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PERIPHERAL BLOOD MONONUCLEAR CELLS INJECTION FOR THE TREATMENT OF CHRONIC EPICONDYLITIS

CASE SERIES - 12TH MAR 2019

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Chronic Epicondylitis

6 months
follow-up

8 patients

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RATIONALE

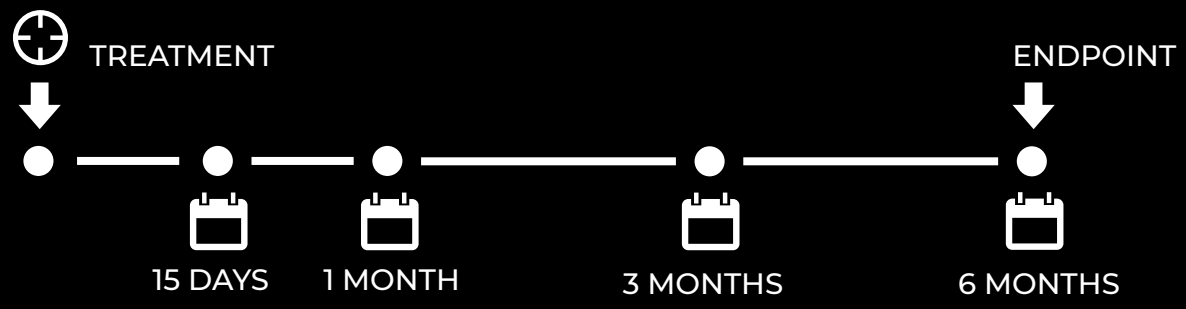
Tendinopathy is a degenerative disease characterized by pain, swelling, and thickening of tendons. Chronic inflammation and vascular degeneration impair the natural mechanisms of repair, allowing the formation of fibrous tissue that makes tendons more subject to secondary lesions due to substandard mechanical properties (Nichols et al., 2019). Since the increase in the prevalence of tendinopathies in the adult sports population and the high rate of failure in the treatment options, researchers have focused on the biological mechanisms of tendon healing to reduce post-operative lesions re-occurrence and to improve long-term tendon functionality. Overuse and micro-trauma associated with an abnormal microvascular response are the main reasons for failure in tendon repair. Reduction of blood flow leads to a lack of oxygen and nutrients, slowing down regeneration and promoting tissue degeneration – a process exacerbated by aging and over-load. Moreover, angiogenesis is impaired by the release of inhibitor factors by fibroblasts and reduced tenocytes paracrine activity, triggering a vicious circle (Pufe et al., 2005).

Platelet-rich plasma (PRP) is extensively used in tendinopathies treatments because of the therapeutic potential of growth factors that favor tissue regeneration. Intra-tendinous injection of PRP temporarily increases the angiogenic phase and subsequently leads to its rapid reduction, thus accelerating tendon healing (Fitzpatrick et al., 2017; Lyras et al., 2010; Di Matteo et al., 2015). Recently, PRP indications have generated some controversies (Filardo et al., 2018); different preparations of PRP exist, and one main difference is the presence or absence of leucocytes. PRP with peripheral blood mononuclear cells (PBMCs) can ameliorate tendon healing increasing collagen production, exploiting the anabolic potential of monocytes, and avoiding the hazardous reactivity of neutrophils (Yoshida et al., 2013).

Monocytes and macrophages support angiogenesis and arteriogenesis during development, homeostasis, and vessel repair (Cheyne et al., 2019). Monocytes, recruited during vascular damage, adhere to the endothelium, and their number positively correlates with the growth capacity of collateral vessels. In response to hypoxia, endothelial cells and pericytes involved in the tissue damage niche release Vascular Endothelial Growth Factor (VEGF) capable of inducing a robust tissue infiltration of monocytes from the peripheral circulation. Then, cells can release soluble factors, favoring matrix remodeling and neo-endothelium reassembly (Heil et al., 2019; Melgar-lesmes et al., 2016).

The objective of this study is to evaluate the safety and efficacy of PBMCs treatment to promote repair, regeneration, and recovery of the normal functionality of the tendon tissue in patients affected by epicondylitis.

