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Platelet Rich Plasma Treatment Application for Multiple Purposes

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Abstract:

Platelet Rich Plasma (PRP) treatments, a relatively new practice, are used for a variety of medical and clinical treatments. More recently, an increasing number of case studies and research has focused on the efficacy and use of PRP to treat injuries, and potential cosmetic benefits. This article is a compilation of numerous case studies regarding diverse uses of PRP in order to better understand the uses as well as efficacy of the treatment. The applications include: atrophic acne scarring[3], orthopedic care[2], Hepple stage V osteochondral lesion of the talus[5], chronic non-healing ulcers[6], plantar fasciitis[7], skeletal muscle cell migration[10], cyclophosphamide-induced hemorrhagic cystitis[19], and degenerative change of rotator cuff muscles[21].

Introduction/Background:

Research provides medicine with novel treatment practices which benefit patient diagnosis, prognosis, and therapy. One such treatment quickly gaining popularity is the use of Platelet Rich Plasma (PRP) injections. These injections can be used to treat many ailments such as long term pain relief and may even affect healing of injuries.

The treatment of long term pain is always an important factor to consider. There are many patients who have chronic pain that could be caused by a multitude of reasons. Because of this, there is a constant search for new long term pain relief treatments that may be more effective than current treatment options.[11]

PRP injections can benefit many different people. For instance, studies have shown that for sufferers of injuries such as tennis elbow, PRP will outperform local steroids.[17] Also, conditions affected by hypoxia (poor blood supply or low oxygen content) such as tendon and ligament tears; cartilage injuries, bone injuries, and arthritis can be treated with PRP injections. This is due to PRP's ability to improve blood flow to the hypoxic areas.[16]

PRP injections, though gaining popularity quickly, are still not approved by the Federal Drug Administration (FDA) and are surrounded by controversy. This is likely due to the fact the treatment is still not entirely understood and not enough research has been conducted to prove that the treatment is effective. Therefore, even though certain providers offer this treatment as on option, the patient must pay for the treatment entirely out of pocket due to health insurances not covering non FDA approved treatment methods.

PRP Injections:

PRP injection therapy has been used for over three decades. It has been used in the medical field as a recovery agent after dental, orthopedic, and surgical procedures. Over time its uses have grown due to studies showing the injections could be used for treatment of tendinopathy, chronic tendon and muscle injury, and joint degeneration.[12]

PRP is derived from the blood of the patient receiving the treatment. The blood sample taken from the patient is centrifuged to generate a natural concentration of autologous GFs (GFs). Bioactive cytokines and proteins, which are from the platelet's alpha granules, stimulate chemotaxis, cellular migration, proliferation, differentiation, and extracellular matrix production.[13] The proteins also promote the release of angiogenic GFs, which contribute to tissue regeneration and healing.[14]

There are multiple GFs present in PRP. The main GFs are platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), insulin-like growth factor (IGF-1), and fibroblast growth factor (FGF).[15] The advocates of the treatment believe it works with the body's ability to heal itself. They claim that use of patient's organic matter to stimulate the natural healing process of the body should not be unconventional. Also, use of the patient's own organic matter greatly reduces the rejection rate of the treatment.[11]

The critics of the treatment claim that the success stories are results of the placebo effect and see PRP injections as a way to make money.[11] There is the hope that the extended ongoing research of the treatment will help to evaluate its efficacy.

Preparation of PRP Injections:

PRP's are synthesized from the patient's own blood. Therefore, the first step in the process is to extract a small amount of blood from the patient. This is usually around 60 mL. The drawn blood is put through a centrifuge process which separates the platelets from the other cells in the blood. The platelet layer is then extracted from the blood sample in order to be injected into the patient. The extracted platelets are then injected into the location of the injury.[11]

After the injection process, GFs are released in the area of the injection resulting in inflammation which lasts for about three days.[11] The next phase is known as the proliferative phase of healing which lasts several weeks. This is followed by the remodeling phase which results in formation and stabilization of the mature tissue and takes around six months.[11]

For a few days post injection the patient may experience mild pain and/or irritation surrounding the site of injection. The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is discouraged during this time and shouldn't be used until the patient heals, is pain free, achieves full function, or shows evidence of a plateau in these symptoms. Due to the fact NSAIDs can interfere with the healing process initiated by the injections.[18] The typical number of injections administered in a series is three to five. If there is no improvement after the first or second injection there are usually no further injections.[11] As you can see, the type of injury sustained as well as the patient's initial reaction to PRP injection treatment will determine the possibility for future injection treatments.

PRP Case Study Reviews:

Atrophic Acne Scarring:

A study published in the *Journal of Cosmetic Dermatology* observed the effect of PRP injections on atrophic acne scarring. Atrophic acne scarring occurs from abnormal resolution or wound healing after acne inflammation. The study utilized microneedling in combination with PRP in order to reduce acne scarring in a study of 50 individuals.[3] The experiment was conducted by performing microneedling on all patients and on both halves of their faces but by only applying PRP to the right half of the patients face while leaving the left side as the control.[3]

Microneedling is a commonly used treatment for acne scarring and employs a thin fine needle to cause minute injury to the dermis stimulating collagen synthesis. Nerve stimulus of the injury, which is transmitted by electrical signals, initiates the healing process. GFs are released causing immediate inflammation to the site of injury. Fibroblasts then migrate to the area stimulating neo-angiogenesis for 8 weeks to 1 year.[4] The study used platelet rich plasma that was prepared by a double-spin method. The double-spin method simply refers to the use of two cycles of centrifugation. The mean platelet count of the final product was 11.73 compared to the base line of 2.26.[3] The platelet count can heavily affect the final result of the treatment

