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The Role Of Platelet Rich Plasma In Pain Management And Decrease In Opioid Use

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Abstract

Platelet-rich plasma, also known as PRP, has become increasingly popular for the treatment of orthopedic injuries and symptomatic pain that results from such injuries. By promoting a localized inflammatory response, PRP injections increase blood flow to the injured area and expedite the healing process, thereby leading to pain relief. PRP has the potential to be a key player in the future of pain management. However, current evidence of the impact of PRP on pain relief is controversial. This paper aims to review the most current randomized controlled trials evaluating the efficacy of PRP in pain relief in a variety of orthopedic injuries and diseases.

Today's America is confronting an epidemic involving the prescription of opioids for chronic pain. This trend started in the late 90's when pharmaceutical firms began to advertise the use of opioids for non-cancer related chronic pain as a safe alternative (Asim & Juurlink, 2016). Americans experienced a cultural shift in the way pain was viewed and treated. Individuals suffering from chronic pain began to seek opioids in order to achieve pain relief and primary physicians continued to prescribe it. Two decades later, opioid related morbidity and mortality has increased dramatically leading the US Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) to declare the current practice of opioid prescription and the related overdoses an epidemic (Asim & Juurlink, 2016). As professionals who regularly manage pain, anesthetists have an important role in combating overutilization of opioids. Furthermore, alternative and non-opioid methods to treat pain should be explored and incorporated into the anesthetist's practice. Platelet-rich plasma (PRP) has been proposed to decrease pain in patients suffering from musculoskeletal injury and osteoarthritis. Regenerative medicine has adopted this therapy for its ability to produce cell proliferation, healing and consequently, pain relief. With the ability to relieve pain, PRP has the potential to change the future of pain management therapies and reverse the trend of increased opioid use experienced over the last twenty years.

Platelet's Role in Cell Regeneration

Platelets are typically known for their contribution to coagulation and hemostasis. However, these intriguing cells serve several roles in addition to controlling bleeding. As first responders, platelets are the earliest cells to arrive in damaged tissue sites. When activated, they can release more than 300 substances that act in favor of tissue restoration including cytokines, chemokines and growth factors (Goleniewska & Poole, 2014). In addition, platelets recruit

mesenchymal stem cells (MSC) and tissue smooth muscle cells to migrate towards the injured cells. Examination of the dynamic mechanisms of platelets sheds light as to how they may function as a component of PRP in pain management.

Platelets, or thrombocytes, are complex anucleated cells derived from bone marrow cells called *megakaryocytes.* They are composed of an outer phospholipid cell membrane containing glycoproteins, glucosaminoglycans, and coagulation proteins. Microtubules of actin and myosin form a supporting structure, which is responsible for maintaining the platelet shape. The lack of nucleus makes it infeasible for these cells to reproduce. The energy source for these cells comes from their mitochondria and enzymatic system, which is capable of producing adenosine diphosphate (ADP) and adenosine triphosphate (ATP). In addition, they contain two specific types of granules, alfa and gamma, that are responsible for mediating hemostasis. Alfa granules contain fibrinogen, von Willebrand factor (vWF), fibronectin, factors V and VIII, platelet-derived growth factors (PDGF), transforming growth factor-alfa (TGF-alfa) and thrombospondin. Gama-granules contain ADP and ATP, ionized calcium, histamine, serotonin and epinephrine (Grossman & Porth, 2014).

Under physiological circumstances, platelets remain intact, circulating near the vascular wall. Once the endothelial wall is damaged, platelets are activated to secrete their bioactive contents precipitating a cascade of events and signaling, which ultimately culminates into clot formation and hemostasis. Platelets can also be activated by G-protein coupled receptor (GPCR) signaling from substances forming at the site of the thrombus (Goleniewska & Poole, 2014).

In addition to immediate response to disrupted tissue, platelets have a fundamental role in communicating and modulating immunological response, therefore establishing a balance between tissue repair and tissue damage. Chemokines released by activate platelets induce the

recruitment and proliferation of adult stem cells such as CD34-positive progenitor cells, mesenchymal stem cells (MSC), and smooth muscle cells (SMC) and endothelial progenitors, which are important in the process of regulation of apoptosis and cell survival. In a study investigating myocardial regeneration after an infarct, the authors found that injections of progenitor bone marrow cells, derived from both bone marrow and circulating blood, prevented both cardiac cell apoptosis and ventricular remodeling, and reestablished cardiac function (Assmus et al., 2006). Hepatocyte growth factor (HGF), which can also be released by platelets, is considered one of the mediators responsible to MSC migration to damaged cardiac tissue. Therefore, the release of HGF appears to be the mechanism by which platelets mediate the movement of MSCs to targeted areas of injury (Goleniewska & Poole, 2014).

