Article ID: WMC00701 ISSN 2046-1690

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Article ID: WMC00701

Article Type: Research Protocol

Submitted on:22-Sep-2010, 01:34:04 PM GMT **Published on:** 22-Sep-2010, 04:38:52 PM GMT

Article URL: http://www.webmedcentral.com/article_view/701

Subject Categories:ORTHOPAEDICS

Keywords:PRP, Tennis, Elbow, Lateral epicondylitis

How to cite the article: Aqil A , Jacobs L . Physical therapy or Platelet Rich Plasma Injections in the Treatment of Tennis Elbow: A Randomised Clinical Trial . WebmedCentral ORTHOPAEDICS 2010;1(9):WMC00701

Source(s) of Funding:

Funding will be provided by Exactech UK.

Competing Interests:

All participants and researchers declare that they will not have any form of personal funding or incentives given to them for conducting this trial.

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Background

Chronic painful tendon disorders are common in athletic and sedentary individuals. They are common in middle age, and with increasing sports participation at increasing ages (1-4). Tendon regeneration may be improved by injecting autologous growth factors obtained from the patient's own blood. Autologous growth factors can be injected with autologous whole blood or platelet- rich plasma (PRP) (5).

At present there is evidence which suggests conservative treatment such as the use of heavy load eccentric training programmes is effective (6). However conventional conservative therapy is ineffective in around 25% of patients (7). In these patients, surgery can be performed, but it is not always successful, and the post-operative rehabilitation is slow and time consuming (3-4, 6-8). To reduce the need for surgery, more effective conservative therapies are required (5).

Literature Review

Platelets are small, non-nucleated bodies found in the blood whose primary role is in helping maintain haemostasis. Platelets contain within themselves proteins, cytokines and other biologically active factors that can initiate and regulate tissue healing. Plasma is the fluid portion of the blood which contains clotting factors, proteins and ions. Platelet- rich- plasma has a concentration of platelets four times that of normal blood.

There is a great variability of autologous blood preparations which is why wording is very important when describing the bioactive substance used. Unfortunately a number of terms have been used in the literature that refer to isolate and concentrated platelets. The term "platelet concentrate" wrongly implies a solid lump of platelets without plasma. "platelet gel" has also been used but this is also incorrect as gel does not contain the cell adhesion molecules present in a clot.

Bioactive factors in PRP

Platelet rich plasma can potentially enhance healing by the delivery of various growth factors and cytokines from the alfa- granules located in platelets. These include TGF-β, PDGF, IGF- I, IGF- II, FGF, epidermal growth factor, VEGF and endothelial growth factor. It is already known that cytokines have important roles in cell proliferation, chemotaxis, and differentiation. They also have important effects in encouraging angiogenesis. Within the dense granules in platelets are histamine and serotonin, dopamine, calcium and adenosine. These substances have also tissue healing properties by increasing blood vessel permeability and modulating the inflammatory process. Therefore it can be understood why they would be important in tissue healing. Importantly these bioactive substances are present in "normal" biologic ratios in PRP. This is important as tissue healing is an extremely complex process and delivery of simply one exogenous cytokine is not likely to bear an improvement on its own.

Formulation of PRP

Platelet- rich- plasma is made from anticoagulated blood. This is because in clotted whole blood, the platelets become part of the clot. When citrate is added to blood, it binds to ionised calcium and inhibits the clotting cascade.

Centrifugation steps separate the red and white blood cells from plasma and platelets. Further centrifugation then concentrates the platelets separating the PRP from platelet poor plasma. PRP is then clotted to allow delivery to the desired site. This step could pose some compliance problems. This is because bovine thrombin is used in some systems which might lead to some groups rejecting its use. Such groups might include vegetarians or religious groups. In addition there is potential for formation of antibodies by the host against this which can rarely result in an imunomediated coagulopathy. This clotting process also causes activation of platelets which result in the release of their stored growth factors. 70% of which are released within 10 minutes and 100% within one hour. Additional growth factors may be produced by the platelets for the remainder of their lifetime, which varies between 8 to 10 days. We will not be using bovine thrombin for the reasons above. Instead we will

rely on the host releasing their own thrombin for platelet activation.

CURRENT CLINICAL APPLICATIONS

There are a number of studies which document safe and efficacious use of PRP (9). There a number of animal studies, case reports, and small case series in maxillofacial, otolaryngology, plastic general and orthopaedic surgery. Some of these will be discussed later.

