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Ultrasound-guided platelet-rich plasma injections for the treatment of common peroneal nerve palsy associated with multiple ligament injuries of the knee

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Abstract
Purpose Peroneal nerve palsy in traumatic knee dislocations associated with multiple ligament injuries is common. Several surgical approaches are described for this lesion with less-than-optimal outcomes. The present case represents the application of plasma rich in growth factors (PRGF) technology for the treatment of peroneal nerve palsy with drop foot. This technology has already been proven its therapeutic potential for various musculoskeletal disorders. Based on these results, we hypothesized that PRGF could stimulate the healing process of traumatic peroneal nerve palsy with drop foot.
Methods The patient was a healthy 28-year-old man. He suffered peroneal nerve palsy with drop foot after multiple ligament injuries of the knee. PRGF was prepared according to the manufactured instruction. Eleven months after the trauma with severe axonotmesis, serial intraneural infiltrations of PRGF were started using ultrasound guidance. The therapeutic effect was assessed by electromyography (EMG), echogenicity of the peroneal nerve under ultrasound (US) and manual muscle testing.
Results Twenty-one months after the first injection, not complete but partial useful recovery is obtained. He is satisfied with walking and running without orthosis. Sensitivity demonstrates almost full recovery in the peroneal nerve distribution area. EMG controls show complete reinnervation for the peroneus longus and a better reinnervation for the tibialis anterior muscle, compared with previous examinations.
Conclusion Plasma rich in growth factors (PRGF) infiltrations could enhance healing process of peroneal nerve palsy with drop foot. This case report demonstrates the therapeutic potential of this technology for traumatic peripheral nerve palsy and the usefulness of US-guided PRGF.
Level of evidence V.

Keywords Plasma rich in growth factors · Platelet-rich plasma · Drop foot · Common peroneal nerve palsy · Knee · Ultrasound-guided injection

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Introduction

Peroneal nerve injury in traumatic knee dislocations associated with multiple ligament injuries is quite common [25, 28]; in fact, most studies have reported an incidence of 25–36 % of peroneal nerve palsy in these types of lesions [14, 18, 20]. Clinically, these patients present mainly with a drop foot accompanied by pain and a sensory deficit on the anterolateral skin of the leg. Recovery of ankle dorsiflexion is likely in more than 80 % of cases when the nerve

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is in continuity [5, 12, 28], but traction injury may impair nerve conduction even when the nerve is intact. If spontaneous nerve regeneration does not occur within 6 months, it is common practice to surgically inspect the nerve at the site of possible trauma to search for nerve interruption and extraneural impairment [7].

Numerous surgical techniques have been described for the treatment of peroneal nerve palsy after knee dislocation, with non-optimal outcomes. However, the most difficult surgical decision is how to approach the non-conducting but continuous peroneal nerve, and it is often necessary to perform neurolysis and nerve conduction studies. Despite these efforts, full function recovery does not always follow; therefore, novel treatment techniques are demanded to address this issue.

Here, it is described a case patient who was treated during 22 months for drop foot with common peroneal nerve palsy associated with multiple ligament injuries of the knee by applying intraneural injections of plasma rich in growth factors (PRGF), an autologous of platelet-rich plasma (PRP); the patient obtained partial but satisfactory and functional recovery. After reviewing the literature, we noted that there is no case similar to this. In our opinion, it is very stimulating, and our purpose is to report it in order to present a promising treatment for these pathologies.

The patient was informed that data concerning the case would be submitted for publication, and the study was approved by our institutional review board.

Case report

The patient was a healthy 28-year-old man. He is an amateur soccer player who suffered a varus stress trauma following medial-sided impact to his right knee during a soccer match. He was unable to bear weight and was transported to hospital, where he was noted to be in intense knee pain with swelling, subcutaneous ecchymosis in the popliteal fossa and paraesthesia in the lateral calf and the dorsum of the foot. The emergency physician noted a positive varus stress test, positive anterior drawer test and absence of active ankle dorsiflexion and eversion associated with anaesthesia in the peroneal nerve distributing area. Radiograph images of the knee did not show any fracture or dislocation. Magnetic resonance imaging (MRI) showed anterior cruciate ligament and lateral collateral ligament tear with bone bruise of medial femoral condyle and moderate joint effusion.

