Platelet Rich Plasma (PRP) Gel for Wounds on Persons with SCI

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No Commercial support was received for this activity.
Laurie M Rappl, PT, DPT, CWS is an employee of Cytomedix, Inc, Gaithersburg, MD.
Objectives

• Cite 3 physiological differences between denervated and enervated tissues that impair healing in denervated tissues

• Describe the unique components of PRP gel that address the biological needs of recalcitrant wounds regardless of the phase of wound healing

• Describe the benefits that might be achieved with comprehensive wound management and PRP, based on case series evidence
Physiological changes in tissues denervated by spinal cord injury tissues and possible effects on wound healing

Physiological deficits of SCI

- Abnormal vascular reactions
- Decrease in density of adrenergic receptors
- Decreased blood flow
- Decreased blood pressure
- Decreased blood supply
- Decreased PO2
- Collagen catabolism
  - Increase in urinary excretion of glycosaminoglycans (GAG’s)
- Decreased amino acid concentration
- Decrease in enzymes of biosynthesis
- Decrease in proportion of Type I to Type III collagen
- Decreased fibronectin, a glycoprotein for fibroblast activity
Physiology of SCI causes impairment at **every step** of the wound healing process.
Platelet rich plasma

• Release all growth factors, cytokines, chemokines
• PRP products differ according to how they are made
• The Buffy Coat dilemma
• Goal is no WBC’s, no RBC’s
• Low concentration is important
PRP In the Literature
RCT's, Meta-analyses, Reviews


Overlapping Activity of Many Cells From Skin and Blood Contribute to the Phases of Wound Healing

- **Days**
  - 7
  - 14
  - 21

- **Phases**
  - Clotting
  - Inflammation
  - Proliferation
  - Remodeling

- **Cells**
  - Platelets
  - Neutrophils
  - Macrophages
  - Lymphocytes
  - Fibroblasts
  - Endo-epithelium
  - Blood vessel-Keratinocyte
  - Collagen

- **Processes**
  - Re-modeling cross linking
  - Deposition and remodeling
Platelets Degranulate

Centrifugation + thrombin = degranulation

- Platelets
  - Growth Factors
  - Cytokines
  - Chemokines

- Cell growth and migration
- Formation of new tissue
Platelets
Platelets Release A Diversity of Molecules

- **Growth Factors**
  - Growth of fibroblasts and keratinocytes

- **Cytokines**
  - Induce keratinocytes to produce proteases, chemokines, more cytokines

- **Chemokines**
  - Recruit neutrophil, endothelial cell, fibroblast

- **Thrombocidins**
  - Kill bacteria

- **Thromboxanes**
  - Increase platelet aggregation, increase blood pressure, vasoconstriction

- **Serotonin**
  - Vasoconstriction

- **Clotting Factors**
  - Activation of thrombin to cleave fibrinogen to fibrin (clot glue)

- **Fibrinogen**
  - Undergoes cleavage to fibrin (clot glue)

- **Thrombin**
  - Cleavage of fibrinogen, activation of additional platelets and activation of mast cells

- **Proteases**
  - Begin to clean up surrounding tissue

- **Protease Inhibitors**
  - Inhibit destruction of clot
Overlapping Activity of Many Cells From Skin and Blood Contribute to the Phases of Wound Healing

- Days 7, 14, 21
- Clotting
- Inflammation
- Proliferation
- Re-modeling cross linking
- Collagen Deposition and remodeling
- Platelets
- Neutrophils
- Macrophages
- Lymphocytes
- Fibroblasts
- Endo-epithelium
- Blood vessel-Keratinocyte
- Blood vessel-Keratinocyte

Tensile Strength
PRP products differ: Centrifuges

Affects # and viability of platelets
Variabilities in centrifuges and PRP’s

• Rotor angle, radius
• Acceleration, speed, deceleration – 3k to >7k rpm’s
• Length of time of centrifugation – 1-45 minutes
• Number of spins
• Method of activation of platelets – thrombin, thrombin with calcium chloride, calcium chloride, baproxobin, freezing to lyse the cell membrane
• Ratio of blood to activation factor
Variabilities in PRP’s

- Post-centrifugation blood components used –
  - plasma
  - plasma + the buffy coat
  - plasma + buffy coat + top layer of red blood cells
- Additional components added to PRP – e.g. Vit C
- Inclusion or exclusion of WBC’s, RBC’s
- Injected vs topically applied
- Resulting concentration of platelets – \(1.3X – 16+X\)
Are all PRP’s alike? No.

Much of the reported variability in wound healing outcomes following the use of PRP likely is due to the diversity of devices, methods, and clinical strategies used to obtain and apply PRP derived products.

Arora, Ramanayake, Ren, & Romanos, 2009
Eppley, Woodell, & Higgins, 2004
Ficarelli, et al., 2008
Smith & Roukis, 2009

Studies not interchangeable.
“What was the method of making the PRP?”
Buffy coat dilemma

- Platelet-poor plasma
- Buffy coat (platelets and white blood cells)
- Red blood cells
Spin Determines Where Platelets Lie – and with whom

Long (>5 min)
Slow (<5000 rpm)

Pushes platelets into buffy coat with WBC’s and RBC’s
Spin Determines Where Platelets Lie – and with whom

Long (>5 min)
Slow (<5000 rpm)
Pulls platelets into buffy coat with WBC’s and RBC’s

Short (<5 min)
Fast spin (>5000 rpm)
80% of platelets in plasma, leaves leukocytes in buffy
What we know:
WBC’s and RBC’s Detrimental

WBC’s (Leukocytes)
- MMP’s
  - Degrade matrix
  - Reactive oxygen species

RBC’s (Erythrocytes)
- Free radicals
  - Inflammation
  - Tissue destruction

Eliminate WBC’s and RBC’s from PRP
What we know: Dose Response

Dose Response

Examples of Receptors with Demonstrated Bell-Shaped Dose Response:
- EGF
- FGF-2
- VEGF
- IL-8
- TGF-Beta
- MIP-1

More is Not Better

Increased Concentration →
Downregulation and Desensitization!
What we know: Lower Concentration is Important

Poor old platelet-poor-plasma (PPP) is very beneficial

- Plasma
  - Fibrin
  - Fibronectin Scaffold
  - Albumin
  - MMP Inhibitors

- Structure for cell migration

- Block neutrophil spread
- Block release of damaging free radicals
- Inhibit destructive protease activity
One method:
10-minute process, 1.3x PRP

1. Phlebotomy
   Small volume blood draw from patient the day of application

2. Separation
   Fast short centrifugation separates RBC’s and WBC’s from platelet rich plasma (PRP)

3. Processing
   PRP is processed and easily activated at the point of care using the Wound Dressing & Reagent Kits

4. Application
   Gel is applied topically in a thin contact layer to the wound bed and covered with a thin film and secondary dressing of choice
End product: Gold

No WBC’s or RBC’s
Platelet rich plasma

• Release all growth factors, cytokines, chemokines
• PRP products differ according to how they are made
• The Buffy Coat dilemma
• Goal is no WBC’s, no RBC’s
• Low concentration is important
To analyze the effects of autologous, low-concentration (1.3x) platelet rich plasma (PRP) gel on recalcitrant pressure ulcers and trauma wounds in patients with SCI to incite the wound healing process.
Design

- Non-randomized, prospective case series
- 18 sites – 10 LTAC’s, 2 outpatient wound care centers, 1 home health, 6 DME supplier to LTC and home health
Inclusion criteria

• Any open, cutaneous wound that the clinician determined was not progressing in healing
• Wounds that could have a majority clean wound bed just prior to application of the product
• Wounds without clinical signs and symptoms of active infection.
• Patient with spinal cord injury
Exclusion criteria

- Malignancy in the wound bed
- Current use of chemotherapy
Data gathered

- Patient age
- Previous wound duration
- Wound area $L \times W \times .7854$ (ellipse)
- Wound volume $(L \times W \times .7854) \times D$
- Undermining – measured at 3, 6, 9, 12:00, added together
- Sinus tracts/tunneling (ST/T) – length
Subjects

- 20 patients
- 20 wounds

- Mean Patient Age - 49.2 yrs. (27 - 75)
- Mean Previous Wound Duration – 79.4 wks (8 - 416)
## Wound Location and Depth

<table>
<thead>
<tr>
<th>Body Site</th>
<th>0 to &lt;0.5 cm</th>
<th>0.5 to &lt;1.0 cm</th>
<th>1.0 to &lt; 2.0 cm</th>
<th>2.0 to &lt; 8.5 cm</th>
<th>Total wounds per body site</th>
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</thead>
<tbody>
<tr>
<td>Ischial tuberosity</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Sacrum/Coccyx</td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Legs/Feet</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>Total per wound depth</strong></td>
<td>3 (2)</td>
<td>3 (2)</td>
<td>7 (6)</td>
<td>7 (5)</td>
<td><strong>20 (15)</strong></td>
</tr>
</tbody>
</table>

(# specified as “Full Thickness”)
Previous Wound Duration vs. 1.3x PRP Gel Treatment Time

![Bar graph showing the comparison between Previous Wound Duration and Topical PRP Treatment Time. The graph indicates a significant difference, with Previous Wound Duration at 79.4 weeks and Topical PRP Treatment at 3.4 weeks.]
Baseline Wound Data

- **Area** - avg. 25.6 cm² (0.2 – 151)
- **Volume** - avg. 53.4 cm³ (0.2 – 344)
- **Undermining** – avg. 7.0 cm (4.8 – 9.0)
- **ST/T** – avg. 5.0 cm (1.5 – 7.5)
Volume and Area Reductions
3.4 wks with 4 treatments

<table>
<thead>
<tr>
<th></th>
<th>% Reduction</th>
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<tbody>
<tr>
<td>Volume</td>
<td>56</td>
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<tr>
<td>Area</td>
<td>47.9</td>
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<tr>
<td>Undermining</td>
<td>31.4</td>
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<tr>
<td>Sinus tracts/tunnelling</td>
<td>26.1</td>
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</table>
Undermining Reductions
2.6 wks with 3.5 treatments

<table>
<thead>
<tr>
<th>Measure</th>
<th>Reduction</th>
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<tbody>
<tr>
<td>Volume</td>
<td>56%</td>
</tr>
<tr>
<td>Area</td>
<td>47.9%</td>
</tr>
<tr>
<td>Undermining</td>
<td>31.4%</td>
</tr>
<tr>
<td>Sinus tracts/tunnelling</td>
<td>26.1%</td>
</tr>
</tbody>
</table>

N=4
Sinus Tracts/ Tunneling Reductions
In 1.5 wks with 2.3 treatments

<table>
<thead>
<tr>
<th></th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>56</td>
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<tr>
<td>Area</td>
<td>47.9</td>
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<tr>
<td>Undermining</td>
<td>31.4</td>
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<td>Sinus tracts/</td>
<td>26.1</td>
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<tr>
<td>tunnelling</td>
<td>N=3</td>
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Responders:
% of subjects responding per segment

<table>
<thead>
<tr>
<th>Segment</th>
<th>Response</th>
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<tbody>
<tr>
<td>Volume</td>
<td>90%</td>
</tr>
<tr>
<td>Area</td>
<td>90%</td>
</tr>
<tr>
<td>Undermining</td>
<td>75%</td>
</tr>
<tr>
<td>Sinus tracts/tunnelling</td>
<td>100%</td>
</tr>
</tbody>
</table>
Right Ischial Pressure Ulcer

Arrows Indicate Extent of Undermining

L = 4.7 cm  
W = 4.2 cm  
D = 2.3 cm

Wound Duration: 2 yrs
Healed: 1 Month

Core Wound Measurements (CWM)

<table>
<thead>
<tr>
<th>Measurement Date</th>
<th>Area</th>
<th>Volume</th>
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<tr>
<td>3/11/2002</td>
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<tr>
<td>3/14/2002</td>
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<td>3/26/2002</td>
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<td>3/28/2002</td>
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<td></td>
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<tr>
<td>3/31/2002</td>
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<td></td>
</tr>
<tr>
<td>4/5/2002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5 PRP Treatments
Left Lateral Leg – SCI patient

Wound Duration: > 1 yr
Healed: 7 weeks

Core Wound Measurements (CWM)

7 PRP Treatments
97% volume reduction
Tendon covered
Left Ischium
>3 Months Duration

Baseline – Tunnel 4.7 cm

7 Days – Tunnel 2.5 cm
Conclusion

• 1.3x PRP Gel (autologous, non-concentrated, platelet rich plasma gel) appears to be an effective adjunct in the treatment of recalcitrant wounds in patients with SCI.
• Response was fast and robust.
• Denervated tissues are at a physiological disadvantage for healing.

• PRP’s vary depending on method of manufacture. Results cannot be carried from one study to another.

• Low concentration PRP without RBC’s or WBC’s seems to be beneficial to SCI pressure ulcers.
Platelet Rich Plasma (PRP) Gel for Wounds on Persons with SCI

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