AN APPROACH TO CHRONIC SPINE AND MUSCULOSKELETAL PAIN

The Need For A Hybrid Subspecialty

We live in a time of pain crisis in America. One hundred million adults are affected by chronic pain in the US. In 2010 the cost of pain associated with reduced worker productivity increased over $560-$635 billion. The annual cost of pain is now greater than that of heart disease, cancer, and diabetes. Conventional methods of pain treatment include pain medications, other drugs, and surgery, all of which have been problematic. It is commonplace for interventional spine physicians to ablate nerves off the spine by radiofrequency thermal lesioning. However, nerves regenerate and the pain returns, requiring additional procedures.

There is an ever-increasing need for physicians with a hybrid subspecialty to address this problem. Nationally there is a shortage of board-certified pain physicians. It is rare to find interventional pain physicians who utilize state-of-the-art, minimally-invasive surgical procedures with a focus on regenerative medicine while also being knowledgeable in integrated practices that can provide alternatives for the chronic pain population. The focus of our practice is on integrated pain medicine and regenerative approaches to orthopedic and musculoskeletal conditions. This article introduces our patients, and prospective patients, to a few basic principles utilized within our practice.
A Regenerative Approach

A regenerative medicine approach does not focus on ablating nerves and tissues to relieve pain. Instead, it focuses on stimulation of connective tissue regeneration whenever possible. There are many regenerative medicine techniques that we use within our practice. For brevity’s sake, we will only discuss a few of these methods here. In this article, we will cover five basic regenerative approaches.

We utilize the following methods in our practice to stimulate cellular and connective tissue regeneration:

1. Classic prolotherapy, utilizing dextrose-based solutions
2. Utilization of hormones to stimulate change in tissue and to modulate pain
3. Platelet-rich plasma, utilizing the growth factors from platelets as a stimulus for repair
4. Bone marrow aspirate concentrate (BMAC) as a means of capturing and transplanting stem cells to stimulate tissue repair
5. Adult, adipose-derived stem cell therapy as another means for possible tissue regeneration

Why Is A Regenerative Approach Needed?

I will first use the example of the chronic back pain patient. As I often tell patients, there are three ways in which we develop instability in our joints. On rare occasions an individual may have congenital hypermobility of joints that can lead to instability and chronic pain. These individuals are “born loose.” The majority of us, however, either break down and develop instability over time (“worn loose”), or have traumatic injuries that can lead to ligamentous damage and instability (“torn loose.”) Commonly we see a combination of traumatic injury superimposed over long-standing degeneration.

We all develop degenerative disc changes in our spine. Some of us suffer little mechanical consequences from this degeneration. Others develop changes within the disc that alter the mechanical behavior of spinal segmental motion. Subtle joint instability can increase the load and stress on the joints of your spine as well as compromise the ligaments that support them. The increased translational movements allowed by the degeneration and attenuation of the ligaments causes mechanical dysfunction and ligamentous pain.
As I have stated earlier, most pain physicians will block the nerves that innervate the ligaments and ablate them with thermal energy. But what if it were possible to strengthen the spinal ligaments and stabilize the spine? As a chiropractor early in my career, I could relieve a patient’s pain with such conditions, but the pain would recur. I became painfully aware of why this occurred. I knew it was caused by instability of joints secondary to either trauma, degeneration, or both. Because of recurrent pain, patients continued to return for repeat manipulation and treatment.

I built a gymnasium in my office so that patients could strengthen the core muscles that stabilize the spine, in an attempt to correct segmental instability and prevent recurrent spinal segment dysfunction. The strengthening and exercises certainly helped, but could not correct the intrinsic instability that was at the root of the problem.

Spinal surgeons commonly treat instability by surgical spinal fusion. Physical medicine and rehabilitation physicians prescribe more medication and more physical therapy. Anesthesiology pain physicians inject cortisone, perform epidural injections, and nerve ablation procedures. This may help temporarily, but patients find themselves returning for the same treatment repeatedly. The cost of this care is staggering.

When I discovered that there were physicians scattered around the world practicing regenerative medicine techniques that could resolve some of these problems I realized I was in the wrong profession and returned to school to retrain. It cost me another 14 years of postgraduate education, training, and experience to master these methods. What I share with you now is an understanding that comes from years of frustration and experience dealing with thousands of chronic pain patients over the years.