Lateral Epicondylosis

Lateral epicondylosis (LE) also known as “tennis elbow” is a common and important condition of the upper extremity (9-12). There are many conservative treatments which have been used in the treatment of LE. These include rest, eccentric exercise, and corticosteroid injections. More recently only physical therapy in the form of eccentric exercises have only been found to give good long term results. However there still remains a subset of patients who regardless of therapy, suffer long term pain and disability lasting up to two years (13-15).

The pathology of LE, is hallmarked by the presence of degenerative changes including neovascularity and disorganised collagen fibres(16-17). The exact mechanism of degeneration in patients with LE, is still unclear. However proposed aetiological models propose mechanical, vascular, neural, and “failure of healing” (18). Autologous whole blood injections have been used for medial and lateral epichondyloses and plantar fasciitis (19-21). However it is PRP which is rapidly gaining clinical popularity and is being promoted as the ideal autologous biological blood-derived product that can be exogenously applied (22-23). When compared with traditional treatments such as corticosteroids PRP seem to perform better. A non-randomised trial found that patients with LE who were given PRP injection, improved by a mean of 81% by 27 weeks. At a mean of 25.6 months, authors reported a 93% pain reduction compared with baseline. In contrast controls only reported a 17% improvement at 4 weeks (22). A recent systematic review on the treatment of LE with four injection therapies has found that Both PRP and whole blood and its products was safe and all studies reviewed failed to identify any serious or adverse events for the use of PRP (9). This review has suggested that future trials should compare these injection treatments with the eccentric exercise (9) to determine which is the most effective. Another systematic review has been conducted recently which has investigated autologous injections in chronic tendonopathy. This has also concluded that although current evidence shows signs of promise, there are still no high quality studies evaluating PRP (5). A recent double- blind randomised control trial has compared PRP with corticosteroid injections for LE. PRP has been proven to give better, long term results and hence currently the question is whether PRP or physiotherapy is the more superior treatment (24). Unfortunately there are no randomised trials comparing these two treatment modalities. We aim to compare physical therapy eccentric exercises with PRP injection in a randomised single blinded control trial.

Ethical considerations

This ethics proposal will aim to show that this trial will provide valuable information in the management of a common and debilitating condition while protecting the rights and interests of research participants.

Aims and Objectives

To investigate the efficacy of physical therapy compared with injections of platelet- rich- plasma (PRP) injections for the treatment of tennis elbow over the course of 52 weeks.

Type of Study

Radomised Control Trial.

Methods

This study will be single blinded as it is not possible to blind subjects to the treatment they receive. Once the physician deems that the patient requires treatment he/she will explain the trial to the patient. It is the responsibility of the physician to gain informed consent for the subject to be admitted into the trial so long as they meet the inclusion criteria. The patient will be made aware that the level of their care will not alter whether they consent to entering the trial or not and that they may freely exit the trial at any point. They will also be made aware that both treatments do work but this trial is to determine which is the more effective as current research is inconclusive on this.

Randomisation

Once the patient has given consent they will be given a random sealed envelope with instructions for their treatment. The patient will not be allowed to disclose treatment to the physician.

The instructions will guide the patient to being allocated to an injection clinic where a single injection

of PRP will be given. Alternatively they will be seen in a physiotherapy clinic when the patient will start a regime of eccentric training exercises. A total of eight physiotherapy sessions will be given. Patients allocated to the PRP arm of the study will have a sample of their own blood taken using the Recover System (Biomet Biologics, Warsaw, Indiana). A total of 27mls of blood will be collected in a 30ml syringe which already would contain 3mls of sodium citrate. A desktop centrifuge with disposable cylinders will be used to isolate the platelet rich fraction from the anticoagulated blood. The PRP would then be buffered to physiological pH using 8.4% sodium bicarbonate. A total of 3 ml of PRP will be injected into the patient.

Injection Technique

A total of 1ml of PRP will be injected into the area of maximum tenderness and the remaining 2mls into the extensor tendon in a fanning motion using the same puncture hole so as not to cause unnecessary pain. No other equipment would be needed and all the injections carried out by the same independent person certified for blood management. The time between collection of the blood sample and administration of the injection would be no longer than thirty minutes to maintain standardisation and freshness of the sample.

