REVIEW ARTICLE

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Treatment of tendinopathy: is there a role for autologous whole blood and platelet rich plasma injection?

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SUMMARY

Background: Chronic tendinopathies are a common source of disability and can be recalcitrant to conservative measures, which once exhausted may necessitate operative intervention. Blood and platelets, in particular, are a rich source of factors necessary for tissue healing. Autologous blood injections (ABI) are thought to promote tendon healing, but have been explored clinically in only a few limited studies. However, recently they have attracted media attention in relation to the world of professional athletes and sports-related injuries. **Method:** We review the evidence base for this technique using the available literature on PubMed. **Conclusion:** Refractory chronic tendinopathy may be responsive to ABIs, but the data available to date are limited by quality and size of study, as well as length of follow up, and are currently insufficient to recommend this modality for routine clinical use.

Review Criteria & Message for the Clinic

There is currently much interest and media hype concerning autologous blood injections for the treatment of sports injuries, including chronic tendinopathy. This study reviews the basic science theory and exposes the paucity of evidence base behind this treatment modality. Although, *in vitro* and animal studies look promising, as do early clinical results, good quality, long-term data from large studies is still lacking. Until this is forthcoming, it does not have a deserved place among treatment modalities for chronic tendinopathy.

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Disclosures
None.

Methods

Literature search in PubMed (covering period from commencement to January 2010) of English and German language articles and Cochrane Central Register of Controlled Trials (through to January 2010), using the key search terms tendinopath*, autologous, blood, injection, platelet rich plasma, elbow, patella, achilles, plantar fasciitis, rotator cuff. Reports not cited in the aforementioned databases were searched using Google© search engine and the same key words. Both authors then screened the titles and abstracts for relevance – they were excluded where no clinical outcomes were reported, as were animal studies, conference abstracts and internet publications of lesser quality. Those evaluating the treatment modality under review in humans were included. Levels of evidence included – levels 2–4. No level 1 evidence had been published at the time of this review. This overview is based on 526 patients from 15 studies (Table 1).

Introduction

Tendinopathy, characterised by pain, weakness and stiffness, describes a common injury affecting a variety of tendons. It is often multifactorial, its aetiology related to abnormal joint mechanics or stiffness, with repeated trauma leading to intrasubstance degeneration, microtears and failure of healing (1–3). Pathologically, these conditions are characterised by fibroblast proliferation, vascular hyperplasia and disorganised collagen, more commonly termed angiofibroblastic hyperplasia, with little or no evidence of inflammation (4,5). There is no consensus on the ideal treatment of most tendinopathies. Conservative management includes rest, anti-inflammatory medications, analgesia, orthotics, physical therapy, local steroid injections, extracorporeal shock wave therapy and surgical debridement for refractory symptoms (4,6).

Autologous blood injection (ABI) for tendinopathy, is a relatively new treatment modality, that has been explored recently. It aims to directly deliver growth factors contained in blood to the injury site, to act as humoral mediators and biological catalysts in the healing cascade promoting tissue repair and regeneration. The procedure has been recognised by NICE, although the latest (January 2009) guidelines state that currently there is insufficient evidence for its routine use outside the setting of audit and research (7). The World Anti-Doping Agency bans (Prohibited List 2009) the use of ABIs (section M1)

Table 1 Summary of included key clinical studies on autologous blood injection for tendinopathy in humans

