

## Review

## Timing of Platelet Rich Plasma Injections During Antithrombotic Therapy

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The use of platelet rich plasma (PRP) spans across many fields owing to its role in healing and as a natural alternative to surgery. PRP continues to grow however much of the literature is anecdotal or case report based and there is a lack of controlled trials to evaluate standards for PRP. The International Cellular Medical Society (ICMS) has developed guidelines to help with the safe advancement of PRP; however there remains a gap in literature concerning the timing of PRP injections in patients who are on antithrombotic therapy. The importance of an intact platelet surface membrane allows for the appropriate release of the healing bioproteins and growth factors granting PRP therapy its efficacy. This along with the proliferation of differentiated cells, enhancement of collagen synthesis, early angiogenesis and revascularization help promote the benefits of regeneration. The intrinsic and extrinsic pathways of the coagulation cascade are valuable in that disruption of this mechanism or prematurely activated platelets may result in limited efficacy. Anticoagulants and antiplatelet drugs are commonly used in patients who are candidates for PRP. As antithrombotic agents affect platelet stability, they will have an effect on PRP efficacy and must be discontinued at an appropriate time frame prior to injection therapy. Understanding the pharmacokinetics and platelet effects can help guide discussion on the proper timing of discontinuation and resumption of a particular antithrombotic agent. With future research, the establishment of clinical practice guidelines concerning PRP and antithrombotic therapy can help structure safe and efficacious means in which to promote healing and regeneration in a growing patient population.

**Key words:** Platelet rich plasma, antithrombotic therapy, coagulation, platelet activation, regenerative medicine, growth factors

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**P**latelet rich plasma (PRP) has been well documented in many fields after it was first used by Ferrari et al in 1987 to avoid blood transfusions after an open heart operation (1). Initial popularity touted PRP as a safe and natural alternative to surgery. By having a powerful effect of modulating cytokines, growth factors, and bioactive proteins, PRP procedures have continued to expand with the goal of healing and regeneration (2). The elective procedure is generally considered for subacute and chronic conditions; most healing slows by 6 – 12 weeks after an injury (3). Some of the more common uses for PRP include tendinopathies, ligament sprains, muscle strains, joint osteoarthritis, failed conservative treatment of entrapment neuropathies, and non-union fractures

(4-6). Many patients who are candidates for PRP therapy will also be on concomitant antithrombotic therapy (7). The pharmacokinetics of each particular agent needs to be examined with longer acting anticoagulants requiring greater intervals between dosing and procedures. Further studies and testing are clearly needed to further elucidate the timing of PRP injections during antithrombotic therapy.

### **PRP**

PRP therapy systems have several ways in which they are prepared and performed. One of the most commonly used techniques is the double spin method. In this method there is the use of blood plasma from the patient's whole blood that has been processed to

contain a high concentration of platelets and associated growth factors. The patient's whole blood is first spun down using a centrifuge in order to allow removal of the red blood cells. At that point a second centrifuging is performed which allows the removal of the platelet rich layer. The use of an anticoagulant, while not taken systemically, is needed in the processing of PRP in order to prevent spontaneous activation. Numerous agents have been utilized including heparin, citrate, acid citrate dextrose (ACD), and citrate-theophylline-adenosine-dipyridamole (CTAD). Heparin is not typically used as it activates platelets in-vivo. Sodium citrate has also been used, but recent research has shown that it may decrease the number of dense granules and promote earlier lysis and more spontaneous activation. ACD is utilized and the platelets have more dense granules and lower spontaneous activation. CTAD has 3 combined platelet antagonists and has been used in hematologic studies. There has been a push for its use in PRP production because of decreased spontaneous activation and an increase in the amount of growth factor released (8). In terms of purposefully activating the PRP, many practitioners will use either thrombin or calcium chloride which causes the release of growth factors, signaling molecules, cytokines, integrins, coagulation proteins, and adhesion molecules (9,10). Growth factors have been shown to be extremely important in wound healing and in the wound regeneration process (11). Some of the essential growth factors include transforming growth factor beta (TGF- $\beta$ ), 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) (12) (Table 1). These factors have been shown to increase or enhance bone and soft tissue healing through a variety of ways including proliferation of osteoblast and epidermal cell differentiation, stimulating collagen synthesis, and enhancing early angiogenesis and revascularization (13,14). It is important to note that data on

antithrombotic agents acting on these growth factors are severely lacking, and more research is needed to better determine more specific interactions between particular agents and growth factors.