The results of the experiment were assessed both by an independent dermatologist as well as by the patients' satisfaction. The final percentage of improvement for both halves of the face was then taken from mean quantitative scores. The results are shown in the three figures below (Figure 1-3).[3]

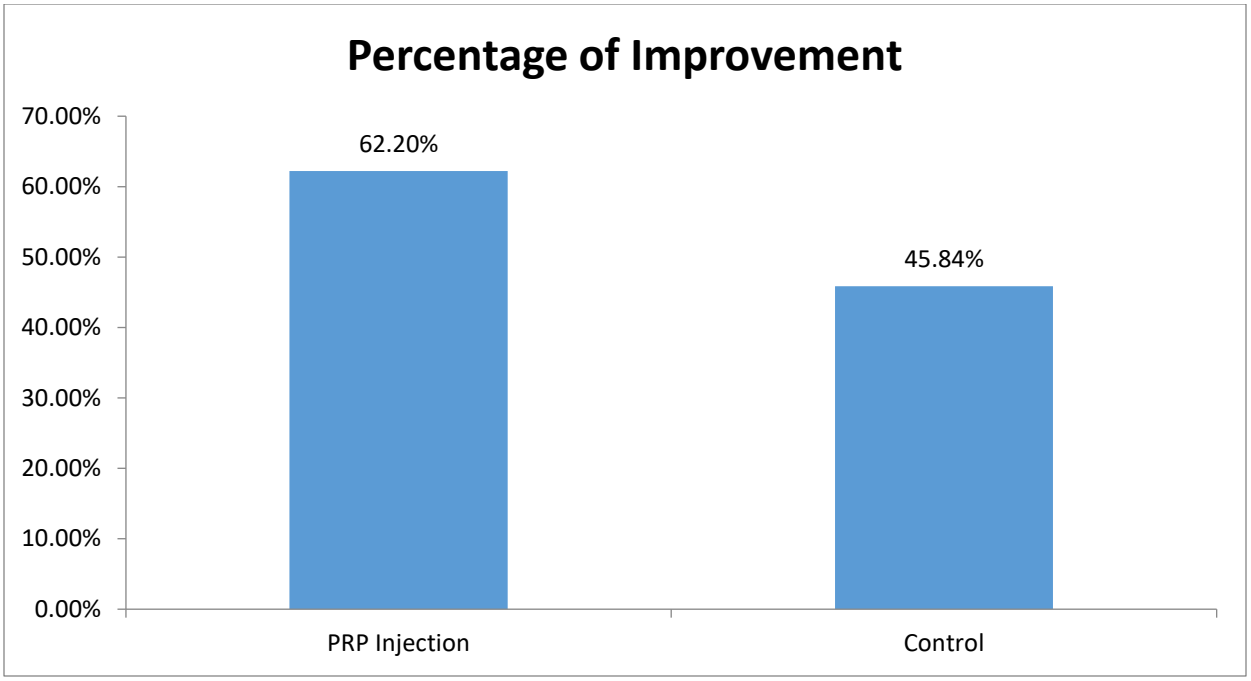

Figure 1: Overall percentage of improvement in acne scars among both the control and PRP group.[3]

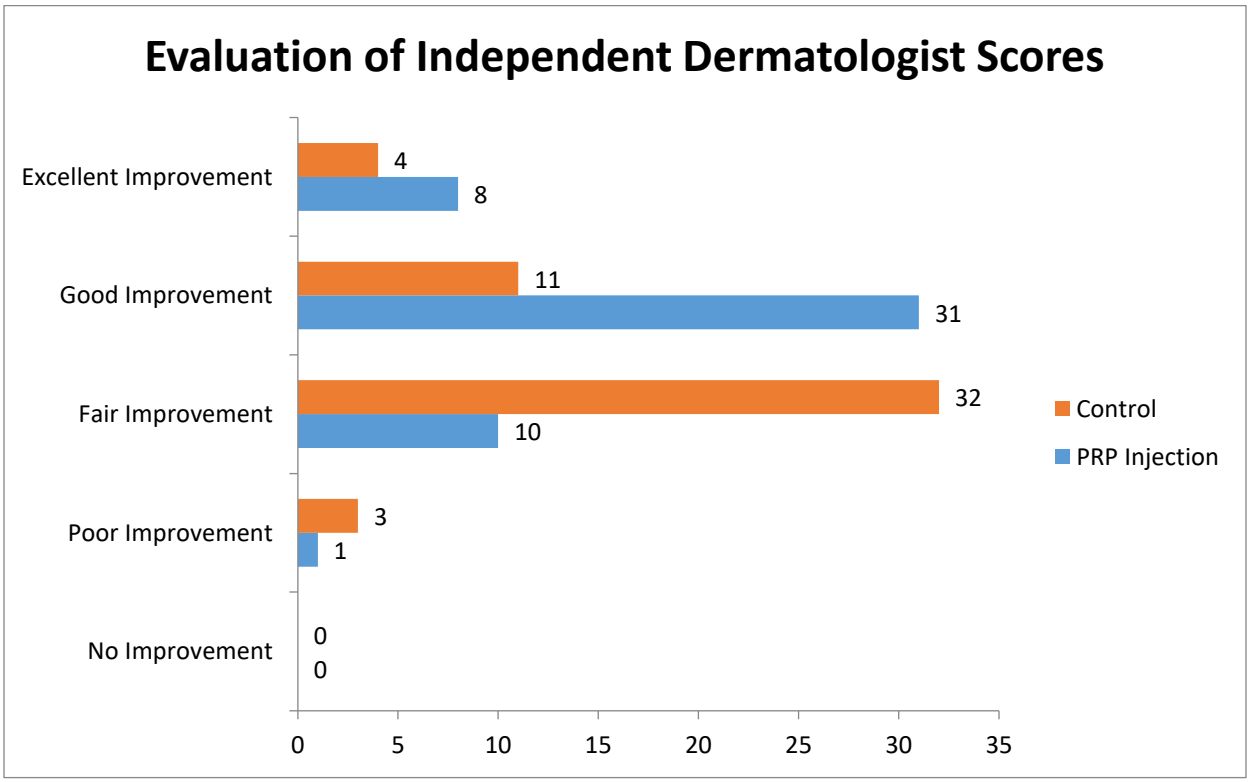

Figure 2: Number of patients falling into each category of improvement decided by expert independent dermatologist.[3]