Study details	Level of evidence*	Key findings
Randomised controlled trials		
De Vos et al. (2000)	2	*n* = 54
JAMA		Self selected group of patients with Achilles tendinopathy
Stratified, block randomised, double blind, placebo controlled trial		Saline or platelet rich plasma injection, followed by eccentric exercise programme
Single centre		After adjustment for baseline scores no difference between treatment groups for VISA scores, satisfaction or return to sport
		No groups without exercise programme for comparison
Lee et al. (2007)	2	*n* = 64 (three lost to follow up thus 61 analysed)
Foot Ankle Int		Comparing autologous whole blood and corticosteroid injections in chronic plantar fasciitis
Prospective randomised controlled trial		Significant improvement ($p < 0.0001$) in VAS and tenderness threshold for both groups at 6 weeks and 6 months, greater improvement ($p = 0.094$) in corticosteroid group
Single centre		Second injection required in 6.5% (corticosteroid group) to 10% (autologous blood group)
		Greater incidence postinjection pain in blood injection group (53.3%) than steroid group (12.9%)
Kiter et al. (2006)	2	*n* = 44
J Am Podiatr Med Assoc		Consecutive patients presenting with chronic heel pain
Prospective randomised controlled trial		Comparing LA with dry needling vs. LA and steroid vs. LA and autologous whole blood injection
Single centre		All groups had significantly improved ($p < 0.001$) VAS scores after multiple injections, however, no difference between the groups
Non-randomised controlled trials/cohort studies		
Mishra et al. (2006)	2	*n* = 140 (patients with elbow epicondylar pain screened for enrolment in study)
Am J Sports Med		20 failed conservative management for chronic elbow epicondylitis of which 15 received platelet rich plasma vs. 5 received LA
Unblinded prospective study		
Single centre		Improved VAS (60% vs. 16% at 8 weeks) and Mayo Elbow Performance scores (52% vs. 14% at weeks) up to 6 months
		> 90% returning to normal activities, work and sport at 26 months
		60% drop-out rate in 'control' group
Reviews		
Rabago et al. (2009)	3	*n* = 208 (of which 109 on autologous blood injections)
Br J Sports Med		Comparison of autologous whole blood, platelet rich plasma, polidocanol and prolotherapy injections for lateral epicondylitis
Systematic review		All modalities showed improved VAS ($p < 0.05$), disease specific questionnaires, biomechanical elbow function and ultrasonic appearances
		Limitation of small sample sizes acknowledged, follow-up varied (9–108 weeks)
Case series		
Kon et al. (2009)	4	*n* = 20
Injury		Refractory patellar tendinopathy
		Improved VAS, Tegner activity, Medical Outcomes Study 36-Item Short Form after 3 injections of platelet rich plasma
		80% were satisfied, 70% complete or marked resolution at 6 months
Moon et al. (2008)	4	*n* = 24
Ann Acad Med Singapore		Chronic elbow tendinopathy
		Autologous bone marrow injection for lateral and/or medial epicondylitis after arthroscopic debridement
		Improved VAS and Mayo Elbow Performance scores in all patients
James et al. (2007)	4	*n* = 44
Br J Sports Med		Chronic patellar tendinopathy treated with autologous blood injection and dry needling
		At 15 months significant improvement in pain and function, improved ultrasound appearance in 22/24 knees
		6% failure of response – surgery
Connell et al. (2006)	4	*n* = 35
Skeletal Radiol		Refractory lateral epicondylitis
		Ultrasound guided autologous whole blood injections with dry needling
		Improved Nirschl and VAS scores ($p < 0.001$) at 4 weeks and 6 months
		Temporary pain and stiffness reported (25/35)

Table 1 (Continued)

Study details	Level of evidence*	Key findings
		Failure in 6% patients Some ultrasonographic evidence of tendon reparation
Suresh et al. (2006) *Br J Sports Med*	4	$n = 20$ Refractory medial epicondylitis treated with 2+ autologous whole blood injections/dry needling 85% had improved VAS ($p < 0.001$) and Nirschl scores ($p < 0.001$) at 4 weeks and 10 months Improvement in ultrasonographic tendon parameters ($p < 0.001$ for neovascularity and hypo-echoic changes, $p = 0.006$ for number of interstitial tears)
Barrett et al. (2004) *Podiatr Today*	4	$n = 9$ Ultrasound guided platelet rich plasma injection for chronic plantar fasciitis 77.8% patients were successfully treated with complete resolution of pain up to 1 year follow up Reduced thickness of plantar bands noted postinjection
Edwards et al. (2003) *J Hand Surg (Am)*	4	$n = 28$ Refractory lateral epicondylitis treated with up to three autologous whole blood injections No ultrasound guidance or dry needling Reduction in pain and Nirschl scores at mean of 9.5 months – 79% no pain even during strenuous activity 2/28 patients required narcotic analgesia for temporary postinjection pain 4% failure requiring surgery
Case reports		
Logan et al. (2006) *Am J Phys Med Rehabil*	4	$n = 1$ Patient with spastic hemiplegic cerebral palsy and refractory plantar fasciitis Successfully treated with autologous whole blood injection, botulinum injection and night splint Doubtful importance as difficult to attribute improvement to blood injection

