

# Questions and Answers about Prolotherapy Updated From a 2009 Interview

Q: "What is prolotherapy and why is it called prolotherapy?"

Dr. Reeves: Prolotherapy is a method of injection treatment designed to stimulate healing. The term "prolo" comes from the term proliferate which means to make new cells. Because prolotherapy involves making new cells grow or regenerate, another description of the treatment is regenerative injection therapy. There are other ways to make things regenerate of course but the key word in prolotherapy is injection. This is a nonsurgical treatment. Therefore, injection that causes new cell growth can be termed prolotherapy.

Q: How long has this been around? I mean how old is prolotherapy?

Dr. Reeves: The concept of creating or stimulating new growth and repair has been around since the time of the Pharaohs. Nearby the tomb of Amenhotep III is a pictorial description of how he tarried to treat his lame horses by applying heat to their foot ligaments. Much like foot aches in humans, if horse foot ligaments became weak the horses become lame and may have to be put down. Heat was used to irritate the ligaments in the foot of the horse and stimulate repair. That was the early history of using irritation to promote healing. Another example was from the 1600s on the French battlefield when oil was dripped into a wound to stimulate more rapid healing by irritation. If you could not lift your sword you could not defend yourself. The key was speed of healing. If it was not for the process of inflammation, none of us would heal even the smallest cut. It is life-threatening if we lose the ability to react to injury by inflammation. In about 1930 several physicians, primarily in the United States, began to use various solutions to create a temporary stimulation for repair. One of those solutions used years and years ago was simple dextrose solution. So, the use of dextrose dates back at least till then.

Q: What does prolotherapy actually do to ligaments and tendons that are damaged?

Dr. Reeves: Those that use prolotherapy realize that the typical repair process after an injury leads to approximately an 80% repair. In other words, the original strength of the ligament or tendon or integrity of the cartilage has some damage that is not completely repaired or made fully normal. Over time, with additional injuries, large or small, the amount of total injury becomes enough to start creating pain. We can't force someone to repair by causing actual injuries because they don't fully repair. The advantage of prolotherapy is that you don't tear anything and you don't stretch anything. Instead, you simply inject something that makes the body sense that repair needs to occur and then the process begins. A tendon or ligament is much like a rope. If you're going to

strengthen a rope you can't just pull on the rope to make it stronger. A rope will fray when you do that. To make a rope stronger you need to add strands to the rope. After a solution is injected, called a proliferant solution, new rope material or new "strands of rope" are laid down along the weak area. This new rope material thickens the rope that is already there, but it is important to know that the new rope material is immature and filled with water molecules. It is called procollagen. The term pro means immature. As the baby collagen or procollagen matures it loses the water in its structure and, as it does that, it naturally tightens. This is how a stretched out and weakened rope in sprain and strain can be changed back into a thicker and tighter rope. The body does not appear to allow over-tightening, so it has not been the experience of those doing prolotherapy that ligaments and tendons become too tight. Cartilage is a different structure type but has its own way of responding.

Q: Are there different methods used in prolotherapy?

Dr. Reeves: Well, as mentioned, the initial way that prolotherapy was done was to create an inflammation and this can occur by simply using a needle. When a needle penetrates a cell, it disrupts the lining of that cell. That lining is called a cell membrane. The cell membrane is made up of little fats called lipids and these are released into the fluid around a cell. These lipids create inflammation which is a signal for repair cells to begin their work. A needle can also cause a little bit of bleeding. There are tiny veins and capillaries all over our body and you can stimulate a little bleeding with needle contact. Blood has many thousands of specialized structures called platelets. When these are released into an area they are also inflammatory and stimulate a repair effect. This is one reason why bruises are actually good. So even a little bitty needle can do this without injecting anything at all. If you inject something that creates an additional repair effect, that will result in a more powerful response. Dextrose is the most natural and most common solution injected in prolotherapy. We have all heard of glucose which is what we measure in our blood when we have diabetes. Glucose comes as a right or left mirror image. Dextrose is the right mirror image of glucose and is the one found in humans. So, when I say dextrose, listeners can substitute the term glucose. Dextrose is a simple sugar that has six carbon atoms. It's like a hexagon and is what our cells use for energy. Injecting dextrose appears to be somewhat like piling raw materials outside a factory. Having an abundance of raw materials is a signal for the factory to turn on and start producing something. When you inject dextrose around a cell it makes ligament, tendon and cartilage cells produce special proteins that are potent stimulators of repair. In summary there are needle effects and bleeding effects that stimulate healing and an effect of the solution itself.