My first discovery in regenerative medicine was the technique of prolotherapy, over twenty years ago. I was introduced to it via Robert Klein, MD, a rheumatologist, and Bjorn Eek, MD, an orthopedic surgeon at Sansom Clinic in Santa Barbara, California. They were utilizing an injection technique that they claimed caused collagen and connective tissue proliferation in the ligaments that support the spine and joints.

I have to admit this was met with skepticism on my part, since I had never heard of such technology. Having practiced as a chiropractor prior to my medical training, I knew that segmental instability and attenuation of ligaments was a common cause of chiropractic and rehabilitation exercises failing to resolve my patients’ pain. Was it possible to regenerate connective tissues of the spine and joints?
It turned out that this injection treatment, directed at these ligaments, tendons, and connective tissues was, in fact, effective. I sent dozens of my patients to these doctors and was astounded by the outcome. The physical medicine and orthopedic institution where I was employed was concerned that I would bring “alternative” or “complementary medicine” procedures into the institute without evidence to support its use. Thus, despite my interest, our institution abstained from using this method of treatment until we could further study its potential benefit.

Another physical medicine and rehabilitation specialist and I started conducting our own clinical study, in 1994, of our own patient population. Our intent was to validate whether or not this method was effective, and we set up stringent criteria for an outcome study. Patients who entered the study had to first fail our best attempts at conservative treatment. Patients must have failed 3-6 months of physical therapy and 12-16 visits of chiropractic manipulation. They must also have failed medication management (including non-steroidal, anti-inflammatory medications, analgesics, muscle relaxants, and antidepressants) and injection procedures, such as trigger-point injections, epidural blocks, and corticosteroids. They had to have chronic pain of significant duration. In order to consider the patient improved by our treatment they had to have had their last prolotherapy injection procedure one year prior to the date of their re-evaluation. This was all to make sure that we far exceeded any potential placebo effects from the treatment. You may be interested to know that this patient population had, on average, been in chronic pain for 6.7 years. The average number of injection treatments utilizing prolotherapy was 6.4.

In re-evaluation, one year following their last treatment, 70% of these patients with low back pain reported an average of 72% improvement and 96.4% of our cervical spine patients reported improvement. This was a population who had failed all forms of conventional treatment. It was fascinating to us that cervical spine patients did better than low back pain patients and we were to later find out why. (I will address this in a separate article on chronic neck pain, available on my website.) The results were astounding. From that day forward we began to utilize this method of treatment in our practice and have continued to use it for the last 20 years.

**PROLOThERAPy**

**What Is Prolotherapy?**

Prolotherapy was a word coined by James Hacket, MD, a surgeon in the 1950’s. The word comes from the Latin ‘proles,’ which means to stimulate growth. Over the last 150 years, there have been a variety of agents discovered to stimulate growth and proliferation of collagen tissue. Prolotherapy is the process of injecting various substances into ligaments and tendon attachments for the purpose of proliferating the collagen in these connective tissues. This form of treatment
is directed to ligaments and connective tissue to help heal chronic injury and improve the attenuation of ligaments that occurs secondary to progressive degeneration of the disc.

**How Does Prolotherapy Work?**

To answer this question we must first understand how collagen is made in the body. Collagen is made by a specialized cell called a tissue fibroblast, shown in the picture to the right. These specialized cells contain the genetic programming to manufacture collagen. Collagen is a specialized protein that is one of the most supportive structures in living cells and tissues. Fibroblasts typically lie dormant in tissues and are activated with tissue injury. They are activated by cell-to-cell communication and chemical signals. These chemical signals, or signaling messengers, typically are released by injured cells. If you cut yourself in the kitchen and begin to bleed, the cells that you have cut release chemical messengers called growth factors into the surrounding tissues. These substances stimulate the dormant fibroblast to become active. Fibroblasts can move through tissue and “weave” a web of collagen in response to injury. Their job is to repair tissue damage. If you want to stimulate fibroblasts to action and cause these cells to lay down collagen and repair connective tissue, it can only be accomplished by utilizing this special cell-to-cell signaling. The substances we use to accomplish this cell signaling are called growth factors.

