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Platelet-rich plasma injection for tennis elbow: did it ever work?

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ABSTRACT

Platelet-rich plasma (PRP) is a commonly used treatment for tendinopathies such as tennis elbow despite the questionable evidence of its efficacy. A recent Cochrane review suggests that it likely does not provide clinically meaningful benefits in people with tennis elbow. In this viewpoint, we discuss how lack of regulation allowed aggressive marketing and clinical use without normal phases of drug development and approval process or rigorous evidence of benefits. Since several phases of development were bypassed, we still do not know the optimal preparation method and dosing of PRP for tendinopathies. Furthermore, several clinical trials compared PRP with other interventions although it was unclear if PRP was better than placebo and these comparisons created distraction rather than improved understanding of its effects.

Key messages

What is already known

- Platelet-Rich Plasma (PRP) injection is widely used to treat tennis elbow symptoms.

What are the new findings

- Cochrane review found moderate certainty evidence that PRP does not provide patient-important benefits compared with placebo in people with tennis elbow.
- Flaws in the interpretation of preclinical and clinical research as well as active marketing resulted in widespread use despite lack of benefits.
- The benefits of novel treatments should be assessed in rigorous trials before implementation.

RECENT EVIDENCE: WHERE ARE WE NOW?

On any given day, lateral epicondylitis affects 1%–2% of middle-aged people and is associated with substantial healthcare and societal costs.[1 2] Glucocorticoid injection has been a mainstay of treatment, but its benefits are short-lived.[3] With a lack of alternative options and a shift to focussing on regenerative outcomes, many front-line clinicians have turned to less regulated and what are perceived to be more risk-free treatments, such as platelet-rich plasma (PRP).

Our recent Cochrane review found insufficient evidence to support the ongoing use of autologous blood or PRP injections in the treatment of tennis elbow.[4] Estimates from eight placebo-controlled trials sit firmly above the null effect for both pain (MD 0.16, 95% CI −0.3 to 0.6, 0–10 scale; n=523) and function (MD 1.9, 95% CI −1.3 to 5, 0–100 scale; n=502).

The prospects of widely used PRP injections turning out to be the holy grail for tennis elbow are tenuous at best. Furthermore, PRP injections did not show superiority compared with autologous blood injections (four trials, 292 participants), undermining the rationale for selling the centrifugation kits that concentrate the growth factor (GF)-filled platelets.

BIOLOGICAL RATIONALE: HOW WAS IT SUPPOSED TO WORK?

Despite advances in our understanding of tendon biology, the exact mechanism for pain in tennis elbow is unclear. In response to hypoxia and tissue injury, cytokines and growth factors (GFs) are released, and a complex, sequential cascade results in neovascularisation and synthesis of poorly organised tendon tissue.[5 6]

The biological rationale for PRP injection is that platelets contain several GFs and other potentially active proteins, so when delivered to sites of injury, it is hypothesised to promote the repair process. Animal and cell studies have shown that PRP may confer several effects on tendons: it increases vascularity, tenocyte proliferation and collagen synthesis.[7] However, this is not what tendinopathic tissue is devoid of. Although PRP has been demonstrated to promote tendon healing in in vitro studies, evidence from acute injuries and cultured cells may not apply to human tendinopathy.[7]

CLINICAL SCIENCE: WHAT WENT WRONG?

Many factors have contributed to the widespread adoption of PRP into clinical practice in the absence of rigorous evidence support its use. Since PRP is not considered a medication or medical device, the robust oversight, clinical trial and approval processes, normally required for the adoption of a new treatment/

device into clinical practice, were not followed. Consequently, several early phases of the development pathway were bypassed. For example, the optimal doses of the different cytokines, immune cells and proteins being delivered in PRP or how frequently they should be administered is still unclear.[8] Clinical trials have therefore been limited by the variability of PRP preparations and delivery protocols used, limiting the generalisability of results.

