USE OF AUTOLOGOUS PLATELET CONCENTRATE (APC) IN PLANTAR FASCIOSIS AND ACHILLES TENDINOPATHY

ABSTRACT

Autologous platelet concentrate (APC) has been used in lower extremity wounds, oral and maxillofacial surgery with positive results for some time. There is limited data on the use of APC in foot and ankle ailments such as tendonitis, plantar fasciitis and other inflammatory conditions. A retrospective analysis of the efficacy of APC in the treatment of plantar fasciosis and Achilles tendinopathy in the foot and ankle was evaluated in 61 subjects comprising a total of 70 feet. The subjects were given one injection up to a maximum of four subsequent injections of APC. The subjects were followed for up to one year and their pain level was evaluated using a visual analog scale. In the group of plantar fasciosis 63% of the subjects showed improvement in symptoms after APC with no further treatment needed. In the group of Achilles tendinopathy 62.5% of the subjects showed improvement in symptoms after APC with no further treatment needed. APC seems to enhance primary healing, reduce healing time and have fewer complications than traditional treatments of degenerative conditions in the foot and ankle.

USE OF AUTOLOGOUS PLATELET CONCENTRATE (APC)

IN PLANTAR FASCIOSIS AND ACHILLES TENDONOPATHY

Definitions

Plantar fasciosis is pain at the site of attachment of the fascia and the calcaneus. Plantar fasciosis may involve acute or chronic stretching, tearing, and degeneration of the fascia at its attachment site. Achilles tendinopathy is degenerative changes in the substance of the tendon with pain or fusiform swelling 2-6cm proximal to insertion in the calcaneus. The authors did not use the terms plantar fasciitis or Achilles tendonitis because these conditions are not inflammatory but degenerative pathology.

PLATELET ANATOMY AND BIOLOGY

Platelets are the smallest of the blood cells, and are formed in the bone marrow.[1] They reside intravascularly for 5 to 9 days[2] until removed by macrophages[1]. The average platelet count ranges from 150,000-300,000/μL of circulating blood.[3] Each platelet houses a number of cellular structures that contain glycogen, lysosomes, and two types of granules: dense granules and α-granules. Dense granules contain ADP, ATP, serotonin, and calcium. α-granules contain more than 30 bioactive proteins, which have a fundamental role in hemostasis or wound healing.[1]

PLATELET FUNCTIONS

Platelets are nonthrombogenic in the resting state and require activation before they function in hemostasis and wound healing. Activation occurs when platelets become exposed to damaged blood vessels and contact directly with various extracellular proteins after tissue injury and/or surgical stimuli.[2,4] Once they are activated, they change shape and develop pseudopods, which promote platelet aggregation and subsequent release of the granules contents.[4] Within 10 minutes after clotting, platelets begin actively secreting proteins. More than 95% of the pre-synthesized growth factors are secreted within the first hour. They continue to synthesize and secrete additional growth factors for the remaining several days of their life span.[2]

GROWTH FACTORS

The main growth factors contained in these granules are platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), vascular endothelial growth factor (VEGF), and epithelial growth factor (EGF).[4] PDGF is the first growth factor to start nearly all wound healing. The main function of PDGF is stimulation of cellular replication (mitogenesis). It activates macrophages, resulting in debridement of the surgical or traumatic site. PDGF also promotes angiogenesis.[2] TGF-β has stimulatory effects on the proliferation of osteoblast precursor cells and bone collagen synthesis. In addition, it activates fibroblasts to

induce collagen formation, endothelial cells for angiogenesis, chondroprogenitor cells for cartilage, and mesenchymal cells in an effort to increase the population of wound healing cells.[2] VEGF promotes angiogenesis.[4] EGF promotes cell differentiation and stimulates epithelial/mesenchymal mitogenesis and endothelial chemotaxis/angiogenesis.[4]

WHAT IS AUTOLOGOUS PLATELET CONCENTRATE or PLATELET RICH PLASMA?

