Platelet Rich Plasma and Stromal Vascular Fraction as Therapeutic Agents for Pain Management: A Primer for Physicians

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Abstract

This paper collects the current therapeutic approaches to pain management using the new treatment modalities Platelet Rich Plasma (PRP) and Stromal Vascular Fraction (SVF) and is intended as a primer for physicians considering the addition of stem cell (SC) related treatments to their practices. Most studies have found little or no adverse effects and have suggested that PRP is a safe, minimally invasive treatment for many painful conditions. Further, autologous adipose derived stem cells (ADSCs) display immunosuppressive properties and low immunogenicity, their capacity to secrete trophic factors augments the therapeutic and corrective outcome in a wide range of applications and ADSCs are abundant at approximately 500 times the naturally occurring levels found in bone marrow (BM) and can be retrieved with fall less morbidity.

Keywords: Adipose-derived stromal/stem cells, Adipose tissue, Mesenchymal stem cells, Platelet rich plasma, Regenerative medicine, Stem cells, Stromal vascular fraction

Mandated Prescribing Changes Have Resulted in a need for Effective Alternatives in Pain Medicine

It was reported in 2015 that approximately 92 million adults in America used prescription opioids, or about 38 percent of the population, took a legitimately prescribed opioid. [1]

On March 15, 2016 the "CDC Guideline for Prescribing Opioids for Chronic Pain" was posted online in the Mortality and Morbidity Weekly Report (MMWR) as an early release. It was promoted as a method for improving the way opioids are prescribed via clinical practice guidelines so as to ensure that patients would have access to safer, more effective chronic pain treatment, while at the same time, it would seek to reduce the numbers of people misusing or overdosing from these drugs. [2]

On September 13, 2018 the CDC released another report concluding that 50 million Americans, just in excess of 20% of the adult population, endure chronic pain. Of those, almost 20 million patients experienced "high-impact chronic pain," severe enough to frequently limit their life or work activities. [3] Many in our professional ranks have observed a correlation between weaning medication doses downward and increased patient pain burden.

Also in September, 2018 the results of a survey of 6,300 adults were reported, in which nearly two thirds suffered with neck or back pain so intense that they had sought a health care provider for relief, and 54% said that the neck or back pain had persisted for at least five years. But it is of interest to understand that in this cohort, 78% disclosed that they would prefer to try alternative methods of pain management prior to taking drugs.

Alternatives recommended in the CDC Guidelines and others, i.e., acupuncture, counseling, chiropractic adjustments, physical therapy, medical devices, nutritional supplementation and other non-narcotic medication, had previously been implemented and were either a functioning part of an integrated pain management protocol or had been found inadequate and already discarded.

On July 10, 2018, FDA Commissioner, Scott Gottlieb, M.D., issued the disparaging statement, "In most circumstances, opioids should only be used for the treatment of acute pain and prescribed for short durations of time."

Since 2011, when orders for opioids peaked, prescriptions have subsequently dropped 43%, [4] due to the chilling effects of new rules and regulations and a changing political climate. Diminished dosing has resulted in intensified stress for many patients, in association with their escalating pain intensities. Thus, thoughtful practitioners have been looking for viable alternatives to assist in management of pain burden.

It is now clear that new modalities for the control of pain are immediately required.

The Rise of a New Kind of Medicine

Fortuitously, medical science had become aware of and has been developing regenerative procedures, stem cell (SC) technology and platelet-rich plasma therapeutics, making use of the bioactive molecules taken from within our own bodies, which appear to be effective in offering salutary benefits to chronic pain sufferers. [5]

In regenerative medicine, autologous adult stem cells (ASCs) are the most promising of the cell-based therapies. Traditionally, BM was considered the premier source of SCs and peripheral blood secondary thereto. However, as a new source of multipotent stem cells, human adipose tissue has developed a preeminent position and ADSCs are now deemed most suitable for application in regenerative therapies. Their advantages over mesenchymal stem cells (MSCs) derived from other sources, includes easy and repeatable harvesting via minimally invasive techniques producing low morbidity.

ADSCs are often paired with PRP in SC therapy. PRP is aka autologous conditioned plasma. It is a concentrate of platelet-rich plasma protein extracted from whole blood and thereafter it is necessarily centrifuged to separate the red blood cells and white blood cells, while concentrating the platelets in the plasma. As a concentrated source of platelets and autologous conditioned plasma, PRP contains several different important growth factors and other cytokines.

