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Platelet-rich plasma: a case study for the identification of disinvestment opportunities using horizon scanning

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Abstract

Objective. This paper discusses the potential for horizon scanning to identify low-value, inappropriate clinical practices that deliver minimal benefit to patients and represent a considerable financial burden on the health system.

Methods. Platelet-rich plasma (PRP) was identified by routine horizon scanning as a potentially innovative treatment alternative for osteoarthritis of the knee. A rapid, non-systematic assessment of the evidence pertaining to the safety and effectiveness of PRP compared with nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of osteoarthritis of the knee was conducted.

Results. The evidence base supporting the use of PRP for the treatment of osteoarthritis was poor. No comparative studies were identified that compared the use of PRP to NSAIDs, the current treatment option for osteoarthritis of the knee in Australia. Despite the lack of effectiveness evidence, the use of PRP injections was rapidly increasing in the private sector using an inappropriate Medicare Benefits Schedule item number.

Conclusions. This assessment highlights the potential of using established horizon scanning methodologies to identify targets for full or partial disinvestment of ineffective, inefficient or harmful clinical practices.

What is known about the topic? PRP is rapidly diffusing in the private health system in Australia, however the use of a Medicare Benefits Schedule item number meant that this practice was being subsidised by the public reimbursement of treatment fees.

What does this paper add? Traditional horizon scanning tends to identify technologies for health systems to invest in. The evidence on the effectiveness of PRP was examined with the purpose of exploring investment in an innovative treatment that may have reduced the number of invasive procedures being performed in the public hospital system. The current evidence base does not support the use of PRP injections for the treatment of osteoarthritis. It does, however, support the use of horizon scanning as an inexpensive methodology to identify possible disinvestment targets associated with potential patient harm and high health service expenditure.

What are the implications for practitioners? Practitioners should be aware that public funding for the injection of PRP should not be used for the treatment of osteoarthritis.

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Background

The Health Policy Advisory Committee on Technology (HealthPACT) was created in 2003 under the auspices of the Medical Services Advisory Committee (MSAC) and comprises representatives from all Australian state and territory health departments, the Australian Department of Health and Ageing, the MSAC, the Therapeutic Goods Administration, the Department of Veterans' Affairs, and New Zealand's National Health Committee. HealthPACT's primary role is to conduct horizon scanning (HS) of the peer reviewed and grey literature, using a methodology previously described,[1] in order to proactively identify new and emerging medical devices and practices that may impact, positively or negatively, on the public health systems of Australia and New Zealand. By providing an early warning system in the form of summarising the preliminary safety and effectiveness evidence, as well as regulatory, ethical and potential workforce and training issues, HealthPACT informs jurisdictional decision-making to assist in the appropriate introduction of new and emerging health technologies. Recently the focus of HealthPACT has shifted to specifically assessing those technologies that may reduce public hospital admissions, readmissions, length of stay and patient waiting lists, while still maintaining optimal patient care. In addition, HealthPACT has recognised that health services need to develop a disinvestment methodology that can identify obsolete, ineffective, high-cost, low-volume technologies that may deliver inappropriate care to patients.

Osteoarthritis is one of Australia's nine national health priority areas,[2] affecting over 1.6 million Australians and accounting for more than A$1221 million in annual direct health expenditure, the majority of which is attributed to hospital-admitted patient

services and out-of-hospital medical services.[3] Intra-articular injections of autologous platelet-rich plasma (PRP) were identified in February 2013 through routine HS as an innovative treatment alternative for patients with osteoarthritis of the knee. PRP is used widely in the private sector in Australia, primarily in sports medicine clinics,[4–8] for the treatment of soft tissue injuries and anecdotally its use for the treatment of patients with osteoarthritis, particularly of the knee, is increasing.

It has been suggested that by addressing tissue damage early, the use of PRP may result in a reduced number of arthroscopy and arthroplasty procedures being conducted in the public hospital system. A preliminary assessment of the evidence describing the use of PRP (the intervention) compared with standard treatment, usually nonsteroidal anti-inflammatory drugs (NSAIDs; the comparator), for the treatment of osteoarthritis of the knee was therefore commissioned.

Methods

The main component of a HealthPACT assessment is a brief summary of the evidence pertaining to the safety, effectiveness and, if available, the cost-effectiveness of the technology in question. Unlike a traditional health technology assessment (HTA) used to inform public reimbursement decision-making through the MSAC process, this assessment is not systematic, but rather uses a hierarchical approach to the most recent published evidence. That is, the strongest level of evidence, according to the National Health and Medical Research Council levels of evidence,[9] is included first. If no randomised controlled trials or comparative studies are identified by the search strategy, then evidence from the largest case series is included. Due to the rapid nature of HealthPACT assessments, the quality of included studies is not appraised and the results of included studies are reported in a narrative form. The pooling of results and a statistical analysis is not usually possible due to the lack of data and the heterogeneous nature of studies describing new and emerging health technologies.

