Arthrex Autologous Conditioned Plasma-Double Syringe System

Introduction

Arthrex has developed a new product designed to extract platelet concentrate solution from a patient's own peripheral blood, which will enable the surgeon to apply biologic factors directly at the point of care in soft tissues. A specially designed and patented double syringe and the elimination of a second centrifugation step make the Arthrex Autologous Conditioned Plasma Double Syringe (ACP-DS) system easy to use.

Growth Factors (GFs) in Tissue Healing

Table 1 below highlights the prominent growth factors (GFs) involved in tissue healing. Studies over the past 10-15 years have shown the utility of these individual GFs, either produced synthetically or obtained from another source. Since ACP and other platelet rich plasma (PRP) solutions are a combination of biologically relevant GFs concentrated from the patient's own blood, they are an attractive option for treatment and are being heavily studied for clinical use.

Factor	Name	Origin	Effects
IGF-1	Insulin-like growth factor	Activated platelets	Stimulates osteoblast proliferation & differentiation
EGF	Epidermal growth factor	Activated platelets	Stimulates epidermal cell proliferation & differentiation, angiogenesis
VEGF	Vascular endothelial growth factor	Leukocytes	Angiogenesis, osteoblast chemoattractant
PDGF	Platelet-derived growth factor	Activated platelets	Mitogenesis of mesenchymal stem cells (MSCs)
TGF-β	Transforming growth factor-beta	Activated platelets	Stimulation of DNA synthesis

Table 1 – GFs important to healing of soft and hard tissues

When injury occurs, blood immediately rushes to the site and comes in contact with damaged collagen. This indicates the start of the wound healing process. Blood contact with collagen stimulates platelets within the blood to degranulate and release GFs such as PDGF, VEGF, and fibroblast growth factor (FGF), resulting in hematoma or clot formation. PDGF activates the appearance of neutrophils and macrophages within the first hour of injury to start clearing the wound site. PDGF, TGF-β, VEGF, and EGF activate fibroblasts to appear at the wound site and start the production of type III collagen to replace the damaged tissue. After 7-10 days, type I collagen normally found in tissue replaces the type III collagen, and wound healing proceeds to completely replace all intermediate tissues, normally within 21-28 days post-injury. As shown here, platelet concentrate products have the potential to augment soft tissue healing by concentrating GFs all at once in one location and possibly accelerating the normal wound healing process.

Production of ACP-DS Solution

Figure 1 illustrates the ACP-DS process. In step 1), 1 mL of anticoagulant citrate dextrose solution A (ACD-A) is drawn into the larger 10 mL syringe. ACD-A is a mixture of citric acid, sodium citrate, and dextrose which acts as an anticoagulant by binding free calcium in the blood. In step 2), 9 mL of the patient's peripheral blood is drawn into the larger syringe. In step 3), the entire syringe containing the whole blood is centrifuged at 1500 rpm for 5 minutes**.** This separates red blood cells (RBCs) from the platelet-containing plasma solution, but does not separate what is within the plasma further. In step 4), 3 mL of the platelet concentrate solution is carefully drawn into the smaller syringe, with care taken to not draw up any RBCs into the smaller syringe. In step 5), the smaller syringe is unscrewed from within the larger syringe. Finally in step 6), the ACP is ready to use at the point of care. What makes this system so attractive is the lack of a second centrifugation step, while still having a platelet concentrate solution in an easily removable syringe for application.