In normal healing of the musculoskeletal system, the repair response begins with the formation of a blood clot and with degranulation of platelets (15). This degranulation then causes the release of the growth factors and cytokines which trigger the expansion of local progenitor cells as well as the chemotaxis of inflammatory cells. It is thought that about 100% of the growth factors are released within the first hours, of which 70% are secreted in the first 10 minutes of activation (16). It is posited that through the use of PRP, the body's physiologic healing process can be enhanced after a musculoskeletal injury. Augmentation of this healing process by PRP has been demonstrated by increased proliferation of stem cells and fibroblasts (17). In order for these intact platelets to mediate their effects they must undergo degranulation. Naturally occurring platelet activation occurs when there is a break in the endothelium. Collagen, thromboxane A<sub>2</sub>, ADP, and thrombin are all factors that can trigger the activation, with thrombin being the most potent activator. Activation of PRP is typically done via calcium chloride or thrombin allowing for soft adhesion (18). As the majority of the platelet substances are contained in alpha granules (in addition to dense granules and lysosomes), when activated there is exocytosis of the granules and their subsequent release into the extracellular environment (19,20). It is important to ensure that the platelets are intact after centrifugation or the growth factors could be diluted and lost in the plasma. As the growth factor receptors remain on the platelet surface membrane, platelet activation P selectin can be measured to ensure integrity (21).

### Coagulation Pathway

After an endothelial injury to a vessel, the coagulation pathway starts almost instantly in normal individuals. Primary hemostasis occurs with platelets forming a plug at the injury site while secondary hemostasis occurs via a complex cascade with the goal of fibrin strand formation helping to strengthen the platelet plug. As previously mentioned, PRP efficacy stems from the integrity of the platelet membrane and inactivation until the timing of the PRP (22). If the coagulation pathway is disrupted and the platelets are activated prematurely, PRP may not work as predicted. It is for this reason that an in depth knowledge of the coagulation pathway is needed.

**Table 1. Growth Factors in PRP.**

<b>Transforming growth factor beta (TGF-<math>\beta</math>)</b>
<b>Platelet-derived growth factor (PDGF)</b>
<b>Insulin-like growth factor (IGF)</b>
<b>Vascular endothelial growth factor (VEGF)</b>
<b>Epidermal growth factor (EGF)</b>
<b>Fibroblast growth factor-2 (FGF-2)</b>



literature guiding the timing of PRP injections during antithrombotic therapy is severely lacking. Due to the importance of the platelet and their granular content effects in PRP, it is clear that agents interfering with the platelet plug, particularly factor 8, von Willebrand factor, fibrinogen, and thrombin, can affect the efficacy of treatment. For this reason we aim to focus practitioner and patient emphasis on the safety, efficacy, and education of PRP injections in relation to commonly used antithrombotic agents. Taking into account the half-life of a drug is important as it takes about 5 half-lives in order for a drug to be cleared from the system.

Warfarin, with a half-life of 20 – 60 hours should be held 4 – 5 days prior to PRP injection. In order to maintain the efficacy of the PRP injection, resumption of therapy may be initiated 2 hours after the procedure (26).

Heparin, with a half-life around 1.5 hours may be held 2 – 4 hours prior to injection and may be restarted one hour after. There should be no contraindications up to 5000 units twice daily (27).

Low molecular weight heparin therapeutic dosing should be held for longer than 24 hours while prophylactic dosing should be held for 10 – 12 hours prior to the procedure. Therapeutic dosing can be resumed after 24 hours post procedure and prophylactic dosing 6 – 8 hours after (28).