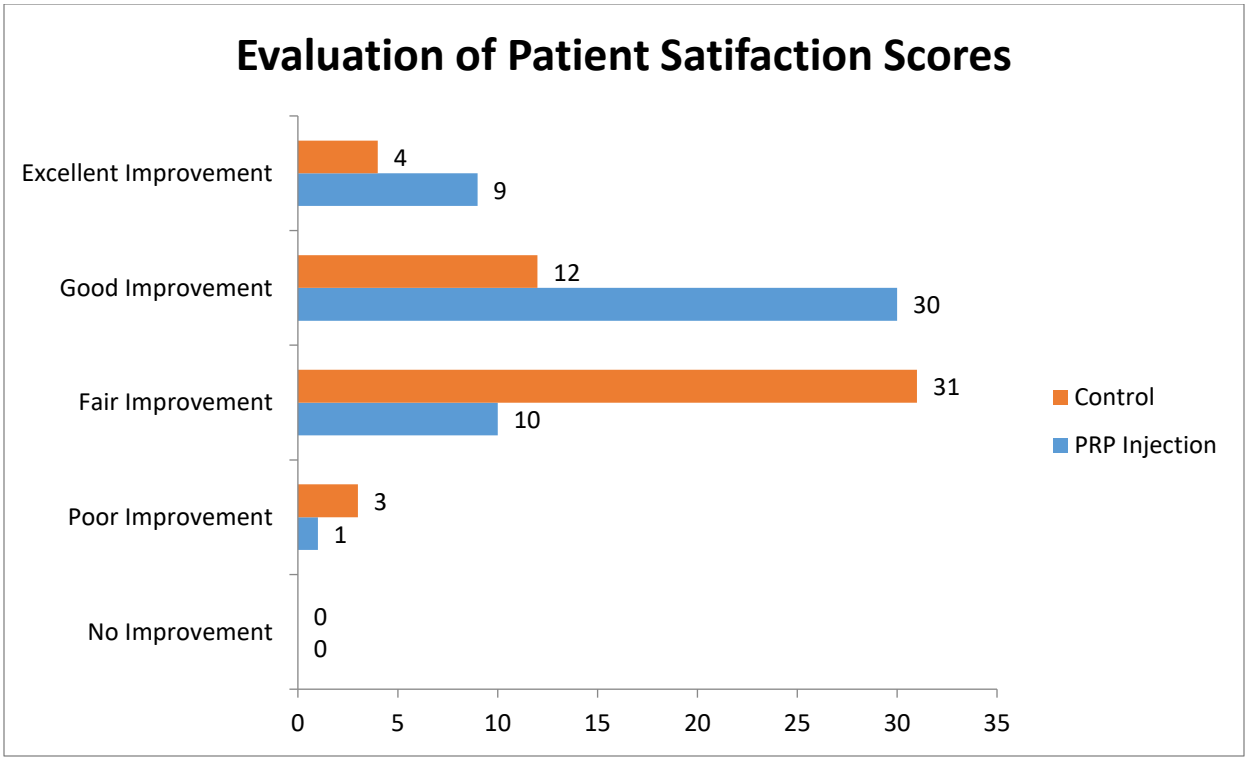

Figure 3: Number of patients falling into each category of improvement based on self-reported satisfaction.[3]

Orthopedic Care:

The use of PRP treatments in orthopedics is an expanding field. Injuries in orthopedics can keep people out of work or leisure activities. These injuries include knee osteoarthritis, lateral epicondylitis, ulnar collateral ligament (UCL) injuries, patellar and Achilles tendinosis, muscle injuries, and others.[2]

Research conducted by the *Medical Research Archives* discovered the efficacy of PRP treatment in orthopedic injuries. The conclusions drawn from this research state "PRP, as a biologic therapy, presents the possibility of benefit to multiple musculoskeletal injury sites".[2] The article goes on to discuss the efficacy of the treatment in certain injuries. For instance, use of PRP in knee osteoarthritis has proven to have significant benefits in many studies.[2] Also, PRP use in lateral epicondylitis treatment has been shown to be effective.[2]

Other injuries such as patellar tendinosis and UCL tears have limited evidence supporting the use of PRP as treatment; moreover, most evidence points toward not using PRP treatment on partial Achilles tendon tears or tendinopathy. Studies of PRP therapy for muscle injuries, ACL, and rotator cuff tendon repair currently show mixed results of efficacy.[2]

Hepple Stage V Osteochondral Lesion of the Talus:

Osteochondral lesions of the talus (OLTs) have presented a great challenge to foot and ankle surgeons. OLTs also often cause pain and disability in those affected. A classification system for OLTs was invented by Hepple and colleagues in 1999. The system contains five stages that are measured through Magnetic Resonance Imaging (MRI) manifestation.[5]

Stage V OLTs is characterized by the formation of a subchondral cyst, making the treatment process much more difficult.[5]

The PRP preparation was completed using the WEGO Platelet-Rich Plasma Preparation Kit (WEGO Ltd, Shandong, China). Blood (40ml) extracted from each patient was centrifuged (2000 rpm, 10 minutes) to produce a standard 3-4 mL of plasma. The PRP was formed into a scaffold to place on the lesion.[5]

There were 14 patients involved in the study (10 males and 4 females) and an average age of 39 years (range, 21-57). All of the wounds healed without complication. Of the 14 patients, 13 continued through all follow ups (averaging 18 months). The 14th patient stopped follow-ups after the suture removal.[5]

PRP scaffold has proved to be a viable new method of cartilage repair. There are possible benefits of scaffolding as opposed to injections of PRP, the scaffold gives the ability to repair and restore cartilage with congruence along the curvature of the talus.[5] (NEED SOME KIND OF CONCLUDING SENTENCE).