In the role of cell apoptosis, platelets can regulate the balance between cell death and survival. One of the pathways involving apoptosis is promoted through a cytokine called tumor necrosis factor (TNF). Platelets contain several TNF related ligands including CD-95, DC154, Apo2-L, Apo3-L and LIGHT, which potentially regulate apoptosis through signals from nearby cells. In addition, platelets have the ability to release high mobility group box 1 (HMGB1), a protein released by necrotic cells that regulates immune response and cell death (Gawaz & Vogel, 2013).

Anti-apoptotic properties are another way in which platelets can promote tissue repair. This mechanism is exerted through anti-apoptotic activity of several mediators including the previously mentioned HGF, stromal cell-derived factor 1(SDF-1), serotonin, ADP and HMGB1 (Gawaz & Vogel, 2013). Gawaz and Vogel (2013) explain that whether a platelet will induce or inhibit apoptosis will depend on the amount of receptors and surface expression presented by that specific cell along with particularities of the target cell.

What is PRP?

The idea of utilizing this potent and natural cell as a way of promoting tissue healing has appealed to various medical specialties, giving rise to PRP technology and therapy. Platelet-rich plasma or PRP is a nonspecific term used to define plasma product originated from a sample of whole blood that contains platelet concentration greater than baseline. Blood levels of platelets vary from 150,000 to 450,000 platelets per microliter of blood (Metcalf, Mandelbaum, & Mcllwraith, 2013). The platelet concentration in PRP products differs depending on the platelet-concentrating machines utilized. They can be lower concentrating machines (>1x -3 x baseline) or higher concentrating machines (>4 x –9 x baseline) (Mautner et al., 2015). The most effective therapeutic platelet concentration for cell regeneration is yet to be determined, since distinctive studies have achieved different results. Moreover, Mautner et al. (2015) highlighted that the ideal platelet concentration has other variables, including the type of tissue being treated, the stage of wound healing, and/or whether the goal is to achieve direct promotion of tissue healing versus the initiation of stem cell recruitment.

PRP Classification

PRP is prepared through a process called differential centrifugation. In this process, distinct cellular components with their unique specific gravity are separated through an acceleration force. Two common processes are the PRP and the buffy-coat methods. In the PRP method, two centrifugations are utilized. The initial centrifugation separates red blood cells (RBC), while the second centrifugation results in the concentration of platelets. First, a given volume of whole blood is spun resulting in three layers: an upper layer containing platelets and white blood cells (WBCs), a middle layer containing high levels of WBCs, also called the buffy coat, and a bottom layer that comprises predominantly of RBCs. Pure PRP is produced from a

second spin of the upper layer and the more superficial portion of the buffy coat. The second spin will result in an upper portion containing platelet-poor plasma (PPP), which should be removed. PRP is originated from the lower one third of volume during the second spinning, which is approximately five milliliters of plasma. On the other hand, the buffy coat method comprises the gathering of the buffy coat, which is rich in platelets and WBCs after whole blood is centrifuged at a high speed (Dhurat & Sukesh, 2014).

PRP classification and terminology vary significantly depending on its composition. Thus far, PRP classification lacks uniformity. Dohan-Ehrenfest et al. (2014) suggested that a consensus be formed. The authors proposed the following classification to be the most current: Pure platelet-rich plasma (P-PRP), also known as leucocyte-poor PRP, lacks leucocytes and consists of a low-density fibrin network. Leucocyte and PRP (L-PRP), on the other hand, is prepared with leucocytes along with a fibrin network after activation. Pure platelet-rich fibrin (P-PRF), or leucocyte-poor platelet-rich fibrin, preparations do not contain leucocytes but do present with a high-density fibrin network. They are in gel form and cannot be injected. Lastly, leucocyte and platelet-rich fibrin (L-PRF), or second generation PRP, contains leucocytes and high-density fibrin network (Dohan-Ehrenfest et al., 2014). Although the authors report this classification to be a consensus, Mautner et al. (2015) questioned the completeness of the current taxonomy system. According to the researchers, there is not one system that incorporates all of the PRP properties, which determine a PRP's abilities and effectiveness. Furthermore, the researchers suggest that PRP classification should contain specific information in regards to the concentration of platelets, leukocytes along with their neutrophil content, red blood cells and whether or not exogenous activating agents were utilized. This system is proposed to be called

PLRA (platelet count, leukocyte presence, red blood cell presence, and use of activation) and may benefit standardization along with interpretation of future research.

