Arthrex ACP™ Double Syringe System

Autologous Conditioned Plasma
Biologics has a solid history in Europe and some use in North America

- Now gaining in popularity for orthopedic applications
- Coining of the phrase “Regenerative Medicine”

Why?

- Increasing older population wants to maintain active lifestyle
- We treat areas with limited blood supply and slow cell turnover
- Greater demands on surgeons to produce more rapid return to sport
Serious challenges for use of biologics in orthopedic applications

A system must:
- Be affordable
- Cannot add significant time to the procedure
- Be easy to use

Corporate and Scientific Challenges
- Regulatory control
- Cost and time for development
- Quantifying results
Our Answer - ACP

- **Autologous Conditioned Plasma**
- Platelet concentrate for use in orthopaedic applications
- Increased concentration of platelets and growth factors which are associated with the healing process
What Exactly Is ACP?

- An easy to use system that concentrates platelets and growth factors within a plasma layer separate from red and white blood cells.
- Growth factors and other molecules within the plasma layer may modulate healing.
What Does ACP Look Like?

- Easy system to use
- Minimal additional capital equipment
- Additional procedure time of ~5-10 minutes
What Do Other Systems Look Like?

- Blood + anticoagulant
- 1st centrifugation
  - RBC
- Plasma
- 2nd centrifugation
  - PPP
  - PRP
  - RBC

- Complicated systems that require rep support
- Expensive capital and expensive kits
- Additional procedure time (15 - 30 minutes)
FDA Clearance

Indications for Use Form

Indications for Use

1) Indications for Use Form

510(k) Number: RN074009
Device Name: Arterian Double Synergy (ACG) System

This Double Synergy (ACG) System is used to facilitate the safe and rapid preparation of autologous platelet-rich-plasma (PRP) from a small sample of blood at the patient's point of care.

The PRP can be mixed with autograft and all bone prior to application to an orthopedic surgical site as deemed necessary by the clinical use requirements.

Prescription Use: AND/OR

The symptoms of the disease for which the device is intended are as follows: [List of symptoms here.]

Concomitant use of this device with other drugs or devices is not recommended without prior consultation with a medical professional.

Date: December 30, 2008

Decree, OCTOT

G75, 5030, 03

510(k) Number RN074009

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510(k) Number RN074009
Using ACP in Medical Practice

Syringe, ACD-A, and cap

Withdraw blood + mix with ACD-A

ACP ready to use

Centrifuge 1500 rpm for 5 min

Transfer plasma into smaller syringe and unscrew
Using ACP in the OR

Syringe, ACD-A, cap, and sterile bucket

ACP is transferred into sterile basin on sterile field. A sterile 5 cc syringe is used to recover ACP and use at the point of care.

Scrub nurse withdraws blood + mixes with ACD-A

Transfer plasma into smaller syringe and unscrew

Scrub nurse places syringe into bucket and passes closed bucket to circulating nurse

Circulating nurse opens cap and scrub nurse removes sterile syringe

Centrifuge 1500 rpm for 5 min
ACP platelet concentration
PRP concentration is patient-specific

- Pietrzak and Eppley, 2005; Weibrich *et al.*, 2001;
- Anitua *et al.*, 2004

- Dependent on injury, patient condition, processing variables
  (single vs. double spin, PRP volume, etc.)

- **Not necessary to have high concentration for effective healing**

- **Higher GF concentrations can be detrimental to healing**
Anitua’s definition of platelet concentration

- Whole blood baseline – \( 1.5 - 2 \times 10^5 \) platelets / \( \mu L \)
- Minimum \( 3 \times 10^5 \) platelets / \( \mu L \) – 2X PRP

2 - 3X ACP concentration modulates healing

- Other systems use similar concentrations
  - Plasma rich in growth factors (PRGF) – Spain
  - Clinaseal centrifuge - US
  - Nahita centrifuge - Spain
Marx’s definition of PRP concentration