Q: How natural is prolotherapy?

Dr. Reeves: If you inject dextrose you are basically injecting fuel for the body cells. The cells of course transport the dextrose inside them so that within several hours the body has already used the glucose up in that area. Therefore, there is nothing left behind that is unnatural. However, the cell, once it begins the repair process, continues that

process. Those that are unaware of how prolotherapy works often think you are using a placebo when you inject dextrose because most are aware that dextrose is a simple sugar and then using sugar water by injection is like taking a sugar pill. The reason why dextrose by injection is not a placebo is because you're not taking it in your mouth and your insulin doesn't have the ability to drop the dextrose concentration. So, it's like you're bypassing your stomach. You're putting a high level of dextrose around the cell. In order to stimulate the cells to produce the growth proteins you only need to surround the cell with one half percent dextrose. If you listen to television programs about emergency rooms or hospitals you realize they use dextrose in 5% or more concentration. Therefore, we can stimulate healing by injecting only a fraction of that, and typically we use 12.5% to 15% dextrose for prolotherapy. Compared to injection in an IV, which distributes and dilutes dextrose rapidly, injection in a local area around a ligament or tendon or in a joint keeps the level of dextrose high for several hours. The DNA in local cells begin to produce new proteins for growth within about 20 to 30 minutes.

Q: It has been said that prolotherapy works on soft tissue. What is soft tissue and what types of musculoskeletal conditions does prolotherapy work best on.

Dr. Reeves: The simplest way of describing soft tissue is a part of our body that is not hard when you knock on it. Bones are really hard when you knock on them. Cartilage, compared to bone, is soft tissue, and cartilage cells also begin to produce repair proteins, called growth factors, when exposed to dextrose. Growth factors, once produced, hook onto the outside of cells that you want to repair. When they hook on they send a signal to the cell's DNA to begin a repair or growth process. Bone cells do not respond to dextrose, and do not respond to the growth factors produced by soft tissue cells. Therefore, repair can be stimulated in ligaments and tendons and cartilage without causing a bone response. That is good because we don't want more bone spurs. Pain in chronic sprain or strain in arthritis is contributed to very heavily by degeneration in either ligament, tendon, or cartilage, or it can be due to the little nerves being oversensitive in that area. A very exciting area of research is based on the understanding that nerves are soft tissue also. It appears as though nerves that have been abnormal for a long time in an area of chronic pain can be stimulated to repair and begin behaving normally by exposure to dextrose. So, while you are treating the damage in ligament, tendon or cartilage, at the same time you are treating the nerves that are over sensitive in the area so that they begin to act more normally and thus produce less pain.

Q: It sounds like you're getting a dual effect really in that you're not only treating the actual problem with the tendon or ligament but you're also getting an effect on the perception of pain. Would that be safe to say?

Dr. Reeves: That's what's been so particularly exciting because when a person hurts long enough in an area the nerves in that area become abnormally sensitive to pain. There is a term for that called "wind up " when nerves are over sensitive, it is like your

football team is facing another team called pain. When you have nerves that are oversensitive it is like your football team has no linebackers. When the opposing team sends a pain that gets through your line of scrimmage you have no linebackers to keep the pain from getting to your brain. This explains how the person that has chronic pain can hurt in an area of pain even with stimulation that would not normally hurt, like touch. Another way of describing this is like a baseball player with a glove on and the glove gets smaller and smaller and cannot catch as many balls as it used to. It has been thought that once patients become oversensitive that there are permanent changes in the brain and spinal cord that cannot be changed. However, it appears that some of the change is actually in the nerves that we can reach and that, by stimulating the cell to become healthier, the oversensitivity can actually be reversed. You can understand why we are excited about the potential that prolotherapy offers for pain even of several decades.

Q: When do you start to use prolotherapy? Is there such a thing as being too late?

Dr. Reeves: What we have found is that regardless of the number of years that a patient has had chronic pain, a high percentage of patients still respond with pain and functional improvement. A rough estimate would be that 80% respond in a very good or excellent fashion with pain less than a year and 70% with pain of twenty to thirty years. Things become more complicated with pain for many years but it does appear that with this reversal of the nerve irritability and repair of the structures that the amount of years a person has hurt does not matter as much as we thought. Your question was "Is it ever too late?" The other end of that question is – "Is it ever too early?" The general approach has been to let the body do its own natural healing process for several months before you use prolotherapy. That's logical of course. However, in the future and even in the present we will be able to accelerate the process of healing and increase the likelihood of healing in more significant injuries. This is particularly critical in athletes that are in a hurry to get back to sports. Therefore, treatment that enhances healing that the body is already trying to do on its own is another use of prolotherapy.