In Vitro Study

Tendon injuries resulting from repeated mechanical strain commonly produce a significant amount of discomfort. PRP has been proposed to facilitate the regeneration of tendons after this mechanical stress. Given the histological similarity between human tendons and rats, a study has investigated the effects of platelet-rich clot releasate (PRCR) on proliferation of adult rat tendon stem cells (TSC). PRCR is an active releasate of PRP (Chen et al., 2012). In the study, patellar and Achilles tendons were stretched, simulating the tendon injuries commonly experienced by adult humans, and then cultured in adipogenic, chondrogenic and osteogenic mediums with and without PRP. The researchers found that cell proliferation was significantly higher when PRP was utilized. Treatment with PRCR increased levels of collagen types I and III, which are responsible for tendon regeneration, while reducing levels of adipocytes that are responsible for calcifications and the development of tendon disease (Chen et al., 2012).

Current Application

The use of PRP has been specifically explored in regenerative medicine and, most recently, in the orthopedic setting due to its potential effects on bone proliferation and healing. As previously explained, platelet-rich plasma stimulates the migration of mesenchymal cells, and specific to the osteoarthritic joint, it can increase the level of epithelial cells to the injected area, resulting in collagen formation and consequent osteoblast migration (Smith, Gassmann, & Campbell, 2007). This effect promotes a pro-healing environment especially in joints and ligaments that normally have limited vascularity. With the promotion of healing, PRP has the potential to reduce pain and improve function. The beneficial properties of PRP in healing and

consequent pain management have been researched. Controlled trials have investigated its clinical application on various joints commonly linked with chronic pain including: lateral epicondylitis, rotator cuff, knee joint, intervertebral disc, nerve injury and in the osteoarthritic process. Examination of these controlled trials will allow anesthesia providers to be aware of appropriate settings in which PRP may be used as an alternative to opioids in pain management.

Lateral Epicondylitis

Lateral epicondylitis is a painful condition caused by overuse or strenuous exercise (Krogh et al., 2013). This condition is also known as tennis elbow and it is commonly present in tennis players. Krogh et al. (2013) investigated whether PRP was more effective than placebo or glucocorticoid (GC) in relieving pain in adults suffering from this condition. Sixty patients were randomized into three groups. Twenty participants were allocated to each group. The researchers used the Patient-Rated Tennis Elbow Evaluation (PRTEE), ultrasound changes, a numeric pain scale and a verbal rating pain scale to evaluate the results. The PRP utilized had approximately eight times the patient's baseline platelet concentration.

The researchers found that PRTEE pain scores had enhanced improvement in the glucocorticoid group versus saline and PRP group at one month. At three months, however, there was no significant statistical difference between the groups. Ultrasound evaluation revealed a decrease in tendon thickness in the glucocorticoid versus PRP and saline. Tendon thickness increased in both PRP and saline groups. The researchers concluded that PRP and glucocorticoid were not superior to the placebo group. Of note, the study had a significant dropout rate at the three-month mark and the researchers were unable to complete data collection at the 12-month mark. Overall, this study was unable to find benefits in the use of both PRP and glucocorticoid therapy.

In a previous study, Peerbooms, Sluimer, Bruijn, and Gosens (2010) compared PRP to corticosteroid injections in one hundred patients suffering from chronic lateral epicondylitis. This randomized controlled trial found that PRP was superior to corticosteroids in pain reduction. In this study, Disabilities of Arm, Shoulder, and Hand (DASH) along with VAS scores were obtained to evaluate results at weeks four, eight, twelve, twenty six and fifty two. PRP was prepared according to Recover System guidelines. The researchers, however, did not indicate whether one or two spinnings were performed, nor did they specify the presence of leukocytes.