Five days after the trauma, he underwent surgery. It was performed through a lateral knee approach by fixing the avulsed ends of the lateral collateral ligament and posterolateral capsule, tying down all these structures with three suture anchors at their femoral origin. Popliteus tendon was fixed within a bone tunnel at his femoral attachment. The common peroneal nerve was found elongated but continuous. No limited neurolysis of the peroneal nerve was performed at that time. After the surgery, the patient was immobilized with a knee-stabilizing brace and a drop foot ankle brace.

The first electromyography (EMG) was carried out 15 days after the trauma; it revealed axonal non-excitability between proximal and distal injured nerve area of the fibular head, with a profusion of positive sharp waves and fibrillations in the muscles peroneus longus and tibialis anterior in relation to a severe axonotmesis. Tinel's sign was found just below the fibular head and reflected to the first web space of the foot. The proposed treatment consisted of pregabalin, vitamin B and E complex and rehabilitation programme that included percutaneous electrical stimulation, weight bearing, assisted active range of motion and progressive resistance exercises.

Nine months after the trauma, the patient still had a drop foot. Serial EMG showed partial denervation for peroneus longus as well as complete denervation for tibialis anterior and extensor hallucis longus, with no signs of reinnervation. At this time, the patient had been proposed for a tibialis posterior transposition surgery at the hospital. Ten months after the trauma, the patient was introduced to our clinic for second opinion. We recognized evident muscle atrophy in the anterior and lateral muscular compartments of his right leg. Varus stress test in extension and in 30 degrees of flexion was observed with little positive improved function in comparison with the contralateral knee. Positive Lachman test with a mild pivot shift was found. The patient presented evident drop foot with an inability for ankle dorsiflexion and eversion, being forced to wear a drop foot ankle brace to walk. A partial recovery of sensory loss in the anterolateral aspect of the lower lateral two-thirds of the leg and the dorsum of the foot was observed. Positive Tinel's sign was found at the fibular neck without distal progression. MRI at the moment showed anterior cruciate ligament tear, postsurgical changes in the posterolateral corner lesion and continuity of the common peroneal nerve throughout its course.

Based on previous experience in the treatment of musculoskeletal injuries [21] and encouraged by the promising results from animal studies [8–10, 24, 29], we proposed intraneural US-guided PRGF injections before performing tibialis posterior transposition surgery. Eleven months after the trauma, we performed a first injection.

Plasma rich in growth factors (PRGF) preparation

A total of 36 mL of peripheral venous blood was withdrawn into 9-mL tubes containing 3.8 % (wt/vol) sodium

citrate. Blood was centrifuged at 580*g* for 8 min at room temperature (PRGF®-Endoret®, BTI Biotechnology Institute, Vitoria, Spain). The upper volume of plasma, which contains a similar platelet count to that of peripheral blood, was drawn off and discarded in a collection tube. The 2-mL plasma fraction, located just above the sedimented red blood cells, but not including the buffy coat, was collected in another tube and carried to the injection room ready for use. This plasma contains a moderate enrichment in platelets (2- to 3-fold the platelet count of peripheral blood) with scarce leucocytes [2]. To initiate clotting, calcium chloride (10 % wt/vol) was added to the liquid PRGF aliquots just before injection. All procedures were performed under sterile conditions.

US-guided injection technique

An 8.0–13.0-MHz multi-frequency linear probe (12L-SC, Venue 40 Musculoskeletal, GE Healthcare) was used. US examination was performed by an experienced radiologist before each injection. Diagnosis of the injured site was based on the continuity, echogenicity and thickness of the common peroneal nerve. First, the probe was aligned repeatedly with the long, short axis of the common peroneal nerve at the site of positive Tinel's sign (Fig. 1). Once the lesion was located, the injection was performed using a 22-gauge needle (25 mm) just below the probe to allow visualization of the needle and ensure intraneural infiltration of PRGF (Fig. 2). Three to eight millilitres of the autologous preparation was injected gently with slow speed within the epineurium and also around the common peroneal nerve, changing the entry point of the needle along the lesion. Serial injections of PRGF were programmed. We started with one series of three intraneural injections with 2-week intervals followed by a monthly injection according to the clinical outcome and EMG results. The injections were performed in an outpatient clinic without any anaesthesia. All procedures were performed by one experienced orthopaedics surgeon under sterile conditions.