*As per Centre for Evidence Based Medicine (http://www.cebm.net/index.aspx?o=1025).
LA, local anaesthetic; VAS, visual analogue score; VISA, Victorian Institute of Sports Assessment.

and products containing growth factors (section S2) in sports medicine as the presence of factors such as growth hormone, insulin-like growth factor 1 and mechano growth factor are seen as potential performance enhancing substances (8). Platelet-derived preparations were not explicitly listed and application under the International Standard Therapeutic Use Exemption (ISTUE) could be made. This stance changed 1 January 2010, with growth factors affecting muscle, tendon or ligament status, and platelet derived preparations administered by intramuscular route being explicitly listed in the Prohibited list (S2). Other routes of administration of platelet-derived products require a declaration of use in accordance with the ISTUE. These applications may be limited by the current level of evidence. The International Olympic Committee has also recently acknowledged the possible benefits, but also potential misuse of products containing growth factors, engaging scientific advisors to monitor new developments in this field (9). We review the available literature, and evidence surrounding its use in chronic tendinopathy. Its use in acute ligament and muscle injuries, fractures, bone healing, osteoarthritis and acute cartilage repairs is outside the scope of this review (10–12). A brief review of the basic science of growth factors is also provided.

Basic science of tendinopathy and growth factors

There is ample literature on tendon injury and healing, as well as the basic science of growth factors. Our intention is to highlight the salient points related to ABIs, rather than provide an exhaustive review. Tendon repair and regeneration involves three overlapping stages (1,13–16). The acute inflammatory stage is characterised by haematoma formation, migration of blood cells into the injury site, phagocytosis of necrotic material, release of pro-inflammatory cytokines and angiogenic factors and fibroblast recruitment. Within days the proliferative stage begins with continued recruitment and proliferation of fibroblasts, which are primarily responsible for collagen (largely type 3) and proteoglycan synthesis, as well as other components of the tendon extra-

cellular matrix. During the final remodelling stage approximately 6 weeks post injury, type 3 collagen decreases, with an increase in type 1 collagen and its mechanical reorganisation (to run in longitudinal bundles), as well as reduced glycosaminoglycan synthesis. With consolidation (for up to 10 weeks), repair tissue changes to more fibrous tissue, then gradually changing into scar-like tendon tissue whilst maturing over a year. Normal physiological use of the tendon further induces remodelling and acquisition of final tendon stability and strength.

On a more molecular level, several growth factors are known to be important in the activation and regulation of musculoskeletal tissues, including initiation and acceleration of tendon repair and regeneration, by recruiting stem cells, stimulating fibroblast proliferation, migration and collagen production, and helping induce neovascular growth (angiogenesis) (17,18). They are small peptides secreted by many tissues including haemopoetic stem cells, platelets, white blood cells, polymorphonuclear leucocytes, connective tissue and solid organs. By binding to cell surface receptors, activating specific intracellular signalling pathways via DNA synthesis and expression (i.e. transcription of specific regulatory genes), they influence the growth, differentiation and development of these cells. These signalling molecules may act independently or synergistically with other growth factors (18,19). They have a short half life and quick systemic lavage (17,20), with a subsequently limited duration of action (hours to days) and hence need to be placed close to the site of the lesion – either by direct injection, impregnation on scaffolds or sutures, or gene therapy (21). The latter involves delivering genetic material (encoding growth factors) to cells usually via viral vectors by *in vivo* or *ex vivo* transfection, to alter and promote the growth factor production (16). Although this enables more prolonged exposure to growth factors, studies have been limited to animal models on transected tendons (19). Growth factors have been extensively reviewed in the literature and those implicated in tendon healing are summarised in Table 2 (13,14,17–19,22–28).