The researchers found that 24 out of 49 patients in the corticosteroid group and 37 out of the 51 patients in the PRP group presented improved VAS scores. DASH scores had similar results with the PRP group showing the most significant improvement. The authors highlighted that the glucocorticoid group had better results initially, which then declined. In contrast, the PRP group showed progressively better results. Peerbooms et al. (2010) explained that glucocorticoid use could produce short-term relief, which is followed by structural changes in the tendon resulting in relapse. This study highlighted the temporary pain relief achieved with corticosteroids, which comes with tendon deterioration over time. PRP, in contrast, offered a more sustainable pain relief without compromising tendon integrity, and more importantly, through structural redevelopment.

Rotator Cuff

Castrini et al. (2011) evaluated the efficacy of platelet-rich fibrin matrix (PRFM) in augmenting healing after a surgical rotator cuff repair. The researchers randomized eighty-eight patients with a rotator cuff tear who were scheduled for an arthroscopic repair. The subjects were divided into groups 1 and 2. Group 1 included individuals who did not receive PRP injections, while group 2 contained those who received PRP. Evaluations started from the day of surgery,

and follow-up continued for an average of twenty months. Shoulder pain, daily level of activity, range of movement and power was evaluated using the Constant Murley Score (CMS) system. In addition, the researchers obtained Magnetic resonance imaging (MRI) to evaluate the anatomical appearance of the tendons and differentiation from partial to complete tears. MRI offered information regarding tendon size, thickness and alterations of signal intensity. PRFM was produced through two centrifugations. The investigators did not reveal the actual number of platelets in the final PRFM product.

Results revealed a significant improvement between preoperative and postoperative scores in both groups, however one was not found to be superior to the other. Group 1 improved from 43.2 to 89.2, while group 2 had scores going from 42 to 88.4. Although MRI images failed to show a difference in tendon size and thickness between the two groups, better alterations in tendon signal intensity was found in the PRFM, suggesting a positive effect. Overall, this study does not support the use of PRFM as a way to augment surgical rotator cuff repair. The researchers highlighted that their results are applicable to small or medium rotator cuff tears, and that it is possible that PRP may be beneficial to large or massive tears. In addition, a different PRP preparation may be of greater benefit. The authors could not compare the results since this was the first randomized control trial evaluating PRP therapy for post-surgical repair of rotator cuff tears.

Another randomized clinical study evaluating the effects of PRFM on rotator cuff healing was conducted by Rodeo et al. (2012). The researchers studied 79 patients undergoing rotator cuff repair. The participants were allocated to a group who received surgical repair with PRFM and another who underwent standard surgery without PRFM. Tear sizes to be repaired varied. The PRFM group incorporated individuals presenting with small tears (10), medium-sized tears

(20), and large-sized tears (10). On the other hand, the control group had 10 patients with small tears, 19 with medium-sized tears and 10 with large tears. Evaluation tools included ultrasound images, manual muscle testing (MMT), the L'Insalata shoulder score and the American Shoulder and Elbow Surgeons (ASES) patient survey.

According to the results, the mean preoperative MMT ratio of the operated to the non-operated extremity was 0.69 in the control group and 0.74 in the PRFM group. No statistically significant difference was found. ASES scores in the control group increased from 54.74 prior to surgery to 96.43 one year after surgery. The PRFM group reported an increase from 56.22 to 91.3, respectively. Ultrasound images, and ASES and L'Insalata scores had no statistically significant difference. Ultrasound findings did suggest that size of tears is a determinant of the outcome. For instance, at 12 weeks median tears showed superior healing: 55.6% of large tears, 71.4% of the small tears, and 81.8% of median tears were intact.

In agreement with Castrini et al. (2011), this study does not support the application of PRFM on tendon-bone interface at the time of surgical repair of rotator cuff tears. The researchers did not find a statistic difference. Study limitations include a lack of information about the composition of actual PRFM received by each patient. In addition, the authors explained that the ultrasound evaluation was rather early and that tendon healing could have occurred over time. The researchers also considered the follow-up period to be short.

In contrast to the above studies, and in a more recent analysis evaluating the benefits of PRP in rotator cuff tears, Shams, El-sayed, Gamal, and Ewes (2016) compared injections of corticosteroid to PRP in 40 patients with symptomatic rotator cuff tear. The study included patients suffering from persistent shoulder pain for at least three months and presenting with MRI evidence of partial supraspinatus tear, one of the rotator cuff tendons. Twenty individuals

were allocated to the PRP group and another twenty to the corticosteroid group. Outcomes were measured using the ASES, CMS, the Simple Shoulder Test (SST) and the VAS scores. Patients were assessed after six weeks, twelve weeks and six months of the initial treatment. PRP was obtained using MyCells Autologous Platelet Preparation System.