- Whole blood baseline – $1.5 - 2 \times 10^5$ platelets / $\mu$L

- Minimum $1 \times 10^6$ platelets / $\mu$L - 5X PRP
The science of ACP
Healing Cascade

- a – Hematoma with platelet activation
- b – Invasion of cells and proliferation of paratenon
- c – Vascular and neuronal ingrowth
- d – Loose collagenous callus formation
- e – Mechanical stimulation
- f – Maturation and remodeling

Taken from Aspenberg, Int Orthop 2007; 31(6): 783-9
Most systems concentrate RBCs and WBCs – why this is bad


  - Activated WBCs release MMPs that degrade matrix and reactive oxygen species that destroy anything close by - can lead to inflammation


  - Lysed RBCs release free radicals, similar to WBCs, that destroy anything close by – good for bacteria, not good for platelets

Why is this resultant PRP RED?
What Are Platelets?

- Fragments of cells derived from megakaryocytes in bone marrow that live between 5-9 days
  - They do not contain a nucleus
  - Contain growth factors and other molecules to modulate healing and hemostasis
  - Platelets release growth factor-containing α-granules into plasma
Platelet Activation

- Releases growth factors and other cytokines from α-granules
  - Calcium chloride or any other calcium salt
  - Thrombin
- Centrifugation activates platelets, but to much smaller extent
All PRP systems require the addition of an anticoagulant (ACD-A)

- These additives drive down the pH and dilute the end product
- Why is this a problem?
- Possible solution to add sodium bicarbonate

When to use or not to use?
- <30 minutes - no need
- >30 minutes - use ACD-A, will stay for 4 hours
Growth Factors

- Promote collagen formation
- Stimulate angiogenesis
- Modulate matrix formation
### Growth Factors in ACP

<table>
<thead>
<tr>
<th>Growth Factor</th>
<th>Phase in Which Most Active</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>Inflammation, proliferation</td>
<td>Promotes proliferation and migration of cells, stimulates matrix production</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Inflammation</td>
<td>Regulates cell migration, proteinase expression, fibronectin binding interactions, termination of cell proliferation, stimulation of collagen production</td>
</tr>
<tr>
<td>VEGF</td>
<td>Proliferation, remodeling</td>
<td>Promotes angiogenesis</td>
</tr>
<tr>
<td>PDGF</td>
<td>Proliferation, remodeling</td>
<td>Regulates protein and DNA synthesis at injury site, regulates expression of other growth factors</td>
</tr>
<tr>
<td>bFGF</td>
<td>Proliferation, remodeling</td>
<td>Promotes cellular migration, angiogenesis</td>
</tr>
<tr>
<td>EGF</td>
<td>Proliferation, remodeling</td>
<td>Stimulates proliferation and differentiation of epidermal cells, stimulates angiogenesis</td>
</tr>
</tbody>
</table>

How does ACP compare?
## Comparison of ACP vs. PRP

<table>
<thead>
<tr>
<th></th>
<th>Arthrex ACP</th>
<th>Other PRP Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume drawn</strong></td>
<td>10 mL</td>
<td>60-120 mL</td>
</tr>
<tr>
<td><strong>Is anticoagulant (ACD-A) necessary?</strong></td>
<td>No: if ACP is used within 30 minutes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Centrifugation steps</strong></td>
<td>1X</td>
<td>1-2X</td>
</tr>
<tr>
<td><strong>Centrifugation time</strong></td>
<td>5 min</td>
<td>15-30 min</td>
</tr>
<tr>
<td><strong>Does it concentrate red and white blood cells?</strong></td>
<td>No: &lt; whole blood levels</td>
<td>Yes: &gt;= whole blood levels</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>$150</td>
<td>$350-900</td>
</tr>
<tr>
<td><strong>Harvest volume</strong></td>
<td>2-5 mL</td>
<td>6-10 mL</td>
</tr>
<tr>
<td><strong>Growth Factor Concentration</strong></td>
<td>~5X -25X</td>
<td>~5-10X</td>
</tr>
<tr>
<td><strong>Mode of action</strong></td>
<td>Growth factors released by platelets, mixed with proteins and electrolytes in plasma</td>
<td>Growth factors released by platelets</td>
</tr>
<tr>
<td><strong>Platelet concentration/μL</strong></td>
<td>300,000 – 500,000</td>
<td>500,000 – 1,000,000</td>
</tr>
</tbody>
</table>
## Comparison to Other Systems