Blood and platelets, in particular, provide the richest source of these growth factors, storing and releasing them from their cytoplasmic ά-granules (25,29,30). Platelets are one of the first cells to arrive at a site of injury, and can be activated by a large number of bioactive molecules, including thrombin, which in itself has stimulatory properties in common with growth factors. This and their capacity to release a multitude of growth factors means they are being explored as a delivery tool for growth factors and role in soft tissue healing (10,31). The technique of deriving platelet-rich plasma (PRP) preparations was developed in the 1990s for use in maxillofacial surgery, although its use has since spread to orthopaedic and plastic surgery, limb and myocardial ischaemia and ophthalmology (32,33).

Outline of the procedure

Prior to the procedure ultrasonography (USS) assesses the state of the tendon, and identifies the location of intrasubstance tearing. Blood is withdrawn from the patient by standard aseptic venesection usually from the antecubital fossa and after a few minutes injected into the area of tendinopathy (2–5 ml depending on tendon size). Local anaesthetic and ultrasound guidance are typically employed, and the injection may be preceded by dry needling. This involves repeatedly passing the needle into tendon substance to create fenestrations, thereby disrupting fibrils and causing internal bleeding, and has long been known to reduce myofascial and musculoskeletal pain (34,35). Ultrasonic guidance allows accurate targeted injection into the sites of sonographic abnormality (alteration of echo texture, interstitial tears, neovascularity). Partial or full thickness tears are a contraindication to this method.

There are three commonly utilised techniques encompassed by the phrase 'ABI' – autologous whole blood injection, PRP and autologous conditioned serum (ACS) (22). With autologous whole blood injection, up to 5 ml of blood is withdrawn and injected directly into the area of tendinopathy, with no additional processing. PRP is prepared from whole blood (20–60 mls) which is centrifuged to concentrate platelets in plasma, although its specific elements have not been clearly defined in the literature, with platelet preparations differing between studies (11,36). It usually requires the addition of an anticoagulant to prevent premature activation of the platelets. Alternatively, ACS involves incubating whole blood with glass beads, then centrifuging it to obtain serum which contains the released cytokines and growth factors (37). The latter has mainly been investigated in context of muscle strains rather than tendinopathy (38). Following the procedure, protocols vary, but the patient may use the limb normally, avoiding excessive or strenuous exercise/use for several weeks, be splinted or undergo a formal rehabilitation programme.

Areas of clinical application

Growth factors are an exciting prospect in the treatment of tendinopathy as a result of their ability to stimulate the healing cascade of musculoskeletal

Table 2 Summary of growth factors playing a role in tendinopathy

	Site of release	Action
Transforming growth factor-β (TGF-β_1)	Many cells	Cellular proliferation Cellular migration Cell-matrix interactions Collagen synthesis (types 1 and 3)
Basic fibroblast growth factor (b-FGF)	Fibroblasts Inflammatory cells	Angiogenesis Cellular proliferation Cellular migration Cell-matrix interactions
Platelet derived growth factor (PDGF)	Platelets	Expression and interaction of other growth factors Cellular proliferation Angiogenesis Collagen synthesis
Insulin-like growth factor type-1 (IGF-1)	Platelets Plasma Liver	Cellular proliferation Cellular migration Collagen synthesis Extracellular matrix synthesis (e.g. proteoglycans) and remodelling
Vascular endothelial growth factor (VEGF)	Platelets	Neovascularisation/angiogenesis Increases capillary permeability Establishment and maintenance of epitenon and endotenon vasculature
Epidermal growth factor (EGF)	Platelets	Cellular proliferation Chemotaxis
Bone morphogenetic protein 12 (BMP-12)*	Platelets	Increased collagen type-1 expression
Cartilage-derived morphogenetic protein (CDMP)*†	Chondrocytes	Collagen synthesis (tendon-like tissue) Bone and cartilage formation

*Member of TGF-β superfamily.
†Also known as BMP-13 (CDMP-2) and BMP-14 (CDMP-1).

tissue. Numerous animal and human studies have investigated the effects of autologous whole blood injections and PRP in tendinopathy, and whether the laboratory findings can be translated into clinical results. Our review is intended to be comprehensive, focusing on those studies involving human subjects.