Platelet rich plasma (PRP) is a volume of autologous plasma that has a platelet concentration above baseline.[1,3,5] Marx states that the working definition of platelet rich plasma is a 5-ml volume of plasma that contains 1,000,000 platelets/μL because various studies have shown bone and soft tissue healing enhancement with this concentration.[3] Lesser concentrations are unable to be relied upon to enhance wound healing, and greater concentrations have not yet been shown to further enhance wound healing.[1,6]

PREPARATION OF PLATELET RICH PLASMA

There are various blood separation techniques to obtain platelet rich plasma. Marx describes the technique that uses a double centrifugation technique to concentrate platelets from autologous blood. The red blood cells are separated from the plasma in the first spin. Then, the second spin will separate the platelets and white blood cells together with a few red blood cells from the

plasma. This spin produces the PRP and separates it from the platelet poor plasma (PPP). PRP collected from a single spin would produce a mixture of PRP and PPP, and have very low platelet counts. Regardless of the rate of centrifugation or the time of centrifugation, a single spin cannot adequately concentrate platelets, because the red blood cells will interfere with the fine separation of the platelets.[3]

Eppley, et al. states that the method of platelet-rich plasma preparation has a potentially significant impact on the different levels of platelet recovery and activation.[7] Platelet activation during preparation of the platelet concentrate can result in early α-granules release and loss of the growth factors during the collection process. It is therefore critical to recognize that each platelet-rich plasma preparation method may differ in regard to platelet number, platelet activation rates, and growth factor profiles. Sufficient characterization of the effects of differing platelet-rich plasma preparation methods has not been thoroughly performed.[7]

LITERATURE REVIEW

There are numerous studies showing the effects of platelet rich plasma on bone healing, non-healing ulcerations, tendon injuries, and plantar fasciitis besides other uses in maxillofacial and dental surgery. One of the reasons for the wide spread use of PRP is that platelets contains a variety of growth factors which

have different functions. The following is a review of some of the recent studies involving platelet-rich plasma.

Bone healing: Yazawsa, et al. studied the bone formation ability of platelet rich plasma in rabbits. They applied PRP to a 1-mm wide slit defect in rabbit mandible. They concluded, based on the histological study, that PRP can promote bone formation in a timely way from the initial stages.[8] Kawasumi, et al. studied the effect of platelet concentration in platelet-rich plasma gel on the regeneration of bone. Rat bone-marrow cells embedded in different concentrations of platelet-rich plasma gel were cultured. PRP's potential for proliferation and osteogenic differentiation was analyzed. Also, the cultured rat bone-marrow cells with platelet-rich plasma of variable concentrations were transplanted into the distraction gap and the quality of the regenerate bone was evaluated using a rat limb lengthening model. They concluded that a higher concentration of platelets in the platelet-rich plasma gel stimulated the proliferation of rat bone-marrow cells, although the rate of differentiation of osteoblasts was not accelerated. Also, rat bone-marrow cells with a higher concentration of platelets in the platelet-rich plasma had the most favorable effect on osteogenesis in the rat limb-lengthening model.[9] Simman, et al. studied the role of platelet-rich plasma in the acceleration of bone fracture healing in rats. Following creation of open femur fractures, PRP was applied. They reported that radiographic and histological analyses showed enhanced bone formation.[10] These studies show the positive effect platelet rich plasma has on bone healing. However,

some studies have shown negative effects of PRP. Ranly et al. investigated the effect of PDGF on the ability of human DBM to induce bone formation in a nude-mouse muscle-implantation model and examined whether PRP, which contains PDGF, also stimulates osteoinduction in this model. They reported that PDGF and PRP are unlikely to improve the osteoinductive ability of DBM at a non-bone site; PDGF reduced bone formation in a dose-dependent manner. Also, PDGF retarded the resorption of DBM in a dose-dependent manner. PRP reduced osteoinduction by human DBM.[11] Ranly et al., states that if platelet-rich plasma does enhance bone-healing in some application, the effect is not due to an osteoinductive property of the platelet-rich plasma itself.[12]