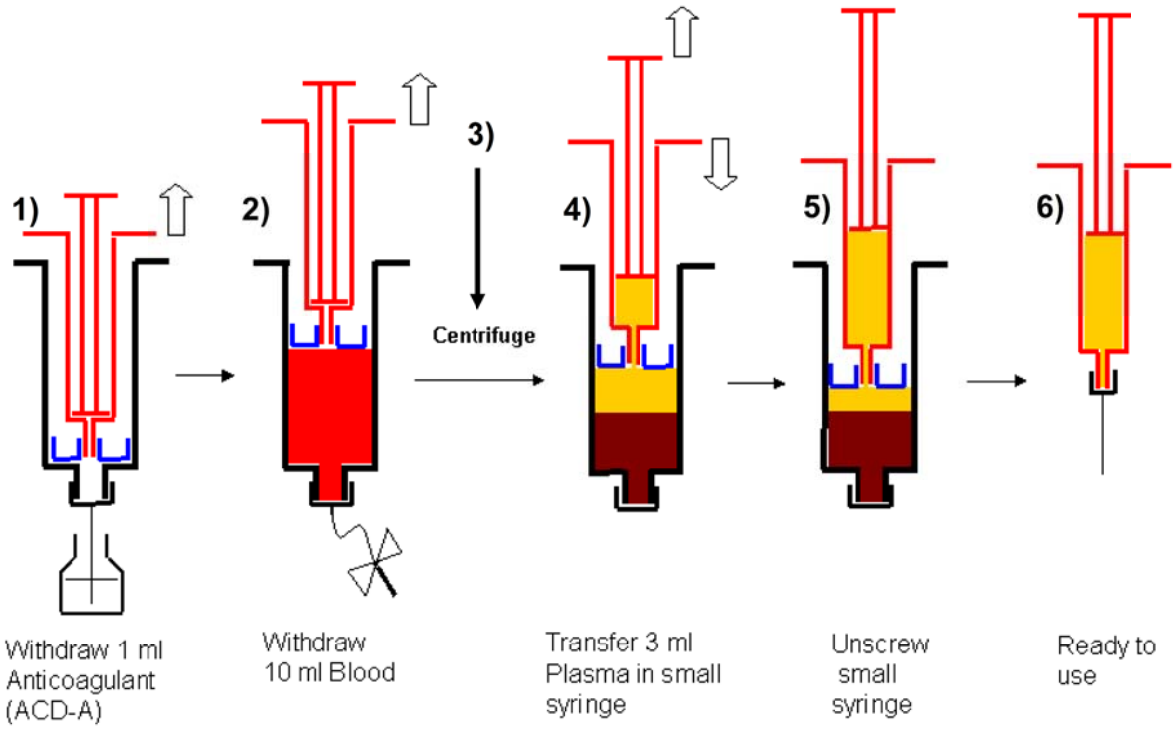

Figure 1 – Steps in production of ACP using double syringe system

Studies with ACP-DS Solution

An initial study compared platelet and GF levels in ACP solution vs. whole blood in humans [1]. ACP solutions contained concentrated platelets 2-3X above baseline levels in whole blood, while PDGF was 25X, EGF was 5X, VEGF was 10X, and TGF-β was ~5X above baseline levels. An important aspect of ACP is the elimination of leukocytes, as proteases and hydrolases within white blood cells can degrade ACP [2]. This is confirmed in the same study.

A human clinical study performed in Bonn and Hamburg, Germany used ACP clinically for healing of cartilage lesions [3]. Doctors administered intra-articular doses of ACP into grade II-IV cartilage lesions once a week for 6 weeks. This led to a 54-60% improvement in WOMAC pain, physical activity, and stiffness scores 4-6 months after the first administration of ACP.

Table 2 below highlights upcoming studies involving ACP in both animals and humans.

Type of Study	Location	Indication
Animal	Italy	Sheep osteoarthritic (OA) injuries
	Germany	Rat tendon healing
	Germany	Minipig primary ACL repair
	United States	Equine suspensory tendon
Clinical	Germany	OA injuries
	South Africa	Lateral ligament sprains
	Italy	OA injuries using MRI imaging
	*Canada	Acute and chronic Achilles tendon repair

Notes:
* - ACP was recently approved for use in humans in Canada

Table 2 – List of upcoming studies involving ACP

Comparison to Other PRP Products

Table 3 shows a comparison of various platelet concentrate products on the market. Most of the systems mentioned in the chart below have been used clinically in humans for successful outcomes in plastic and cosmetic surgery [4], dental procedures [5], and orthopedic procedures in the elbow [6]. Platelet concentrate products have also been combined with biomaterials such as hydroxyapatite [7] or gelatin [8].

Since the formation of platelet concentrate can depend on patient and processing variables that could interact with each other, there is no real range for platelet concentration over baseline. Therefore, each individual patient may require a different concentration for treatment to be effective [9]. Even with these caveats, a concentration of $1x10^6$ platelets/μL or greater and 3-5X platelet concentration over baseline [10] has been recommended for a platelet concentrate solution to be effective in healing. These values have come from the study of various platelet concentration products and procedures.