Two Important Mixed Cell Fractions: Stromal Vascular Fraction and Platelet Rich Plasma

Our discussion will focus on the two important mixed cell fractions and begin by reviewing important characteristics of the adipose derived cells. We have learned that dense regions of MSCs associated with vascular structures form at sites where adipose tissues develop. We are also aware that MSCs transform into unipotent adipoblasts which eventually develop adipocytes. Adipose tissue can expand via hypertrophy of existing fat cells as well as through the generation of new adipocytes. Thus, a SC population must be responsible for replacing mature adipocytes. This SC population is the source of the ADSCs.

Because ADSCs are multipotent, they can differentiate into various cell types including, e.g., adipocytes, cardiomyocytes, hepatocytes, neural cells, osteocytes, pancreatic β-cells, and vascular endothelial cells. ADSCs display immunosuppressive properties and low

immunogenicity, making them ideal for transplantation to sites of pain and injury. Also, their capacity to secrete trophic factors augments the therapeutic and corrective outcome in a wide range of applications. [6] Further, ADSCs are abundant at approximately 500 times the naturally occurring levels found in BM when comparing similar aliquots of harvested product. [7] Taken together, the beneficial attributes of ADSCs make them most relevant for clinical purposes. A nonexpanded adipose tissue product is produced during the process of harvesting ADSCs and contains human adipose SCs aka stromal cells. Expansion is the process that allows SCs to be grown in culture to produce higher concentrations. Expansion engenders the risk of lost viability, unfavorable differentiation and acquisition of viruses.

Now, considering platelets, which are non-nucleated bodies, they are formed by BM precursor cells aka megakaryocytes and are resident in peripheral blood. They cannot replicate, their lifespan is 5-9-days. They are activated when exposed to damaged blood vessels and aggregate at the site, forming a clot. A normal Platelet count ranges from 150,000/ul to 350,000/ul. [8]

While most physicians have an appreciation of platelets as blood cells with several roles to play in the body; and their most commonly thought of function is the promotion of coagulation via clotting factors to control hemorrhage. However, platelets also contain a host of bioactive molecules found in α-granules. The bioactive molecules include growth factors and numerous other compounds designed to help heal wounds, e.g., adhesive proteins, fibrinolytic factors, proteases and anti-proteases, basic proteins and membrane glycol proteases. In fact, platelets release more than 30 bioactive proteins that initiate or regulate homeostasis and/or tissue healing. This is the reason why PRP is such a powerful modality to relieve pain and promote healing.

PRP is a concentration of 1,000,000 platelets/ul in approximately 5 ml of plasma. PRP is considered rich plasma when it contains a 3 to 5-fold increase in growth factor concentration. It is used clinically for problems requiring increased concentrations of growth factors and secretory proteins that enhance the healing process on a cellular level. PRP enhances recruitment of other cells to the affected area.

The bioactive molecules found in α-granules of platelets include growth factors, adhesive proteins, clotting factors, fibrinolytic factors, proteases and anti-proteases, basic proteins and membrane glycoproteases.

Growth factors identified in PRP include:

- Connective tissue growth factor (CTGF). Platelets source CTGF through endocytosis from extracellular environment in BM. The Function of CTGF is to promote angiogenesis, cartilage regeneration, fibrosis and platelet adhesion
- Endothelial cell growth factor (ECGF) for proliferation, angiogenesis
- Basic fibroblast growth factor (bFGF), producing angiogenesis, fibroblast proliferation. bFGF targets blood vessels, smooth muscles and skin fibroblasts, resulting in cell growth and differentiation of chondrocytes and osteoblasts and it is Mitogenic for mesenchymal cells, chondrocytes and osteoblasts
- Insulin-like growth factors I and II (IGF I and II), leading to cell proliferation, maturation, bone matrix synthesis. IGF targets bone, blood vessels, skin and fibroblasts, causing cell growth, differentiation, recruitment and collagen synthesis with PDGF.

- Platelet derived epidermal growth factor (PD-EGF) required for cell proliferation. PD-EGF targets blood vessel cells, outer skin cells and fibroblasts. Its functions include cell growth, recruitment, differentiation, skin closure and cytokine secretion.
- Platelet derived growth factor alpha and beta (PDGF-α and β), active in chemo-attraction, cell proliferation. PDGF targets fibroblasts, smooth muscles, chondrocytes, osteoblasts and MSCs to cause potent cell growth, recruitment, produce blood vessel growth, granulation and to encourage growth factor secretion, matrix formation with bone morphogenic protein (collagen and bone).
- Transforming growth factor beta 1(TGF β1), necessary to promoting matrix synthesis and
- Vascular endothelial growth factor (VEGF) needed for angiogenesis. TGF targets blood vessel tissue, outer skin cells, fibroblasts and monocytes and the TGF-gene family includes bone morphogenetic protein, osteoblasts. TGF Functions in blood vessels, collagen synthesis, growth inhibition, apoptosis, cell death and differentiation and activation. VEGF targets blood vessel cells, stimulating Cell growth, maturation, new blood vessel growth and functions in Anti-apoptosis, anti-cell death capacities.