The intervention

Platelets are crucial for tissue repair and vascular remodelling, with the first stage of normal wound healing immediately following injury or insult being inflammation where activated platelets adhere to the site of injury releasing various growth.[10,11] It is thought that the delivery of activated platelets via an intra-articular injection of PRP will reduce inflammation, provide pain relief, improve function and stimulate cartilage regeneration at the site of injury, in this case the worn cartilage area of the knee.[10]

PRP is prepared by drawing 30–60 mL of whole blood from the patient, which would yield a concentrated platelet layer of ~3–6 mLs of PRP after centrifugation.[11] A 3–5 times baseline concentration of platelets is regarded as a therapeutic dose (baseline platelet concentration of $200 \times 10^3/\mu L$ concentrated to $1000 \times 10^3/\mu L$ in PRP).[12] Several one-step commercial PRP preparation systems are available on the market or a standard bench-top centrifuge may be used, however using this method is likely to activate the platelets and reduce the yield slightly.[11]

As PRP is generally prepared at point-of-care, once isolated it is injected immediately into the joint, usually under ultrasound guidance. Local anaesthetic is not usually applied as the effect on platelet activation is unclear.[11,13] Some practitioners advocate activating the platelets before 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.[14] Patients may be advised to avoid the use of NSAIDs 2 weeks pre- and post-PRP procedure so as not to inhibit the inflammatory response of the growth factors,[11] however, there is little clinical evidence to support the negative effect of NSAIDs on PRP therapy. Patients with platelet dysfunction conditions and thrombocytopenia are contraindicated for PRP therapy.[14]

The comparator

The mainstay of treatment for osteoarthritis is the management of symptoms with medications 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 nonselective or selective NSAIDs such as celecoxib, meloxicam, ibuprofen, diclofenac and naproxen.[15]

Intra-articular injections of hyaluronic acid into the fluid of the knee joint to reduce pain and improve mobility have been proposed as a treatment to manage osteoarthritis.[15] Although some studies demonstrated a positive benefit with hyaluronic acid injection, recent studies have reported the same level of pain reduction after injection with hyaluronic acid as placebo.[16] Viscosupplementation with hyaluronic acid was rejected for public funding by the MSAC in 2003 due to a lack of evidence.[17] This position has been vindicated by a recent statement by the American Academy of Orthopedic Surgeons that the treatment of patients with severe knee osteoarthritis with hyaluronic acid could not be recommended 'based on high-quality evidence that hyaluronic acid injections were not associated with clinically meaningful improvement in symptoms compared with placebo injections.'[18] A recent study found that injections with hyaluronic acid were costly and had limited clinical benefit.[18] Similarly, intra-articular injection of corticosteroids, which may be offered for pain relief in osteoarthritis patients,[16] was also rejected by the MSAC for public funding in 2011.[19]

Arthroscopic debridement to remove debris from around the knee joint may also be offered, 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 osteoarthritis.[20]

Results

The evidence base supporting the use of PRP for the treatment of osteoarthritis was poor. Of the three comparative studies included in this assessment, two used hyaluronic acid, an inappropriate comparator for the Australian setting.[21,22]

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

The remaining comparative study randomised 78 patients with bilateral early osteoarthritis of the knee (156 knees) into three groups: those who received a single PRP injection ($n = 26$, 52 knees); those who received two PRP injections 3 weeks apart ($n = 25$, 50 knees); and controls ($n = 23$, 46 knees) who received a

single placebo injection of normal saline.[23] There was no significant difference in the baseline characteristics in the three study groups. Assessment was conducted at 1.5, 3 and 6 months by an observer blinded to treatment status. PRP was prepared from 100 mL of whole blood, activated with calcium chloride with a mean number of 239×10^7 platelets injected per knee without local anaesthetic.

Adverse events including syncope, dizziness, headache, nausea, gastritis, sweating and tachycardia were reported in 6/26 (23%) and 11/25 (44%) of patients in the single and double PRP injection groups, respectively. No adverse events were reported in control patients. There was a significant association between experiencing an adverse event and the number of platelets that were injected. Patients who experienced an adverse event were injected with a higher average number of platelets compared with those who did not have an adverse reaction ($253.5 \pm 102 \times 10^7$ vs $195.7 \pm 90.6 \times 10^7$; $P = 0.02$).