Wound healing: Driver et al., studied to determine the safety and effectiveness of treating diabetic foot ulcers with more than 4 weeks duration with PRP gel versus a control treatment with normal saline gel. They reported that PRP gel is safe for use in the treatment of non-healing diabetic foot ulcers. They also reported that PRP gel-treated wounds are significantly more likely to heal than control gel-treated wounds. Treating wounds with PRP or saline gel resulted in healing in 6 weeks, although almost twice as many PRP treated wounds healed in that time frame.[13] McAleer et al. treated 33 chronic lower-extremity wounds with at least 6 months duration with PRP. Wound closure and complete epithelialization was achieved in 20 wounds, 75% or greater wound closure was obtained in 3 wounds, 50-74% closure in 3 wounds, and 25-49% closure in 2 wounds. Mean time to complete closure

was 11.15 weeks.[14] Schade and Roukis studied split thickness skin graft (STSG) healing in high-risk patients with the use of PRP. A majority of the patients had diabetes. They concluded that the use of PRP to STSG recipient sites seems to enhance primary healing and reduce the time to more than 90% healing in patients with well-controlled medical comobidities.[15]

Tendon injuries: Aspenberg and Virchenko studied the effectiveness of platelet concentrate injection in Achilles tendon repair in rats. The injection increased tendon callus strength and stiffness by about 30% after 1 week, which persisted for as long as 3 weeks after the injection. The mechanical testing indicated an improvement in material characteristics such as greater maturation of the tendon callus, which was confirmed by histological study.[16] de Mos et al. studied human tenocytes were cultured 14 days with several different concentration of PRP or PPP. They analyzed cell amount, total collagen, and gene expression of collagen, matrix metalloproteinase, and vascular endothelial-derived growth factor, and transforming growth factor at day 4, 7, and 14. The results showed that PRP, but also PPP, stimulates cell proliferation and total collagen production in human tenocyte cultures. However, they also showed that PRP, but not PPP, increased the expression of matrix-degrading enzymes and endogenous growth factors. According to the authors, these effects on tenocyte behavior might accelerate the catabolic demarcation of traumatically injured tendon matrices and promote angiogenesis and the formation of a fibrovascular callus.[17]

Plantar fasciitis: Barrett and Erredge studied the effectiveness of PRP injections in chronic plantar fasciitis. Nine patients had 3cc of PRP injected into a symptomatic heel under ultrasound guidance. The ultrasound measurements showed a reduction of the thickness of the symptomatic plantar fascia. Six out of nine patients achieved complete resolution of symptoms after 2 months. None of the patients experienced any complications from the treatment. In addition, at one year, seven of nine patients had complete resolution of their plantar fascial pain for a 77.8 percent success rate.[18]

PATIENTS AND METHODS

Study Group: A retrospective analysis was performed looking at two groups of patients who were treated with autologous platelet (APC) injections for their foot and ankle condition. The first group had a diagnosis of plantar fasciosis. The second group had a diagnosis of Achilles tendinopathy.

The study period was from December 2006 to October 2008. The plantar fasciosis group had a total of 53 subjects with 62 feet. The Achilles tendinopathy group had a total of 8 subjects with 8 feet. There were 18 males and 43 females in the study. The age range was from 30 to 95 years with mean of 51.49 years. Co-morbidities included DM, HTN OA, Hypothyroid, etc. (Table 1). Five of the plantar fasciosis subjects had received previous surgery for their condition. Two of the Achilles tendinopathy subjects had received previous surgery for their

condition.

Injection Protocol: Prior to initiation of treatment, the subject's foot and ankle pain was evaluated using a visual analog scale. Informed consent was obtained. In the antecubital fossa of the subject's arm a suitable vein was identified and 20cc of the subject's own blood was drawn aseptically (Picture 1). The blood was then transferred to tubes (Picture 2) and centrifuged at 3200 RPM for 15 minutes (Picture 3). After centrifugation, the blood was separated into platelet poor plasma, platelet rich plasma (APC), and RBC's. Approximately 3cc of APC was yielded after centrifugation (Picture 4). The authors did an analysis of platelet concentrations of one subject's blood in single spin verses double spin using Harvest system. It was found that a single spin produced 1,254,000/μL of platelets where as double spin produced 2,017,000/μL of platelets. The single spin concentration is consistent with previous studies and so a single spin was used as the standard in this study. The subject's symptomatic foot or ankle was anesthetized with a peripheral nerve block using 2% plain lidocaine. The 3cc of APC was then injected aseptically into the affected area of the foot or ankle.