In the 1930’s, physicians who were the early orthopedic medicine pioneers of this technology started off using Sylnasol—a fatty acid and rather caustic, inflammatory substance—to stimulate connective tissue proliferation. Years later, George Hackett, MD and Gus Hemwall, MD coined the term “prolotherapy” and, more importantly, figured out a rather simplistic way to stimulate fibroblasts. They began utilizing dextrose sugar to cause the release of these growth factors. The dextrose sugar also improved patient safety in contrast to the more caustic chemicals previously utilized.

Gus Hemwall, MD specifically is credited with the use of dextrose-based solutions for this purpose. I had the privilege of meeting him many years ago when he was in his 90s. He theorized that you could extract growth factors from your own cells by causing an osmotic shock to the cell with the dextrose sugar.
I will attempt a simplistic description of the basic theory behind the process. First one must understand the general concepts of osmolarity and osmosis. Within each cell there are dissolved solutes such as sodium, potassium, chloride, and various other proteins and ions. There are also dissolved solutes outside the cell. A delicate balance of solutes is created by a very complex process within the cell that keeps certain ions outside the cell and certain ions inside the cell.

The cell’s outer membrane allows water to pass freely in and out. With a balanced solution of 5% both in and outside the cell it is said to be in equilibrium, meaning that an equal amount of water is flowing in and out of the cell. This is why we use a 5% solution of dextrose for IV fluids (which we call D5W, meaning dextrose 5% in water.) If we were to use a 1% solution surrounding cells, the concentration of solutes inside the cell would be higher than that outside. Thus, water would flow into the cell, causing it to swell up and burst. If we were to use a 25% solution, then the concentration would be too high outside of the cell. This would cause water to flow out of the cell, shrinking it. It is with this process of osmosis that our discussion begins.

If we inject dextrose sugar at a concentration of 25% outside the cell there is now far more solute outside the cell, thus exerting an osmotic effect in which water will flow through the cell membrane to the outside environment in an attempt to re-establish equilibrium. The cell membrane shrinks and the cell bursts, releasing growth factors into the surrounding tissues. Remember, these growth factors are chemical signals that stimulate local dormant tissue fibroblasts to once again become active. It is a signal to the fibroblasts that cells have been injured and that tissue needs to be repaired.
This led early prolotherapists to begin utilizing simple dextrose sugar to stimulate the production of collagen by simply turning on local tissue fibroblasts. That technique has been the foundational principle of prolotherapy ever since. This stimulus, when precisely targeted by injection into damaged connective tissues, can stimulate repair of a particular connective tissue. Fibroblasts have the unique ability to knit new collagen into the existing collagen, thereby strengthening the ligamentous structure. Your own cells do the repair work and it is your own connective tissues that are proliferated. There are no steroid anti-inflammatory medications used in the process. In fact, steroids are counterproductive to tissue healing. Steroids breakdown proteins and are not used in regenerative therapies. We do just the opposite, utilizing the natural inflammatory response of your body to stimulate healing.

I often ask my patients during the course of a consultation whether or not they have ever had a severe sprained ankle or know someone who has. After a severe sprain the ankle is never the same. You have an unstable joint that frequently is re-injured and never feels quite as stable with activity as it was before. The reason for this is that ligaments are damaged or stretched beyond their ability to repair. Utilizing targeted stimulus of dormant tissue fibroblasts provides a means of stimulating connective tissue repair. This repair can be targeted to the sacroiliac joints of the lumbar, thoracic, and cervical spine facet joints as well as other joints and tendons in the body.

OTHER TYPES OF REGENERATIVE THERAPY INJECTIONS

Hormones Used As Stimulus For Connective Tissue Repair

Another method of stimulating connective tissue repair and modulating pain is with the use of hormones. This was first introduced in 2010 by one of my early mentors, Thomas Raven, MD, from Colorado. When I first heard that Dr. Raven was utilizing testosterone and human growth hormone as a means of connective tissue regeneration I thought he had lost his mind. I was extremely skeptical, but I have known him to be a very objective physician and not someone who exaggerates or makes extraordinary claims about any form of treatment. After a lengthy discussion with Dr. Raven I decided to try this on a few, select patients. After significant success with the treatment, I was encouraged to explore it further. I then selected 30 patients and followed Dr. Raven’s protocol. I was very surprised to see the excellent results that we obtained on these 30 patients. Now, having had the opportunity of treating hundreds of patients with this method, I am convinced that he discovered an important therapeutic tool. My goal is to begin randomized clinical trials as early as next year to evaluate this method of treatment under controlled conditions.
Why Testosterone?