Q: Can you elaborate on prolotherapy with platelet rich plasma a little more?

Dr. Reeves: Prolotherapy is a method of injection treatment designed to stimulate healing. I previously mentioned that the needle can cause a little bleeding which can stimulate healing because that is the effect of blood exposure. The most common type of platelet rich plasma currently is one in which the red cells and white cells have been removed, leaving the clear plasma of the blood with platelets. Platelets contain growth factors that are already made and ready to begin work immediately when they are activated. If PRP is injected in an area of disrepair, you have a very powerful stimulant for healing. In the PRP are also some stem cells. The exact potency of PRP has not been compared with dextrose but PRP is likely several times more potent than dextrose. However, it cannot be used in large areas because it can only be made in a limited volume. Injection of PRP is most certainly injection designed to stimulate healing so it is another way prolotherapy can be performed.

Q: Are PRP and stem cell injection variations of prolotherapy?

Dr. Reeves: Yes, however many were hoping that insurance coverage could occur more readily if they simply called them PRP injection and stem cell injection. However, further research is needed, and that hope has not been realized.

Q: When injecting for arthritis, why are injections given both inside and outside of the joint

Dr. Reeves: Joints are more complex because they can have a number of pain sources. An example of the importance of treating pain sources both inside and outside the joint is seen in patients that still have pain after a joint replacement because they still have pain sources outside the joint itself. For this reason, whenever we talk about treating joint such as a knee or a shoulder for example, we're talking about how to inject the joint itself and also the key ligaments and tendons around the joint. More recently we are also treating some of the nerves around the joint. By doing so we address every source of pain for a more complete pain relief.

Q: What do you think of steroid injection?

Dr. Reeves: We don't want to dismiss steroids completely. They have their place, particularly for the type of inflammation based on the arachidonic acid pathway. There are certainly conditions that are inflammatory and very quickly respond to steroid injections. However, as a cause of chronic pain, nerve-based inflammation rather than arachidonic acid pathway inflammation is predominant. Since the mid-1980s, pathologist (doctors who specialize in understanding why diseases happen and what they look like under a microscope) began to comment that in chronic pain there are typically very few inflammatory cells. They suggested that the term "osis"; e.g., tendinosis, or "opathy"; e.g., tendinopathy, are both more appropriate than using the term "itis". Since the basic problem is not an it is, steroids typically help only temporarily after the first time.

Q: What about myofascial pain? How does that relate to the need for prolotherapy?

Dr. Reeves: Myo means from muscle and fascia is the connective tissue around muscle fibers. Myofascial pain therefore means pain from muscles or their connective tissue. In the 1980s and somewhat continuing today, many physicians and therapists thought the source of pain in chronic pain was from the muscles themselves. Pain of course is from nerves, not muscle, but those nerves supply the muscle as well, and muscles are very reactive to nerve inflammation. We all know that people in chronic pain tend to have tight muscles. That tightness itself can be counterproductive, and there are many skillful therapists that use a variety of techniques to treat myofascial pain, and find success doing do. The two limitations with this are when the ligaments and tendons are weak and painful enough (due to its nerves) that the muscle reflexly persists in

tightness, or when the nerves that supply the muscle are inflamed or compressed sufficiently that they will not allow the benefits to hold up after treatment.

Q: What about active release therapy or acupuncture? Do they do the same thing?

A: They do similar things. Active release therapy is a valuable approach to chronic pain that identifies areas of compression of nerves and stretches nerves to help them move better, and practitioners are often excellent at both releasing nerves and retraining proper movement in athletes. Acupuncture has stood the test of time, and the areas of penetration/entrapment of nerves appears to correlate closely with most of the acupuncture points (and the area of trigger points in myofascial pain), and the use of needle placement has substantial effect on the nerves at those locations. The same limitations apply to these treatments as with myofascial therapy in that neither active release nor acupuncture directly repair damaged structures, and nerve dysfunction may be present at deeper levels in areas that cannot be effectively stretched or that the needles can reach or get to. However, it should be emphasized that active release therapy (ART), muscle retraining/reconditioning, acupuncture, and manipulation are quite valuable. Each treatment can be effective alone, depending on the type of damage present. There are many very talented practitioners out there.