Subjects were given aftercare instructions including; non-weight bearing for the first 48 hrs and limited weight-bearing subsequently for the next week. Utilization of a CAM walker in some subjects for the first week was prescribed. Some subjects developed post-injection pain and were advised to take either

NSAIDs, acetaminophen, or prescribed narcotic pain medication. Subjects were monitored at one week post treatment, two weeks post treatment, one month post treatment, two months post treatment, three months post treatment, six months post treatment and one year post treatment. At the time of this study however not all subjects had reached six months post treatment or one year post treatment. At each follow-up visit pain was evaluated using visual analog scale and/or interview of the subjects. Subsequent APC injections were given at the follow-up visit if no relief of pain had occurred, up to a total of 4 injections. Time interval in between injections varied from one week to several months.

RESULTS

Plantar Fasciosis Group: This group comprised 54 subjects and 62 feet. Thirty-nine of the feet (63%) were treated with APC alone and had improvement in pain or no further intervention. Nine of the feet (14%) did not experience improvement with the APC and went on to have steroid injections. Fourteen of the feet (22.9%) did not experience improvement with the APC and went on to have surgical intervention (Figure 1).

Pain was assessed using a visual analog pain scale or by interview on scale 0-10 with 0 being no pain and 10 being the worst pain imaginable. The mean pain level pretreatment for the 39 feet that did not require further intervention was 8.87. The mean pain level post treatment for the 39 feet was 2.41. Fourteen of the

39 feet (35.8%) had no pain after APC+ treatment. Three of the 39 feet (7.6%) had no change in their pain but did not want further treatment (Figure 2).

The number of APC injections given varied from one up to four. In the group of feet that APC alone was required 25 feet (64.1%) had one injection, while 9 feet (24%) had two injections, 3 feet (7.89%) had three injections, and two feet (5.26%) had four injections. In the group of 9 feet that required steroid injection after APC, 8 feet (88.9%) received one injection of APC and one foot received two injections of APC. In the group of 14 feet that went onto surgery after APC injection, 10 feet (71.4%) received one injection of APC and 4 feet (28.6%) received two injections of APC.

Achilles Tendinopathy Group: This group was made up of 8 subjects and 8 feet. Five of the feet (62.5%) were treated with APC alone and had improvement in pain. Three the feet (37.5%) did not improve with APC and required surgical intervention (Figure 3).

Pain was assessed using a visual analog pain scale or by interview on scale 0-10 with 0 being no pain and 10 being the worst pain imaginable. The mean pain level pre-treatment for the 5 feet that did not require surgery was 8.2. The mean pain level post-treatment for the 5 feet was 3.7 (Figure 4). Four of the feet had adjunctive treatment with AFO, CAM walker, or orthotics for an extended period. One of the feet improved without additional adjunctive treatment. In the group

of Achilles tendinopathy that went onto surgery, all had been treated with adjunctive use of CAM walkers.

The number of APC injections given to this group varied from one up to three. In the group that APC alone was required 1 foot (20%) had two injections, and four feet (80%) had three injections. In the group of 3 that required surgery after APC, all feet had been given one injection.

DISCUSSION

The age range of the participant's reflect the findings of a non-randomized study of the conditions. In addition, the co-morbidities of the participants reflect those seen in the general population of individuals with these foot and ankle conditions.

Analysis of the data did not detect a relationship between the participants' feet that had previous surgery before APC treatment and those that had not. Participant's feet that previously had been treated with cortisone injections before APC did not seem to be associated with their outcome nor did the use of foot orthoses.

Pain at the injection site was noted once the anesthetic wore off in both the plantar fasciosis group and the Achilles tendinopathy group. At the one week follow-up there was an increase in pain level which subsided at subsequent follow-ups. It was observed that the full effect of the APC injection was not seen

until approximately one month following the procedure. Due to this significant increase in pain after the APC injection several of the participants who opted for surgical intervention or other treatment did not want to wait for the full outcome of the APC to take effect. Some participants were given post injection prescriptions of either NSAIDs, Acetaminophen or narcotics to help with pain control and compliance.