Platelets also produce various other active biological products including:

- Adhesive Proteins
    - Fibrinogen: Blood clotting cascade (fibrin clot formation)
    - Fibronectin: Binds to cell surface integrins, affecting cell adhesion, cell growth, migration and differentiation
    - Vitronectin: Cell adhesion and chemotaxis
    - Thrombospondin-1: Inhibition of angiogenesis.
- Clotting Factors: All play a role in actual clot formation and actual fibrin clot formation.
    - Factor V
    - Factor IX, XI
    - Protein S
    - Antithrombin
- Fibrinolytic Factors
    - Plasminogen: Plasmin production (leads to fibrinolysis)
    - Plasminogen activator inhibitor: Regulation of plasmin production
    - A-2 Antiplasmin: Inactivation of plasmin.
- Proteases and Antiproteases
    - TIMP-4: Regulation of Matrix degradation
    - Metalloprotease-4: Matrix degradation
    - α-1 Antitrypsin: Inhibits wide variety of proteases and enzymes.

- Basic proteins
    - Platelet factor 4: Inhibits angiogenesis
    - β-thromboglobulin: platelet activation and Inhibition of angiogenesis
    - Endostatins: Inhibitors of endothelial cell migration and angiogenesis.
- Membrane Glycoproteins
    - CD 40 Ligand
        - Inflammation and synthesis of Interleukins
        - Integrin production
        - Platelet endothelial cell adhesion

        - Cell signaling
        - Modulation Integrin activation molecule-1 on WBCs
    - P-selectin
        - Vascular cell adhesion molecule, aids in binding and recruitment of WBCs to inflamed tissue. [9]

Despite the highly complex nature of the bioactive molecules associated with platelets, most studies have found little or no adverse effects and have suggested that PRP is a safe, minimally invasive treatment for many painful conditions. [10]

How are the Stromal Vascular Fraction and Platelet Rich Plasma Harvested?

The population of the stromal vascular fraction (SVF) cells, obtained from the autologous abdominal adipose tissue, possess potential tissue regenerative capability. Because SVF cells are secured during micro-liposuction, the SVF also contains other cell types, e.g., endothelial and mesenchymal progenitor cells, leukocyte subtypes, lymphatic cells, pericytes and vascular smooth muscle cells. These SVF cells are handled such that they retain a consistent and duplicable content of heterogeneous cells. Following processing, the administered adipose-derived SVF cells can differentiate into various tissue types, encourage neovascularization, replace irreparable cells and restore injured tissues. [11] Although various methods have been developed for obtaining the SVF,[12] the most common approach or current methods of isolating ADSCs follows along this pattern. First of all, the recumbent patient is prepped and draped in the usual sterile manner, leaving the operative site of the abdomen accessible. Typically, lidocaine subcutaneous anesthesia has been selected to make the patient comfortable, during the harvesting of subcutaneous adipose. The technique is referred to as standard tumescent liposuction with lidocaine. [13]

The tumescent technique for local anesthesia requires that a copious volume of a very dilute cocktail of saline, lidocaine, epinephrine and sodium bicarbonate be injected into the subcutaneous abdominal fat prior to liposuction. The technique aids in fat removal, decreases bleeding, swelling and bruising and improves post-operative recovery, allowing patients to return home sooner. The term tumescent is appropriate here, because it means swollen and firm. With the tumescent technique, the targeted areas literally become swollen and firm. This technique results in extensive and long-lasting local anesthesia of the skin and subcutaneous fat. Because this method of liposuction injects the largest amount of medication and allows for the use of a smaller cannula to suction out the fat, the patient doesn't require general anesthesia. [14]

It should be mentioned that, while it is the most commonly employed anesthetic, lidocaine may have a negative impact on ADSC survival. However, the results of a recent study suggest that the average percentage of live SVF cells could be increased and the average number of viable ASC would also be raised, due to significantly reduced SVF and ASC apoptosis in the lipoaspirate, if ropivacaine was used instead of lidocaine. [15]

