



Regenerative Injection Therapy

By Michael N. Brown, DC, MD, DABPMR-PAIN. Reprinted with permission.

The need for a hybrid subspecialty trained physician for the chronic spine and musculoskeletal pain patient:

We live in a time of pain crisis in America. 100 million adults are affected by chronic pain in the US.¹ 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.¹ Conventional methods of pain treatment include pain medications, other drugs and surgery, which have been problematic. It is commonplace for interventional spine physicians to ablate nerves off the spine by radiofrequency thermal lesioning. Nerves regenerate and the pain recurs requiring additional procedures. There is an ever increasing need for a physician "subspecialty hybrid." There is a national shortage of board-certified pain physicians and it is rare to find interventional pain physicians who utilize state of the art minimal invasive surgical procedures but whose focus is regenerative medicine, and are also knowledgeable in integrated practices that can provide alternatives for the chronic pain population. The focus of our practice is "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.

Regenerative medicine procedures for the chronic spine and musculoskeletal pain patient: A "regenerative medicine" approach does not focus on ablating nerves and tissues to relieve pain but rather focuses on stimulation of connective tissue regeneration whenever possible. There are many regenerative medicine techniques that we use within our practice. For brevity we will only discuss a few of the methods that we most commonly utilize. We will discuss five basic regenerative approaches in this article. We utilize these 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 modulate pain
3. Platelet Rich Plasma utilizing the growth factors from platelets as a stimulus for growth factors from the 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 of joints. What that means is that on rare occasions an individual may have a congenital hypermobility of joints that can lead to instability and chronic pain. These individuals are "born loose". The majority of us either breakdown 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 of 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

cause 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 was possible to strengthen the spinal ligaments to stabilize the spine? As a chiropractor early in my career, I could relieve a patient's pain with such conditions but the pain would reoccur. I became painfully aware why this occurred; I knew this 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.

The spinal surgeons commonly treat instability by surgical spinal fusion. The physical medicine and rehabilitation physicians prescribe more medication and more physical therapy. The anesthesiology pain physicians inject cortisone, perform epidural injections, and nerve ablation procedures which 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. That cost me another 14 years of postgraduate education and years of training and experience to master the 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 20 years ago. My first exposure to prolotherapy was via Robert Klein, MD, a rheumatologist and Bjorn Eek, MD, an orthopedic surgeon at Sansom Clinic, located in Santa Barbara California. They were utilizing an injection technique that claimed to cause collagen and connective tissue proliferation in ligaments that supported the spine and joints. I have to admit this was met by skepticism on my behalf since I had never heard of such a 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 failure of chiropractic and rehabilitation exercise to resolve some of my patient's pain. Was it possible to regenerate connective tissues of the spine and joints? It turned out that this injection treatment directed to these ligaments, tendons and connective tissues was in fact effective. I sent dozens of my patients to these doctors and was astounded at 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.

Therefore, despite my interest in this concept our institution withheld this method of treatment until we could further study its potential benefit. Myself and another physical medicine and rehabilitation specialist set forth to conduct our own clinical study in 1994 of our own patient population. We needed to validate whether or not this method was effective. We set up stringent criteria for an outcome study.

Patients that entered the study had to first fail our other best conservative efforts. Patients must have failed 3-6 months of physical therapy, 12-16 visits of chiropractic manipulation, medication management including non-steroidal anti-inflammatory medications, analgesics, muscle relaxants, antidepressants and injection procedures such as trigger point injections, epidural blocks and corticosteroid injections. 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 injections procedure one year prior to the date of their re-evaluation. This was a way 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 an average chronic pain of 6.7 years. The average number of injection treatments utilizing prolotherapy was 6.4 visits. Following the last injection treatment one year later the patients were each re-evaluated to determine how they

were doing. At this one-year point, 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 an article on the chronic neck pain posted on the website. The results were astounding, from that date forward, we began to utilize this method of treatment in our practice, and have continued to use it for the last 20 years.

What is Prolotherapy?

Prolotherapy was a word coined by James Hackett, MD a surgeon in the 1950's. The word comes from proles - which means to stimulate growth in Latin. Over the last 150 years, there has 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. The fibroblasts are activated by cell to cell communication and chemical signals. The 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 these 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 initially used Sylnasol, a fatty acid and rather caustic and inflammatory substances 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 the growth factors. The dextrose sugar also improved patient safety in contrast the more caustic chemicals previously utilized. Gus Hemwall, MD specifically is credited for the use of dextrose-based solutions for this purpose. I had the privilege of meeting him many years ago when he was in his 90's. 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 am going to try and simplistically describe the basic theory of how the process of osmosis is used to stimulate connective tissue repair.

The first thing that you need to understand is the 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 most important concept is that there needs to be an equal solute concentration inside and outside the cell for the cell to remain in equilibrium. The solute concentration inside and outside the cell is 5%.