<table>
<thead>
<tr>
<th>Device Name</th>
<th>IGF-1 Increase</th>
<th>TGF-β Increase</th>
<th>VEGF Increase</th>
<th>PDGF-AB Increase</th>
<th>PDGF-BB Increase</th>
<th>EGF Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthrex ACP</td>
<td>1X</td>
<td>4X</td>
<td>11X</td>
<td>25X</td>
<td>6X</td>
<td>5X</td>
</tr>
<tr>
<td>Biomet GPS™</td>
<td>1X</td>
<td>3.6X</td>
<td>6.2X</td>
<td>N/A</td>
<td>5.1X</td>
<td>3.9X</td>
</tr>
<tr>
<td>Harvest® SmartPrep2™</td>
<td>N/A</td>
<td>4.4X</td>
<td>4.4X</td>
<td>4.4X</td>
<td>N/A</td>
<td>4.4X</td>
</tr>
<tr>
<td>DePuy Symphony II</td>
<td>N/A</td>
<td>3-6X</td>
<td>2-3X</td>
<td>4-5X</td>
<td>N/A</td>
<td>4-6X</td>
</tr>
<tr>
<td>Medtronic Magellan™</td>
<td>N/A</td>
<td>4-6X</td>
<td>3-6X</td>
<td>6-10X</td>
<td>N/A</td>
<td>8-10X</td>
</tr>
<tr>
<td>Cascade Fibrinet</td>
<td>5-10X*</td>
<td>5-10X*</td>
<td>5-10X*</td>
<td>N/A</td>
<td>5-10X*</td>
<td>5-10X*</td>
</tr>
</tbody>
</table>

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

* Fibrinet growth factor levels monitored over a 7 day period - all others were baseline
Our Competition’s Story

- What are they going to say?
  - Lower platelet concentration levels
  - The product from ACP is PPP
    - Not true!
  - Delivery method: To clot or not?
    - Using thrombin = immediate release of GF
    - Kit design (Micromedics’ FibriJet parts)
  - Where are the studies?
Key Features and Benefits

- Affordable
- Easy to use and short procedure time
- Requires less blood than conventional PRP systems
- Anticoagulant not necessary in all cases
  - Less dilution
  - More natural pH
- Reduced level of RBC and WBCs vs. baseline
- Similar GF concentration to other systems
Gelling agent powder – 4800-5000 IUs (International Units)
Gelling agent liquid – 5 mL of 10% solution
Mix 1000 IUs of gelling agent powder with 1 mL of gelling agent liquid (1000 IUs/mL ratio of powder/liquid)
- 5000 IUs of powder to 5 mL of liquid
- 10000 IUs of powder to 10 mL of liquid
- This creates the gelling agent solution
Mix 1 mL of PRP with 0.1 mL of gelling agent solution to create a clot/gel (10:1 ratio of PRP/gelling agent solution)
- Can be prepared with syringe mixer system or in sterile cup
- If clot prepared in sterile cup, transfer clot to dry sterile cup after forming to make it more solid
Two Program Options

If the capital equipment is placed and disposables $200
- Minimum purchase $8,000 in disposables over 12 months
- Disposables convert to $150 after minimum purchase is met

If the capital equipment is placed and disposables $150
- Minimum purchase $8,000 in disposables over 12 months
- Reduced commissions until minimum purchase is met

Capital Equipment Cost $7K

Distributorship may purchase capital under conventional Arthrex capital agreement
Coding / Reimbursement
Arthrex recommends that you check with your insurance provider or payer for reimbursement.
ACP Procedure Pearls
ACP Pearls