At follow-up 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 one injection and those who received two.

Several case series were identified that described the use of PRP to treat patients with osteoarthritis of the knee.[13,24–28] Although 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.

The largest case series described the results of 261 patients injected three times with PRP at 2-week intervals. At 6-month follow-up, clinically significant improvements in arthritis scores, quality of life (SF-36), and functional scores were reported when compared with baseline values, with no adverse events described.[28]

The case series with the longest follow-up period reported on 91 patients who received three injections of PRP given at 3-weekly intervals. A decrease in pain and an increase in function scores were reported after 12 months when compared with baseline. Results at 24 months were still significantly improved over baseline but had begun to approach baseline levels.[24]

A small case series of 65 patients with various grades of osteoarthritis was described by Jang *et al*. Patients received a single PRP injection. At 6 months pain scores were reduced compared with baseline, however at 9 and 12 months these scores had begun to increase (no statistical value given). Those patients with a milder form of osteoarthritis had a more sustained period of pain relief.[26]

Discussion

The evidence base to support the practice of PRP injections for osteoarthritis of the knee was poor, informed by studies that use an inappropriate comparator for the Australian setting (hyaluronic acid) or by case series evidence. All research included in the present study 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 main adverse event reported being short-term pain following injection due to inflammation. Although there is some evidence that PRP injections may provide some symptomatic relief, there is no evidence that PRP injections alter the natural progression of osteoarthritis and it is unlikely that the use of PRP will result in changes to clinical practice in the treatment of osteoarthritis at the public hospital level.

What is of interest, however, is that this HealthPACT assessment highlighted a high-volume, low-value healthcare practice with the possible inappropriate use of the Medicare Benefits Schedule (MBS) item number 13703: 'administration of blood, including collection from donor', which attracts an MBS fee of A$119.50.[8] In the period from July 2011 to June 2012, there were 5480 services performed using this MBS item number. For the period July 2013 to June 2014, this figure had risen to 30 452 services, representing an increase of over 450%, with the majority of services being performed in NSW (9559) and Victoria (15 085).[29] Although it is difficult to directly ascribe this large increase in activity to the use of PRP injections alone, it is also difficult to explain the sudden increase in activity and the concomitant increase in costs to the public health system with MBS fees totalling in excess of A$3.6 million.

Since the commissioning of this assessment, the MSAC reviewed the wording of MBS item number 13703, which has been amended to read 'transfusion of blood, including collection from donor' since 1 January 2015, meaning a Medicare rebate is no longer payable for injections of PRP.[8] For the 6-month period from this 1 January 2015 to July 2015, the number of services performed using item number 13703 has markedly reduced to 3521. If this number is extrapolated out to a 12-month period, this would represent a decrease of 76% from 2014, representing a saving of A$2.8 million to the public health system.

This assessment highlights the potential use of horizon scanning to serendipitously identify potential targets for disinvestment of ineffective, inefficient or harmful clinical practices. Much research and debate has centred on identifying a method for routine disinvestment. In Australia, the Comprehensive Management Framework has systematically reviewed existing MBS items to ensure value for money and improve health outcomes for patients using a process akin to conventional HTA where the safety, clinical effectiveness and cost-effectiveness evidence is systematically reviewed in addition to significant stakeholder engagement. With limited healthcare resources, these reviews may be considered time consuming and expensive. Elshaug *et al*. attempted to develop a strategy to enable the identification of low-value clinical services via an 'environmental scan' of the literature,[30] and although the project identified 156 potentially ineffective services, it was time-consuming and resource dependent.

Horizon scanning is a system already in place used to proactively identify new healthcare technologies but may serendipitously identify full or partial disinvestment targets, presenting opportunities to enhance quality of care and improve patient safety, while also resulting in health system savings. Horizon scanning assessments are rapid and consider the most recent evidence, ensuring timely advice to jurisdictions using few resources.

Recently HealthPACT has identified potential high-volume targets for partial disinvestment, including: routine vs clinically-

indicated replacement of peripheral intravenous catheters;[31] the overuse of catheter ablation for atrial fibrillation;[32] and overuse of the implantation of inferior vena cava filters in the prevention of pulmonary embolism.[33]

Conclusion

Horizon scanning for disinvestment can be run in parallel with horizon scanning for investment and represents a relatively inexpensive yet effective methodology. As such, funding a dedicated disinvestment horizon scanning program may represent a good investment for policy-makers. Although it is difficult to change some entrenched clinical practices, assessments such as these represent a starting point for much-needed conversations between clinicians and policy makers around established clinical practices to work together to minimise the use of low-value practices.

Competing interests

None declared.

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