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 on the cell. When this occurs water will flow through the cell membrane to the outside environment in an attempt to equilibrate the concentration differences. 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 basically a signal to the fibroblasts that cells have been injured and that tissue needs to be repaired. Early prolotherapist began utilizing simple dextrose sugar as a means to stimulate release of tissue growth factors to stimulate proliferation of collagen by simply turning on local tissue fibroblasts. That technique once discovered has been the foundational principles prolotherapy ever since. When fibroblasts are activated they move into the region of the chemical signal and begin to lay down connective tissues (collagen). This stimulus when precisely targeted in damaged connective tissues can stimulate repair.⁵

Fibroblasts, once stimulated by cell signaling from the growth factors released in the area lay down bands of collagen in the tissues. Fibroblasts have the unique ability to knit collagen into the existing collagen thereby strengthening the ligamentous structure.

Utilizing simple sugar and the powerful effects of osmosis allows a physician to target a specific connective tissue with precise injection and stimulate local tissue fibroblasts. This causes proliferation of collagen and connective tissue at the targeted site of injection. The repair is your own cells doing the work. 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.

Actually, we do just the opposite. We utilize 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 sprain of an ankle or know someone who has. Anyone who has had a severe sprain knows that the ankle is never the same. You have an unstable joint that frequently is reinjured and never feels quite as stable with activity as prior to the sprain. 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 METHODS 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 Colorado2. When I first heard that Dr. Raven was utilizing testosterone and human growth hormone as a means of connective tissue regeneration I personally 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 and 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 on these few individuals, I was encouraged to explore this modality of treatment further. I then selected 30 patients and followed Dr. Raven's specific protocol.

I was very surprised to see the excellent results that we obtained on these 30 initial patients. Now, having had the opportunity of treating 100's of patients with this method I am convinced that he has discovered an important therapeutic tool for the future. 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 firsthand 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 orthopedic and rehabilitative medicine background did not afford me the exposure to such a large population of the patients undergoing this type of treatment. My exposure to Dr. Mark's treatment methods for over a decade afforded me an 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. That was my first exposure. 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 below². 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 and multiple aspects of the cell machinery that controls transcription, etc³. You can watch this process on youtube at www.youtube.com video: G- protein receptors.

Initially we utilized a combination of human growth hormone and testosterone for tissue repair. We began to realize very soon that the human growth hormone provided no significant additional benefit as compared to testosterone alone. By utilizing a water- soluble testosterone (aqueous testosterone) specially microionized to micro-particles we were able to deliver a cost-effective injection solution. The other concept 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

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 clinical control trials where we have compared the outcome to placebo injections utilizing this technique. There is a huge void in research in this area and a great need for further research in this regard.

What is our experience utilizing testosterone as a means of reconstructive injection therapy? Dr. Raven initially reported his own personal experience in 2010². He reported that testosterone seemed to work quicker with less post injection soreness than the traditional osmotic solutions previously utilized by most prolotherapy practitioners. Having now treated hundreds of patients with this technique myself, I tend to concur with his empirical experience. I am in agreement that this seems to bring about a rapid response in the majority of my patients.

Patients will still experience soreness and will typically require 1-3 days to recover from the soreness of the injections, similar to other prolotherapy injections. We have

injections, typically, a patient would not receive over a single milligram of testosterone; therefore, the patient experiences no systemic effects. The reason for using such low doses is that we are trying to elicit a local tissue effect and not a systemic effect.

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 and eliminate hype, over exaggerations and provide a clear understanding of 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. Platelets are responsible for sticking to each other and stopping initial bleeding after injury. Once activated they also initiate the clotting cascade as well as release numerous growth factors which stimulate the proliferation of collagen connective tissue, new blood vessels and 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 a healing cascade in soft tissue injuries such as abrasions and lacerations.

The rationale therefore 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), fibroblastic growth factor -2 (FGF-2), which have the potential to enhance healing, grafting and connective tissue repair. The specific attributes of these growth factors are not as important as the basic understanding 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.⁴

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 to promote the release of additional growth factors. This has been used for example to accomplish the following:

1. Stimulating articular chondrocyte proliferation and healing cartilage defects in joints^{5,6}.
Thus is currently being used to influence proliferation of cartilage in arthritic joints.
2. Healing of chronic wounds^{7,9}.
3. Enhancing healing and pain reduction in shoulder arthroscopic surgery^{10,11}. Surgeons wanting to take advantage of the healing power
4. of platelets are injecting platelet rich plasma into the shoulder after surgery to enhance healing.
5. 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 pathology. The use of a patient's platelets has now had become a powerful biologic tool for the orthopedic and musculoskeletal
6. clinician to affect tissue healing^{12,14}.

What exactly is platelet rich plasma? Platelet rich plasma is typically prepared by obtaining the patient's own blood via an IV. The blood is then transferred in a special centrifuge tube and put through a series of centrifuge processing that allows us to separate your red blood cells and white

blood cells from plasma and platelets. We then take the plasma and platelets and further centrifuge them to concentrate platelets. We then add back some of your own plasma to create a custom concentrate platelets and plasma based on what procedure we are planning.