The number of injections given was variable from one up to four. In the plantar fasciosis group, the majority of participants (43 feet or 69.4%), received one injection. This includes the participants who went on to surgery. This raises the question of whether or not the participants who went on to other treatments would have improved with the APC injection if given more than one injection, since 14 feet (37.2%) that improved with APC alone had multiple injections. In the Achilles tendinopathy group, three of the participants (38%) received one injection and four participants (50%) received three injections. The results in the Achilles tendinopathy group also point to the efficacy of multiple injections although the study size is small.

In a randomized controlled trial evaluating the effectiveness of steroid injection compared with local anesthetic for heel pain, Crawford et al[19] had mean pain scores of 5.6 at beginning of trail and 2.4 at the 6 month follow-up. They found no statistically significant difference in pain reduction after the one month

follow-up. The mean pain scores seen post-treatment are similar to those observed in this study among the plantar fasciosis group.

In a trial evaluating APC in nine patients with plantar fasciitis Barret, et al [18] found that there was an average reduction in the medial band thickness of 2.29 mm at three months. At the one year follow-up 77.8% of the patients had complete resolution of their plantar fascial pain. The results point to the effectiveness of APC in the treatment of plantar fasciitis and plantar fasciosis even though the study size is small. None of the patients had complications related to the APC injection [18].

In a randomized control trial evaluating injection modalities of APC, cortisone and peppering technique Kiter, et al [20] found that there was no statistically significant difference between the groups related to improvement in symptoms.

To date, a review of the literature did not find any human studies on Achilles tendon and APC. As noted previously, Aspenberg and Virchenko [16] studied the effects of platelet concentrate injection on Achilles tendon repair in a rat model. Their findings in the rat model demonstrate the improved healing and strength that platelet concentrate gives to the Achilles tendon. In this study, which had a small sample size but human subjects, 62.5% had improvement of their symptoms with APC injection and required no further treatment.

There were no complications observed in this study in both the plantar fasciosis group or in the Achilles tendinopathy group. The adverse effects of cortisone injections are well documented including fat pad atrophy, fascia/tendon rupture, cutaneous depigmentation and cutaneous atrophy.

The authors acknowledge that there are limitations of this study. They include no standardization of post-injection care, variable time interval between injections, variable number of injections, absence of inclusion/exclusion criteria, and the small study size of the Achilles tendinopathy group.

CONCLUSION

This article provides a basic knowledge of platelet biology and function. The authors also presented the findings of a study that demonstrate the efficacy of APC in plantar fasciosis and Achilles tendinopathy. A review of the literature show great potential of the application of autologous platelet concentrate on various conditions. However, further studies and research need to be done in order to support the positive effects of platelet rich plasma, especially in the foot and ankle pathologies. To begin with, there is no standardization for APC preparation technique. Various preparation techniques of APC will produce different platelet counts, depending on the system used, or whether a double- or single-centrifugation technique is utilized. The duration of centrifugation may also provide different platelet counts. In addition, it is not yet well understood

what the optimal concentration of platelet is that will provide the best outcome. The effects of too high or too low of platelet concentration are still unknown. Moreover, potential complications or side effects caused by APC have not been studied extensively.

The study that was presented shows the potential of APC injection to treat various foot and ankle pathologies. The investigators felt it is necessary to understand the efficacy of APC in comparison to other treatments. In the case of plantar fasciitis, it is compulsory to know whether or not APC would be effective in cases of acute or chronic plantar fasciosis. Therefore, more well-controlled studies from various aspects are necessary to support the positive effects of autologous platelet concentrate.