I have spent many years working with Denise Mark, MD, an internal medicine physician who specializes in bioidentical hormone therapies in Carmel, California. I began to see first-hand the advantages of using various hormones, including testosterone and human growth hormone, in health and wellness. This has become quite popular amongst integrative medical physicians throughout the world. My own orthopedic and rehabilitative medicine background did not give me exposure to a large population of patients undergoing this type of treatment. However, my exposure to Dr. Mark’s treatment methods for over a decade afforded me the opportunity to observe countless patients utilizing her hormone balance techniques.

Clearly, our empirical experience with Dr. Mark is that her patients seemed to heal better when deficiencies in hormones were corrected. Upon further investigation of growth hormone and testosterone, I began to realize that these hormones have significant effects on the earliest phases of wound healing in tissue repair. Testosterone and growth hormone play a role in regulating cell functions and stimulating protein production (a slow process called genomic effects).

The non-genomic effects of these hormones may be helpful in stimulating connective tissue repair by releasing signaling molecules alerting cell wall flexibility, modifying pain perception, stimulation blood flow to the site, and other effects described below. These hormones are used for cell signaling as second messengers to set off changes within the cell. This is done by attaching a cell receptor on the cell membrane and activating a specialized protein inside the cell, called a G-protein. The G-protein regulates metabolic enzymes, ion channels, transporters, multiple aspects of the cell machinery that controls transcription, etc. There is a youtube video of this process that you can watch titled “G-Protein Receptor Activation Video” (https://www.youtube.com/watch?v=xT0mAQ4726s).

The nongenomic effects of testosterone are illustrated here. Notice the relationship of the G-protein’s receptor (GPCR) to the ion channel and the MAP kinase pathway. These pathways play an important role in fast cellular responses known as non-genomic signaling. The sex hormone binding globulin receptor (SHBG) also uses the G-protein to stimulate the cyclic-AMP pathways which supply energy to many other fast-acting pathways.
Initially, we utilized a combination of human growth hormone and testosterone for tissue repair. We began to realize very soon, however, that the human growth hormone provided no significant additional benefit as compared to testosterone alone. By utilizing a water-soluble testosterone (aqueous testosterone), specially micro-ionized to micro-particles, we were able to deliver a cost-effective injection solution. The other thing that is important to understand is that we use extremely low doses. In a 6cc syringe we may only utilize 0.1mg! Even with multiple injections, typically a patient would not receive over a single milligram of testosterone. Thus, while there is a local tissue effect, the dosage is too low for the patient to experience any systemic effects from the injected testosterone.

CELLULAR-BASED THERAPIES IN REGENERATIVE MEDICINE:

Is There Research To Support The Use Of Testosterone For Pain And Connective Tissue Repair?

Although there is significant basic science research on the biochemistry and cellular effects of testosterone, and we can apply this research to clinical applications, we do not have randomized, clinically-controlled trials where we have compared the outcome to placebo injections utilizing this technique. There is a huge research gap in this area and it is my hope that this will soon be remedied.

What Is Our Experience Utilizing Testosterone As A Means of Reconstructive Injection Therapy?

Dr. Raven, in 2010,\textsuperscript{2} reported that testosterone seemed to work more quickly and with less post-injection soreness than the osmotic solutions previously utilized by most prolotherapy practitioners. Having now treated hundreds of patients with this technique myself, I tend to concur with his observation. The response in the majority of my patients has been rapid.

Patients will still experience soreness from the injections and will typically require 1-3 days to recover from that soreness, similar to other prolotherapy injections. However, we have noticed that the soreness seems to be milder than that experienced with the dextrose prolotherapy injections.
FROM PLATELETS TO STEM CELLS

Platelet-Rich Plasma Injection (PRP)

The use of the healing power of growth factors contained within platelets is not new. We have known for many years that there may be hidden potential for their use in clinical practice. My initial interest began 18 years ago when we were conducting experiments on the effects of platelet-derived growth factors on the spinal discs of goats. At that time there were very few physicians experimenting with the therapeutic use of platelets. Now, 18 years later, it has become one of the hottest topics in musculoskeletal injection therapy.

As a physician researcher, I continue to remain focused on regenerative therapies. I feel compelled to educate patients, eliminate hype and exaggerations, and help others tell fact from fiction concerning these new therapies as they enter the healthcare marketplace.

