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Abstract

Complex Regional Pain Syndrome (CRPS) is a poorly understood and treated pain syndrome that typically occur after limb trauma. CRPS affects the peripheral nervous system with dysregulation of the sympathetic system, aberrant inflammation, vasomotor dysfunction and poorly adapted neuroplasticity. This report describes two female patients aged 37 and 46 years, disabled with CRPS Type 1 and 2 for about 10 months and 60 months duration respectively, subsequent to ankle injury. They were treated with ultrasound guided autologous liquid photo activated platelet rich plasma (PAPRP) and were followed up for 3 months and 13 months respectively. There was meaningful clinical improvement in pain, restoration of peripheral neuropathy and striking improvement in sympathetic dystrophic symptoms of nocturnal swelling and skin discolouration.

Possible mechanisms of action of PAPRP in CRPS include correction of sympathetic dysregulation, neoangiogenesis, neuropeptide and cytokine mediated anti-inflammatory effect, neural regeneration and macrostructural augmentation of damaged cartilage and ligaments. There is an urgent need for large studies to evaluate the safety and efficacy of PRP in CRPS.

Case Report(s)

Case 1: A 46 year old office worker, smoker of ten cigarettes a day, weighing 112kg, sustained a right ankle injury in 1998, in 2008 and suffered for five years in pain. At one stage she underwent arthroscopy debridement. Pain persisted and she had intravenous lignocaine infusions with partial relief for three weeks at one stage. She had pain after walking for a few minutes accompanied by skin discolouration and altered sensation of the right dorsal ankle and foot. She also complained of right ankle instability. Flexion of toes was considerably limited due to pain provocation. Foot and ankle disability index (FADI) score was 46.2. She was on Pregabalin 350 mg a day and Tramadol 600 mg a day. On examination there was mild cutaneous oedema of the right foot with altered sensation to touch in the distribution of the superficial peroneal nerve (see figure 1). There was no hyperalgesia in the dorsum of the foot. There was apprehension to ankle joint movement for fear of pain aggravation. There was localising tenderness of the lateral talar neck at the talonavicular joint and the overlying soft tissues. Further tender areas were present in the posterolateral ankle joint recess at the calcaneofibular ligament (CFL) and distal fibula (prior avulsion) ankle and at the anterior tibiofibular syndesmosis. A diagnosis of chronic ankle instability with chronic regional pain syndrome in the distribution of the superficial peroneal nerve was made. Written informed consent was obtained after full explanation of the procedure, complications and possible outcomes. A series of ultrasound guided (GE Logic 9, 9MHz probe) injections of 4-8cc autologous PRP (BCT, REGEN Labs, Switzerland) was performed about two to four weeks apart into the talonavicular joint, anterior talofibular ligament (ATFL) and anterior tibiofibular
syndesmosis. Symptoms of peroneal neuropathy gradually improved over the first couple of months with progressive improvement in her mobility. At eight months she reported improvement in the treated areas. However she suffered persisting pain in the untreated posterolateral ankle in the region of the CFL. The CFL was treated with the same technique described above with autologous PRP (BCT, REGEN Labs, Switzerland) that was photo activated for ten minutes (Adilight 2, Adistem Ltd Hongkong). At 13 months followup, her symptoms of pain improved and for the first time in five years she was able to walk up to forty minutes. She reported improved range of movement of the ankle joint comparable to the asymptomatic side. She was able to flex her toes without pain provocation. There was normal sensation with no pain in the dermatomal distribution of the superficial peroneal nerve. She reported improved subjective sensation of ankle stability. FADI score had improved to 64.4 with an absolute improvement of 39.5%. She reduced Tramadol from 600mg pre PRP to 450 mg per day post PRP. She also reduced Lyrica 350mg per day pre PRP to 300mg per day post PRP.

**Case 2:** A 37 year old female volunteer firefighter, mother of two dependant children, weighing 107kg, ex smoker of two years, sustained an inversion injury and a hairline fracture of the ankle requiring a plaster for two weeks in January 2013. This was complicated by deep vein thrombosis. Two months later she had surgical reconstruction of the lateral collateral ligaments and was in a below knee plaster cast for nine weeks. In July 2013, within a day of plaster removal the right foot swelled up with a reddish blue discolouration. Since then she used crutches to walk. At presentation to the author in February 2014 she was on Pregabalin 150 mg in the morning and 75 mg at night, Tramadol 200mg slow release BD and Amitriptyline 50 to 100mg nocte. Medications made her sleepy during the day. She walked with crutches and struggled with transfers. There was marked localising tenderness to the right tibiofibular syndesmosis, CFL, ATFL, peroneus and achilles compartment. There was severe allodynia of the anterior medial/anterolateral lower leg and dorsum of the right foot, progressively worsening from proximal to distal. Lower limb discolouration and swelling typically occurred at the end of the day (see figure 2). Written informed consent was obtained after full explanation of the procedure, complications and possible outcomes. A series of ultrasound guided (GE Logic 9, 9MHz probe) infiltrations of 8cc autologous PRP (BCT, REGEN Labs, Switzerland) photo activated for ten minutes (Adilight 2, Adistem Ltd Hongkong), was performed at two week intervals into the right anterolateral gutter with percutaneous tenotomy of the ATFL on one occasion and infiltration into the posterolateral gutter and percutaneous tenotomy of the CFL subsequently. Two weeks later, 5cc of PRP prepared from clotted platelet rich plasma and 7cc of PRP (Adistem Ltd, Hongkong), photo activated for ten minutes (Adilight 2, Adistem Ltd Hongkong), was placed into the right anterior ankle joint recess under ultrasound guidance twice, two weeks apart. After the first four weeks (following the first two PRP treatments) the patient reported significant improvement in nocturnal skin discolouration and swelling (see figure 2 & 3). At three months review since PRP treatment, she was able to stand for longer and perform day to day activities with a noticeable change in her gait.