Chronic Non-Healing Ulcers:

Non-healing ulcers are defined as spontaneous or traumatic lesions which are typically in the lower extremities and are unresponsive to therapy or which persist without healing despite care.[6]

The PRP in this case study, done by the *Journal of Biomedical Science*, was prepared using an advanced rapid point-of-care technology (Res-Q^{TM} 60 PRP system) (Thermogenesis Corp, USA). The system takes peripheral blood (40-60 mL) and centrifuges it. The result is 7 mL of PRP […]. The mean (±Standard Deviation) platelet count increased nearly fivefold in the final PRP product (from 261.91 x 10^3 (±125.31)/µL to 1177.35 x 10^3 (±787.95)/µL). Also the post-processed red blood cell (RBC) count was less than pre-processed whereas the post-processed white blood cell (WBC) count was more than the pre-processed (Figures 4,5, and 6).[6]

There were 24 patients in the study (16 males and 8 females), each one with differing etiology of their wound/ulcer. Each patient was given one dose of PRP injections around the periphery of the wound. The ages ranged mainly from 40 to 80 with only one patient younger than 40 years.[6] Results of the study stated that all of the patients involved showed healing of their wound/ulcer and 17 of the 24 showed wound size reduction of more than 90%. Also, 3 of the 24 showed a reduction in wound size of 80-90%. Overall, there was a significant reduction in all patients' wound sizes (Figure 7).[6]

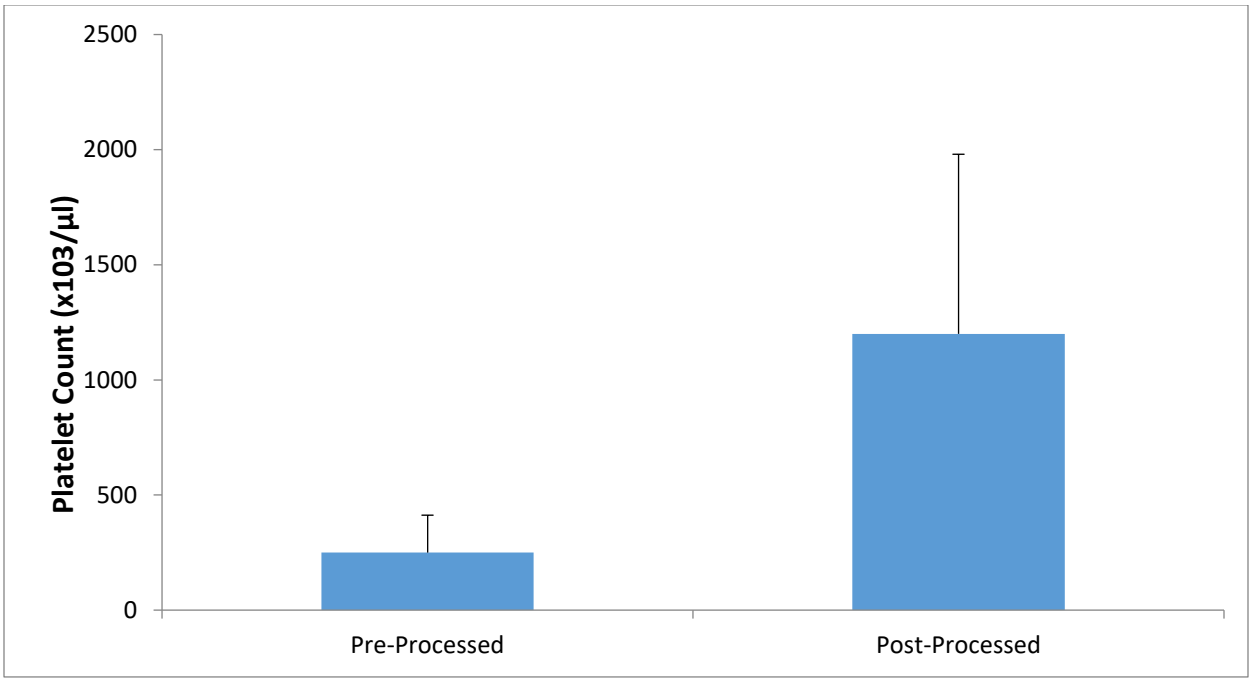

Figure 4: Platelet count distribution at pre- and post- processing.[6]