Results demonstrated significant improvement in ASES, CMS and SST shoulder scores along with reduced pain as shown through VAS scores in both groups. PRP was superior to the corticosteroid group only at 12 weeks. MRI findings were not significantly different between the two groups.

Corticosteroid therapy has been utilized in the short-term management of pain in patients with rotator cuff pathologies. The use of steroid injections, however, carries complications such as tendon weakness, which are not found with the injection of autologous blood, or PRP. The researchers found that PRP injections are as effective as corticosteroid for pain relief. The conclusions represent a positive outcome for PRP supporters, suggestive of PRP as an alternative to corticosteroids as it provides similar pain control without the possibility of tendon weakness. Limitations to the study include the fact that injections were not guided by ultrasound; therefore, the accurate placement of the injection could not be confirmed.

Knee Injury and Osteoarthritis

Aggarwal, Shashikanth, and Marwaha (2013) researched whether platelet-rich plasma reduces postoperative pain, along with promotion of wound healing and prevention of blood loss in patients who underwent knee arthroplasty. The study included 40 participants; 17 individuals were allocated to the intervention group who received PRP injections and 23 participated in the control group. Patients were followed for a total of six months and outcomes were measured

based upon the amount of opioids used along with VAS, WOMAC and Knee Society Score (KSS) scores.

The researchers found a statistically significant decrease in pain and amount of narcotics used, as well as an improvement in range of motion, KSS and WOMAC scores. The authors suggested that pain reduction was a result of the achievement of faster hemostasis and an expedited healing process. The intervention group had 24.39 % lower WOMAC scores than the control group at 6 weeks and 24.79% lower score at 12 weeks. Overall, the researchers support the use of PRP for pain control, reduction in blood loss and reduction of use of narcotics.

Another study evaluating the impact of PRP in pain reduction for patients suffering from knee osteoarthritis was conducted by Patel, Dhillon, Affarwal, Marwaha, and Jain (2013). The researchers hypothesized that PRP improved symptoms of knee osteoarthritis (OA) including reduction in pain. The participants were 78 patients with bilateral knee OA who were randomized into three groups. The cohort on group A received one single PRP injection, group B received two, and group C, the control group, received saline injections. The outcome was measured through WOMAC and VAS scores, as well as patient satisfaction. Patients were followed from baseline to six weeks, three months, and six months. The PRP injected was leukocyte free and contained a platelet count of about 310 thousand per ml.

The scholars found a significant decrease in pain from baseline in PRP groups. Overall, the mean pain decreased from baseline. At six months, an increase in pain levels was noted which was still lower than baseline. Both WOMAC and VAS were lower in groups A and B, but without a difference between them, indicating that a single injection of PRP was as effective as two injections. Patient satisfaction was also significantly higher in the PRP groups than in the control group. The researchers' findings support the use of PRP in patients with knee OA. The

authors explain that some of the benefits decrease over time and suggest that a continuous regimen might be beneficial. Limitations to the study include the fact that some patients had bilateral knee OA and both knees received the same treatment. It would have been interesting to compare results of two different treatments in the same patient. The researchers highlight that issues with patient blinding would have occurred had they chosen to use different treatments on the same patient.

More recently, Smith (2016) studied the effects of PRP on pain resulting from knee osteoarthritis. The researcher conducted a randomized, double blind, placebo-controlled clinical trial sanctioned by the Food and Drug Administration (FDA). The trial included 30 participants who had a documented diagnosis of OA for at least six weeks and were suffering from moderate pain. The placebo group received saline injections while the treatment group received injections of autologous PRP. The same individual who administered the injections prepared the syringes. Participants underwent three intra-articular injections of three to eight milliliters of either saline or PRP weekly. Patients were followed for 12 months. The PRP produced was leukocyte-poor platelet-rich plasma (LP-PRP).

