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Platelet-Rich Plasma: A Review of the Science and Possible Clinical Applications

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educational objectives

1. Define the mechanism of action of platelet-rich plasma and how it is derived.
2. Summarize the role of platelets in the healing cascade.
3. Discuss animal and human data regarding platelet-rich plasma and tissue healing.
4. List the potential clinical applications of platelet-rich plasma.

During the past several decades, advances have been made in the treatment of musculoskeletal disorders. Many of these advances have been the result of improvements in diagnostic imaging and surgical techniques. While it is possible to repair soft tissues reliably during surgery, the long-term outcomes are not always as successful as the immediate surgical result. One of the primary reasons for suboptimal surgical outcomes is the fact that surgical fixation (anchors, screw, sutures) will eventually fail if the repaired structures cannot heal themselves and regain their native strength.

Recently, attention has shifted towards optimizing the biology of the healing environment in an attempt to stimulate the body's natural healing process and improve outcomes. The structures that we are trying to repair, eg, the rotator cuff or meniscus, often are of poor vascularity and have limited capacity to heal. Methods that hold the potential to improve the biological milieu at the repair site have become available over recent years. One of these methods is the use of platelet-rich

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Table

Growth Factors in Platelet Rich Plasma

Transforming growth factor beta (TGF- β)
Platelet-derived growth Factor (PDGF)
Insulin-like growth factor (IGF)
Vascular endothelial growth factor (VEGF)
Epidermal growth factor (EGF)
Fibroblast growth factor-2 (FGF-2)

plasma. Platelet-rich plasma can be used in both the nonoperative and operative settings to improve or stimulate the healing response. The focus of this article is to review the current literature pertaining to platelet-rich plasma and to discuss its potential role in the treatment of musculoskeletal pathology.

PLATELET-RICH PLASMA – WHAT IS IT?

Platelet-rich plasma is essentially plasma that has been processed to contain a high concentration of platelets and growth factors. Platelet-rich plasma is derived from a patient's whole blood. The blood is spun down in a centrifuge, which allows the red blood cells to be removed. Most systems require a second centrifuging step to create the final product. Once the red blood cells are removed, the remaining plasma is again centrifuged, which allows the platelet-rich layer to be extracted. The platelet-rich plasma can then be activated with thrombin or calcium chloride. This activation step causes the platelets to begin releasing growth factors. Platelet-rich plasma can also be injected in its inactivated form allowing it to be activated once it is within the body.

There are many different proprietary methods of creating platelet-rich plasma but the essential concepts behind creating the platelet-rich plasma are similar for each system. The platelet-rich plasma contains platelets as well as specific growth factors (Table). These growth factors include:

transforming growth factor beta (TGF- β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and fibroblast growth factor-2 (FGF-2). Many of these factors have been shown to enhance one or more phases of bone and soft tissue healing. Insulin-like growth factor is thought to stimulate osteoblast proliferation and differentiation. Platelet-derived growth factor, EGF, and FGF-2 have been shown to stimulate proliferation of osteoblastic progenitors as well as to affect the mitogenesis of mesenchymal stem cells and to stimulate epidermal cell proliferation. Transforming growth factor beta is believed to stimulate collagen synthesis. Angiogenic factors, including VEGF and FGF-2, are believed to enhance early angiogenesis and revascularization.¹

MECHANISM OF ACTION OF PLATELET-RICH PLASMA

In order to understand the mechanism of action of platelet-rich plasma, it is necessary to review the normal healing process of musculoskeletal tissue. The repair response of musculoskeletal tissues starts with the formation of a blood clot and degranulation of platelets. This degranulation of platelets releases growth factors and cytokines into the local environment. This in turn results in chemotaxis of inflammatory cells as well as the activation and proliferation of local progenitor cells.²⁻⁸

It is believed that platelet-rich plasma can augment or stimulate healing by turning on the same biological healing process that normally occurs in the human body after musculoskeletal injury.⁹⁻¹⁴ In vitro studies have demonstrated that platelet-rich plasma can enhance the proliferation of stem cells and fibroblasts in a controlled study of platelet-rich plasma versus platelet-poor plasma.¹⁵

PLATELET-RICH PLASMA – ANIMAL DATA

Several studies have examined the effects of platelet-rich plasma on tissue

healing. A recent study on a rabbit model of osteochondral injury demonstrated that platelet-rich plasma had a beneficial effect on osteochondral healing.¹⁶ In this study, 48 osteochondral defects were created in the trochlear groove of rabbits. The rabbits were then divided into 3 groups: (1) left untreated, (2) treated with autogenous platelet-rich plasma in a poly-lactic-glycolic acid (PLGA), or (3) with PLGA alone. After 4 and 12 weeks, the specimens were assessed by macroscopic examination, microcomputed tomography, and histological evaluation. The platelet-rich plasma-treated group was found to have improved cartilage and bone formation and a stimulatory effect of platelet-rich plasma on osteochondral formation was observed.