Lateral elbow epicondylitis

Lateral epicondylitis is characterised by microfibroangioblastic changes to the common extensor origin (in particular extensor carpi radialis brevis). Several studies look at the use of ABI in this common condition.

Connell et al. (39) performed dry needling with autologous whole blood injection under ultrasound guidance in a cohort of 35 patients with refractory symptoms (mean duration 13.8 months). In 33 patients, visual analogue score (VAS) and Nirschl scores decreased significantly in the short term (4 weeks and 6 months), with ultrasonographic evidence of tendon reparation (reduction in tendon thickness, interstitial cleft formations, anechoic foci and neovascularity). However, no tendon returned to a normal appearance and evidence of residual tendon abnormality did necessarily correlate to symptoms. The procedure failed in 6% of patients, and all received multiple injections (74% two injections, 26% received a third injection). The two failures were excluded from pain analysis, which may have favourably skewed the results towards blood injection.

Similar results were noted in a case series of 22/28 patients who received up to three autologous whole blood injections (without dry needling or ultrasound guidance) (40). Prestudy symptoms existed for at least 3 months, and patients had tried numerous conservative measures, including steroid injections (eight patients). Although this was a prospective study, it studied a self-selected group of patients. The consecutively recruited patients were offered numerous options and those who selected ABI were analysed in the study. The study methodology thus introduced inherent subject bias. Postoperatively, stretching began after 3 weeks of splinting. Further

injections (nine patients) were offered every 6 weeks if pain relief was not satisfactory. At a mean follow up of 9.5 months (6–24 months) reduction in pain and Nirschl scores was noted, with complete pain relief (by 3 weeks maximum benefit) even during strenuous activity in 79% of patients; 4% failed treatment and required surgical treatment.

Ghani et al. (41) in their case series of 26 patients with refractory symptoms (mean duration 2.1 years) found improved pain and Nirschl scores at an average of 8 months follow up. Most patients received one injection of autologous whole blood, with nine patients requiring two. Overall, 15 (58%) returned to all activities, seven returned to modified activities and four avoided strenuous activities altogether.

Moon et al. (42) also noted significant improvement in VAS and Mayo elbow performance scores in the short term (8 weeks and 6 months) following autologous bone marrow plasma injection, for chronic elbow tendinopathy (mean duration of symptoms 15 months). It involved a more invasive procedure of sampling and centrifuging bone marrow plasma taken from the iliac crest, and injecting (no dry needling) this around the lateral or medial epicondyle after arthroscopic debridement. Postoperative physiotherapy was instigated after 2 days of immobilisation. All 24 patients noted improvement in their pain and function, with no complications related to the procedure.

Mishra et al. (43) performed a prospective cohort study on 140 patients with elbow tendinopathy of at least 3 months duration. In the 20 patients who failed their conservative management, 15 received a single injection (with dry needling) of buffered PRP, whereas the five patients in their 'control' group received simple bupivacaine. There was no blinding, and hence placebo effect and bias contributing to the results is a possibility. Prior to treatment symptoms had existed for an average of 15.3 months in the study group, thereby reflecting the more severely affected patients in the cohort. Postoperative physiotherapy included stretching and strengthening exercises. A statistically significant improvement was noted in the VAS and Mayo elbow performance score of the PRP cohort compared with the 'control group' at 8 weeks, this improvement persisted at 6 months, with no complications. At 26 months, 99% of the PRP group had returned to their daily living activities and 94% their work or sporting activities. However, this was a non-randomised controlled trial of a small number of patients. Additionally, only patients who had the blood injection were followed up beyond the first 8 weeks as over 60% of those patients in the control group had dropped out, prohibiting further direct comparison.

A recent systematic review of the literature (44) looking at four different injection therapies supports the use of autologous whole blood and PRP injections, as well as polidocanol (a vascular sclerosant) and prolotherapy, with all modalities showing improved VAS scores, disease-specific questionnaires, biomechanical elbow function and ultrasonographic appearances, although the authors acknowledged that the reviewed evidence was limited by small sample size.

