks and alternatives to help them make better decisions regarding their care. Claims examiners and case managers utilizing available tools of UR, Peer Review, or IME, when applicable, can help facilitate evidence based care.

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