Clinical course after the first injection

Three months after the first injection, EMG showed polyphasic motor unit potentials at voluntary recruitment and electrical elicited neurographic motor response, signs of (partial) reinnervation for tibialis anterior and peroneus longus muscles. There was also an improvement in US image, appreciating less hypoechogenicity and less cross-sectional area compared to previous examination. Furthermore, Tinel's sign progressed and sensitivity improved.

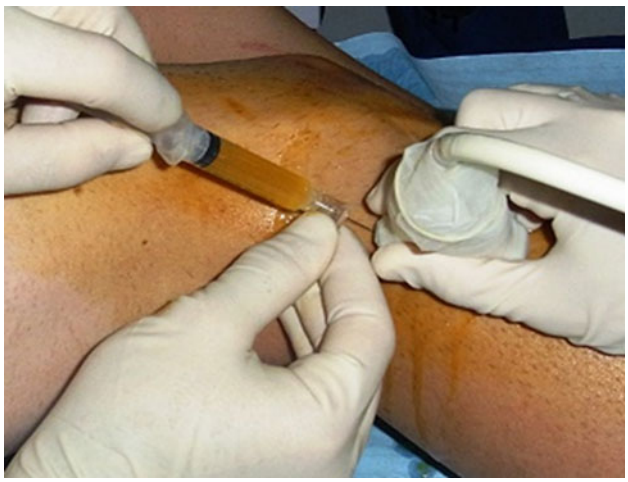

Fig. 1 US-guided plasma rich in growth factors injection for common peroneal nerve. The procedure was performed in sterile conditions in an outpatient setting. The multi-frequency linear probe was aligned with the long axis of the common peroneal nerve, and a 22-gauge needle (25 mm) was inserted into the common peroneal nerve

Since the first infiltration, we applied injections in a proximal direction to the lesion and in the injured site, noting with US image how the PRGF spread along the nerve.

At 5 months after the first injection, with a total of 5 injections, the patient reported subjective clinical improvement (strong and sensitivity) and EMG showed a progressive improvement of reinnervation for both peroneus longus and tibialis anterior muscles. The following infiltrations were distal to the lesion. At 9 months after the first injection, with a total of 7 injections, he was able to walk without orthosis and even run up to 7 km.

At present, 23 months after the first injection and 33 months after injury, the patient is satisfied with the functional recovery. The manual muscle testing (MMT) is 3 out of 5 for tibialis anterior and extensor hallucis longus, and 5 out of 5 for peroneus longus and extensor digitorum longus, graded on the Medical Research Council scale, while before treatment scores were 0 out of 5 for tibialis anterior and extensor hallucis longus, and 1 out of 5 for peroneus longus and extensor digitorum longus. Sensitivity demonstrates almost full recovery in the peroneal nerve distribution area. EMG controls at 30 and 33 months after infiltration show complete reinnervation for the peroneus longus and a better reinnervation for the tibialis anterior muscle compared with previous examination. Based on these data, we decided to continue with more injections, which were again proximal to the lesion since the patient showed better response (Fig. 3). There were no adverse events associated with this treatment.