Platelet-rich plasma has also been demonstrated to improve the healing of acute traumatic wounds when comparing a group that received platelet-rich plasma gel to their wounds versus a group that did not.^{17,18} Schabel et al¹⁸ examined the effects of platelet-rich plasma on equine tendons and found enhanced gene expression of key matrix molecules suggesting that the application of platelet-rich plasma enhanced healing of tendons in this model.

Aspenberg and Virchenko¹⁹ also demonstrated that the application of platelet-rich plasma improved healing in a rat Achilles tendon rupture model. In this study, a rat model of Achilles tendon ruptures was created by transecting the Achilles tendon and removing a 3-mm segment. At 6 hours post transection, a platelet concentrate was injected percutaneously into the hematoma. The mechanical properties of the treated tendon was compared to controls and the treated tendons were found to have increased tendon strength and stiffness by 30% after 1 week, which persisted for 3 weeks after the injection. Improvement was noted in the maturation of the tendon callus in the treated tendons.

A recent study on the effects of platelet-rich plasma on a patellar tendon resection model in rabbits also demonstrated a statistically significant increase in tendon



strength in the early phase of healing.²⁰ The authors resected the central portion of the patellar tendon in 40 skeletally mature New Zealand White rabbits. They then treated half the rabbits with platelet-rich plasma and half served as a control group. The histology and biomechanical properties were evaluated at 14 and 28 days after treatment. At 14 days after treatment, the platelet-rich plasma group was noted to have a 72.2% increase in load to failure and a 53.1% increase in stiffness compared to controls. At 28 days no statistically significant differences between the platelet-rich plasma and control groups were found. The authors concluded that platelet-rich plasma has a strong effect in the early phase of tendon healing.

PLATELET-RICH PLASMA – HUMAN DATA

Human data regarding the efficacy of platelet-rich plasma is more limited. In an *in vitro* study of human tenocytes, de Mos et al²¹ demonstrated that platelet-rich plasma stimulated cell proliferation and collagen production laying out the pathway by which platelet-rich plasma may enhance healing in human soft tissues. The authors cultured human tenocytes for 14 days in a control medium, a platelet-rich plasma environment or a platelet-poor plasma environment. At day 4, 7, and 14, cell amount, total collagen, and gene expression of collagen I alpha 1 (COL1) and III alpha 1 (COL3), matrix metalloproteinases (MMPs), vascular endothelial-derived growth factor (VEGF)-A, and transforming growth factor (TGF)- β 1 were analyzed. The authors concluded that platelet-rich plasma, but also platelet-poor plasma, stimulates cell proliferation and total collagen production. Platelet-rich plasma, but not platelet-poor plasma, increased the expression of matrix-degrading enzymes and endogenous growth factors. In addition, they concluded that platelet-rich plasma, and perhaps platelet-poor plasma, might accelerate the process of callus formation and angiogenesis in an injured tendon.



Figure: Platelet-rich plasma being applied to an osteochondral fragment before and after fixation.

Mishra et al²² compared patients receiving bupivacaine injection versus platelet-rich plasma injection for patients with chronic elbow tendinosis. They noted a 60% decrease in visual analog pain scale (VAS) scores in the platelet-rich plasma group versus a 16% decrease in the control (bupivacaine) group.

Further evidence backing the efficacy of platelet-rich plasma on tendinosis can be seen in a study by Filardo et al.²³ The authors treated 15 patients with chronic patellar tendinosis with multiple platelet-rich plasma injections and physical therapy. They then compared this group to a similar group treated with only physical therapy. An improvement in clinical outcome was seen in the platelet-rich plasma group when comparing the Tegner and pain scores to the group that did not receive platelet-rich plasma. Several studies address the use of platelet-rich plasma on soft tissue pathology currently underway and more data should become available over the next several years.

CLINICAL RELEVANCE

Platelet-rich plasma likely has the ability to stimulate and enhance healing of soft tissue injuries in humans. Nevertheless, its exact role in the treatment of musculoskeletal disorders remains to be determined. We are in the infancy of evaluating platelet-rich plasma in clinical trials and deriving evidence based guidelines by which to use platelet-rich plasma. In addition, the use of platelet-rich plasma as described in this article is not FDA approved.