Pain reduction was the primary outcome of this study, as evidenced by WOMAC scores. The PRP group had improvement on WOMAC scores from week two until the end of the study. On the other hand, the placebo group had improvement only in the second month. This was the only time that the placebo group showed decreased pain level, which the authors suggested would be consistent with the placebo effect. Overall the study provides evidence that PRP reduces pain and decreases stiffness in knee osteoarthritis patients.

In addition to corticosteroid therapy, platelet-rich plasma injections have been also compared with hyaluronic acid (HA). HA is a component of the synovial fluid. Osteoarthritis

causes a decrease in the physiological production of HA, which results in mechanical deterioration and degeneration of the joint (Raeissadat et al., 2015). The use of HA in the osteoarthritis setting has been studied and used vastly. Raeissadat et al. (2015) compared the effect of PRP and HA in knee osteoarthritis. Participants included 160 patients aged 40 to 70. The PRP group received two intra-articular injections at a four-week interval, and the HA group received three doses of HA at one-week intervals. The patients were assessed for pain, joint stiffness and function through the WOMAC questionnaire. In addition, physical and mental health information was obtained through a Persian Version of Short Form-36 (SF-36). PRP was prepared via the Rooyagen Kit, which involves separation of white and blood cells and results in platelet concentration of about five times greater than the baseline.

The researchers found that PRP was effective in pain management and overall improvement of joint function, and when compared to HA, PRP had greater effects. The measures of the study were subjective, which limits the study. An objective evaluation such as MRI studies could have strengthened the results. Another limitation to the study was the lack of a placebo.

The comparison between intra-articular injections of PRP and HA continued in a study by Filardo et al. (2015). The authors investigated 189 individuals. The PRP group included 94 patients while the HA group included 89. They were followed at two, six, and twelve months after the last treatment. Measure tools included: International Knee Documentation Committee (IKDC), Knee Injury and Osteoarthritis Outcome Score (KOOS), EuroQol Visual Analog Scale (EQ-VAS) and Tegner score. The PRP final product had about 4.6 times more platelets and 1.1 times more leukocytes than whole blood.

The investigators found a statistically significant improvement in all scores for both PRP and HA groups. However, there was no meaningful difference between the two groups. The researchers emphasize that both treatments proved to be effective in a modest manner. This study validates the use of PRP as an alternative to HA, demonstrating that PRP is as effective as HA in pain relief.

Intervertebral Disc Pain

In addition to joint pain, PRP can be beneficial in the management of lumbar or low back pain. Previous animal studies have demonstrated the ability of a single PRP injection to cause disc regeneration and healing (Gullung et al., 2011). Human trials started in 2015 with a study by Tuakli-wosornu et al. (2015). In this study, the authors randomized 58 participants. The control group received intradiskal injections of contrast in place of PRP. Progress was evaluated based on Functional Rating Index (FRI), Numeric Rating Scale (NRS) and questionnaires with 36 short health surveys. PRP was produced via Harvest Technologies Corporation. The researchers did not specify the details of preparation and final platelet concentration.

The researchers found a significant improvement in the PRP group. At eight weeks, FRI and NRS scores were significantly better on the PRP group. On the other hand, the control group did not present significant changes in pain or function scores. Patients in the treatment group reported greater satisfaction with the treatment (56%) versus 18% in the control group. Limitations to the study included the lack of longer follow up period on the control group. The two groups were compared at eight weeks, and subsequent follow up only included the PRP group. Greater differences between the two groups may have been apparent if a longer follow-up had taken place.

Acute Muscle Injury

PRP has also been utilized for the recovery and pain management of acute muscle injury. Bubnov, Yevseenko, and Semeniv (2013) investigated the effects of PRP in muscle injury and pain relief in professional athletes. The researchers randomized 30 participants into groups A and B. Group A received PRP injections under ultrasound guidance along with conservative treatment. Conservative treatment included immobilization, physiotherapy and anti-inflammatory therapy. Group B, on the other hand, received only conventional therapy. Muscle injury was identified through ultrasound examination. Patients were followed weekly from the day of treatment for one month. Outcomes were evaluated based on muscle function, regenerative changes identified through ultrasonography, and VAS scores. The authors did not specify how the PRP was processed.