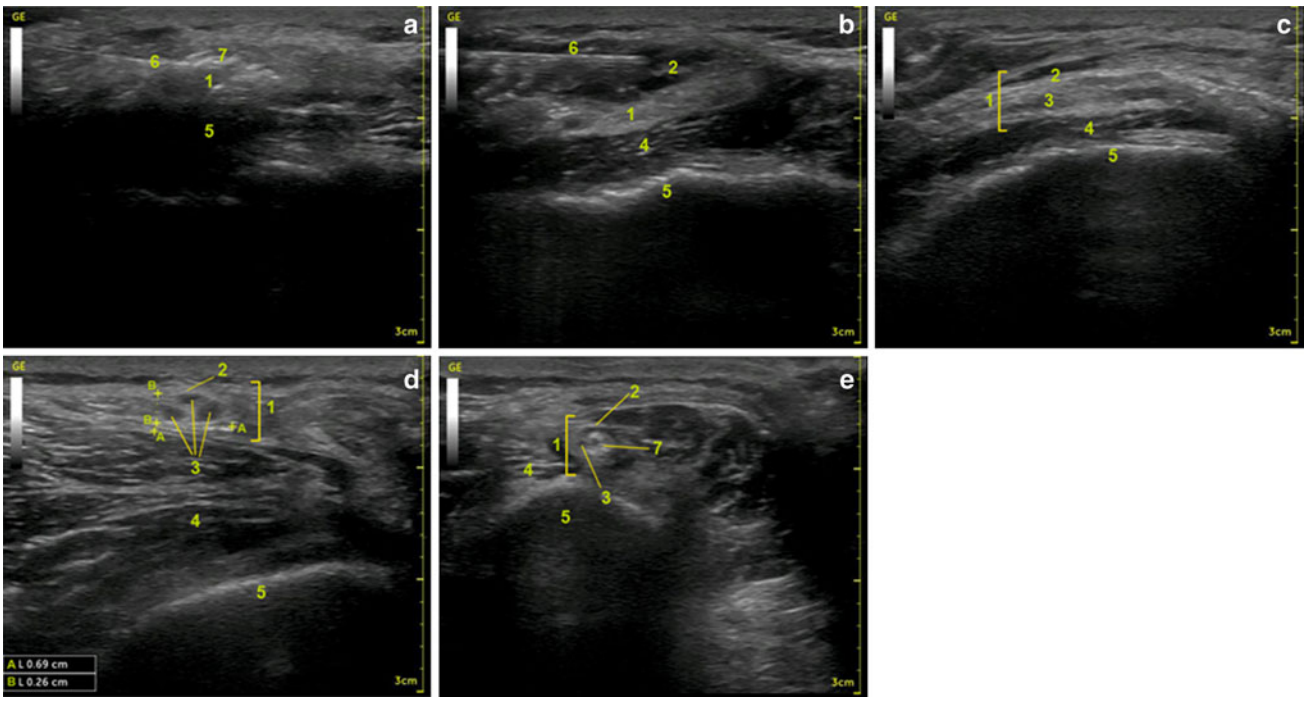

Fig. 2 Plasma rich in growth factors was injected at the proximal site and peri-epineural area of the nerve lesion. The accuracy of plasma rich in growth factors infiltration was confirmed by direct visualization of US imaging. Intraperineural infiltration; long section (**a**). Intraepineural infiltration; long section (**b**). Nerve after infiltration; long section (**c**). Nerve before infiltration; cross section (**d**). Nerve after infiltration; cross section (**e**). *1*: nerve, *2*: perineurium, *3*: nerve trunk, *4*: muscle, *5*: bone, *6*: needle, *7*: PRGF

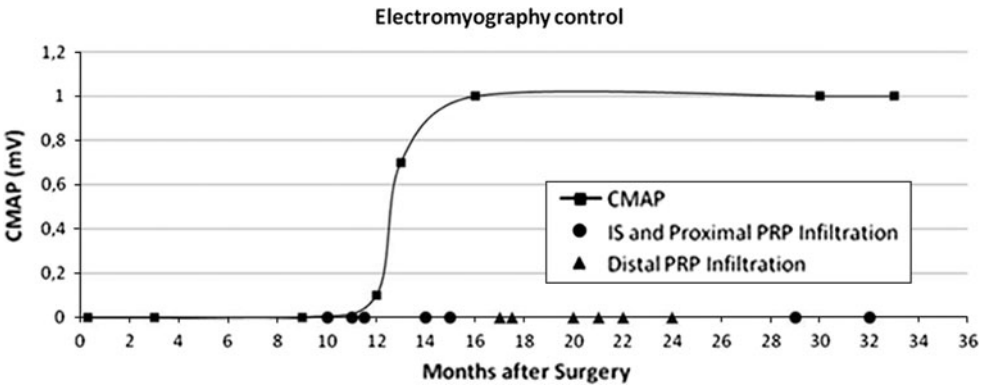

Fig. 3 Electromyographic control from surgery up to date. *CMAP* compound muscle action potential, *IS* injured site, *Dis* distal of the injured site, *Prox* proximal of the injured site

Discussion

For almost one decade, our group has characterized PRGF technology and has studied its therapeutic potential for various musculoskeletal disorders [1, 11, 16, 22, 23]. PRGF is an autologous biological therapy based on using the patient's own plasma and platelet-derived growth factors for regenerative purposes that stimulate processes such as angiogenesis, cell proliferation and migration [3] and improve nerve regeneration in different manners.