Medial elbow epicondylitis

The less common medial epicondylitis is characterised by similar histopathological changes, but to the common flexor origin (usually flexor carpi radialis and pronator teres). There is less data evaluating blood injections in these patients. We found only one study specifically evaluating medial epicondylitis. Suresh et al. (45) demonstrated a statistically significant reduction in VAS and Nirschl scores in 17/20 patients (85%) with refractory symptoms (mean duration 12 months) at both 4 weeks and 10 months. All patients had two autologous whole blood injections, except two (10%) who required a third; dry needling was performed. Ultrasonographic parameters improved significantly following injection, although none of the treated tendons returned to a normal appearance, corroborating findings in lateral epicondylitis (39). The three failures were awaiting surgical intervention. No complications were noted in their cohort of patients.

In Moon's study (42), some of the study patients had medial epicondylitis (five isolated, four medial and lateral sides involved) with improved VAS and Mayo elbow performance scores, although a comparison in outcomes between medial and lateral epicondylitis was not drawn. Mishra's study (43) also included 1/15 patients with medial elbow tendinopathy and although the study group's VAS and Mayo elbow scores improved overall, these patients' results were not separately discussed.

Achilles tendon

Chronic Achilles tendinopathy is considered a troublesome injury to treat and non-surgical treatment is unsuccessful in about 25% of patients (46). Histopathological findings reveal increased vascularity and vascular proliferations in biopsies of patients with degenerate tendons or spontaneous ruptures, with increased expression of vascular endothelial growth factor receptors, VEGFR-1 and VEGFR-2 (47). These results showed that the possible targets for VEGF, an important inducer of neovascularisation, are expressed in degenerative tendon tissue, and may

thus be useful in therapy. Increased expression of transforming growth factor-β (TGF-β) and insulin-like growth factor type-1 has also been seen in animal models following shockwave treatment to Achilles tendons, leading to tendon regeneration (48). Numerous animal studies (23,49,50) have noted potential benefits of ABIs, although clinical application of the methods developed in these experimental models is lacking.

Sanchez et al. (51) performed a small study on augmentation of surgical Achilles tendon repair with platelet rich fibrin matrix (six patients), and retrospectively compared this with patients receiving a non-enhanced repair. No complications were noted and patients receiving the matrix had significantly better range of movement, with earlier return to gentle running.

De Vos et al. (52) performed a stratified, block randomised, double blind, placebo controlled single centre trial on 54 patients with clinically diagnosed tendinopathy (symptoms present at least 2 months). Stratification was based on preinjury activity levels and patients either received saline or PRP injection followed by an eccentric exercise programme. Although Victorian Institute of Sports Assessment (VISA) – Achilles scores improved significantly within the PRP group after 24 weeks, once adjusted for baseline VISA scores and duration of symptoms, there was no difference between the treatment groups at 6, 12 and 24 weeks. There was also no significant difference in patient satisfaction or number returning to their desired sport. The authors felt the clinical improvement seen in both groups was likely to be secondary to the eccentric exercises. Some limiting factors in this study include the self-selected group of patients, who sought active participation in the study, absence of ultrasonographically confirmed tendinopathy, and lack of a PRP group without eccentric exercises.

Patellar tendinopathy

This is a common condition characterised by anterior knee pain and tenderness around the inferior pole of the patella. Although there is some evidence from *in vitro* (26) and animal models (53) that growth factor supplementation and autologous whole blood injections enhance patellar tendon healing and strength, few human studies on ABI in patellar tendinopathy exist.

A case series (54) looking at 44 consecutive patients (47 knees) with USS confirmed patellar tendinopathy (mean duration of symptoms 12.9 months), investigated the response to dry needling and autologous whole blood injection (two injections 4 weeks apart). Following the second injection, a specific physiotherapy regime was implemented. Knee function and pain were determined using a validated questionnaire (VISA score) and ultrasonographic findings (21 patients, 24 knees only) were documented at a mean of nearly 15 months post-treatment. Treatment failed in three (6%) patients overall – these required surgical decompression. Those (24/47) assessed ultrasonographically had significant reduction in tendon thickness (92% of patients), echo texture (92%) and resolution of interstitial fissures (58%), although neovascularity did not routinely increase as the authors expected. Notably, numerous clinicians were involved and thus operator experience may have been variable, and the independent effects of dry needling and ABIs could not be differentiated. No untoward events relating to treatment were commented on.