First signs of possible benefits of PRP in the treatment of tennis elbow were published in 2006.[9] A non-randomised comparative study including 20 participants found that by 2 months, there was a 60% reduction in pain in the active group (n=15), increasing to 93% by final follow-up at 25 months. This compared with only 16% reduction in the control group (n=5) by 2 months and most of the control subjects left the study to seek active treatment. This may seem impressive, but regression to the mean and natural course could explain most of the improvement in the active group. Furthermore, non-randomised studies are known to overestimate the benefits of experimental interventions.[10]

Instead of widespread clinical use, we should have conducted rigorous efficacy trials. However, only two of the following 18 randomised trials published during the next decade compared PRP with placebo. The remarkable effect in the first non-randomised study was elusive when tested in a blinded trial: Krogh *et al* found no difference between saline and PRP, and Mishra *et al* found a significant difference only in a dichotomised pain outcome in a subset of participants at post hoc time point.[11 12]

Trials using various active controls (corticosteroid injection, shock wave therapy, laser, polidocanol injection, surgery) did not improve our understanding of the effects of PRP since the effect of comparators is unclear.

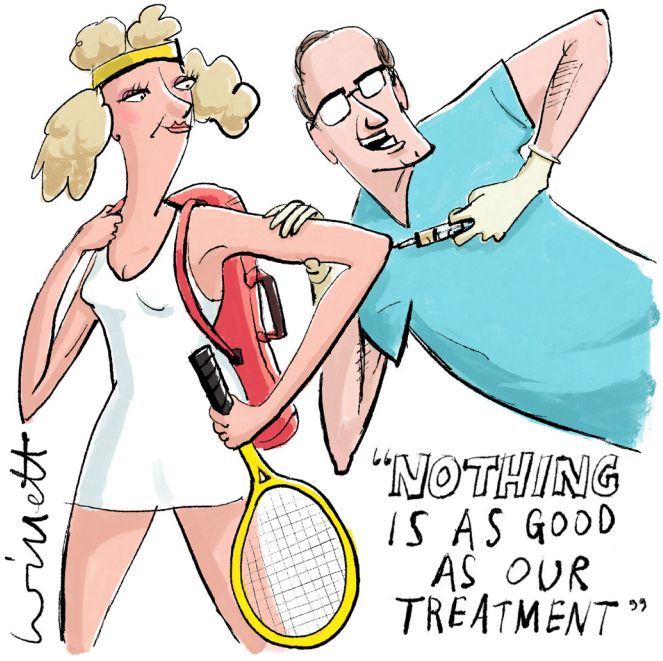

Figure 1

Nevertheless, comparisons against corticosteroid injection and the pioneer studies[9 12 13] convinced many, while some authors remained sceptical[14]—and with hindsight, rightfully so.

Despite lack of convincing evidence PRP was heavily marketed to the public. High-profile sporting celebrities and campaigns have promoted its 'natural' and 'regenerative' properties. While no significant harms have been reported, it does appear there is an ethical blind spot and regulatory loophole allowing this unproven and high-cost treatment to be offered to patients.

WHAT CAN BE LEARNED?

The PRP case study highlights deficiencies in the regulatory space that have allowed the widespread use of this unproven therapy. With freedom comes responsibility—but the case of PRP and several other novel treatments, such as vertebroplasty and arthroscopic partial meniscectomy, illustrates the vulnerability of the current system.[15 16]

Another key takeaway is that if treatments show no benefit over placebo, studies with active comparators provide no meaningful information and constitute research waste and a source of distraction. For example, a recent review concluded that PRP injections may be an alternative to surgery for treating tennis elbow although neither PRP nor surgery has demonstrated benefits.[17 18]

Despite our improved understanding of tendon biology, we still lack an effective intervention to treat tennis elbow symptoms. Before adopting new treatments that, such as PRP, turn out to be no better than doing nothing (figure 1), we should demand rigorous evidence of efficacy, safety and cost-effectiveness. Meanwhile, we should continue to inform patients of the favourable natural history of this condition.

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