Currently, we have little more than animal data, early human data and anecdotal evidence by which to guide us. The use of platelet-rich plasma is probably best relegated to soft tissue injuries such as tendon ruptures and tendinosis.

In the author's experience, platelet-rich plasma has been successful in treating lateral epicondylitis and multiple types of tendinosis and has also been used to treat acute soft tissue injuries in elite athletes (medial collateral ligament sprains, ulnar collateral ligament sprains). The



author has also used platelet-rich plasma to augment healing of displaced osteochondritis dissecans lesions when there is little bone attached to the loose fragment (Figure). In this setting, where there is no bone attached to the cartilage fragment, healing would not normally be expected to occur. The hope is that the use of platelet-rich plasma may make it possible to allow some of these loose osteochondritis dissecans fragments to unite with the subchondral bone and regain stability. It is important to mention that while the author has used platelet-rich plasma on both ligaments and cartilage injuries, there is no data demonstrating its success in such applications.

CONCLUSION

Platelet-rich plasma is a new technology that may prove to have numerous applications in the treatment of musculoskeletal injuries. Platelet-rich plasma has the ability to promote soft tissue healing in vitro and it is likely that this will translate into improved healing in human trials as well. However, due to the paucity of human data, caution must be taken in the use of platelet-rich plasma in areas where currently only anecdotal evidence is available. ●

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Platelet-Rich Plasma: A Review of the Science and Possible Clinical Applications

1. **Platelet-rich plasma contains growth factors that have been shown to:**
 - A. Disrupt early angiogenesis.
 - B. Enhance only soft tissue healing.
 - C. Stimulate osteoblast proliferation.
 - D. Have a detrimental effect on epidermal cell production.
2. **The normal healing process of musculoskeletal tissue:**
 - A. Involves the activation of all growth factors.
 - B. Does not use the body's inflammatory response.
 - C. Ends with degranulation of platelets.
 - D. Involves activation and proliferation of local progenitor cells.
3. **In an animal model (Aspenberg and Virchenko), a transected rat Achilles tendon treated with platelet-rich plasma showed:**
 - A. No improvement in tendon callus formation.
 - B. Complete rupture of the tendon.
 - C. Increased tendon strength and stiffness.
 - D. Increased tendon elasticity.
4. **In a study by Mishra et al, patients receiving a platelet-rich plasma injection for chronic elbow tendinosis:**
 - A. Noted a greater decrease in pain scores versus those who received a bupivacaine injection.
 - B. Noted no difference in pain.
 - C. Had increased pain for 7 days, then reported complete resolution of pain.
 - D. Had worse Tegner scores post-platelet-rich plasma injection.
5. **When comparing platelet-rich plasma to platelet-poor plasma in a human in vitro study (de Mos et al):**
 - A. Platelet-poor plasma does not stimulate cell proliferation.
 - B. Only platelet-rich plasma increased the expression of matrix-degrading enzymes and endogenous growth factors.
 - C. Platelet-poor plasma significantly slows the process of callus formation in an injured tendon.
 - D. Both platelet-rich plasma and platelet-poor plasma stimulates cell proliferation and total collagen production.
6. **While much research still needs to be performed, the area where platelet-rich plasma has the most documented clinical success to date is:**
 - A. Soft tissue injuries.
 - B. Accelerating fracture healing.
 - C. Spine fusions.
 - D. Osteoarthritis.
7. **Platelet-rich plasma does not contain:**
 - A. Platelet-derived growth factor.
 - B. Red blood cells.
 - C. Vascular endothelial growth factor.
 - D. Fibroblast growth factor-2.
8. **In a recent study on the effects of platelet-rich plasma on a patellar tendon in a rabbit model:**
 - A. Platelet-rich plasma was shown to provide maximal tendon strength after 28 days.
 - B. Platelet-rich plasma was shown to increase tendon strength in the early phase of healing.
 - C. There was no difference in tendon strength between platelet-rich plasma and the control in the early phases of healing.
 - D. The control group showed a larger increase in tendon stiffness compared to the platelet-rich plasma group.
9. **Platelet-rich plasma is created from a patient's whole blood by:**
 - A. Combining the whole blood with fresh-frozen plasma.
 - B. Keeping the whole blood at a temperature of 5°C for 24 hours.
 - C. Centrifuging, which allows the red cells to be removed.
 - D. Vigorously shaking the syringe of whole blood for 1 minute.
10. **The current clinical knowledge base would suggest that the best use of platelet-rich plasma is in which situation:**
 - A. Never.
 - B. On all Achilles tendon ruptures.
 - C. On all cervical spine fusions.
 - D. In selected cases of soft tissue injuries.