Fondaparinux is a synthetic factor Xa inhibitor with a half-life of 17 – 21 hours. The agent should be held between 36 – 42 hours prior to PRP injection and may be resumed 6 – 8 hours post procedure (29).

Rivaroxaban was the first direct factor Xa inhibitor and has a half-life of 5 – 9 hours. It should be held 22 – 26 hours prior to injection and may be restarted 4 – 6 hours post procedure (30).

Apixaban, also a direct factor Xa inhibitor, has a half-life of 9 – 14 hours and should be held 26 – 30 hours prior to injection. It may be restarted 4 – 6 hours post procedure (31).

Dabigatran is a direct thrombin inhibitor, with a half-life of 12 – 17 hours, should be held for 7 days and may be restarted 5 days post PRP therapy. Other direct thrombin inhibitors such as argatroban and bivalirudin are administered intravenously and are short-acting, so they may be discontinued relatively close to the initiation of the procedure (32).

P2Y12 receptor blockers are contraindicated only if there is concomitant dual antiplatelet therapy.

Clopidogrel, with a half-life of 7 – 8 hours, should be held for 7 days prior to injection.

Ticlopidine, with a half-life of 12 hours, should be held for 14 days prior to injection.

Prasugrel, with a half-life of about 7 hours, should be held for 7 – 10 days prior to injection.

Ticagrelor, with a half-life of 7 hours, should be held for 5 days prior to injection.

The P2Y12 receptor blockers may be restarted 6 hours after injection (33-36).

GP IIb/IIIa inhibitors such as Tirofiban, half-life of 2 hours, and Eptifibatide, half-life of 2.5 hours, should be held 4 – 8 hours prior to procedure (37,38).

Abciximab has a half-life up to 30 minutes however its platelet function effect can last up to 48 hours, so the drug should be held 24 – 48 hours prior to injection (39).

The GP IIb/IIIa inhibitors may be re-dosed 2 hours after injection.

Aspirin should be discontinued for about one week prior to PRP therapy as it irreversibly inhibits platelet cyclooxygenase. The platelet effects can be seen for the duration of the platelet life span, 8 – 9 days.

Comparatively, non-steroidal anti-inflammatory drugs (NSAIDs) reversibly inhibit platelet cyclooxygenase. Typically utilized in short-acting form, these NSAIDs should be held the day prior to the procedure; depending on the half-life of the specific agent (40).

## DISCUSSION

PRP therapy has been well-documented across many sub-specialties in medicine. Its applicability to promote healing and regeneration continues to drive its expansion in subacute and chronic conditions. In the expanding cohort of patients, many PRP therapy candidates will also be on antithrombotic therapy. While there is limited literature on the timing of PRP injections during antithrombotic therapy, understanding the pharmacokinetics and platelet effects can help guide discussion on the proper timing of discontinuation and resumption of a particular antithrombotic agent (41).

The efficacy of PRP has partly been attributed to multiple growth factors and bioactive proteins in platelets that stimulate wound and soft tissue healing (13,17). It is through the proliferation of differentiated cells, enhancement of collagen synthesis along with early angiogenesis and revascularization that PRP continues to show benefits of regeneration. These benefits are maintained in intact platelet cells. Platelet activation starts first with adhesion mediated through purinergic receptors on the platelet surface. Then, through a cascade system with mitochondrial hyperpolariza-

Table 2. Summary of Recommendations.