Why Platelets?

Platelets are very complicated and dynamic cells involved in a myriad of biologic processes in your body. They stick to each other and stop initial bleeding after injury. Once activated, they initiate the clotting cascade. They also release numerous growth factors that stimulate the proliferation of collagen, connective tissue, new blood vessels, tissue regeneration, and healing. The growth factors contained within platelets provide a powerful stimulus for tissue healing and regeneration. It is your platelets that are often responsible for initiating healing in soft tissue injuries such as abrasions and lacerations.

The rationale for utilizing platelets is to take advantage of the myriad of growth factors derived from platelets that alter healing response and tissue regeneration. These growth factors include TGF-β, platelet-derived growth factor (IGF), vascular endothelial growth factors (VEGF), epidermal growth factor (EGF), and fibroblastic growth factor -2 (FGF-2). These have the potential to enhance healing, grafting, and connective tissue repair. The specific attributes of these growth factors are not as important to understand as the fact that these growth factors can dramatically influence the way connective tissues heal and proliferate. The use of these growth factors to influence regulatory function for healing has sparked significant interest in orthopedics.

What Are Platelets Capable of Doing?

The growth factors derived from your platelets have been shown to promote the migration of small blood vessels into the tissue and pluripotent, autogenous stem cells into an area. This
promotes the release of additional growth factors. It has been used, for example, to accomplish the following:

1. Stimulating articular chondrocyte proliferation and healing cartilage defects in joints.\textsuperscript{5,6} As such, it is currently being used to influence proliferation of cartilage in arthritic joints.
2. Healing of chronic wounds.\textsuperscript{7,9}
3. Enhancing healing and pain reduction in shoulder arthroscopic surgery.\textsuperscript{10,11} Surgeons wanting to take advantage of the healing power of platelets are injecting platelet-rich plasma into the shoulder after surgery to enhance healing.
4. Stimulating fibroblasts and collagen proliferation. Because I have been working with previous treatment methods utilized to proliferate connective tissue and heal tendons and ligaments, I became extremely interested in the potential of this treatment as another option for my chronic pain patients who suffer from tendon and ligamentous injury and degeneration. The use of a patient’s platelets has now become a powerful biologic tool for the orthopedic and musculoskeletal clinician to affect tissue healing.\textsuperscript{12,14}

**What Exactly Is Platelet-Rich Plasma?**

Platelet-rich plasma is typically prepared by obtaining the patient’s own blood via IV. The blood is then transferred into a special centrifuge tube and processed to separate your red and white blood cells from plasma and platelets. This plasma and platelet combination is processed further in the centrifuge to concentrate the platelets. We then add back some of your plasma to create a custom concentrate of platelets and plasma for the particular procedure we are planning.

We currently utilize EmCyte technologies and centrifuge systems. We feel they offer some of the highest quality platelet-rich plasma preparations available.

One of the most appealing aspects of this treatment is that you are utilizing the patient’s own blood. At no time are the blood, blood elements, or cells utilized coming from someone else. This eliminates any worry or risk in regards to the spread of infectious diseases, such as hepatitis and HIV. Utilizing the patient’s own blood is considerably safer. It is also one of the most natural therapies I have ever encountered.
What Is It Being Used For?

The use of platelet-rich plasma injection for the purpose of wound healing and treatment of tendinopathy has become more commonplace in orthopedics and sports medicine.\(^7, 12, 15-19\) This form of treatment has been shown to be highly effective in treating tendinitis/tendinopathy, which is what sparked my interest.

Tendinitis/tendinopathy is a rather complex subject. This method of treatment is not a panacea or cure for all joint and soft tissue pain syndromes. It is, unfortunately, far from that. However, in carefully selected individuals, it is a powerful biologic tool. There is a subset of individuals who develop persistent pain despite well-accepted treatment methods. These individuals often have temporary relief with corticosteroid injections but, unfortunately, the pain returns. Mirisha et al. an orthopedic surgeon at Stanford University popularized this technique when he published a linear study on the effect of platelet-rich plasma injection on chronic tendinosis for lateral epicondylitis (tennis elbow).\(^20\) He was able to demonstrate, in patients who have failed conservative treatment (including injection treatment), a 81% success rate utilizing platelet-rich plasma injection. Around the same time, we began to utilize PRP extensively in multiple orthopedic applications.