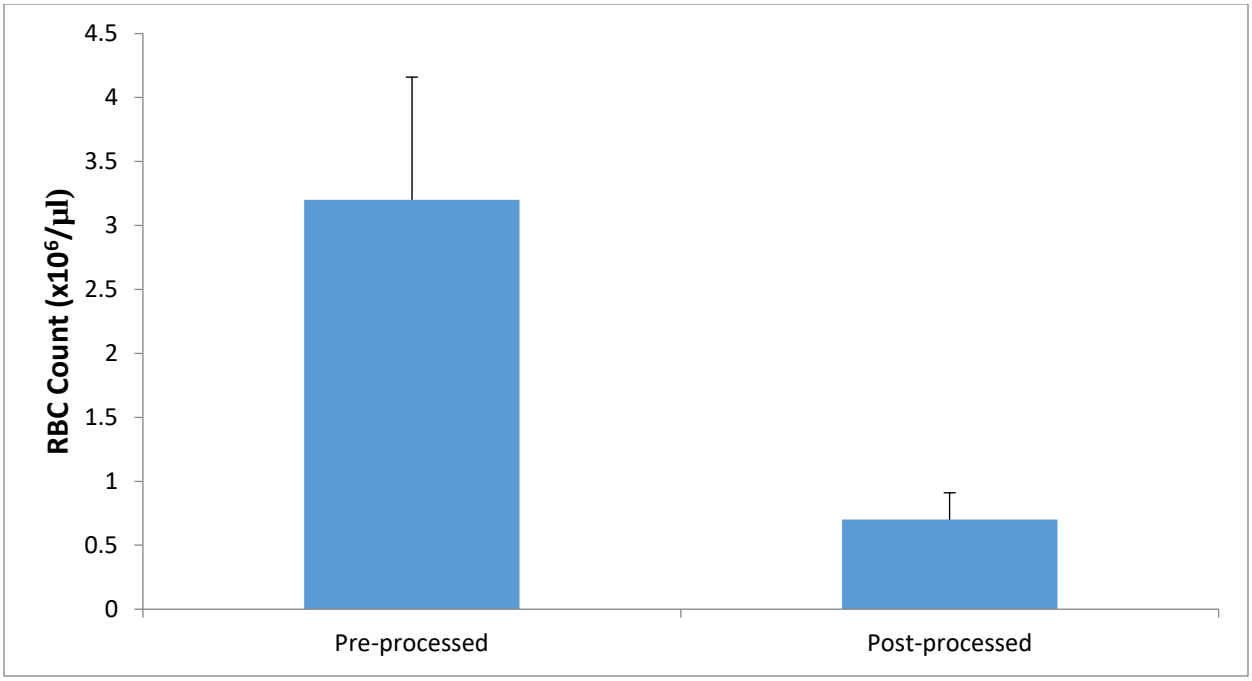

Figure 5: Distribution of Reduction in RBC content in Pre- and Post-processed PRP.[6]

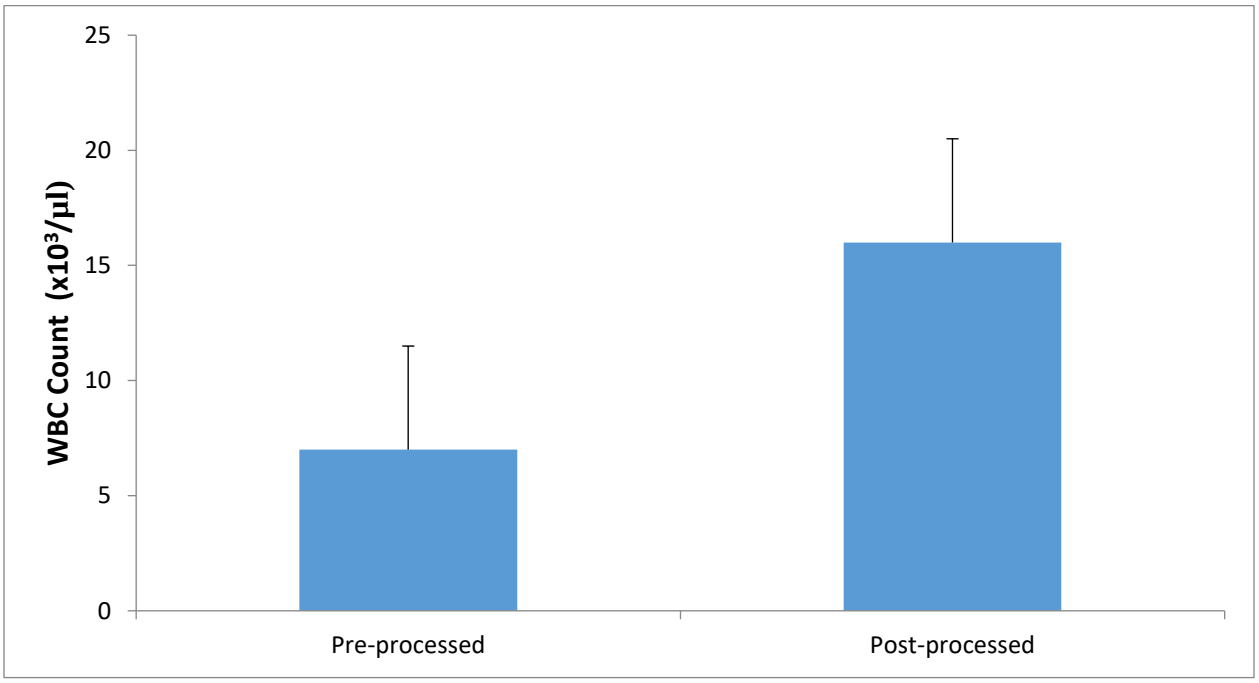

Figure 6: Distribution of WBC counts in pre- and post- processed PRP.[6]