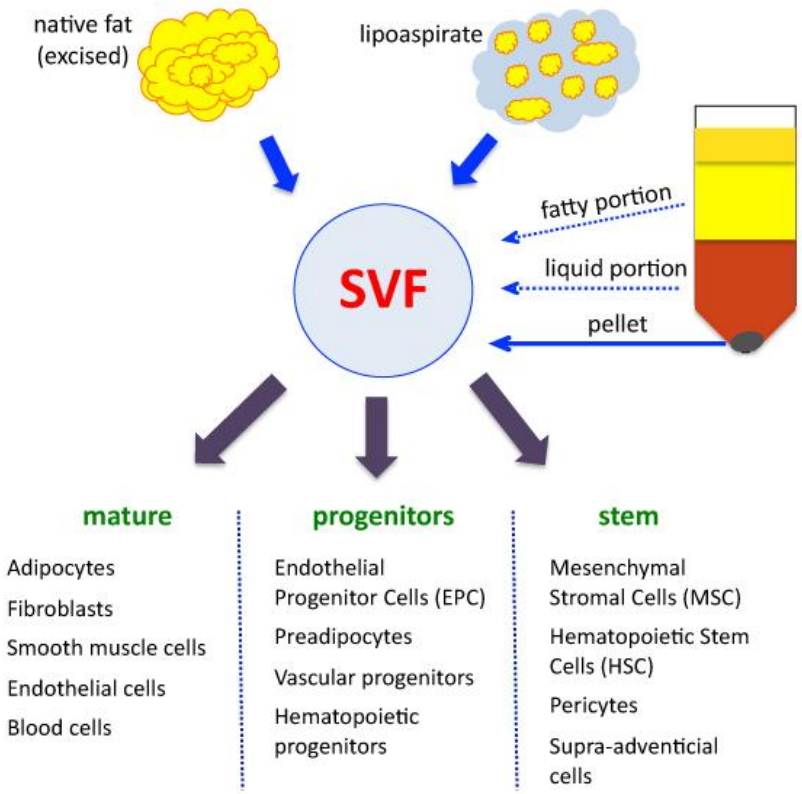
Further evaluation of ropivacaine in the tumescent procedure would be recommended to determine if the probable benefits continue to outweigh any potential shortfalls.

Tumescent liposuction is performed, using a brisk back and forth motion within the anesthetized abdominal subcutaneous fat, producing finely minced tissue fragments. Modern liposuction is routinely performed using a 3mm (O.D.) sterilized suction curette and the blunt tip cannula may be used in conjunction with a twist-and-lock syringe. Designed to maintain suction without user interface, the syringe produces the partial vacuum or suction effect during the liposuction procedure with this small, blunt-tip cannula.

Liposuction is more of an art than a surgical procedure. It entails a practical application of medical knowledge with caution and craftsmanship; The cannula moves parallel to the fat plane with the opening directed away from the operator.

The barrel withdrawal motion, within the syringe, needs to be smooth and steady until the piston reaches the end stop of the syringe. Then, the clinician grips the piston and twists 1/4-turn clockwise. When locked, the syringe will ensure adequate suction throughout the procedure. The special vacuum pressure syringe offers the clinician the opportunity to lock the plunger in variable positions, thereby reducing hand fatigue. The liposuction procedure continues until approximately 60 ml of fatty tissue has been extracted using the specialty suction curette and the twist-and-lock syringe. [16]

Following collection, the lipoaspirate can now go directly to washing without first having to be minced. Washing is performed a couple of times in order to remove hematopoietic cells and unwanted residues.



Procured from "Breaking down fat: Composition of stromal vascular fraction" • Alexy Bersenev • May 18, 2013

After washing, enzymatic digestion is undertaken with collagenase. An alternative approach to collagenase is lecithin application. Seaman et al suggest that adipose tissue can withstand an *ex vivo* time period of up to two hours, using collagenase experimentally and clinically to isolate the stromal vascular fraction, with no significant effect on adipocyte viability. [17] However, to ensure freshness and higher quality of the derived ADSCs, shorter time periods of 30-60 minutes appear prudent. Following the enzymatic breakdown, the adipose is subjected to centrifugation, which is required to separate the SVF out. Following isolation of the SVF and washing cells, it is necessary to do a final filtration via centrifugation leaving the ADSCs prepared in final suspension, at the bottom of the tube. This concentrated accumulation of cells is referred to as the pellet.

The general cellular composition of the pellet is distributed approximately as follows: hSCs = 2%, Pre/Endothelial = 7%, Pericyte/Smooth muscle = 2%, Fibroblasts = 47%, Other = 33% and Adipose SCs = 2-5%. Physicians can make use of PRP as a solitary agent or in combination with the SVF to encourage healing and to reduce inflammation. Scientists surmise that by injecting into areas of inflammation or tissue damage with high concentrations of platelets, it may encourage wounds to heal. Examples of tissues that PRP has been applied to include tendons, ligaments and muscles. [18]

Growth factors and other bioactive molecules from platelets perform a meaningful role in SC research and therapy, and therefore, in pain management. The role of PRP and the benefit of combining the growth factors with SCs has a powerful effect on relieving suffering.