More recently, a small prospective uncontrolled series (55) of 20 male athletes who had failed conservative treatment for a mean of 20.7 months, had improved VAS, Tegner activity and Medical Outcomes Study 36-Item Short Form, after receiving three injections of PRP at 15 day intervals. No adverse outcomes were reported, with 80% patient satisfaction, and 70% complete or marked resolution of symptoms.

Plantar fasciitis

Chronic plantar fasciitis has an unpredictable response to treatment. A case report of a young lady with spastic hemiplegic cerebral palsy who had refractory (5 months duration) plantar fasciitis and was treated with a combination of autologous whole blood injection into the plantar fascia and botulinum injection into the gastrocnemius, reported improved pain and ankle dorsiflexion (56). Postinjection stretching exercises and night splinting were employed. The improvement remained at 1 year follow-up. As ABI was used in addition to other treatment modalities, the improvement cannot be confidently attributed to it. A prospective randomised controlled trial of 64 patients (57) comparing corticosteroid to autologous whole blood injection found a statistically significant reduction in VAS and improved tenderness threshold for both groups, although improvement was better in the corticosteroid group at 6 weeks and up to 6 months. A small number of patients in both groups required a second injection at 3 months. Postinjection pain requiring analgesia was noted in 53.3% of the blood injection patients, compared with 12.9% of those receiving steroids. A further small, prospective randomised study

of 44 patients compared the infiltration of local anaesthetic (LA) with dry needling, LA with autologous whole blood or LA and corticosteroid at 6 months and found an improvement in all groups, but no statistically significant difference in VAS between them (58). Multiple injections were performed in all three groups, although it was noted that none in the corticosteroid group required a third injection. Barrett and Erredge (59) reported on nine patients who underwent ultrasound guided PRP injection after a 90-day wash-out period, with six patients achieving complete resolution of pain within 2 months. A further patient achieved complete pain relief after a second PRP injection, as did another patient who received a corticosteroid injection outside of the study parameters. Overall, 77.8% of the patients were successfully treated, although it is worth bearing in mind that this was a small, uncontrolled study.

Rotator cuff

There is paucity of evidence in the literature for use of autologous blood products in cuff pathology. Human subacromial bursal samples taken at the time of surgery for rotator cuff repairs show increased expression of interleukin-1, tumour necrosis factor-α, basic fibroblast growth factor and TGF-β when compared with similar specimens taken from patients with anterior shoulder instability, suggesting involvement of growth factors in rotator cuff pathology (60). Increased VEGF expression is also known to occur in cuff pathology, possibly accounting for the pain and synovial proliferation encountered (61). Although they are known to be pathological, there is evidence to suggest that growth factors may also be therapeutic in cuff pathology.

In animal models, repair of transected rotator cuff tendons augmented with bone morphogenetic protein 12 (62,63) or cartilage-derived morphogenetic protein 2 (64) have shown greater volume of newly formed bone and soft tissue, as well as greater load-to-failure, stiffness and strength. Whilst tissue augmentation secondary to growth factors occurs, clinical correlation and published studies on humans are limited. PRP-augmentation of arthroscopic rotator cuff repairs improves pain and functional outcome (65). Further clinical studies assessing ABI for tendinopathy and intratendinous delamination tears are awaited.

Safety of the procedure

Potential adverse effects of injections include allergic reaction, infection, injury to adjacent (neurovascular) structures, bruising at the injection site, pain and stiffness, and tendon rupture. Most studies reported no untoward events. Temporary pain (comparable to steroid injections, occasionally requiring narcotic analgesia) and stiffness were most commonly reported (39,40). Pain is associated with the first stages of tendon healing, which take up to 3 months, and is thus not an unexpected feature of blood injection treatment. Most studies reported no adverse or long-term effects, although some failed to disclose the presence/absence of side effects. Study designs to date are additionally limited by small numbers and short term follow up.