Others have suggested a concentration of $3x10^5$ platelets/μL and 2-3X platelet concentration over baseline has the potential to be effective in healing [9, 11]. A group based in Spain has developed autologous plasma rich in growth factors (PRGF), which has a 3X concentration increase in platelets over baseline [12]. This technology is very similar to ACP due to its utilization of a single spin technique, similar platelet

concentration, and elimination of leukocytes. This group has shown the clinical utility of PRGF in arthroscopic cartilage avulsion repair [13], where the patient was able to return to athletic activity 18 weeks after surgery. Using PRGF in Achilles tendon repair in 6 athletes resulted in significant drops in the functional recovery times for walking, running, and training compared to control repairs [12]. PRGF was also found to have a positive effect on healing in ACL arthroscopic procedures [14]. *In vitro*, human tenocytes cultured with PRGF have a significant increase in proliferation compared to control and platelet poor plasma (PPP) cultures [15]. There were also significant increases in PDGF, TGF-β, and VEGF levels in PRGF cultures compared to PPP cultures.

Device Name	Platelet Increase	% Platelet Recovery	PDGF Increase	VEGF Increase	TGF-β Increase	EGF Increase
Arthrex ACP	***2-3X***	***75***	***10-25X***	***2-3X***	***3-4X***	***4-6X***
[1]Biomet GPS™	8X	85	5.1X	6.2X	3.6X	3.9X
[2]Harvest® SmartPrep2 BMAC™	4.4X	72	4.4X	4.4X	4.4X	4.4X
[3]Depuy Symphony II	4X	72	4-5X	2-3X	3-6X	4-6X
[4]Medtronic Magellan™	5.1X	70	6-10X	3-6X	4-6X	8-10X
[5]Cascade Fibrinet	4-5X	60-70	5-10X	5-10X	5-10X	5-10X
[6]Cobe Cardiovascular Angel	4.3X	76	N/A	N/A	N/A	N/A
[6]PPAI Secquire	1.6X	31	N/A	N/A	N/A	N/A
[6]Emcyte GenesisCS	10X	68	N/A	N/A	N/A	N/A

Notes:
1. GPS – From Eppley *et al*, Plast Reconstr Surg, 114: 1502, 2004 and Biomet website
2. SmartPrep2 – From Harvest Technologies brochure
3. Symphony II – From Depuy White Paper
4. Magellan – From Medtronic brochure
5. Fibrinet – From Cascade Medical brochure, presentation, and White Papers
6. Angel, Secquire, and GenesisCS – From http://www.perfusion.com/perfusion/prpdevicesummary.asp

N/A. Data not available from vendor

Table 3 – Comparison of major platelet concentrate systems available

Another group out of Spain compared two PRP systems, one with a double spin vs. single spin centrifugation technique [16]. Both techniques resulted in similar platelet concentrations (2-3X) after the first spin. Even though the double spin samples produced a platelet concentration of 3.52X - not much higher than the single spin samples - the values had a larger range, and much more variability, than those obtained with a single spin. Transmission electron microscopy (TEM) images confirmed that neither system damaged or activated platelets, although some platelet activation was evident in the double spin samples.

Other studies have shown that solutions with 2-3X platelet concentration can lead to an increase in bone-implant contact after 4 weeks when delivered into titanium screw

surgical sites *in vivo* [17], as well as an increase in proliferation of human osteoblasts and gingival fibroblasts *in vitro* [18]. There is sufficient evidence that a 2-3X platelet concentration over baseline has the potential to be effective in healing.

Use of PRP Products in Veterinary Applications

As shown above in Table 2, ACP studies are being conducted in animal models. In general, PRP systems have been used clinically in veterinary applications, mostly in horses and dogs. Application of PRP has been shown to return horses with midbody suspensory ligament desmitis (MSD) back to racing after 32 weeks, and they were able to make as many starts as comparison horses [19]. PRP has also been shown to increase expression of decorin and other associated tendon matrix molecules, while not increasing catabolic factors such as MMP13 in equine tendon explant cultures [20, 21].

ACP can be used successfully to treat soft tissue injuries in animals by concentrating platelets in autologous blood. These platelets are shown to release growth factors important in healing.

References

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