A step-by-step protocol is essential for obtaining PRP, and its many growth factors. Treatment with PRP begins with phlebotomy, withdrawing blood from the person being treated. A physician or laboratory technician will withdraw 30-60 ml blood of venous blood, from a vessel in the upper extremity, using a 25-gauge butterfly needle. The patient's venous blood is collected, in yellow top tubes in which calcium citrate was added in order to ionize the calcium and to inhibit the clotting cascade.

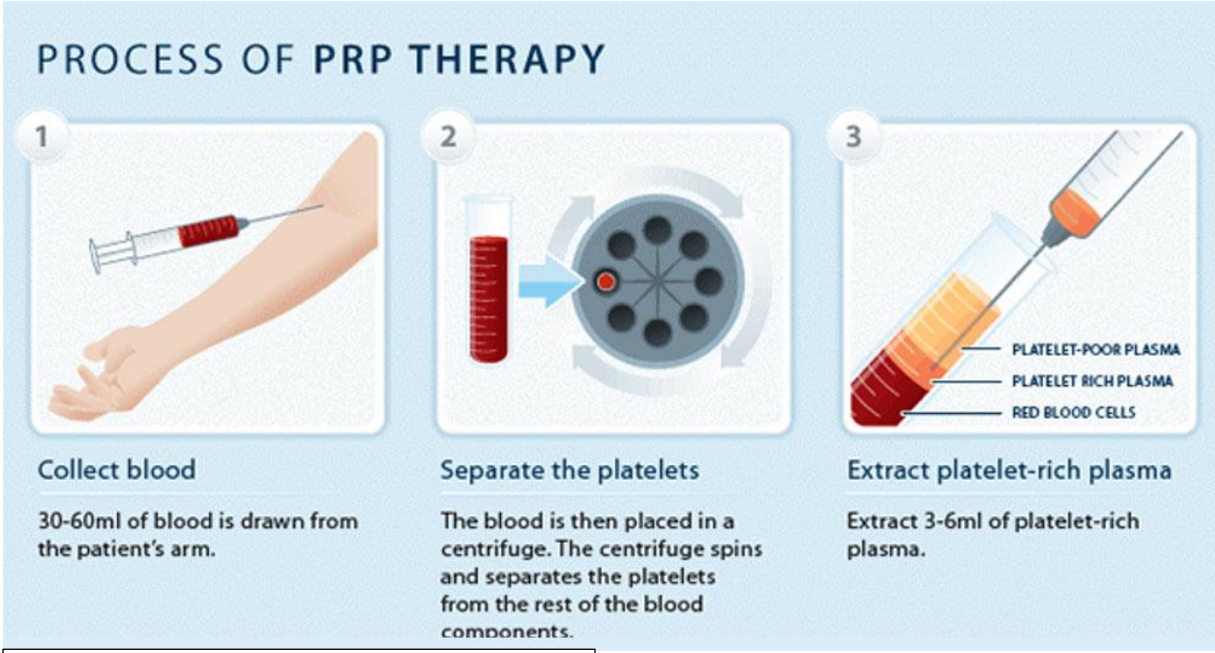
The blood that is obtained is placed into a centrifuge to separate platelets from other blood components, such as the leukocytes and erythrocytes and to concentrate the platelets creating the PRP, which can then be extracted as a 3-6 ml aliquot for direct injection into the area in need of treatment. One should be aware that the centrifuging technique will be adjusted based on whether one desires to collect PRP with a high white cell count, low white count or without white blood cells. Also, please recall that leukocytes will contribute to inflammation. Spin parameters related to centrifuge RPMs, number of spins and time spent centrifuging may vary depending on the composition of the product you are attempting to obtain [19]

The clustering of platelets, following centrifugation, in the PRP and, thereby, the consolidation of growth factors is noted to be 5 to 10 times more concentrated than usually found in unprocessed blood. It is theorized that this concentrating effect contributes to enhanced healing.

Some physicians collect all the yellow PRP portion that is suspended above the red hematocrit, while others will collect just the enriched lower portion of yellow PRP just above the buffy coat.

Growth factors present in the PRP encourage SCs to grow in number and differentiate into various types of tissues.

The concentration of platelets in the PRP is then injected into the area of the person's body that requires treatment.



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Common painful musculoskeletal conditions that have been treated with PRP include:

- Shoulder disorders such as bursitis and rotator cuff repairs
- Tennis elbow, Achilles tendinitis and heel spur syndrome
- Muscle tears, strains and trigger points
- Meniscal tears in the knee
- Mild to moderate degenerative arthritis located in various joints of the body and
- Painful spinal disorders. [20]

While PRP is used primarily in musculoskeletal medicine and in orthopedics, procedures for ischemia or wound healing also are amenable to PRP injections.