METHODS



Symptomatic Chronic Epicondylitis
With no intra-tendinous hyper-vascularization, tendon thickening, and osteitis-dependent edema adjacent to enthesis

Monocytes (PBMCs)
2 ml w/ 18G needle under ultrasound guide

8 patients

VAS
Modified Mayo Elbow score

MRI
Ultrasounds (B-mode and Power doppler)

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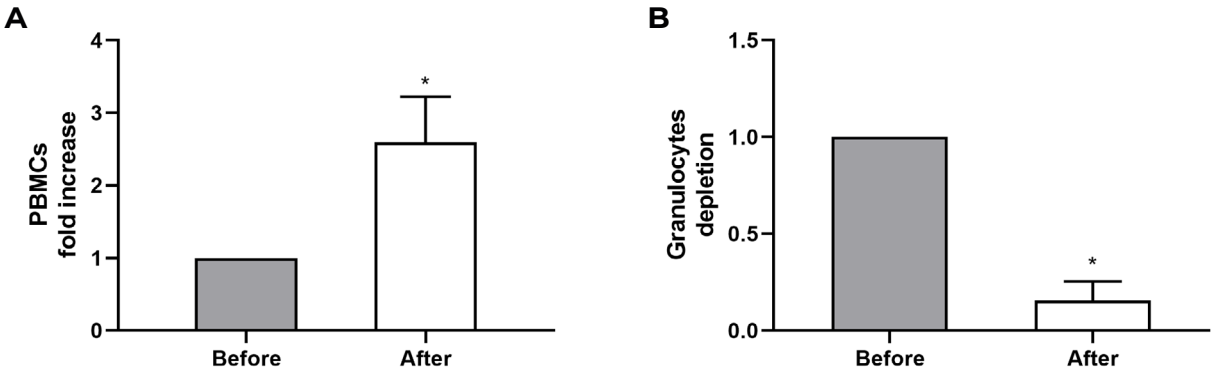
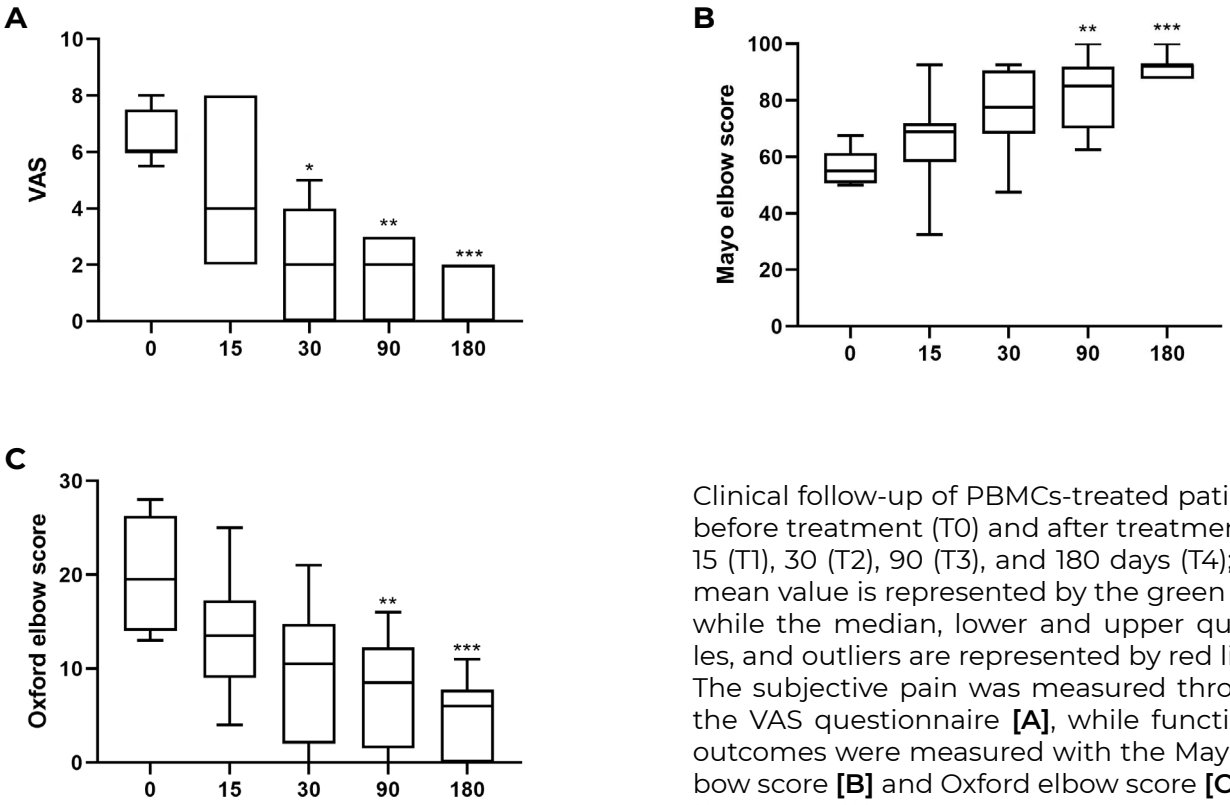
BLOOD COUNT TESTS