We currently utilize EmCyte technologies and centrifuge systems which we feel offers some of the highest quality platelet rich plasma preparations available.

One of the most attractive parts of this treatment is that you are utilizing the patient's own blood. At no time is there any other individual's blood, blood elements or cells utilized during this process. This eliminates any worry or risk for spread of infectious disease such as hepatitis, HIV, et cetera. Utilizing the patient's own blood is the beauty of this therapy. Therefore, the only things being injected into your body are elements of your own blood! This represents one of the most natural therapies I have ever encountered.

What is platelet rich plasma 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 in this treatment. Now, 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 have recurrent pain. 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) at 81% success rate utilizing platelet rich plasma injection. About 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 using periodically injections of PRP into the disc a 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 for similar reasons in the cervical spine with success as well when patients have not responded as expected with 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. It was anticipated that the use of platelet rich plasma may in fact 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.

Is platelet rich plasma injection covered by insurance?

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

STEM CELL THERAPIES FOR SPINE AND JOINT PAIN PATIENTS

We have currently now became affiliated with a research Consortium working under a 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 his 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 that issue in more detail in our article "beyond stem cell therapy".

Stem cell therapies are not magic. It requires an understanding of when to use them and when not to. Not everyone can benefit. It is not like you can regenerate a new joint. There are simply biological tools to enhance healing of certain types of orthopedic conditions.

What are the risk and potential complications of prolotherapy?

I think is the most appropriate way to answer the question in regards to potential complications and precautions regarding prolotherapy injection is to look 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 1092. Out of the 494,845 patients there were 66 minor complaints reported, of these; 24 were reported as allergic reactions, 29 cases of resolved spontaneously without emergent care. 14 cases out of a 500,000 cases reported persistent or transient nerve impairment from accidental nerve injection.

Daganais, et al in 2006 studied 472 reports of adverse events from orthopedic medicine injections; 5 of these patients had nerve injury, the vast majority had spinal headaches postinjection, 123 cases were reported to be pneumothorax and 73 or temporary medication reaction. 27 had some bleeding and 9 patients were reported to have a "non-severe spinal cord insult".

The statistics are both national and international studies that group all

orthopedic medicine injections together and does not separate out those who are non- MDs nor does it separate out those who are not experienced and well trained for this procedure and those who were not. To summarize the side effects and potential complications are:

Postinjection 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 in inconvenience but certainly not incapacitating.

I think the best way to look at postinjection soreness and flare is to look at a bell curve. Looking at the bell curve the majority of the population falls within the light blue or yellow region, which means that the majority of individuals 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 at all. 1-3% will experience more than expected soreness and discomfort which of course can last greater 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 the patient undergoing any type of spinal injection procedure that there may be increased pain which could persist. I simply have not seen it clinically.

1. Reaction to medication:

The predominant medications used for prolotherapy besides simple dextrose sugar are local anesthetics. We typically utilize lidocaine, one of the common local anesthetics. We warn the patient that they could have a reaction to local anesthetic specifically lidocaine. If there is a known allergy or adverse side effect of using lidocaine we typically changes classes of anesthetics. I carry several types of anesthetics within the practice at all times in order to overcome this potential problem. Other reactions to medications are always possible.

2. Allergy:

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

3. 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 rather interesting that infection complication is rather low. Notice 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 as they do to the cells that you inject into to do the prolotherapy to begin with. Therefore, either the small needle size or the potential bacteriostatic nature of the dextrose that we use could be responsible for such a low infection rate in prolotherapy procedures.

4. Accidental neurologic or vascular injury:

This is always one of the biggest concerns with any interventional spine procedure. Prolotherapy and all of the regenerative injection therapies require precise injections to accomplish the therapeutic goals desired. It is my opinion that injections such as these should be done by professionals with appropriate training and experience. We would suggest that one should carefully evaluate the credentials and specialty training experience of the physician you 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. We use the smallest gauge needle possible (typically a 27 gauge). We use the shortest needle possible to reach the target to tissue 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 and it makes it safer to walk 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. Your treating physician has to be extremely careful in doing these procedures so you should consider the training and background of the doctors you choose to see for these procedures. 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.

5. 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, which can collapse a lung. This may require insertion of a chest tube to correct. Of the 29 cases reported by Dr. Dorman in his study all of the cases resolved spontaneously. We take pain-staking efforts and special precautions prevent this type of complication when working over the ribs.

We often use fluoroscopy or x-ray guidance to do the 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 the years I have used this technique.

6. Accidental dural puncture:

There is a fibrous sac full of cerebral spinal 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 the leak".

IN SUMMARY:

Regenerative injection therapies are not new but with the emergence of modern imaging and image guided procedures is a recent rapidly growing field. This will likely continue to grow more popular as new stem cell technology becomes available. In considering the relative few complications reported compared to the number of procedures done it has been considered a safer procedure 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.

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