Outcome Measures

The outcome measures will include a visual analogue pain score (VAS), Disability of the Arm, Shoulder, and Hand score (DASH), as well as a disease specific score. The disease specific score will take the form of the Patient- rated Tennis Elbow Evaluation Questionnaire (PRTEE), which has been validated in assessing this disease (36). Assessments will be carried out prior to commencement of treatment, at 1 month, 3 months, 6 months and at the one year mark after commencement of treatment. In this study the hypothesis that injection of PRP increases the recovery of patients with LE compared with those treated with eight sessions of eccentric physiotherapy will be tested. Confidentiality of subjects and their personal details will be protected at all times. All data collected will be inputted into a secure database. This will only be accessible by members of the research team with a password.

Inclusion criteria:

All patients recruited to the study will be of minimum age 18 with a clinical diagnosis of tennis elbow, for a minimum duration of six weeks. All participants must freely volunteer to enter the trial without coercion.

Exclusion criteria:

1. Patients who had received other treatments over the course of the last six months. (This would include steroid injections but not oral analgesia).
2. Bilateral elbow symptoms
3. Cervical radiculopathy
4. Any other elbow joint pathology
5. Peripheral nerve involvement
6. Previous surgery to the elbow
7. History of dislocation, fractures, or tendon ruptures
8. Systemic neurological disorders
9. Contraindications to PRP
10. Patients not providing informed consent

Interventions: Eight sessions of physiotherapy; PRP injections.

Statistical Analysis and Sample Size

A similar study which looked at steroid injections versus physical therapy calculated that a minimum sample size of sixty participants in each group was required to detect a clinically important difference of 25% in success rate between their two groups, and assuming minimum success rate to be 68% at 52 weeks ($\beta = 0.2$, two tailed $\alpha = 0.05$). They had adjusted by adding 10% to account for any loss to follow up and hence aimed to get 66 volunteers per group. Thus we would require a minimum of 132 if we were to follow the same format a keep 66 volunteers to each group.

Ethical Aspect

Before proposing a study design one must consider ethical theories and principles as well as the current ethical legislation which is in place. These important principles will be discussed here and will justify our proposed method.

The first distinction that must be made is whether this is a therapeutic or non-therapeutic trial. Non-therapeutic trials aim to test health subjects with a treatment to see if it is safe. The subject has very little to benefit from the trial and thus these trials should be held up to greater ethical scrutiny. Therapeutic trials aim to administer a treatment to a subject with a condition, with the aim of improving that condition. This type of trial proposes that the treatment may be beneficial for the patient. Whilst therapeutic beneficence cannot be guaranteed, the intention and aims for this are there. However, good intentions aside, the overriding responsibility of clinical researchers must be to protect participants from unnecessary harm

and to ensure validity of their trials (25). In addition, the clinical subjects, must feel reassured that any treatment is for their potential benefit, likewise that they feel they are being protected from detriment from the proposed treatments. This is crucial in maintaining trust and the professional- patient relationship. If this trust is not maintained, it is likely that the subjects would leave the trial. Legal ramifications are then more likely to ensue (26-27). It has been found that medical research in particular seems to command trust from patients at least initially (28). The perception that medical researchers are highly competent professionals is one possible reason for this. (29-30). It may be that patients believe in the noble motivation of medical research or feel a sense of responsibility to help researchers (31). What ever the motivation of the clinical subject, this trust must be maintained at all cost. The description of the ideas of how this trial should conduct itself is based very much on the “human rights” ethical perspective (32), as is the majority of clinical research now.

There is guidance available which helps medical researchers in designing clinical research trials. In order to maintain patient trust as well as safeguarding patients the declaration of Helsinki, will be used as a framework in designing the methods (33). The declaration was made by the World Medical Association (WMA) and states that its function is to “promote and safeguard the health of patients, including those involved in medical research”. The declaration goes on to say that “the well-being of the individual research subject must take precedence over all other interests”. This means that even if a research project has the potential of doing good to a large population, it still does not hold more importance than the individual interests of the research subject. There is legislation stating rules and procedures that must be adhered to in clinical trials. The Medicines for human use (clinical trials) regulations 2004 is the English based legislation which applies to clinical trials. According to this, all CTIMPs must have permission from an ethics committee as well as a UK licensing authority, the Medicines and Healthcare products Regulatory Agency (MHRA). Therefore this ethical proposal will be submitted not only to the trust ethics committee but to the MHRA also for approval prior to commencing the research (34-35).

Researchers

Only the Authors stated.

Cost Analysis

Funding to be provided by Exactech UK.

Acknowledgement(s)

"AA" and "LJ" were the main authors of this research protocol. Both wrote and reviewed the final manuscript.

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