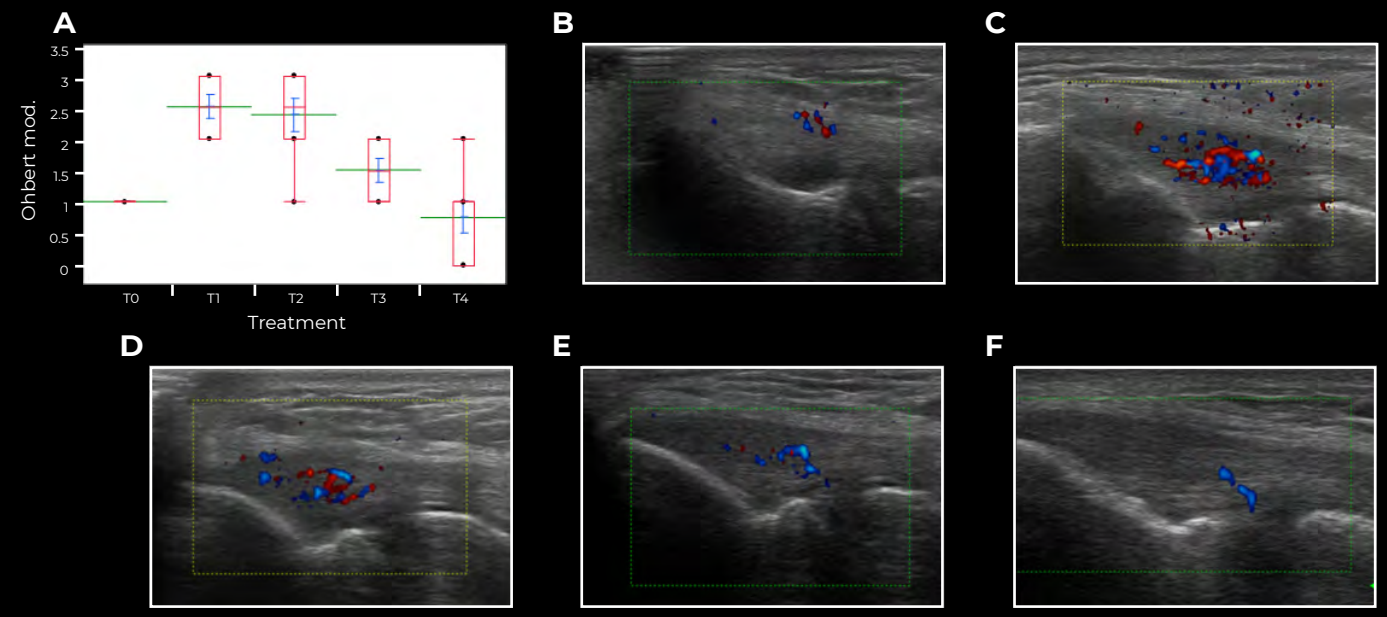
Blood count test for cell quantification before and after Monocytes processing. **[A]** PBMCs total count includes monocytes and lymphocytes. **[B]** Granulocytes total count includes neutrophils, eosinophils, and basophils. * $p < 0.05$