Antithrombotic Agent	Effect	Half-life	Discontinue prior to procedure	Resumption after procedure	Notes
Warfarin	Factors II, VII, IX, X Inhibitor	20-60 hours	4-5 days	2 hours	
Heparin	Indirect Thrombin, Factor Xa Inhibitor	1.5 hours	2-4 hours	1 hour	
LMWH	Indirect Thrombin, Factor Xa Inhibitor	4.5 hours	Prophylaxis: 10-12 hours Therapeutic: 24 hours	Prophylaxis: 6-8 hours Therapeutic: 24 hours	
Fondaparinux	Synthetic Factor Xa Inhibitor	17-21 hours	36-42 hours	6-8 hours	
Rivaroxaban	Factor Xa Inhibitor	5-9 hours	22-26 hours	4-5 hours	
Apixaban	Factor Xa Inhibitor	9-14 hours	26-30 hours	4-6 hours	
Dabigatran	Direct Thrombin Inhibitor	12-17 hours	7 days	5 days	
Clopidogrel	P2Y12 Receptor Blocker	7-8 hours	7 days	6 hours	
Ticlopidine	P2Y12 Receptor Blocker	12 hours	14 days	6 hours	
Prasugrel	P2Y12 Receptor Blocker	7 hours	7-10 days	6 hours	
Ticagrelor	P2Y12 Receptor Blocker	7 hours	5 days	6 hours	
Tirofiban	GP IIb/IIIa Inhibitor	2 hours	4-8 hours	2 hours	
Eptifibatide	GP IIb/IIIa inhibitor	2.5 hours	4-8 hours	2 hours	
Abciximab	GP IIb/IIIa Inhibitor	30 minutes	48 hours	2 hours	*platelet effect can last up to 48 hour
Aspirin	Irreversibly COX Inhibitor	2-30 hours	8-9 days	2 hours	*platelet life span is 8-9 days. Half-life is dose dependent
NSAIDs	Reversible COX Inhibitor	2-10 hours	24 hours	2 hours	*half-life is dose and agent dependent

tion, the platelet morphology undergoes changes. It is then that exocytosis of granules containing growth factors and proteins can be released allowing for PRP therapy's healing effects (21). Medications, particularly antithrombotic agents that modulate or affect the platelet surface membrane integrity can decrease the efficacy of PRP injections. Therefore there is a need to address an appropriate interval in which to discontinue and resume the antithrombotic agent. Once there is more research available it may be possible to categorize medications into high and low risk groups for their potential impairment of PRP based on their mechanism of action.

Taking into account the pharmacokinetics of the particular antithrombotic agent, the half-life can help guide the interval between discontinuation and resumption of the agent as it generally takes about 5

half-lives in order to be cleared from the system (Table 2). Medications such as aspirin exert an irreversible effect of platelets and will require termination prior to injection therapy of 8 – 9 days, the life-span of platelets. Some study protocols held NSAIDs for up to 2 weeks after the procedure while other studies prohibited the use of NSAIDs for 48 hours post procedure (42,43). The lack of uniformity often leads to NSAIDs being held for an undefined period of time in a study protocol with no clear answer on possible resumption (44-46). It has been reported in a single case report, a patient on chronic anti-platelet therapy that could not be held, had excellent results from a series of 3 PRP intra-articular knee injections (47). Regardless, the decision to hold or not hold antithrombotic medications needs to be seriously discussed with the risks and benefits thoroughly examined. So while the literature on the timing of PRP injec-

tion in patients on antithrombotic agents is lacking, it is evident that the efficacy of PRP therapy is dependent on the intact surface membrane.

While there are no other studies looking at the timing of PRP injections during antithrombotic therapy, we offer a backbone on which to base future studies. There is a clear need to examine the efficacy relationship between particular antithrombotic agents and clinical outcomes after PRP. Additionally, studies comparing various intervals are needed to more finely elucidate the adequate timing from discontinuation of the agent to administration of the PRP. With the field of regenerative medicine continuously expanding, the implications for clinicians on this issue will continue to expand.

## CONCLUSION

There is clearly a paucity of literature in regards to the safety, efficacy, and timing of PRP injections in patients with concomitant antithrombotic therapy. The importance of an intact platelet surface membrane allows for the appropriate release of the healing bio-proteins and growth factors granting PRP therapy its efficacy. Antithrombotic agents that affect the stability of platelets will have an effect on PRP efficacy and must be discontinued at an appropriate time frame prior to injection therapy. With future research, the establishment of clinical practice guidelines concerning PRP and antithrombotic therapy can help structure safe and efficacious means in which to promote healing and regeneration in a growing patient population.

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