Previous studies have demonstrated that neurons express PDGF-β, a mitogen and survival factor for Schwann cells with a trophic activity on neurons [8]; its expression is augmented in neurons after peripheral nerve injury, suggesting a role in peripheral nerve regeneration [10]. IGF-1 has been also identified as a neurotrophic factor [9]; Kanje et al. [15] reported the stimulating effect on nerve regeneration of exogenously administered IGF-1, which might enhance the synthesis of proteins and lipids necessary for regeneration. There are also experimental data indicating that some growth factors such as VEGF, TGF-β, PDGF and bFGF can stimulate axonal outgrowth and enhance Schwann cells' proliferation and mitogenesis [24]. All these results tend to suggest how PRGF would enhance peripheral nerve regeneration by stimulating regeneration, remyelination, accelerating axonal transport and Schwann cell proliferation.

On the other hand, several studies have reported that early nerve repair appears to provide better results than late

nerve repair [17]. Hu et al. [13] reported that signs of remyelination or regenerating axons were easily seen 14 days after stretching, which implies that nerve repair starts soon after nerve injury created by distraction. These results indicate that the timing of nerve repair is very important. The injection of PRP to the regenerating nerve fibres immediately after the trauma may benefit the process of regeneration of the nerve fibres. Unfortunately, the common peroneal nerve palsy in this case was chronic when the patient visited our clinic. 11 months after trauma, Tinel's sign had not advanced from the level of fibular neck, serial EMG studies still showed absence of conduction distal from the lesion and complete denervation of peroneus longus and tibialis anterior muscles in relation to a severe axonotmesis, and clinically, the patient presented drop foot and muscle atrophy. Theoretically, these data indicate that spontaneous recovery is not expected at this stage. Although neurolysis and segmental nerve grafting have shown some acceptable results for the treatment of peripheral nerve lesions, the delayed intervention decreases the success rate. Target muscle motor endplate absorption begins at approximately 12–16 months after denervation [27], and associated degenerative changes such as muscle atrophy, shrinkage, deformation and replacement by fibrous tissue necessitate reinnervation by 24 months for optimal function of most muscles [6]. After this period, only a salvage procedure such as tibialis posterior transposition can restore the ankle function. Therefore, we did not consider a surgical nerve exploration but decided to try injecting PRGF for common peroneal nerve before considering tibialis posterior transposition.

Based on several studies of different groups about PRP and nerve regeneration and our experience, we hypothesized that intraneural PRGF injection as well as injection around peripheral nerve may modulate neuronal activity and play a role in regeneration as follows: (1) improving biological environment, which would increase the number of regenerating nerve fibres and consequently promote axonal outgrowth and remyelination and (2) recruiting undifferentiated cells to the site of injury, triggering mitosis and induce angiogenesis. Moreover, although this hypothesis has to be carefully confirmed in an animal experimental model, another possible effect of PRGF factors may be related to the structural aspect, by shifting the histological property of extra- and intraneural tissues from "stiff scar tissue or fibrosis" to "benign soft scar tissue" [4]. This effect might have opened the pass for axonal sprouting from proximal to distal over the injured site; thus, this fact could explain the greater efficacy of proximal infiltrations in the injured site than in distal infiltrations. Therefore, we consider that US imaging of the peripheral nerve is essential to guide the needle for the intraneural PRP injection to locate the appropriate infiltration site [26]. Furthermore, it is useful as a follow-up tool, to evaluate the cross-sectional area and echogenicity of the peripheral nerve lesion over time [19].

At present, 23 months after the first PRGF injection recovery have not been complete, but partial useful recovery has been obtained. Although the patient is satisfied with walking and running without orthosis, a better clinical outcome might have been obtained applying PRGF injections in the early phase of intervention, before degeneration of muscles had begun.

Conclusion

With this case report, a novel treatment is introduced by applying intraneural infiltrations of PRP for common peroneal nerve palsy with therapeutic purposes. In our opinion, this procedure may offer the potential of a new clinical application as well as contributing to elucidate the possible way infiltrations have to be performed. However, it remains unclear, at this stage, what precisely occurred at the site of the peripheral nerve and how PRGF enhances and accelerates the healing of peripheral nerve palsy as it has been depicted. Therefore, further careful clinical follow-up is needed; currently, more systematic animal experiments are in progress to further assess and shed more light on this repair mechanism.

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Conflict of interest Eduardo Anitua is currently scientist at BTI Biotechnology Institute, the company that has developed the PRGF-Endoret Technology. BTI has patents related with PRGF-Endoret Technology.

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