Q: Is there a specific solution that you typically use for prolotherapy?

Dr. Reeves: Typically, about 12.5 to 15% dextrose is what's used for most ligaments and tendons and traditionally many have used 25% dextrose inside joints thinking that the fluid in a joint will dilute the dextrose somewhat. There are other more inflammatory solutions available such as an alcohol called phenol. However, the use of platelet rich plasma in local areas has become more affordable and is more natural than forcing the body to go through more arachidonic acid type inflammation temporarily from more aggressive inflammatory agents.

Q: But isn't dextrose just sugar?

Dr. Reeves: Dextrose has now been shown in randomized/masked clinical trials at the orthopedic laboratory research lab at Mayo Clinic to increase ligament size and strength, even without inflammation. Stains for cartilage after knee injection have indicated some stimulation of cartilage growth. Recent studies have shown a rapid analgesic effect of dextrose without use of anesthetic. Ligament and tendon cells cannot take in dextrose across their cell membrane without producing special proteins called growth factors. Physicians or others who make a comment about dextrose being a placebo are best considered (kindly speaking), "literature challenged" and should spend more time looking at evidence-based basic science literature. See research tabs for more information.

Q: How often would you use a prolotherapy procedure? Let's say for instance that a person comes in with tendinosis of their elbow. How often would you do a prolotherapy procedure on that person?

Dr. Reeves: If you want to be the most cost effective and you have someone who's not having to get back and throw the ball for their team and do a sport immediately, I feel

the most cost-effective way is probably about every two months. Consider what happens when you break a bone. The doctor puts a cast on for 1-2 months. Or if you sprain your ankle you are often told it will take about 2 months to largely heal. First you grow new tissue and then the new tissue takes time to mature. So, if the time is available and there's no huge hurry, two months is okay. If you treat much more often, especially more than once a month I'd probably be using something stronger that would work quicker.

Q: How long is treatment needed? Is this going to be something that's going to have to go on indefinitely or is this something that you know a patient would respond to with maybe two or three treatments?

Dr. Reeves: In most ligament and tendon conditions, once you reach the point where you've got a structure that's tight enough, the symptoms stop and the patients don't need to come back unless they've been injured again. Patients often show improvement after two treatments unless a source of pain has been missed and most require 2-4 treatments total. We like to get ligaments and tendons strong enough to where a person stops hurting and then strong enough to where they can handle the minor injuries of everyday living. Since healing continues beyond two months, if patients become pain and symptom free, the strength of the structure continues to increase further. It is important to remember that nerves supplying the structure being treated are often involved as well and to achieve a "fix" the cause for the poor healing of the structure is treatment of the nerves at the same time. (See PIT information)

Q: What about bone on bone arthritis?

Dr. Reeves: We treat bone on bone arthritis for three primary reasons.

1. Treating pain sources both inside and outside of the knee often markedly reduce or eliminate pain even in bone on bone arthritis in our experience. Happy nerves do not typically hurt, and this is why many with bone on bone arthritis do not present with pain unless the nerves become irritated about their joints.
2. Treating pain sources outside the joint allow the patients that receive total joint replacement to have excellent rehab experiences. Our clinical observations are that, without nerve inflammation outside the joint, pain after surgery is much less.
3. We see patients after total joints who still have pain because nerves in the joint are removed with surgery, but nerves outside the joint are not and they can continue to make the joint stiff.

Q: Does dextrose prolotherapy or PRP or stem cell injection grow cartilage?

Dr. Reeves: All these treatments will likely stimulate some cartilage growth. However, nothing close to resurfacing of the bone has been demonstrated with any regenerative technique. The growth of a little cartilage likely implies that the joint surface is calming, and that is a good thing. Surgery can typically be avoided, particularly if nerves are successfully calmed. However, surgery has its place. For example, loose bone fragments within a joint may need to be removed, pieces of a cartilage may float in the joint and intermittently cause it to lock, and if you have a square peg in a round hole

(especially with very mobile joints like hips and shoulders) replacing the square peg surgically can be critical and make a huge improvement in function. The key is to get the patient to be both aerobic and comfortable with sleep. If that can't occur, a joint replacement is a very nice treatment for many.

Q: What about complications with prolotherapy?