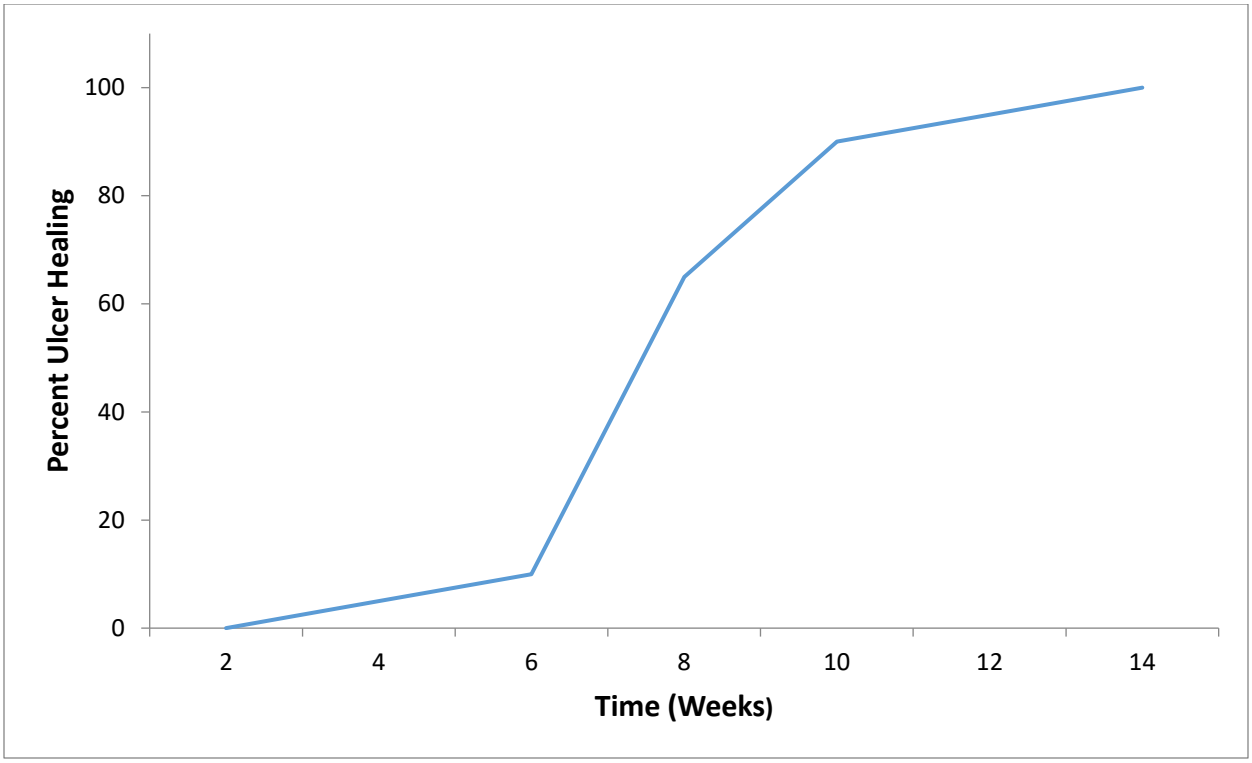

Figure 7: Cumulative ulcer healing time following PRP treatment.[6]

Plantar Fasciitis:

Plantar fasciitis (PF) is a common lesion located in the heel. Professional medical care is needed in approximately 11% to 15% of symptoms. PF can occur in all ages but appears most prominent between the ages of 40 and 60. There is no significant tie to one sex over the other.[8]

A meta-analysis, was conducted and published in *Medicine*, which consisted of a study selection of 26 articles and 9 studies.[9] Of the studies used in the meta-analysis, there were three that reported the American Orthopedic Foot and Ankle Society (AOFAS) scale as the major outcome. They summarized that after 12 weeks, there were no significant differences in results between PRP and non-PRP treatments.[7] Their results were in agreement with two of the studies reported by Foot and Ankle Disability Index (FADI). Additionally two other studies reported by Roles and Maudsley Score (RMS) reflected no significant differences between the PRP and non-PRP groups.[7]

In conclusion, the use of PRP on PF is not the most effective treatment. However, there are some limitations because the article does not specify the quality of the PRP or the method used by each study used in the meta-analysis.

Skeletal Muscle Cell Migration:

Muscle injuries are a very common form of injury. They can originate from sports or could possibly occur from an everyday activity. The current main treatments of muscle injury are non-operative in order to allow the body's natural healing process to occur. Some of these common treatments are rest from activities, compression, ice application, elevation of injured limb, and possibly medication.[10]

The PRP in this article, published in *Wiley Online Library*, was prepared via a two-step manual platelet concentration method. The blood used in the PRP isolation was taken from the heart of the rats used. The blood was then pre-treated with acid citrate dextrose solution and centrifuged (800g, 30 mins) to separate into plasma and erythrocyte fractions. The plasma was the centrifuged (3,000g, 20 mins). The PRP isolated was clotted using 10% thrombin for 30 mins and centrifuged again (5,500g, 15 mins). The final PRP product was filtered using ultrafiltration (0.22μm).[10]

Muscle cells were treated with 0.5%, 1%, and 2% PRP for 24 hours, while there was a control group that received no PRP treatment. The results showed that PRP induced the migration of skeletal muscle cells, dose dependent (see Figure 8).[10]

The electric cell substrate impedance sensing (ECIS) equipment has been created in order to record cell migration activity during in vitro wound healing model without interruption.[10] The normalized impedance revealed an increase in the healing rate of wounds in skeletal muscle cells while treated with PRP (refer to Figure 9).[10]