RESULTS ON FUNCTIONALITY

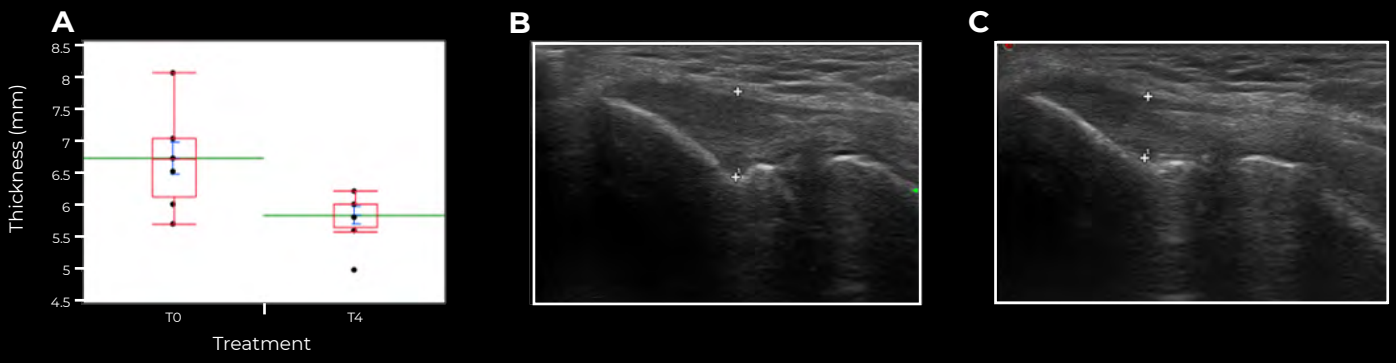


Clinical follow-up of PBMCs-treated patients before treatment (T0) and after treatment at 15 (T1), 30 (T2), 90 (T3), and 180 days (T4); the mean value is represented by the green line, while the median, lower and upper quartiles, and outliers are represented by red lines. The subjective pain was measured through the VAS questionnaire **[A]**, while functional outcomes were measured with the Mayo elbow score **[B]** and Oxford elbow score **[C]**.
** $p<0.005$; *** $p<0.001$

ULTRASOUND FINDINGS



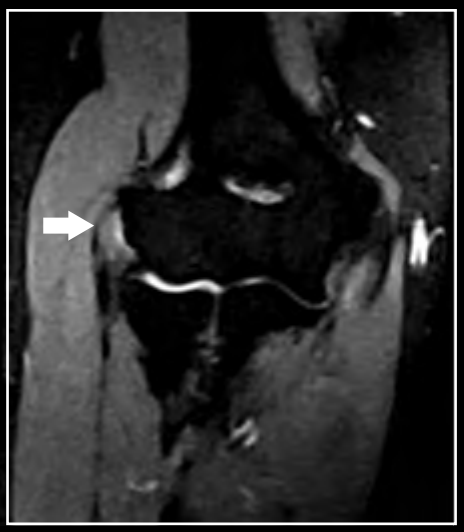
Epicondyle vascularization analysis through modified Ohberg score before treatment (T0) and after treatment **[A]**. Representative Power Doppler ultrasound scans before treatment (T0) **[B]** and after treatment at 15 (T1) **[C]**, 30 (T2) **[D]**, 90 (T3) **[E]**, and 180 days (T4) **[F]**.



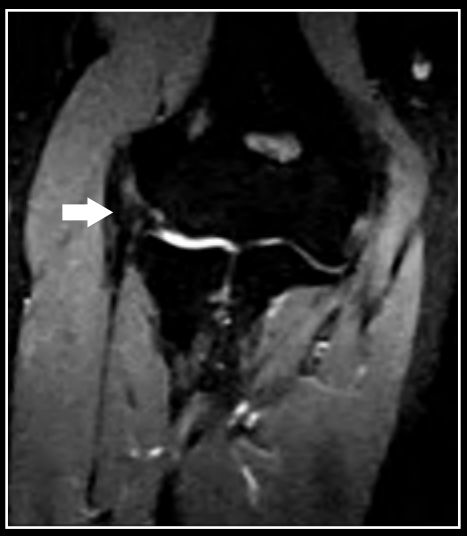
Epicondyle tendon thickness analysis before (T0) and 180 days after treatment (T4); the mean value is represented by the green line, while the median, lower and upper quartiles, and outliers are represented by red lines **[A]**. Representative B-mode ultrasound scans before **[B]** and 180 days after treatment **[C]**.

MRI FINDINGS

A



B



Representative RMI scan of epicondyle tendon before treatment **[A]** and 180 days after treatment **[B]**.

DISCUSSION

We tested the clinical outcome of 8 patients affected by chronic epicondylitis treated with injections of autologous PBMCs obtained with a centrifuge-independent point-of-care medical device.

With Power Doppler ultrasound imaging, we found an increase of intra-tendinous vascularization after PBMCs injection, followed by a physiological decrease. The hypo-vascularization of tendons limits the natural healing mechanisms of the tissue; thus, an angiogenic stimulus can trigger a proper tendon regeneration providing nutrients and oxygen supply and restoring microcirculation homeostasis. This activity may be due to monocytes activity, which releases VEGF and promotes vessel remodeling through endothelial cells re-assembly (Cheyne et al., 2019; Heil et al., 2019; Melgar-lesmes et al., 2016).

The paracrine effect of injected PBMCs may also play a role in pain control (Ogle et al., 2016), explaining the efficacy of the therapy in ameliorating pain and functional symptoms just after 15 days with improving results until 6 months. Decrease of swelling and improved tendon structure, observed with B-mode ultrasound and MRI images, correlate with clinical data and with the finding that macrophages activation likely contributes to the degradation and subsequent repair of injured tendon tissue through an epithelial-to-mesenchymal transition (Sugg et al., 2014).