Discussion

Autologous blood injections for tendinopathy aim to augment the natural healing process of tendon repair and regeneration, by directly delivering growth factors to the site of injury. The biological basis and theory behind ABIs for chronic tendinopathy look promising. Numerous *in vitro* and animal studies suggest beneficial effects of ABIs on the outcome of tendon healing and tendinopathy. However, to date there is little clinical data, and care is needed in extrapolating experimental and animal models to clinical effects in humans. The clinically applicable evidence to date stems mainly from case series and uncontrolled trials, or small, underpowered controlled studies and hence it is difficult to rule out a placebo response. In addition, the differing study protocols make it difficult to compare patient groups and results. These limitations are acknowledged by NICE (7), who have based their latest guidelines on a 'rapid review' of the medical literature and specialist opinion. Their Interventional Procedures Advisory Committee recommends limiting ABI use outside the setting of clinical governance, consent and audit or research.

Although diagnosis of the condition varied, most studies employed some form of imaging modality (ultrasound, MRI). An exception is Mishra et al. (43) who confirmed their diagnoses clinically, and also performed the injections without radiographic guidance [as did Edwards et al. (40)]. In tendinopathy, characteristic features such as macroscopic tears are readily evident on imaging. We feel ultrasonic assessment is beneficial as it helps to guide the needle into the affected area, may aide monitoring the healing process and can exclude large tears that are unlikely to respond to blood injections.

The definition of acute vs. chronic tendinopathy is blurry, with a variable mean duration of symptoms prior to enrolment in the studies – 3 months (40,43) to 15 months (42). This makes comparing the studies difficult. Additionally, degenerate tendon pathol-

ogy, such as that seen particularly in relation to the rotator cuff and Achilles tendon, may be minimally or unresponsive to blood injections. This needs further investigation.

Studies mostly used autologous whole blood, although some used platelet enriched blood (differences in processing techniques) (42,43,51). To date, there is no evidence of any difference between the types of blood products, and more studies are needed to elucidate this. However, some believe that growth factors work in a dose-dependent manner and hence a more concentrated source of growth factors such as that provided by platelet rich products is needed for the technique to be beneficial (18). Alternatively, it may be that the growth factor concentration and/or action is affected by other blood cells (e.g. white blood cells) present in whole blood (36,66). Additionally, PRP generally requires a single injection, whereas autologous whole blood tends to involve multiple injections, as seen throughout the studies. This has implications on cost and patient recovery time.

Dry needling, which itself is thought to have a therapeutic effect in tendinopathy, was employed in many of the studies, and thus in these one cannot confidently conclude that the beneficial effects solely resulted from the blood injection. No study comparing dry needling alone to ABI has been performed, although one study (58) noted no significant difference in improvement between LA/dry needling and LA/ABI. Those studies directly comparing ABI with steroids (57,58) have also not shown a significantly improved response to ABI over more traditional treatment, although in others ABI improved symptoms which had been refractory to steroid injections (39–43,45).

Postinjection protocols (immobilisation vs. physiotherapy vs. nil formal) varied and may have confounded results. Physiotherapy, especially eccentric loading exercises, is likely to play a role during the remodelling stages of tendon repair, and thus should be given due consideration postblood injections (6). Length of follow up also varied from weeks to months, rather than longer term.

In conclusion, early results look promising especially in refractory cases of tendinopathy that have been unresponsive to traditional treatment modalities, but are based on laboratory studies and small clinical studies. Longer term well-conducted studies of sufficient sample size, using validated clinical, radiological and biomechanical measures and biomarkers to reflect tissue healing, are needed to further elucidate this treatment modality and its potential efficacy and safety, and whether it provides advantages to more traditional treatment modalities. Only following this might there be a deserved place among treatment modalities for chronic tendinopathy.

Author contributions

Rebecca J. Kampa: participated on working through the whole document. She was responsible for conception and design, acquisition and analysis of data, as well as drafting of the manuscript. David A. Connell: participated on working through the whole document. He was responsible for conception and design, acquisition and analysis of data. He was responsible for critical revision of the manuscript.

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