Usually, PRP clinical applications are directed to smaller and more acute joints; while SCs are more often combined with RPR, for injection, in more chronic conditions. Nonetheless, epidurals employing PRP have been done by several groups who reported favorable outcomes in spinal conditions. In degenerative disc disease PRP may be injected alone or administered in combination with SCs for intradiscal injection.

Published studies of the clinical use of PRP in human orthopedic conditions report favorable outcomes. For example, Mishra and Pavelko reported on a cohort of 140 patients with chronic elbow epicondylar tendinosis. When non-operative measures had failed in 20 cases, a single

percutaneous injection of PRP was administered to the active group, (n = 15) and bupivacaine was injected into the control group, (n = 5). Eight weeks following treatment, the PRP administered patients noted 60% improvement in their visual analog pain scores v. 16% improvement in the control group (P = .001). [21] Also, a report of PRP therapy having been used as a first line treatment for a severe Achilles tendon tear demonstrated success, from both radiological and functional perspectives, using a non-surgical ultrasound-guided injection. [22]

PRP therapy is founded on the notion that these growth factors can support healing and will enhance recruitment of other cells to the area of involvement. Therefore, PRP is used clinically for problems requiring increased concentrations of growth factors and secretory proteins that enhance the healing process on a cellular level.

The procedure for administering ADSCs and PRP intraarticular is enhanced with the use of a diagnostic ultrasound machine. An ultrasound image increases the likelihood that one locates the appropriate injection site. When injecting the SCs IV, there is no need to use PRP, because platelets are already present in the circulating blood. While IV PRP is not dangerous, it is just not necessary. But when doing a combination IV and orthopedic procedure and you already have the platelets, they can be resuspended in NS and given IV, as well.

An intraarticular injection itself usually takes only 1-2 minutes, multiple trigger point injections or intradermal procedures will take a little longer. The injection site might be tender following the procedure but should not be overtly painful. Some people develop a bruise or small local irritation at the site of the injection.

In the weeks following the procedure, the following instructions may be provided to the patient and will improve the likelihood that the treatment will be effective:

- Avoid strenuous exercise, particularly movements that add pounds force to lower extremity joints, e.g., the knee joint.
- Avoid the use of anti-inflammatory medications, such as aspirin and other NSAIDs. These drugs may interfere with the treatment. Other options exist for any needed pain management.
- Wear a splint for the first few weeks to stabilize the treated joint.
- Some providers even recommend using crutches to avoid putting unnecessary pressure on the hip, knee and ankle joints.
- Acutely following a treatment, applying cold compresses will help to decrease any swelling and reduce pain. Alternating hot and cold packs may be helpful after the first 48 to 72 hours for any residual inflammation.
- Elevation of the joint during bed rest, by sleeping with the affected joint raised upon a few pillows.
- Following all instructions and call with any problems, such as increased pain or if they experience a subsequent fall or other injury.

Following SC treatment, some have found that gentle physical therapy can help enhance range of motion and function to involved joints, decrease the risk of future deterioration and prevent the condition from worsening. Most physicians order physical therapy to begin about 1-2 months after treatment, beginning with passive modalities and advancing modalities as tolerated. [23]

With the passage of the "21st Century Cures Act," essentially fast-tracking biological approaches into the framework of medical care; SC therapy in general, and mixed cell regenerative medicine particularly, involving PRP and ADSCs associated with the SVF has begun development at a accelerated rate. [24] Importantly, a high general level of safety has been reported in recent studies, one gathering data from five treatment centers in the United States, using autologous SC treatments for multiple conditions and another multi-center analysis involving 2,372 adult patients managed with autologous ASC therapy for orthopedic conditions. [25], [26]

Pain Medicine and implementation of Stem Cells for various problems

In the field of Regenerative Medicine, the focus for why SC transplantation is occurring is based on the "what" of therapy. By this we mean, "what" types of conditions are being considered for SC management. Here we see that SCs are being used as a method to prevent a disease or ameliorate chronic or degenerative changes that have developed over time or as the consequence of an injury or trauma. BM transplant is a form of SC therapy that has become commonplace over the years without controversy. Disorders and conditions in which SC treatment is being pursued include Diabetes, Rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, Osteoarthritis, Stroke and Traumatic Brain Injury, Learning disabilities and congenital disorders, Spinal cord injuries, Myocardial infarction, Multiple sclerosis, Cancer, Baldness reversal, Hearing disorders, Crohn's disease, Wound healing and male infertility, amongst others. [27]

The reason for implementing SC transplantation, in the specialty of Pain Medicine; would be based on the "why" of therapy. The reason "why" SC therapy would be considered by a pain specialist would be the alleviation of pain. Pain may be classified in various ways and, for purposes of illustration, we'll review three common types of chronic pain that may all benefit from SC therapy. [28]

Examples of Painful Conditions being Managed with SC therapy

The first category of pain for our consideration is Nociceptive pain. It represents the common response to noxious injury or insult to skin, muscles, joints, ligaments, tendons, bones and viscera. Here we see that cutaneous and musculoskeletal somatic pain is often well localized, while internal organs and smooth muscle pain is usually referred.