According to the results, a 28 % pain relief was achieved within 24 hours after the procedure in the treatment group versus 10% in the group that received conservative treatment only. By the 28th day, pain improved to 93% for group A versus 80% for group B. Improvement in strength and range of motion was statistically significant two weeks post treatment in the PRP group. Regenerative changes started earlier in group A, at seven days. Group B only showed regenerative changes at 14 days in three patients versus 12 in group A. By the end of the study, all patients had regenerative changes. PRP was found to promote faster recovery and pain relief; however, the late outcome was not statistically significant. This finding is of special interest of professional athletes as they seek a faster recovery in order to resume training. Limitations to the study include the size of the cohort and the fact that the study was not double blinded.

Neuropathic Pain

Evidence exists that neuropathic pain can also be treated with PRP injections. Although a review of the literature showed nonexistent randomized controlled trials evaluating the effects of

a PRP in the management of neuropathic pain, Kuffler (2013) discussed the ability of PRP to cause permanent elimination of neuropathic pain if that is applied at the end of injured nerves. The author explained that the inflammatory process created by PRP infiltration promotes axon regeneration.

Seven patients with a total of nine traumatic nerve transections of the arm were included in a small clinical study by Santiago-Figueroa et al. (2011). Ages ranged from 24 to 58 years. In the repair process, a tube of collagen was created using a sheet of collagen that was further attached to the ending of the nerve stumps. Platelet-rich fibrin was then injected into the tube. A verbal pain scale was utilized to quantify the level of pain before and after the repair.

The researchers found significant improvement in pain at one month, and complete resolution of pain by six months. A significant decrease of intake of analgesic was also noted. At six months, six out of seven patients were no longer taking pain medicine. The one patient who had the most severe pain at baseline was able to discontinue the use of opioids and take only a non-opioid analgesic. The researchers concluded that a collagen tube with platelet-rich fibrin causes axon regeneration, therefore successfully decreasing neuropathic pain.

Discussion

The debate does not end in the studies discussed here. The different results among clinical trials evaluating PRP provide a dilemma for health care providers. Indeed, the most appropriate technique and the exact platelet cell count necessary to generate therapeutic outcome is yet to be determined. Whether the presence of leukocytes facilitates or impedes healing is another argument for debate. One side argues that leukocytes potentiate an inflammatory process, which may be maleficent. Conversely, another group reasons that leukocytes play an important role in regulation of healing and inflammatory process for they contain chemokines,

anti-inflammatory cytokines and opioid peptides capable of inhibiting the process of pain. Moreover, the complexity of the discussion may increase even further as the type of leukocytes (lymphocytes, monocytes, granulocytes), along with the amount present, and active state can influence the effectiveness of the PRP produced (Dohan-Ehrenest et al., 2014).

PRP reimbursement is another discussion. Insurance companies refuse to pay for the procedure because it is considered experimental rather than clinically proven. Medicare's coverage is limited to patients undergoing treatment for non-healing diabetic ulcers (Center for Medicare and Medicaid Services, nd). Some consider the lack of reimbursement unfair given the large amount of money that is invested in treatments sometimes considered unnecessary (Bretz, 2015). Bretz speculates that PRP does not have the attention of large pharmaceutical companies, which are able to financially support large trials. PRP research comes from small and independent sources. The actual cost of the therapy is relatively small as the base for its production is the patient's own blood. PRP supporters emphasize that without financial research support, this therapy will continue to be anecdotal. Moreover with the lack of reimbursement physicians will refrain from prescribing it.

Conclusion

In summary, there is contradicting evidence of the beneficial effects of PRP in pain management based on the literature review. This review presented three studies on rotator cuff injuries, one in an acute muscle injury, three in osteoarthritis, one in intervertebral disk pain, two in lateral epicondylitis, and one in neuropathic pain. The results vary among studies, and there is a lack of uniformity in study methodology. More significantly, the method of PRP production varied from study to study, limiting one's ability to compare them. The question of whether PRP significantly reduces pain and improves function in patients suffering from musculoskeletal

injury and disease remains unanswered. Also, distinctive tissues may respond differently. For example, what works for the knee may not work for the elbow or lumbar spine. While the potential for PRP to relieve pain is valid, the formulation of concrete clinical-base evidence is pending and still necessary. Further research with larger sample sizes is paramount. It is necessary that a standard method of PRP production be established. Moreover, determining the appropriate dosing and optimal composition of PRP is imperative. The existing opioid crisis faced by the American population shall be ample incentive for the investment in research that investigates alternative ways to reduce pain. Given all of this information, PRP has the potential to be the future of pain management.

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