Dr. Reeves: Complications are those that you expect from use of a needle. The two that are most important to mention are lung punctures and spinal headaches. For example, I caused a lung puncture about 20 years ago and have injected tens of thousands of ribs since then for pain in the upper back. The key to avoid that while not avoiding important areas in the upper back is the use of ultrasound guidance. Another type of complication is one many people have experienced that have had epidural injections, called spinal headache. That occurs when a small puncture is made through the sac that contains the spinal fluid, and a small leak occurs. That leak fixes itself but it creates a bad headache and nausea when you sit up. This risk is further decreased with the use of ultrasound, but may occur rarely and typically mildly, usually due to altered bony anatomy. Some are born without a bone covering of the spinal canal in all places (spina bifida occulta) and some have had surgery to remove certain bones (laminectomies). Ultrasound can help in these situations as the hole can be avoided.

Some would wonder if infections are common. With appropriate antisepsis (skin preparation and solution preparation precautions) this appears to be exceedingly rare. However, we recommend mask use if the hub of the needle is exposed during injection of a joint of the epidural space while the physician is talking. A rough estimate would be that joint injections may result in infection in every 30,000 injections. Infections in other areas than joints have been minor enough that reports in the literature have not occurred.

Although risks with prolotherapy are quite small overall, the patient needs to have a reasonable indication to take that small risk. For example, I recommend using prolotherapy if the patient has pain or another troubling issue that is significantly affecting their quality of life or sport performance. Other examples of functionally significant issues would include inability to turn the neck fully for checking traffic when changing lanes when driving or a change in walking pattern that may lead to a fall or impaired work performance due to concentration limits related to pain. Pain itself is clearly a risk in everyday living. So, it is important to balance the risks of living with altered protective function due to pain versus the small risk of complications.

Q: What are a few examples of areas treated with prolotherapy (and PIT)?

Dr. Reeves: Since the majority of us all have some chronic pain it may be helpful for me just to take a minute to briefly mention a few common and very treatable conditions. For example, jaw problems or TMJ disorders. This is a very common condition. The patient will complain of grinding their teeth, having some difficulty with their jaw locking

or opening their mouth fully, and may have some headache in the temple area. The jaw may click or pop. That's one of the easiest things to treat with a tiny needle in the jaw and they can feel better quickly. The ligaments of the jaw respond typically with just a few treatments. Another example is patients that complain of migraine or tension headaches. Tension headaches originate from the attachments at the base of the skull and, specifically tendon and ligament attachments there. In addition, most don't realize that the triggers for migraines are often nerves within tendons and ligaments. There's some that just have pure migraines but most people, if you try to heal those ligaments that hook on to the head, will find that their migraines become much less frequent and less severe. Once ligaments and tendons normalize the tendons stop pulling on the base of the head, stiffness decreases, headache improves, and the neck becomes more flexible. Going down the back, we talk about the shoulder such as rotator cuff issues. Rotator cuff tears can stabilize or heal. You just want to be sure that the rotator cuff is not torn completely apart. Patients with elbow pain often have what's called tennis elbow or golfer's elbow which responds nicely to treatment. Loose wrists, painful fingers, and painful thumbs are also conditions we see commonly and treat with success. With respect to the lower body, we talked about knee arthritis. Low back pain is also one of the most common things we treat, as are ankle sprains. As ligaments get weaker they protect the joints less and less. For example, consider a patient who, while walking, has their ankle suddenly turn in without warning and they nearly fall. Ligaments that are loose do not give the proper sensation to tell you if they are being stretched and because of this you can roll the ankle before realizing it. If you inject those ligaments around the ankle with dextrose or other proliferant, the ligaments tighten and then you have proper signals to your body when you're starting to stretch and this will help decrease repeated injuries. So those are just a few brief examples of some of the pain conditions we'll see.

Q: What is needed to advance research faster?

Dr. Reeves: Research in prolotherapy has been largely entirely self-funded for two reasons. One is that there is no profit in dextrose and drug companies have no incentive to fund research. The second is that we want our research to be free of any bias that proprietary support would bring. I tell people that if it wasn't for the scholarships my children got, I wouldn't have done much research. Thankfully, physicians willing to donate their time and finances, have partnered to advance research in many areas, but there is a limit to the type of areas that can be researched without limited outside funding. Obviously, donors to research from those who are cured would be very much appreciated to help those focused on doing the research be able to follow-through with their plan. Two non-profit organization that help fund well-designed research but need funds to do so are the American Association of Orthopaedic Medicine and the Hackett Hemwall Pattern Foundation.

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