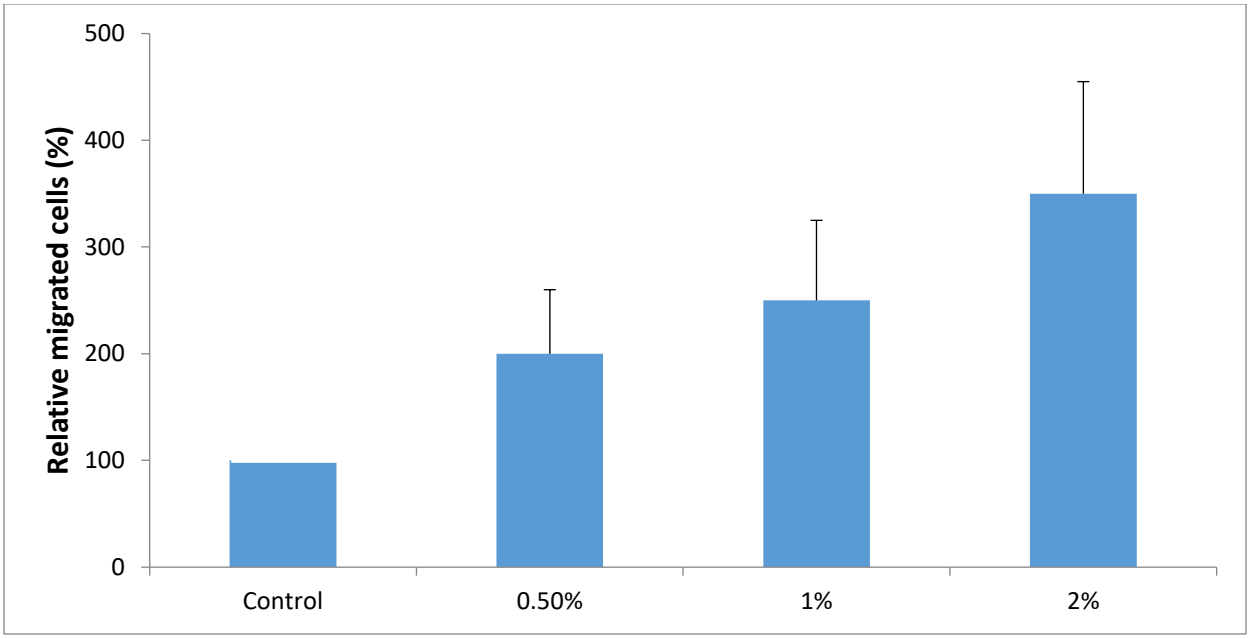

Figure 8: PRP promoted migration of skeletal muscle cells dose-dependently. Skeletal muscle cells were untreated or treated with 0.5%, 1%, and 2% PRP for 24 h. The cell migration was determined by Transwell filter migration assay. Data were presented as mean.[10]

SEM of three independent experiments ($p<0.05$).

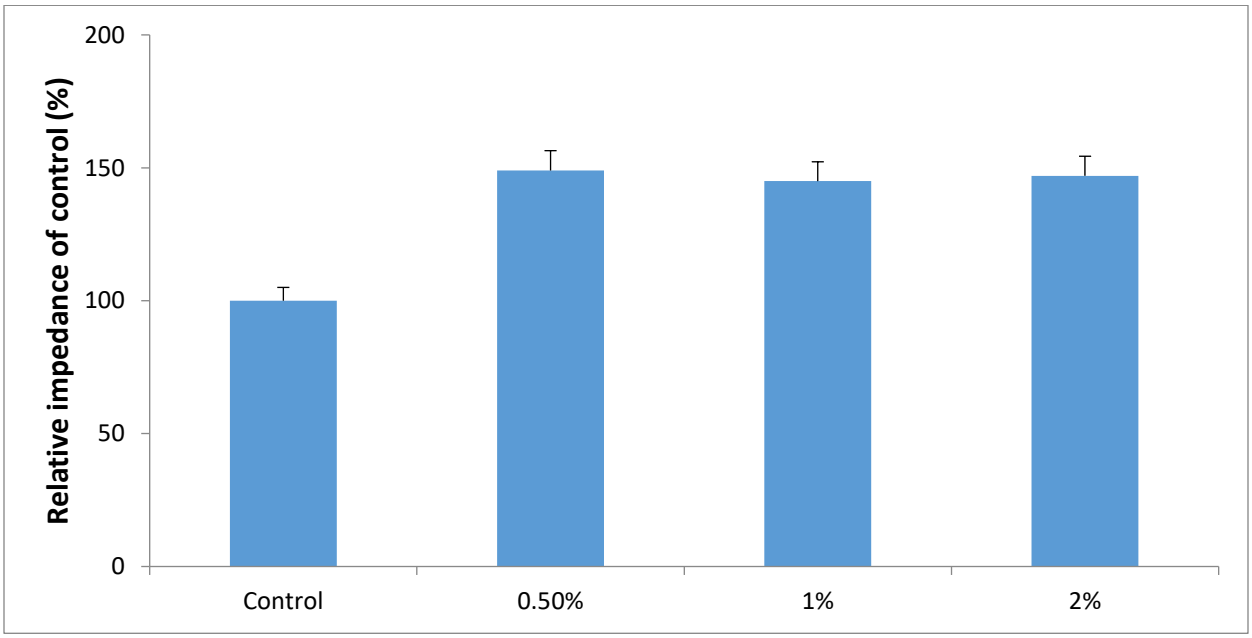

Figure 9: PRP increased wound healing rate of skeletal muscle cells in ECIS model. Skeletal muscle cells were seeded in 8W10E chip and treated with 0.5%, 1%, and 2% PRP for 24 h. The cell migration activities were measured and recorded by ECIS during wound healing process. Data were presented as mean.[1]SEM of mean.[10]

SEM of three independent experiments ($p<0.05$).