Over the last several years I have been utilizing PRP to treat cervical spine, lumbar spine, sacroiliac joint disorders, and even, periodically, using injections of PRP into the disc in certain types of patients with disc disorders. We have utilized PRP injections, for example, in the sacroiliac joint in patients who have reached a symptomatic plateau with excellent success. We have also used this, for similar reasons, with success in the cervical spine when patients have not responded as expected from prolotherapy. The more experience I have with PRP over the years the more I am confident that this treatment method needs to be expanded. I believe this will someday become a standard of care.

Will Platelet-Rich Plasma Replace Prolotherapy?

No, platelet-rich plasma (PRP) will not replace prolotherapy. At one point it was thought that the use of platelet-rich plasma may be a more powerful biologic stimulus for connective tissue repair than prolotherapy injection. PRP use is expanding and, since we have improved PRP laboratory processing, we find ourselves using this method of treatment much more frequently. There are still times, however, in certain clinical situations, where dextrose-based prolotherapy is appropriate to use. This is determined on a case by case basis.
**Are Platelet-Rich Plasma Injections Covered By Insurance?**

Although there may be insurance companies that have been reimbursing patients for platelet-rich plasma injections, we still typically warn our patients that there is no guarantee of reimbursement. Insurance companies continue to be resistant to paying for regenerative injection therapies. Until substantial research is published that forces the insurance companies’ hands, insurance coverage and reimbursement is going to be a continual struggle.

**STEM CELL THERAPIES FOR SPINE AND JOINT PAIN PATIENTS**

We have now become affiliated with a research consortium working under an institutional review board to conduct clinical research in orthopedic application of both mesenchymal stem cells derived from bone marrow and fat. This process involves obtaining a sample of bone marrow blood called BMAC (Bone Marrow Aspirate Concentration) and processing the blood similar to the way in which we prepare PRP. This provides a means to concentrate mesenchymal stem cells from bone marrow blood or aspirate for therapeutic use in certain bone, joint, ligament, and tendon conditions.

Another method that we utilize involves adipose-derived stromal vascular fraction (SVF) mesenchymal stem cells. The cellular complexes are obtained by utilizing an aspiration of your fat tissue. This sample of fat contains high concentrations of stem cells and also provides a means for us to use the cells for therapeutic application in certain orthopedic conditions. We have addressed this issue in more detail in our article “Beyond Stem Cell Therapy.”

Stem cell therapy is not magic. It requires an understanding of when to use them and when not to. Not everyone can benefit from it, and you obviously cannot regenerate a new joint. Stem cell therapy is simply a biologic tool to enhance healing for certain types of orthopedic conditions.

**What Are The Risks And Potential Complications Of Prolotherapy?**

I think the most appropriate way to answer questions about potential complications and precautions regarding prolotherapy injection can be found by looking at real data. The late Thomas Dorman, MD, in 1973, surveyed orthopedic medicine physicians from around the world and obtained the outcomes of 494,845 patients. Of those patients, 343,897 were treated for low back pain and 98,430 for other areas of the spine. 26.85% also reported non-spine peripheral joint injections. The total accumulated years in practice of all practitioners was 1,092. Out of the 494,845 patients, there were 66 minor complaints reported. Of these, 24 were reported as
allergic reactions and 29 cases were resolved spontaneously without emergent care. 14 out of 500,000 cases reported persistent or transient nerve impairment from accidental nerve injection.

Daganais, et al in 2006 studied 472 reports of adverse effects from orthopedic medicine injections. Five of these patients had nerve injury, the vast majority had spinal headaches postinjection, 123 cases were reported to be pneumothorax, and 73 had a temporary medication reaction. 27 had some bleeding and 9 patients were reported to have a “non-severe spinal cord insult.”

These statistics are from both national and international studies that group all orthopedic medicine injections together. They do not separate out those who are not MDs, nor do they separate out those who were not experienced or well-trained in conducting this procedure from those who were. To summarize, the side effects and potential complications are:

1) Post-Injection Soreness

Postinjection pain and soreness, in my opinion, should be expected 100% of the time. Although one of the studies noted above reported only 70% I believe it is closer to over 90%. Prolotherapy utilizes inflammation to heal tissues and, therefore, one can expect to have increased pain for a period of time after the injection. Typically this occurs for a period of 48-72 hours and then resolves. Most patients report the pain as an inconvenience but certainly not incapacitating.