Painful conditions potentially responsive to SC therapy in this category include osteoarthritis, TMJ syndrome, neck and back pain, Tennis and Golfer's elbow, hand and wrist pain, CTS and TFIC tears, CMC and basal hand joint arthritis, tendon and ligament tears, degenerative and herniated discs, persistent pain following failed back surgery syndrome, rotator cuff and shoulder labrum tears, shoulder arthropathy, facet arthropathy and injury, spinal stenosis, spondylitis, sacroiliac joint pain, Hip labrum and tendon tears and arthritis, non-union fractures, osteonecrosis, knee OA, ACL and meniscal tears and foot and ankle injuries. [29]

Neuropathic pain is a second type of affliction commonly seen in various specialties and is initiated or caused by a primary lesion or disease in the somatosensory nervous system. Here, abnormalities of sensation include deficits perceived as numbness, hyperalgesia or allodynia and

paresthesia's or tingling. Also, diabetic neuropathy, postherpetic neuralgia, spinal cord injury and phantom limb pains are characteristic diagnoses. SC treatment has been a beneficial modality to alleviate this presentation of misery. [30]

Inflammatory etiologies of discomfort represent a third common provocateur which occurs from activation, wind-up and sensitization of the nociceptive pain path due to various and sundry mediators released at a nidus of tissue inflammation. Proposed mediators implicated as causative agents include proinflammatory cytokines like TNF-α, IL1α, IL−1β, IL−6, as well as chemokines, reactive oxygen species, vasoactive amines, lipids, ATP, organic acids and such other factors released by infiltrating white blood cells, vascular endothelial cells and tissue resident mast cells. Some examples of inflammatory conditions that mixed cell fractions may be effective for include rheumatoid arthritis, lupus, inflammatory bowel disease and chronic herpetic neuralgia, [31]

Other possible causes of pain such as, tender acupuncture points and somatic dysfunction, e.g., are outside the scope of this paper. [32]

Training Organizations and Programs

There are currently several training programs which have been instrumental in carrying the burden of ensuring that interested physicians are able to become qualified to competently and safely administer SC related therapies. A few are herein summarized as a point of interest.

U.S. Stem Cell Training, e.g., is a SC training organization that endorses a mission dedicated to providing clinicians with regenerative medicine fundamentals, and training in groundbreaking therapies. They offer to physicians' rigorous courses of guidance, in-person, on-site and online. Various aspects of their courses are taught by world renowned stem cell scientist, Kristin Comella, Ph.D. Dr. Comella and her team of qualified clinical staff members enjoy decades of experience. The pricing structure for SC training is very competitive. [33]

Repair, Regenerate and Restore Stem Cell (R3) is a SC association asserting that it is the nation's leader in regenerative therapies, with over 10,000 successful stem cell procedures having been performed nationwide. They query, "Who better to receive training from than the experts" and they offer training on actual patients. R3 Stem Cell offers a 2-Day Training Course designed to help teach procedure skills, protocols, regenerative medicine specifics, image guidance, theoretical education, supplements, marketing techniques and sales techniques. Their leadership brings with them a substantial focus in pain management. [34]

The Advanced Regenerative Medicine Institute (ARMI) presents 2-day SC and PRP training courses, led by an established team of medical experts. Here, physicians and mid-levels can work side-by-side to learn SC science while participating in hands-on training exercises to develop clinical techniques and skills. Clinicians are trained on harvesting, processing and injection techniques, as well as necessary business steps to incorporate SC therapies in the practice. [35]

The International Society for Stem Cell Applications (ISSCA) champions the commitment to educate experienced medical providers on current cellular research and techniques as just the first step in achieving the Conference initiative's goal—to bring cutting edge SC technologies

and regenerative medicine to clinical practices worldwide. Training options include hands-on training and an online course, as well as certification and a Fellowship program. Fees are also competitive at ISSCA. [36]

The American Academy of Anti-Aging Medicine (A4M) is a well-known educational organization that holds two annual World Congresses, each of which attracts 3,000 to 5,000 physicians and other healthcare practitioners. A4M also provides educational workshops, certifications, CME credits, along with specialty symposia focusing on various topics, including regenerative medicine and they oversee a five-module series, referred to as the "Fellowship in Stem Cell Therapy." [37] A4M has been tutoring physicians for almost three decades.