**Discussion**

The pathology of CRPS is thought to be a combination of sympathetic dysregulation, microvascular dysfunction, tissue hypoxia, peripheral neuropathy, increased sensitisation of the central nervous system and cortical disorganisation. Other theories include an autoimmune disorder (5-7), inflammatory disorder (8), small diameter nerve damage (9) and neurogenic inflammation (10). In our patients, the clinical improvement in pain may be partly explained by the anti-inflammatory and regenerative properties of PRP into joints, ligaments, perineural and soft tissues (2-4).

In the second case with CRPS 1, the dramatic reduction in reddish discolouration and swelling, suggests a favourable post PRP treatment effect on the sympathetic dysregulation seen in CRPS. This effect was observed within two to eight weeks after PRP to specific lateral ligamentous structures and subjacent joint recesses. The placement of PRP into these ligamentous structures and the joint recesses does not explain correction of sympathetic dysregulation. Other mechanisms that are likely to reverse within weeks after PRP treatment are a pro inflammatory state mediated via cytokines, neurogenic inflammation mediated via neuropeptides, improved microcirculation resulting in a correction of tissue hypoxia and ischaemia.

In blister fluid assays obtained from patients with chronic CRPS 1, Interleukin-1 receptor antagonist (IL-1 ra), Interleukin-6 (IL-6), Interleukin-8 (IL- 8), Tumour necrosis factor-α, amongst other cytokines were detectable and increased in CRPS 1 affected extremities in comparison to levels obtained from unaffected limbs in the same patients (11). Several cytokines have been implicated in the initiation and
amplification of inflammation and tissue injury. These cytokines, including interleukin-1 (IL-1), IL-6, IL-8 are implicated in an inflammatory response. IL-1 is activated early on in the inflammatory cascade and may be one of the primary targets for therapeutic intervention. IL-1 receptor antagonist (IL-1ra) non-productively binds the receptor on the cell surface, prevents cell signalling and release of IL-1. Photoactivated PRP contains increased levels of IL-1ra, a natural inhibitor of interleukin 1 and modulates a variety of interleukin 1 related immune and inflammatory responses.

In animal models, at fourteen days post treatment, it has been shown that platelet-derived neuropeptide NPY is critical for sustained capillary angiogenesis (12). PRP infiltrations were performed in the second case every fourteen days. On this basis, possible explanations include PRP induced direct local anti-inflammatory effect on neurogenic inflammation via neuropeptides and improvement in ischaemia due to capillary neoangiogenesis.

In case 1 with CRPS 2 the significant improvement of the peroneal neuropathy may be explained by regeneration and remodulation of this nerve. Studies in CRPS affected amputated limbs showed small nerve damage and axonal degeneration (13–15). Modulating the activity of peripheral nerves has shown potential for normalising neuronal activity. This reduces signs of neuropathic pain in animal models and in clinical studies (16). PRP contains insulin growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF). There is evidence that IGF-1, VEGF, neuroimmunophilin ligand and other growth factors including brain-derived growth factor (BDNF) play a significant role in neural regeneration and up-regulation of neuronal nitric oxide synthase (nNOS) (17–25). There is a report on improvement in trigeminal neuralgia after PRP to a branch nerve (4).

As far as the author is aware there are no other similar reports in the English language literature. This paper is not a scientific report. Further studies are required prior to routine clinical use of PRP in CRPS Type 1 and 2.

Conclusion

CRPS is a chronic debilitating condition with an unmet medical need. This case series, describes for the first time in the English language literature, reduction in pain and swelling in patients with recalcitrant CRPS following ultrasound guided serial autologous PRP treatment of the affected limb. Possible mechanisms of action of PRP in CRPS include correction of sympathetic dysregulation, neoangiogenesis, neuropeptide and cytokine mediated anti-inflammatory effect, neural regeneration and macrostructural augmentation of damaged cartilage and ligaments. There is an urgent need for large studies to evaluate the safety and efficacy of PRP in CRPS.

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Illustrations

Illustration 1

Figure 1: Case 1 - CRPS 2. Altered sensation in the distribution of the superficial peroneal nerve in this patient with CRPS: At 13 months follow up after PRP, there was resolution of peroneal neuropathy.

Illustration 2

Figure 2: Case 2 - CRPS 1 - Patient obtained self photographs around the same time of each day between February and April 2014. First panel 20 February before PRP, 20th March after second PRP. Second Panel: 3 April after third PRP, 21st April after fourth PRP. Note the dramatic reduction in swelling, reddish discolouration and shiny skin since treatment with PRP between 20 February and 21 April 2014.
Illustration 3

Figure 2: Case 2 - CRPS 1 - Patient obtained self photographs around the same time of each day between February and April 2014. First panel 20 February before PRP, 20th March after second PRP. Second Panel: 3 April after third PRP, 21st April after fourth PRP. Note the dramatic reduction in swelling, reddish discolouration and shiny skin since treatment with PRP between 20 February and 21 April 2014.