I think the best way to look at postinjection soreness and flare is to think of it as a bell curve. The majority of patients will experience pain that is somewhat of a nuisance for a period of 48-72 hours. But there are outliers: 1-3% will experience very minimal flare, if any. On the other end of the spectrum, 1-3% will experience more soreness and discomfort than most, which, of course, can last longer than 72 hours.

Having performed these procedures thousands of times over the last 20 years I have yet to see a patient who had any residual complaint or increased pain or soreness that did not go away. We always warn patients undergoing any type of spinal injection procedure that there could be increased pain that persists. I simply have not ever seen it clinically.

2) Reaction To Anesthetic

The predominant medications used for prolotherapy, besides simple dextrose sugar, are local anesthetics. We typically utilize lidocaine, one of the most common local anesthetics. We warn patients that they could have a reaction to local anesthetic. If there is a known allergy or adverse side effect to lidocaine we typically change classes of anesthetic. I carry several types of anesthetic at my practice at all times in order to overcome this potential problem.
3) Reaction to Medication

We are careful to ask all our patients about allergies to medications. However, there may be an unknown allergy that is discovered after an injection. We always warn our patients that they could, at any time, have an allergic reaction to medication.

4) Infection

Any time you pierce skin with a needle there is the potential for an infection. We always warn our patients about this potential complication. It is interesting that the number of infections that occur is rather low. Notice that both studies noted above did not report a single episode of infection. The reason for this may not be so obvious. Remember, we are using concentrated dextrose sugar, for the most part. This causes the same osmotic injury to bacterial cells. Thus, the low rate of infection may be due to either the small needle size or the potential bacteriostatic nature of the dextrose that we use in prolotherapy procedures.

5) Accidental Neurologic or Vascular Injury

This is always one of the biggest concerns with any interventional spine procedure, prolotherapy, and all regenerative injection therapies. It is my opinion that injections such as these should be done by professionals with appropriate training and experience. We suggest that patients carefully evaluate the credentials and specialty training experience of the physician they choose to provide this form of treatment. I have completed two interventional spine and pain fellowships and I am board certified as an interventional spine specialist. In addition, I have a history of 25 years of experience with prolotherapy injection techniques.

We take several precautions to reduce the risk of neurological injury. Firstly, we use the smallest gauge needle possible (typically a 27 gauge). We also use the shortest needle possible to reach the target to reduce risk. In addition, if you look at the picture to the right, you will notice the facet joints in the neck overlap each other like shingles on a roof. If you understand this arrangement, you can angle the needle down, making it safer to move down the ligament. Note that, to get into the joint, one would have to angle the needle upward. Since we target the back portion of the ligament, the downward angle is believed to be safer. On larger patients, where it is more of a technical challenge for precise needle placement, I utilize ultrasound to enable precise needle placement for improved safety.
6) **Pneumothorax**

A pneumothorax occurs when the lining of the lung is pierced by a needle and air leaks into the pleural space of the lung field. This can cause a collapsed lung and may require the insertion of a chest tube to correct. Of the 29 cases reported by Dr. Dorman in his study, all of the cases resolved spontaneously. With painstaking care and special precautions we can prevent this type of complication. We often use fluoroscopy or x-ray guidance to do injections over the ribs. We also use ultrasound as another way to guide needles to precise targets overlying ribs. We have never experienced a single episode of pneumothorax in all our years of using this technique.

7) **Accidental Dural Puncture**

There is a fibrous sac full of cerebrospinal fluid throughout the spine. This sac is called the dura. If you accidentally puncture this sac, you can cause a leak of CSF, possibly resulting in a spinal headache. If this happens it is treated with caffeine. On more rare occasions, such a leak may require a procedure called a blood patch. This is where blood from your vein is injected near the leak to patch it.

**CONCLUSION**

Regenerative injection therapies are not new, but, with the emergence of modern imaging and image-guided procedures, it is a rapidly growing field. It will likely continue to grow in popularity as new stem cell technology becomes available. Observing the relatively few complications reported compared to the number of procedures done, it has been considered safer than many other conventional pain management procedures. It offers a well-trained physician countless options in treating musculoskeletal and spine conditions that are typically unresponsive to other, more conventional, therapies.
REFERENCES: