Health Policy Advisory Committee on Technology

Technology Brief

Platelet-rich plasma for the treatment of knee osteoarthritis

August 2013
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For further information, contact the HealthPACT Secretariat at:

HealthPACT Secretariat
c/o Clinical Access and Redesign Unit, Health Service and Clinical Innovation Division
Department of Health, Queensland
Level 13, Block 7
Royal Brisbane Women’s Hospital, Herston Qld  4029
Postal Address: GPO Box 48, Brisbane Qld 4001
Email: HealthPACT@health.qld.gov.au  Telephone: +61 7 3646 9100

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This brief was commissioned by Queensland Health, in its role as the Secretariat of the Health Policy Advisory Committee on Technology (HealthPACT). The production of this brief was overseen by HealthPACT. HealthPACT comprises representatives from health departments in all States and Territories, the Australian and New Zealand governments and MSAC. It is a sub-committee of the Australian Health Ministers’ Advisory Council (AHMAC), reporting to AHMAC’s Hospitals Principal Committee (HPC). AHMAC supports HealthPACT through funding.

This brief was prepared by Linda Mundy from the HealthPACT Secretariat.
Platelet-rich plasma for the treatment of knee osteoarthritis: August 2013

Technology, Company and Licensing

Register ID WP169
Technology name Platelet-rich plasma
Patient indication For the treatment of patients with knee osteoarthritis

Description of the technology

Whole blood consists of a cellular component, red and white blood cells, suspended in the plasma liquid component. The majority of the cellular component consists of erythrocytes or red blood cells (RBC), at approximately 45 per cent of whole blood. The remaining cell fraction represents only one per cent of whole blood volume and may be divided into two cell types: platelets, an integral part of the clotting cascade; and leucocytes or white blood cells, a major component of the immune system (Figure 2). Plasma represents almost 55 per cent of the whole blood volume and contains, amongst others, a mix of proteins including growth factors, sugars, clotting factors and immunoglobulins (Figure 1).

Figure 1 Whole blood separated into 3 distinct layers following centrifugation: erythrocytes, the buffy coat containing platelets and leucocytes and the plasma fraction

Platelets are crucial for tissue repair and vascular remodelling. The first stage of normal wound healing, immediately following injury or insult, is inflammation, where activated platelets adhere to the site of injury releasing growth factors including:

- Growth factors
- Proteins
- Sugars
- Clotting factors
- Immunoglobulins

Figure 2 The components of whole blood and their function

Platelets play a key role in the repair process, contributing to the formation of a fibrin clot, which helps to stabilize the injured area and provide a matrix for tissue repair. The clotting cascade is initiated when platelets adhere to the site of injury, releasing growth factors that stimulate the activation of other cells and the production of extracellular matrix proteins.
- transforming growth factor (TGF-β): promotes formation of extracellular matrix and regulates bone cell metabolism;
- platelet-derived growth factor (PDGF): promotes cell replication, angiogenesis, epithelialisation and granulation tissue formation;
- basic fibroblast growth factor (bFGF): promotes proliferation of endothelial cells and fibroblasts and stimulation of angiogenesis;
- epidermal growth factor (EGF): promotes cell differentiation and stimulates re-epithelialisation, angiogenesis and collagenase activity;
- vascular endothelial growth factor: promotes angiogenesis; and
- connective tissue growth factor: promotes angiogenesis, vessel permeability, and stimulates mitogenesis for endothelial cells.\(^3,4\)

It is thought that an intra-articular injection of platelet-rich plasma (PRP) will deliver activated platelets that may reduce inflammation, provide pain relief, improve function and stimulate possible cartilage regeneration at the site of injury, in this case the worn cartilage area of the knee.\(^3\)

PRP can be prepared at point-of-care by a clinician, nurse or technician. Approximately 30-60mL of whole blood is removed from the patient and centrifuged. Different methods of centrifugation will affect the activation status and concentration of the platelets in the final PRP product. PRP is approximately 10 per cent of the whole blood volume, that is, when 60mLs of blood is drawn, a yield of 6mLs of PRP is expected.\(^4\) A 3-5 times baseline concentration of platelets is regarded as a therapeutic dose (baseline platelet concentration of 200 x 10\(^3\)/µL concentrated to 1,000 x 10\(^3\)/µL in PRP).\(^5\) Using a standard bench top centrifuge, a first spin is used to remove the RBC layer, with a second spin used to yield a more concentrated platelet layer. Using this method is likely to activate the platelets and reduce the yield slightly.\(^4\) Several one-step commercial PRP preparation systems are available on the market: the Magellan® (Arteriocyte Medical Systems, Inc.), the Cascade® (Musculoskeletal Transplant Foundation formerly Cascade Medical Enterprises), the GPS® III (Biomet Biologics), the Angel® (Cytomedix, Inc.) and the SmartPReP® 2 Platelet Concentrate (Terumo Australia Pty Ltd) systems. Although individual characteristics of these systems vary, they all use similar principles and equipment to obtain PRP preparations. Companies such as Biomet market small bench top centrifuges designed to fit specialised PRP centrifugation tubes that have a slanted reservoir to assist in the recovery of platelets (Figure 3).\(^6\)
The Magellan system uses a fully enclosed separation chamber that maintains sterility throughout and uses a dual spin system. A soft spin separates and draws off the RBCs. A hard spin separates and draws off the buffy coat layer from the plasma without activating the platelets prematurely (Figure 4) (personal communication Cellplex Pty Ltd).

As PRP is generally prepared at point-of-care, once isolated it is injected immediately into the joint under aseptic conditions, usually under ultrasound guidance. Local anaesthetic is not usually applied as the effect on platelet activation is unclear. Some practitioners advocate activating the platelets prior to injection with the use of exogenous agents such as calcium chloride, however most protocols rely on the platelets being activated endogenously by the patient’s tissues. Patients may be advised to avoid the use of non-steroidal anti-inflammatory drugs (NSAIDs) 2-weeks pre- and 2-weeks post-PRP procedure.
so as not to inhibit the inflammatory response of the growth factors. However, there is little clinical evidence that taking NSAIDs has a negative effect on PRP therapy. Patients with platelet dysfunction conditions and thrombocytopenia are contraindicated for PRP therapy.

The performance characteristics of PRP preparation systems have been reported to vary. Castillo et al (2011) compared and evaluated the performance of the three main PRP systems. PRP preparations were isolated using each system from whole blood taken from the same five patients at the same time, following the protocol stipulated by each of the companies (Table 1). Final PRP preparations were analysed for growth factor and fibrinogen concentrations, in addition to platelet, leucocyte and RBC counts.

<table>
<thead>
<tr>
<th>System</th>
<th>Whole blood volume (mL)</th>
<th>Centrifuge force, g</th>
<th>Centrifuge time, mins</th>
<th>Final volume PRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cascade</td>
<td>18</td>
<td>1100</td>
<td>6</td>
<td>7.5</td>
</tr>
<tr>
<td>GPS III</td>
<td>55</td>
<td>1100</td>
<td>15</td>
<td>6.0</td>
</tr>
<tr>
<td>Magellan</td>
<td>26</td>
<td>1200</td>
<td>17</td>
<td>6.0</td>
</tr>
</tbody>
</table>

The mean factor concentrations using each PRP system are summarised in Table 2. The overall baseline concentration of platelets was $274 \times 10^3$/mL. Platelet concentrations in the PRP preparations from all systems were significantly higher than baseline. The mean platelet concentration in the PRP preparations using the different systems varied, however there was no significant difference between the platelet concentrations obtained with the three systems. Although platelet concentrations obtained using the Magellen® and GPS® III systems appeared much higher than those obtained with the Cascade®, the standard deviation was high for both of these systems indicating a great deal of variation. There was wide variability in the factor increase in platelet concentration between the three systems. Platelet capture efficiency was significantly higher using the Cascade® and Magellan® systems compared to the GPS® III system. PRP prepared by the GPS® III also had a significantly higher leucocyte concentration compared to the other two systems, which may contribute to therapeutic differences if leucocytes are contributing to the tissue repair process via anti-microbial activity and the production of VEGF. Both PDGF αβ and ββ were significantly higher in PRP prepared by the Magallen® compared to the Cascade® but were not significantly different to those obtained with the GPS® III. VEGF PRP levels were significantly higher when the GPS® III system was compared to the Cascade® but there was no difference between the GPS® III and Magellan® systems. There appears to be considerable variation between the systems and the lack of standardisation in PRP dosing regimens may make it difficult to compare outcomes of studies in the evaluation of clinical effectiveness.
Table 2  Mean factor concentrations using three main PRP systems

<table>
<thead>
<tr>
<th></th>
<th>Cascade®</th>
<th>GPS® III</th>
<th>Magellan®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet concentration x 10³/µL</td>
<td>443.8 ± 24.7</td>
<td>566.2 ± 292.6</td>
<td>780.2 ± 246.5</td>
</tr>
<tr>
<td>Factor increase in platelet conc</td>
<td>x 1.62 ± 0.1</td>
<td>x 2.07 ± 1.1</td>
<td>x 2.8 ± 0.8</td>
</tr>
<tr>
<td>Platelet capture efficiency (%)</td>
<td>67.6 ± 4.1</td>
<td>22.6 ± 11.8</td>
<td>65.5 ± 19.6</td>
</tr>
<tr>
<td>WBC x 10³/µL</td>
<td>1.1 ± 0.2</td>
<td>34.4 ± 13.6</td>
<td>11.0 ± 8.2</td>
</tr>
<tr>
<td>RBC x 10⁶/µL</td>
<td>0.1 ± 0.1</td>
<td>1.5 ± 1.7</td>
<td>0.5 ± 0.3</td>
</tr>
<tr>
<td>Fibrinogen mg/dL</td>
<td>283.8 ± 34.2</td>
<td>286.0 ± 42.7</td>
<td>277.4 ± 30.5</td>
</tr>
<tr>
<td>PDGF-αβ ng/mL</td>
<td>9.7 ± 3.6</td>
<td>18.7 ± 12.8</td>
<td>34.4 ± 10.7</td>
</tr>
<tr>
<td>PDGF-ββ ng/mL</td>
<td>14.8 ± 2.5</td>
<td>23.1 ± 10.1</td>
<td>33.0 ± 8.2</td>
</tr>
<tr>
<td>TGF-β1 ng/mL</td>
<td>0.1 ± 0.08</td>
<td>0.1 ± 0.08</td>
<td>0.2 ± 0.1</td>
</tr>
<tr>
<td>VEGF ng/mL</td>
<td>0.3 ± 0.3</td>
<td>2.4 ± 1.1</td>
<td>1.2 ± 0.8</td>
</tr>
</tbody>
</table>

RBC = red blood cells, WBC = white blood cells, PDGF = platelet-derived growth factor αβ and ββ, TGF = transforming growth factor, VEGF = vascular endothelial growth factor

The Australian Red Cross Blood Service (ARCBS) provide pooled or apheresis (single donor) platelet preparations for transfusion via an intravenous route to patients with clotting disorders or haematological cancers. Since 2008, all platelet components prepared by the ARCBS have been required to be leucodepleted in a bid to reduce, amongst other factors, febrile non-haemolytic transfusion reactions, cytomegalovirus (CMV) transmission risk and transfusion associated graft versus host disease.¹¹ There has been much debate in respect to the pros and cons of using PRP with or without leucocytes. It is thought that white blood cells may contribute anti-microbial activity, which may reduce infection and that they may add other growth factors that could increase the healing response. However, concerns have been raised that leucocytes may release cytokines and other factors that may result in tissue degradation.⁹ Blood products are increasingly under pressure of short supply and are expensive to prepare and store. Although it is feasible, it is unlikely that PRP prepared by the ARCBS would be required for use to treat osteoarthritic patients, and therefore this procedure should not be an added product burden on the ARCBS.

Recently HealthPACT assessed the use of autologous blood injections for soft tissue injuries, a practice that is widespread in the private sector in Australia, particularly for slow healing sporting injuries.¹ This technique involves the injection of a small amount (2-3mL) of whole blood into the injured area in an attempt to stimulate healing via the recruitment of stem cells, increased vascularisation and the production of collagen. Although it appears that, in

addition to whole blood, PRP is also in widespread use in Australia for the treatment of sporting injuries, this current Brief will discuss the use of PRP for the treatment of osteoarthritis.

**Company or developer**

There are several autologous platelet separation systems on the market, including the Magellan® manufactured by Arteriocyte Medical Systems, Inc. (Massachusetts, USA), the Cascade® manufactured by Cascade Medical Enterprises (New Jersey, USA), the Biomet Biologics (USA) GPS® III system, the Angel (Cytomedix, Inc., Massachusetts, USA) and the SmartPReP® 2 Platelet Concentrate System manufactured by Terumo Cardiovascular Systems Corporation.

**Reason for assessment**

An innovative treatment alternative which may repair cartilage damage rather than just reduce symptoms of pain. By addressing tissue damage early, the use of PRP may result in a reduced number of arthroscopy/arthroplasty procedures being conducted.

**Stage of development in Australia**

- Yet to emerge
- Experimental
- Investigational
- **Nearly established**
- Established
- Established *but* changed indication or modification of technique
- Should be taken out of use

**Australian Therapeutic Goods Administration approval**

- Yes  
  ARTG number (s)  
  177960 Magellan  
  (29th November 2010)  
  162190 Terumo  
  (3rd June 2009)
- No
- Not applicable

**Licensing, reimbursement and other approval**

Two PRP systems are currently registered on the ARTG:

- the Magellan®, distributed in Australia by Cellplex Pty Ltd (Victoria), for the separation of bone marrow/whole blood during the preparation of platelet-poor and platelet-rich plasma from a small sample of blood/bone marrow. The Magellan® received US Food and Drug Administration (FDA) approval in June 2003 for point of care use in the preparation of concentrated platelets.
• Terumo Australia Pty Ltd distributes a PRP separation system manufactured by Harvest Technologies (Massachusetts, USA) for the preparation of autologous PRP at point of care. The PRP can be mixed with autograft and allograft bone grafting materials prior to application to an orthopaedic surgical site as deemed necessary by the clinical use requirements.

The GPS® III system was granted equivalence in November 2011 for a predicate technology that received FDA approval in 2008. Substantial equivalence was granted by the FDA in 2002 for the Cascade® system. The Terumo SmartPReP® 2 Platelet Concentrate System granted equivalence in December 2010 for a predicate technology that received FDA approval in 1976.

<table>
<thead>
<tr>
<th>Technology type</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technology use</td>
<td>Therapeutic</td>
</tr>
</tbody>
</table>

**Patient Indication and Setting**

**Disease description and associated mortality and morbidity**

In 2002, Australia declared arthritis, including osteoarthritis (OA), and musculoskeletal conditions a national health priority area. Osteoarthritis is a degenerative joint condition characterised by the wearing down, or breakdown of, the articular cartilage, leaving exposed bone resulting in pain and stiffness (Figure 5).

![Articular cartilage in the knee, drawn by Scott Leighton](image)

Articular cartilage is the thin layer of hard tissue which provides cushioning to the ends of the bones, and acts as a defence mechanism to reduce joint degeneration and bone erosion caused by the friction of movement. Although OA can affect the hands, wrists, spine and
ankles, it most commonly affects the weight-bearing joints of the hip (coxarthrosis) and knee (gonarthrosis). Symptoms include low-grade inflammation, swelling, deformity, tenderness, crepitus, pain, and in advanced stages, loss of mobility and muscle wasting.

OA is more common in females than in males, is more prevalent in individuals aged >55 years, those with a history of joint injury, and is associated with being overweight and obese. Primary prevention measures to delay onset or worsening of OA include maintaining a healthy weight, undertaking regular low-impact physical activity and consuming a healthy diet. Measures to control or manage the symptoms associated with OA include medications and ultimately joint replacement.\textsuperscript{14, 15}

**Number of patients**

In 2007-08 it was estimated that OA affected over 1.6 million Australians, with a population prevalence of approximately 7.6 per cent, which has remained steady since 2001. Almost two thirds of affected individuals are female (Table 3).

**Table 3**  
**Age-specific prevalence of osteoarthritis (%), in Australia 2007-08\textsuperscript{14}**

<table>
<thead>
<tr>
<th>Age group in years</th>
<th>Sex</th>
<th>15-24</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>55-64</th>
<th>65-74</th>
<th>&gt;75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>0.6</td>
<td>1.3</td>
<td>3.5</td>
<td>7.2</td>
<td>15.6</td>
<td>18.1</td>
<td>23.7</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>1.2</td>
<td>1.9</td>
<td>3.4</td>
<td>10.6</td>
<td>26.0</td>
<td>30.9</td>
<td>39.6</td>
<td></td>
</tr>
</tbody>
</table>

In 2009-10 there were a total of 59,118 hospital separations for the principal diagnosis of arthrosis of the knee, with an average length of stay (ALOS) of 5-days, more than double the number of separations for arthrosis of the hip (24,781 with an ALOS of 7 days). The marked difference between the prevalence of OA in males and females is not reflected in these separation figures, with males accounting for 46 per cent of total separations.\textsuperscript{16} For the same period, there were 38,500 surgical procedures for the MDC code I04Z, knee replacement and reattachment, with an ALOS of 7-days.\textsuperscript{17} Data from 2007-08 indicated that for every OA hospitalisation episode, more than one surgical and non-surgical intervention (cognitive, therapeutic or diagnostic interventions) was performed, with an average of 4 interventions per admission (Table 4). More than 4 out of 10 surgical procedures for OA involved a total knee or hip replacement (arthroplasty), with the condition being the major underlying factor in 97 per cent of all hip and knee replacements. The number of hip and knee replacements performed has increased over time, with an increase of 40 and 67 per cent from 2001-01 to 2007-08 for total hip and knee replacements, respectively (Figure 6).\textsuperscript{14}
Table 4  In hospital surgical and non-surgical procedures for OA, Australia 2007-08

<table>
<thead>
<tr>
<th>Measure</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hospitalisations, all OA</td>
<td>86,141</td>
</tr>
<tr>
<td>Number of surgical procedures</td>
<td>100,393</td>
</tr>
<tr>
<td>Total knee arthroplasty</td>
<td>25,970</td>
</tr>
<tr>
<td>Total hip arthroplasty</td>
<td>18,847</td>
</tr>
<tr>
<td>Number of non-surgical procedures</td>
<td>263,068</td>
</tr>
</tbody>
</table>

Figure 6  Trends in total knee and hip replacements for arthritis in Australia, 2000-01 to 2007-08

Speciality  Rheumatology
Technology setting  Specialist hospital, General Hospital

Impact

Alternative and/or complementary technology
Additive and substitution: Technology can be used as a substitute in some cases, but may be used in combination with current technologies in other instances.

Current technology
The mainstay of treatment for OA is the management of symptoms with medication that aim to reduce pain and inflammation, and to increase mobility and slow disease progression. Paracetamol is the most commonly taken medication followed by the use of non-selective or selective non-steroidal anti-inflammatory drugs (NSAIDs) such as

2 The cyclo-oxygenase enzyme, COX-1, maintains the stomach lining and the COX-2 enzyme is part of the inflammatory response. Non-selective NSAIDs block both the COX-1 and COX-2 enzymes. These NSAIDs are effective in treating inflammation but can cause irritation in the stomach. Selective NSAIDs block only the COX-
celecoxib, meloxicam, ibuprofen, diclofenac and naproxen. In 2004 the TGA removed the COX-2 inhibitor (see footnote) rofecoxib from the Schedule of Pharmaceutical Benefits due to an association with cardiac arrest and stroke. This resulted in a concomitant decrease in the number of prescriptions for the COX-2 inhibitor celecoxib. Naproxen and meloxicam are the most commonly prescribed NSAIDs, with more than 1.6 million subsidised prescriptions filled for meloxicam in 2007.¹⁵

Many OA sufferers self-prescribe the use of the dietary supplements glucosamine and chondroitin, which are thought to assist in reducing the breakdown of cartilage. Physiotherapy may also assist with mobility issues.

Viscosupplementation involving the injection of hyaluronic acid³ (HA) into the fluid of the knee joint to improve the lubricating properties of synovial fluid, reducing pain and improving mobility, has been proposed as a treatment to manage OA.¹⁵ Some studies have demonstrated a positive benefit with HA injection, however recent studies have reported conflicting results with HA producing the same level of pain reduction as placebo.¹⁸ Viscosupplementation with HA was assessed by the Medical Services Advisory Committee (MSAC) in 2003 and based on the poor evidence base, public funding for this procedure was not supported.¹⁹

Intra-articular injection of corticosteroids is also an established practice and conducted in OA patients mainly for pain relief.¹⁸ However an application to the MSAC by the Australian Rheumatology Association in December 2011 for a new item number relating to the use of diagnostic joint aspiration and intra-articular steroid injection by rheumatologists in patients with osteoarthritis and inflammatory arthritis was rejected for public funding.²⁰

In the past, many patients may have undergone therapeutic arthroscopic debridement of the knee in an attempt to remove debris from around the knee joint in a bid to prolong the life of the knee and avoid joint replacement. However, there is a large body of evidence that demonstrates that arthroscopy offers no benefit in terms of improvement of pain and function in patients with OA.²¹ In severe cases of OA of the knee, patients may require arthroplasty to replace sections of the joint.¹⁴

**Diffusion of technology in Australia**

The use of PRP to treat soft tissue injuries appears to be widespread in Australia; however its use to treat OA is limited (5-10 cases per week in one practice). The Magellan® system is currently used in two private sports physician practices in Melbourne and is used to treat a small number of OA patients. Magellan® systems are in place at the Royal Hobart Hospital and the Royal North Shore Hospital (NSW) for use during cardiac surgery and for wounds.

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² enzyme, relieving inflammation without causing stomach irritations and may be referred to as COX-2 inhibitors. (AIHW 2010. Medication use for arthritis and osteoporosis.)
³ Hyaluronic acid occurs in the synovial fluid and acts as a protective coating around cartilage cells.
One system is used in the Knox Private Hospital, Victoria, to treat patients with chronic wounds such as diabetic ulcers (personal communication Cellplex Pty Ltd). One practice in Sydney currently uses Terumo PRP kits and is investigating the use of Cytomedix, Inc.’s Angel® kits (personal communication Sydney Sportsmed Specialists). A private practice in Western Australia uses the Biomet system.

**International utilisation**

<table>
<thead>
<tr>
<th>Country</th>
<th>Level of Use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trials underway or completed</td>
</tr>
<tr>
<td>Andorra</td>
<td>✓</td>
</tr>
<tr>
<td>Italy</td>
<td>✓</td>
</tr>
<tr>
<td>Spain</td>
<td>✓</td>
</tr>
<tr>
<td>Slovakia</td>
<td>✓</td>
</tr>
<tr>
<td>USA</td>
<td>✓</td>
</tr>
<tr>
<td>Korea</td>
<td>✓</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
</tr>
<tr>
<td>India</td>
<td></td>
</tr>
</tbody>
</table>

**Cost infrastructure and economic consequences**

In Australia during the period 2004-05, arthritis and musculoskeletal conditions accounted for $4 billion in direct health expenditure, with OA accounting for over a quarter of this expenditure (Table 5). This represents almost a doubling of expenditure from 2000-01 where total costs for OA were $842 million, the majority of which was attributed to hospital-admitted patient services and out-of-hospital medical services.\(^\text{14}\)

**Table 5 Direct health expenditure for OA in Australia, 2004-05**\(^\text{14}\)

<table>
<thead>
<tr>
<th>Health service area</th>
<th>$ million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admitted patient services</td>
<td>898.5</td>
</tr>
<tr>
<td>Out-of-hospital medical services</td>
<td>188.6</td>
</tr>
<tr>
<td>Prescription pharmaceuticals</td>
<td>105.5</td>
</tr>
<tr>
<td>Research</td>
<td>28.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,220.9</strong></td>
</tr>
</tbody>
</table>

Currently practitioners utilise different Medicare Benefits Schedule (MBS) item numbers to perform PRP injections. MBS item number 13703 “ADMINISTRATION OF BLOOD, including collection from donor” (Fee: $119.50) may be used in conjunction with an ultrasound item number. In the period from July 2011 to June 2012, there were 5,480 services performed using the MBS item number 13703, the majority of which were performed in NSW (2,067) and Victoria (2,453).
Private clinics charge varying amounts for injection with PRP. A Western Australian clinic charges approximately $500 per treatment, whereas a NSW clinic has patient out-of-pocket charges of a maximum of $200 for one knee and $240 for both knees (personal communication).

The Magellan® separation unit currently costs A$11,000 and the cost of consumables used in the preparation of PRP vary depending on the final end product. All kits include machine consumables and syringes and prices range from $220 for a PRP kit that doesn’t include anticoagulant to $356 for a kit including anticoagulant. A kit designed to create a PRP gel for cardiac surgery costs $599. All kits are single use only; however one kit may be used for three 60mL preparations from one patient (personal communication Cellplex Pty Ltd).

**Ethical, cultural or religious considerations**

No issues were identified.

**Evidence and Policy**

**Safety and effectiveness**

Of the three comparative studies identified for inclusion in this assessment, two used HA, an inappropriate comparator for the Australian setting. Both of these studies used a series of three, weekly injections of both PRP and HA. Filardo et al used the same PRP preparation which was frozen and thawed, however the efficacy of this approach has not been validated and many practitioners do not advocate this method due to uncertainties in respect to the activation status of the platelets. It was unclear from the methodology described by Spakova et al if PRP preparations were prepared fresh prior to each weekly injection. As these studies used an inappropriate comparator, an in-depth discussion is not provided in this Brief. Although the blinded randomised controlled trial (RCT) by Filardo et al (2012) reported improvements in pain and function scores in patients treated with PRP (n=54) compared to those treated with HA (n=55), these differences were not significant. Higher post-injection pain was noted in those patients injected with PRP compared to HA and this is thought to be indicative of an intense inflammatory response due to the number of platelets injected. The RCT by Spakova et al (2012) randomised patients to receive PRP (n=60) or HA (n=60). Both groups demonstrated a clinically significant improvement in pain and function scores at 3- and 6-months follow-up compared to baseline values; however scores worsened between 3- and 6-months. A between group comparison found that PRP treatment significantly reduced both WOMAC scores for pain, stiffness and function.

\[ \text{WOMAC} = \text{Western Ontario and McMaster Universities Arthritis Index. Is a validated questionnaire that consists of 5 items for pain (score range 0–20), 2 for stiffness (score range 0–8), and 17 for functional limitation (score range 0–68). A high score indicates a worsening of the condition, a lower score indicates improvements in symptoms.} \]
(p<0.01) and pain (p<0.01) at 3-months. Although the paper stated that this effect remained at 6-months, no scores were reported.

No comparative studies were identified that compared the use of PRP to NSAIDs, the current treatment option for OA of the knee.

The remaining comparative study randomised 78 patients with bilateral early OA of the knee (156 knees) into three groups: those that received a single PRP injection (n=26, 52 knees); those who received two PRP injections 3-weeks apart (n= 25, 50 knees) and the control group (n=23, 46 knees) who received a single placebo injection of normal saline (level II intervention evidence). There was no significant difference in the baseline characteristics in the three study groups including age, body mass index, WOMAC scores, visual analogue scale for pain and radiological grading. Assessment was conducted at 1.5, 3- and 6-months by an observer blinded to treatment status. Approximately 100mL of whole blood was drawn from each patient. PRP was not prepared by any of the systems as described in this Brief, but in a bench-top centrifuge and the buffy coat preparation was filtered to remove leucocytes. The mean platelet count was 310 x 10^3/µL and the mean number of platelets injected per knee was 239 x 10^7. Injections, whether they were saline of PRP preparations, took place without local anaesthetic. PRP preparations were activated with calcium chloride. Patients were advised to cease taking NSAIDs during the follow-up period.

Adverse events including syncope, dizziness, headache, nausea, gastritis, sweating and tachycardia were reported in six (22.2%) and 11 (44%) patients in the single and two-PRP injection groups, respectively. There were no adverse events reported in the control group patients. There was a significant association with those patients who experienced an adverse event and the number of platelets that were injected. Patients who experienced an adverse event were injected with an average of 253.5 ± 102 x 10^7 platelets compared to 195.7 ± 90.6 x 10^7 injected to those who did not have an adverse reaction (p=0.02).

At follow-up time points there was no improvement in pain and function scores for control patients, whereas patients in both of the intervention groups demonstrated an improvement, which was evident early but diminished at 6-months. There was no difference between those patients who received a single injection and those who received two. Pain and function increased in the control patients. Pain and function scores are summarised in Table 6.
<table>
<thead>
<tr>
<th>Table 6</th>
<th>Mean score and percentage change in WOMAC scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>Mean score</td>
</tr>
<tr>
<td><strong>Group A: A single PRP injection</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.18</td>
</tr>
<tr>
<td>1.5 months</td>
<td>4.26</td>
</tr>
<tr>
<td>3 months</td>
<td>3.74</td>
</tr>
<tr>
<td>6 months</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td><strong>Group B: 2x PRP injection 3 weeks apart</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>10.62</td>
</tr>
<tr>
<td>1.5 months</td>
<td>4.38</td>
</tr>
<tr>
<td>3 months</td>
<td>4.88</td>
</tr>
<tr>
<td>6 months</td>
<td>6.18</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td><strong>Group C: a single placebo injection of normal saline</strong></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>9.04</td>
</tr>
<tr>
<td>1.5 months</td>
<td>9.48</td>
</tr>
<tr>
<td>3 months</td>
<td>10.35</td>
</tr>
<tr>
<td>6 months</td>
<td>10.87</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>p&lt;0.05 increase</td>
</tr>
</tbody>
</table>

A number of case series were identified that described the use of PRP to treat patients with OA of the knee (level IV intervention evidence).\(^6,26-30\) However, whilst these studies may provide evidence in regard to the safety of the PRP procedure, due to the lack of comparator, they cannot give an insight into the effectiveness of the procedure. These studies did provide before and after measures of pain scores, function and quality of life in the same patients.

The case series by Wang-Saegusa et al (2011) described the results of 261 patients injected three times with PRP at 2-week intervals. At 6-month follow-up, clinically significant improvements in WOMAC, quality of life (SF-36), and functional scores were reported when compared to baseline values, with no adverse events described.

A small case series of 65 patients with various grades of OA was described by Jang et al (2012). Patients received a single PRP injection. At 6-months pain scores were reduced compared to baseline, however at 9- and 12-months these scores had begun to increase (no
statistical value given). Those patients with a milder form of OA had a more sustained period of pain relief.

The case series reporting the longest follow-up period was conducted by Filardo et al (2011) on 91 patients who received three injections of PRP given at 3-weekly intervals (2\textsuperscript{nd} and 3\textsuperscript{rd} injections used frozen PRP). A decrease in pain and an increase in function scores were reported after 12-months when compared to baseline. Results at 24-months were still significantly improved over baseline but had begun to approach baseline levels.

**Economic evaluation**

No cost-effectiveness analyses were identified that described the use of PRP injections in patients with OA.

**Ongoing research**

A RCT was due to be finalised in December 2012 that compared the use of intra-articular PRP and corticosteroid injections in osteoarthritic knees (NCT01381081). This Spanish RCT aimed to recruit 64 patients and will report on the difference from baseline to follow-up (at 1-, 3- and 6-months) of pain visual analogue scale, functional level of the knee, and SF36 quality of life.

Two further RCTs, one in Israel (NCT01270412) and one in France (NCT01697423), are due to commence in the near future, comparing intra-articular injections of PRP and HA, however this is an inappropriate comparator for Australia. In addition, there is one on-going RCT comparing PRP to HA in Italy (NCT01670578). There are three on-going RCTs (NCT01075230, NCT01563380, NCT00826098) comparing the effect of PRP directly following knee arthroplasty to no treatment to evaluate the effect of PRP on blood loss, pain, wound healing and function.

Of note is that there are 11 single-arm studies registered evaluating the use of stem cells in patients with OA of the knee. In addition, there are four RCTs registered evaluating the use of stem cells compared to HA, Plasmalyte-A and acetaminophen. Of interest is the RCT that was completed in December 2012, which compared the use of stem cells to placebo in 40 patients with OA of the knee (NCT01504464).

**Other issues**

PRP has also been proposed as a treatment for OA of the hip. Sanchez et al (2012) reported the use of ultrasound-guided PRP injections delivered to patients with OA of the hip once a week for 3-weeks. In this case series, 40 patients underwent treatment and at 6-month follow-up, 23 (57.5%) patients reported a clinically relevant reduction of pain and 16 of these patients were classified as excellent responders with a demonstrated reduction in pain at 6-7 weeks, which was sustained at 6 months (level IV intervention evidence).\textsuperscript{31}
Sprays or gels prepared from PRP isolates have also been used to treat chronic wounds such as non-healing diabetic ulcers.$^{3,32}$

PRP gels have been proposed as a measure to prevent deep sternal wound infection in patients undergoing cardiac surgery. The gel is prepared in theatre whilst the patient is undergoing surgery. After the whole blood is centrifuged, the majority of the plasma is removed and the coagulation cascade is activated with either calcium chloride or calcium gluconate. The remaining buffy coat is mixed with the small remaining volume of plasma and transferred into a sterile Petri dish. The activated plasma is then added after 10 minutes, and a gel forms. This PRP gel is then applied onto the sternum prior to closure of the subcutaneous tissue. A large comparative study reported that deep sternal wound infection was significantly higher in control patients (10/671, 1.5%) compared to those who received PRP applied inside the sternotomy wound before closure (1/422, 0.20%, p=0.043) (level III-2 intervention evidence).$^{33}$ Several Australian hospitals are currently using PRP gel preparations during cardiac surgery including the Royal Hobart Hospital, Royal North Shore Hospital (NSW) and the Royal Perth Hospital (personal communication Cellplex Pty Ltd).

Of interest is the potential use of autologous mesenchymal stem cell therapy, usually obtained from the bone marrow, in the treatment of OA. Previously a 2-step procedure would have been used that involved a haematologist harvesting the bone marrow by lumbar puncture and expanding stem cell numbers by culturing them in vitro for up to 20-30 days prior to intra-articular injection. The 1-step procedure is similar to that of preparing PRP as the bone marrow is harvested then concentrated directly in the operating theatre before being injected immediately into the joint. A recent review found that the literature reported that the 2-step procedure was more successful in treating larger cartilage defects and is used to treat osteoarthritisic lesions. The 1-step procedure was used for smaller defects and used to treat osteochondral defects.$^{34}$

**Summary of findings**

Platelet rich plasma is used widely in the private sector in Australia for the treatment of soft tissue injuries and its use for the treatment of patients with osteoarthritis, particularly of the knee, is increasing. However, the evidence-base to support this practice is of low-quality, informed by studies that use an inappropriate comparator for the Australian setting (hyaluronic acid) or by case series evidence. Although before-and-after studies describe changes in patients from baseline, case series studies cannot describe the effectiveness of the intervention due to a lack of adequate comparator.

All studies included in this assessment reported short-term improvements in function and a decrease in pain scores; however this effect did not appear to be sustained over a long period of time. The procedure appears to be safe, with the only adverse event reported being short-term pain following injection due to inflammation.
Although there is some evidence that PRP injections provide some symptomatic relief, there is no evidence that PRP injections alters the natural progression of OA.

Randomised controlled trials using a comparator appropriate for the Australian setting are needed to demonstrate the effectiveness of PRP treatment of OA of the knee. In addition, as viscosupplementation with hyaluronic acid was last assessed by the MSAC in 2003, it may be an appropriate time to review the evidence base for this procedure.

A Brief describing the results of treatment of osteoarthritis of the knee with stem cells may be more informative.

HealthPACT assessment

There is currently insufficient evidence to support the use of platelet-rich-plasma injections for patients with osteoarthritis of the knee in routine clinical practice. However, this procedure will continue to be used in the private sector and HealthPACT would encourage practitioners to participate in appropriately designed clinical trials and to collect long-term data. Pain, mobility and pharmaceutical usage data collected from patients who may have undergone repeat injections would be particularly informative. Therefore, it is recommended that further research on this technology on behalf of HealthPACT is not warranted at this time.

Number of studies included

All evidence included for assessment in this Technology Brief has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies 6
Total number of Level II intervention evidence studies 3
Total number of Level IV intervention evidence studies 3

Search criteria to be used (MeSH terms)

Osteoarthritis, Knee/ therapy
Platelet-Rich Plasma
Injections, Intra-Articular

References