Cyclophosphamide-Induced Hemorrhagic Cystitis:

Interstitial cystitis (IC) is a non-infectious disease that has little known about its etiology.[20] Symptoms of IC include, suprapubic pain, urinary frequency, nocturia, and urgency. Though not very common and not life threatening, IC greatly reduces the quality of life.[19]

The PRP in this experiment, published in *Clinical & Investigative Medicine*, was prepared using a two-step gradient centrifugation method. Blood (3 mL) was taken from the tail veins of the rats. The samples were then centrifuged (1600 rpm, 15 mins). The resulting plasma was centrifuged (2800 rpm, 8 mins) to receive the PRP fraction from the platelets and leukocytes. 0.3 mL of the supernatant was used as PRP.[19]

Twenty-four female rats aged 12 weeks were used in the experiment. They were divided randomly into four groups of six (control, sham, cyclophosphamide only-administered (CYP), and PRP-administered 24 hours after CYP administration (PRP). All groups received intramuscular ketamine (50 mg/kg) and xylazine (4 mg/kg) as anesthesia. The control group received no medications and was sacrificed the same day. The sham group was given saline (2 mL) intravesically on experiment day. Both the Cyclophosphamide (CYP) and PRP group received CYP (150 mg/kg) in order to induce cystitis. The PRP group received PRP (0.3 mL) intravesically 24 hours after the CYP injection.[19]

The results of the experiment were measured by the degree of change in hemorrhage, epithelial degeneration, inflammation, edema, and mucosal ulceration between each of the 4 groups. As shown below (Table 1).[19] There is very little difference in change between the CYP and the PRP group. This means the experiment shows that PRP has little to no effect on hemorrhagic cystitis.

	Control	Sham	CYP	CYP+PRP
Hemorrhage	0	0	1.3±0.5	1.0±0.5
Epithelial Degeneration	0	0.2±0.2	2.2±0.3	2.2±0.3
Inflammation	0	0	1.0±0.3	1.2±0.3
Edema	0	0	2.5±0.2	2.3±0.2
Uker	0	0	1.2±0.5	1.0±0.4

Table 1: Edema, hemorrhage, epithelial degeneration, and inflammation on a scale of 0 (normal) to 3 (severe changes). Mucosal ulceration was scored as 0 (normal), 1 (epithelial denuding), 2 (focal ulceration), 3 (widespread epithelial ulceration).[19]

Degeneration Change of Rotator Cuff Muscles:

Rotator cuff injuries plague many people. They can vary in severity and cause shoulder dysfunction. It is also reported that massive rotator cuff tears can cause atrophy and fatty degeneration of rotator cuff muscles.[22] Once muscle atrophy with fatty degeneration takes place following a rotator cuff tear, recovery of the quality of the muscle can be difficult. Even after the tendons are repaired there is often persistently hindered range of motion.[23]

The PRP used in this study was created from obtaining 8 mL of blood from a rat, and 2 mL of 3.13% sodium citrate was added as an anticoagulant. A double-spinning method was used in which the 10 mL blood mixture was centrifuged at 1,500 rotations per minute (rpm) for 10 minutes in order to separate the plasma from the red blood cells. The second centrifugation (3,000 rpm, 10 mins) was conducted in order to separate PRP out of the mixture. This process yielded a 340% increase in platelet count in comparison to the initial (initial counts: 4.8×10^8, product: 1.6×10^9).[21]

The article provides two different versions of the experiment, one done in vitro and the other done in vivo in rats. The in vivo experiment was the focus for this literary review. The in vivo experiment contained a control group and a PRP group. The PRP group received the PRP treatment while the control group did not.[21] The results of the in vivo experiment showed that the group of mice that received the PRP injections showed an increase in myoblast cells, while inhibiting adipogenic differentiation of myoblast cells and suppressing fatty degeneration change in the torn rotator cuff muscles of rats.[21]

Conclusion:

The results of the case studies reviewed vary, some indicating PRP treatment to be effective while others describe PRP treatment as being limited. There were many inconsistencies between the articles including the

process used to prepare the PRP as well as the quality of the final product. The PRP used in the different articles mentioned either used slightly different methods or didn't mention their methods. The same applies to the final PRP product quality. The platelet and growth factor concentrations of the final product are commonly used to evaluate PRP. It has also been suggested that different patients may require different platelet concentrations in order to achieve sufficient results.[24]

There are multiple different systems that can be used to create PRP. These systems include JP200, GLO PRP, MAGELLAN, KYOCERA, SELPHYL, MyCells, and Dr. Shin's System.[24] Each of these systems yield 0.6-3 mL of PRP per whole blood sample (starting samples vary between systems) as well as different concentrations of platelets and GFs. The highest concentration of platelets is achieved by the MAGELLAN system (152.1 x 10^4/μL) while the lowest was from the SELPHYL system (8.8 x 10^4/mL).

There are also GF concentrations that need to be taken into consideration as well. Some of these GFs are PDGF-AB, TGF-β1, and vascular endothelial GF (VEGF). The highest PDGF-AB concentration is achieved from the JP200 system (93.5 ng/mL), while the lowest was the SELPHYL system (12.2 ng/mL). The highest TGF-β1 concentration is found using the MAGELLAN system (1,719.0 pg/mL), while the lowest is found using the SELPHYL system (384.0 pg/mL). Finally, the highest VEGF concentration is obtained from the MAGELLAN system as well (47.0 pg/mL), while the lowest was the SELPHYL system (28.0 pg/mL).[24]

Furthermore, consistent studies on PRP treatment will need to occur in the future in order to render reliable data which will be more reflective of its efficacy as well as its usability. The use of PRP as a treatment can hold many benefits to the patient. Not only can it increase healing rates but it may also reduce pain in certain injuries as well. Also, the fact that it is derived from the blood extracted from the patient means that there is a low possibility of rejection. If the future research points toward PRP treatment being effective, it could result in a more natural way to treat many ailments in the human body.

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