Regenexx and the Centeno-Schultz Clinic (CSC) have advanced the application of SC therapy for orthopedic injuries. In addition to their various educational seminars and symposia, they offer a premier 12 months long "Fellowship program in Interventional Orthopedics and Regenerative Medicine" to qualified candidates. The training is divided up such that 60% is clinical care with a focus on the use of various percutaneous SC and autologous conditioned plasma technologies in regenerative medicine. A focus on new interventional techniques have been developed to precisely place cells in various sites of the musculoskeletal system using ultrasound and fluoroscopic guidance. CSC indicates, e.g., that they pioneered the percutaneous placement of SCs into the ACL ligament.

They credit innovative in-house research to producing a process to dramatically increase the number of SCs able to be isolated from BM in a same day procedure. The remaining 40% of their Fellowship program is devoted to research in which the "Fellow" must complete a research project under CSC supervision and submit the same for publication. [38]

Certification Opportunities

While several opportunities for certification have come forth, this paper will limit its discussion to the American Association of Orthopaedic Medicine (AAOM) and the American Board of Regenerative Medicine (ABRM).

The AAOM is a not-for-profit organization, which provides information and educational programs for physicians (M.D. and D.O.) on the accurate diagnosis and comprehensive nonsurgical treatment of musculoskeletal problems. The AAOM sponsors a qualification process in Interventional and Regenerative Orthopedic Medicine, the "AAOM IROM–C," as a written and practical Certification Examination. Candidates are informed that they must pass the written portion of the IROM–C before they can progress to take the Practical Exam.

The "IROM–C" endorsement installs minimum competency for physicians in the field of regenerative orthopedic orthopaedic medicine. Preparation and passing the certification exam reflects understanding of the requirements related to various forms of treatment dealing with regenerative orthopaedic medicine. Completion of the IROM – C procure educational and professional opportunities for the qualified individual. Certification requirements may be reviewed at the AAOM website. [39]

The ABRM is another institution setting standards needed to promoting excellence in the field of regenerative medicine, related education, research, publication and certification. The certification program is devised to assess knowledge and competency in the field of regenerative medicine with the goal of improved patient care. Successful candidates will be granted the status of "Diplomat" with the American Board of Regenerative Medicine (DABRM). The ABRM Board's literature indicates that the Certification process establishes didactic basic and clinical science competency in the specialty of regenerative medicine. However, ABRM maintains that it does **not** evaluate clinical competency or define a physician's scope of practice within the specialty of Regenerative Medicine.

ABRM is currently only offering board certification for physicians practicing "Musculoskeletal" or "Plastic/Cosmetic Regenerative Medicine" in compliance with local, state and federal guidelines governing regenerative medicine disciplines. Requirements for physician eligibilty to sit for the board examination are listed online at the ABRM website. [40]

Sample Clinics Where SC Therapy for Pain is currently being used

In 2016, it was estimated that at least 570 clinics were then offering this unique treatment approach. UC Davis scientist Paul Knoepfler and University of Minnesota bioethicist Leigh Turner estimate there are now 700 or more SC clinics providing this type of care in the United States, [41] and many thousands of people have already undergone SC treatments.

Provided below is a short listing of facilities offering Stem Cell Therapy to clients with painful conditions for your interest:

- Albano Clinic • 6360 S. 3000 E., Ste 210 • SLC, UT [42]
- Pain Management Center • Intermountain Regenerative Medicine • 2429 Jafer Court • Idaho Falls, Idaho [43]
- Center for Pain Management • 1602 Physicians Drive, Suite 103 • Wilmington, NC. [44]
- Southwest Spine and Pain Center • Multiple locations across UT [45]
- Centeno-Schultz Clinic • 403 Summit Blvd, # 201 • Bloomfield, CO [46]

Conclusion

It has become clear that pressures on current prescribing patterns have resulted in a need for physicians to seek out effective alternatives in the field of pain medicine. Regenerative medicine, clinically applying the healing qualities of SC therapy and PRP has come along at a providential time. In this paper, we have been able to review the two important mixed cell products, the SVF and platelet concentrates. SC therapy and PRP have been found to be useful in mitigating the adverse effects of many painful conditions. The healing characteristics of bioactive molecules produced by platelets were discussed, as well as the therapeutic benefits of ADSCs, which are able to differentiate into various cells in order to restore damaged tissues. Methods of harvesting and processing of ADSCs and PRP were reviewed, as well as the consideration for their application. We discussed a few organizations where training can be obtained, certification opportunities available in this new medical field and ended this writing with a sampling of clinics where SCs and PRP have been taken advantage of to ease painful conditions.

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