- Prior to the case
  - Prime the syringe
  - Make sure the inner syringe is screwed in tightly
- Phlebotomy
  - Blood draw should be performed with a 18-20G butterfly needle
  - Draw blood SLOWLY (1cc / 2 seconds)
- Separate ACP as soon as possible after blood draw
- If using within 30 min of blood draw, do not use ACD-A
- ACP with ACD-A can stay up to 4 hours at room temperature before use, but use is recommended within 2 hours
CENTRIFUGE
UNPACKING & SETUP
EVERY CENTRIFUGE SHOULD HAVE A SHIPPING INSERT LIKE THIS PACKED WITH IT, USUALLY INSIDE THE CENTRIFUGE CHAMBER
INCLUDED WITH ROTOFIX 32A

• SHORT T-HANDLE (E613)
• GREASE FOR ROTOR (4051)
• 13 AMP POWER CABLE (6083)
• PLASTIC EMERGANCY OPEN PIN (E2914)
• TWO SPARE FUSES (E914)
• OPERSTOR’S MANUAL
• SHIPPING INSERT

* Numbers in ( ) are part numbers
REMOVE AND SAVE THE TRANSPORT BOLTS BY UNSCREWING THEM WITH THE T-HANDLE TOOL INCLUDED IN THE ACCESSORY PACK
WHEN INSTALLING THE ROTOR, APPLY A THIN COATING OF HETTICH GREASE ON THE MOTOR SHAFT TO PREVENT ROTOR FROM BINDING TO THE SHAFT OVER TIME.
LINE UP THE SLOTS IN THE ROTOR WITH THE CORRESPONDING DRIVING TAPER ON THE MOTOR
THESE SLOTS REFERENCE THE SLOTS ON THE UNDERSIDE OF THE ROTOR
USE THE T-HANDLE TOOL PROVIDED IN THE ACCESSORY PACK TO TIGHTEN DON THE ROTOR
GREASE EACH TRUNNION AT INITIAL SET-UP...
... AND AT REGULAR INTERVALS. FREQUENCY IS DEPENDENT ON USAGE.
Bucket installation

• MAKE SURE TRUNNIONS ARE GREASED
• ALL FOUR BUCKETS MUST BE INSTALLED
PROGRAMMING THE ROTOFIX 32A

• **USE THE UP AND DOWN BUTTONS TO SET THE TIME AND SPEED**

• **TIME IS IN MINUTES**

• **SPEED IS ___*100**
  
  *(EXAMPLE: 15=1500RPM)*

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![Image of RotoFix 32A centrifuge](image_url)
SUMMARY SET UP STEPS

• UNPACK PACKAGE CENTRIFUGE
• PLUG IN AND TURN ON
• OPEN LID AND REMOVE SHIPPING INSERT
• REMOVE AND SAVE TRANSPORT BOLTS AND RED SPACERS
• GREASE MOTOR SHAFT AND INSTALL ROTOR
• GREASE TRUNNIONS AND INSTALL BUCKETS
• BEGIN CENTRIFUGATION
COMMON ERRORS

• ERROR CODE -1- (tachometer error)
• This is explained in the manual on page 28

Clearing procedure

• Wait for rotor stand still (120 seconds after rotor stops)
• Turn the power off and wait 10 seconds
• Turn the power on
• Check to make sure rotor is installed properly before spinning
COMMON ERRORS

• ERROR CODE -2- (mains interrupt)
• This is explained in the manual on page 28

Clearing procedure

• Wait for rotor stand still
• Open the lid
• Press the start button
COMMON ERRORS

• ERROR CODE -d- (lid lock error)
  • This is explained in the manual on page 28

Clearing procedure

• Wait for rotor stand still
• Turn off the power and wait 10 seconds
• Turn on the power
COMMON ERRORS

- ERROR CODE -F- (tachometer error)
- This is explained in the manual on page 28

Clearing procedure

- Wait for rotor stand still
- Turn off power wait 10 seconds
- Turn on power
- Check to make sure rotor is installed properly before spinning