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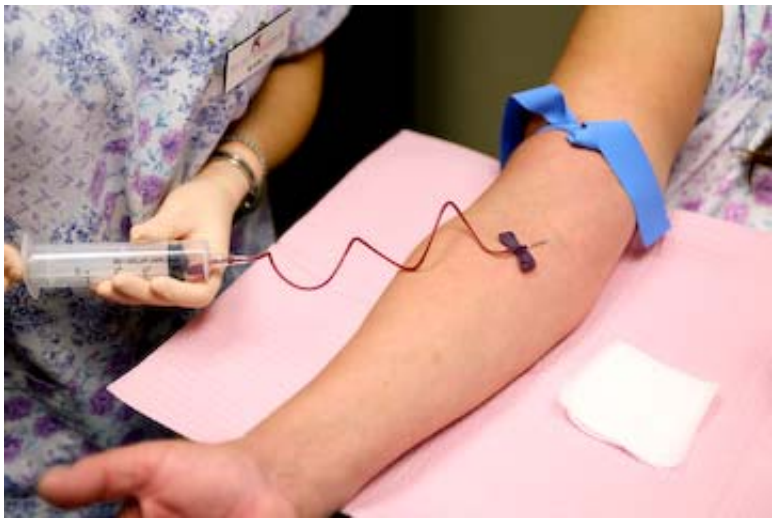
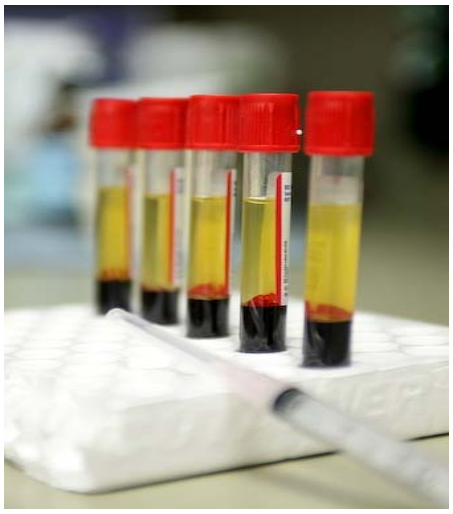
Table 1

Comorbidity	Number of Subjects
Hypertension	10
Diabetes Mellitus	8
Osteoarthritis	7
Hypothyroid	6
Gout	2
Asthma	2
Multiple Sclerosis	1
Fibromyalgia	1
Osteoporosis	1
Bipolar	1
Depression	1
Liver transplant	1
Irritable Bowel Syndrome	1



Picture 1. 20cc of the subject's blood was drawn.

Picture 2. The subject's blood is transferred to tubes for centrifugation.



Picture 3. The blood was centrifuged at 3200 RPM for 15 minutes.

Picture 4. Approximately 3cc of APC was yielded after centrifugation.

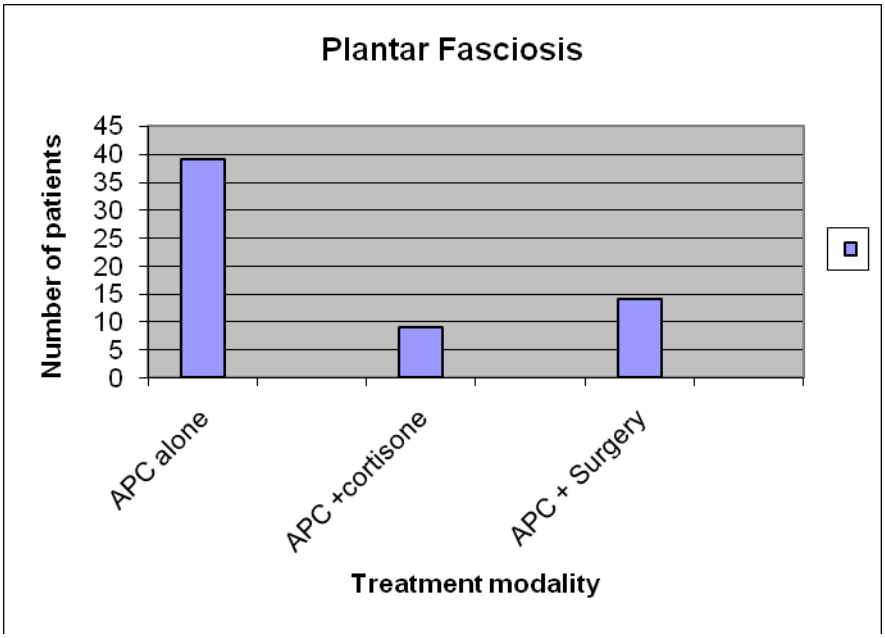


Figure 1

Plantar fasciosis group: 39 of the feet 63% treated with APC alone had improvement in symptoms. Nine of the feet 14% received steroid injections after APC. Fourteen of the feet 22.9% received surgical intervention after APC.

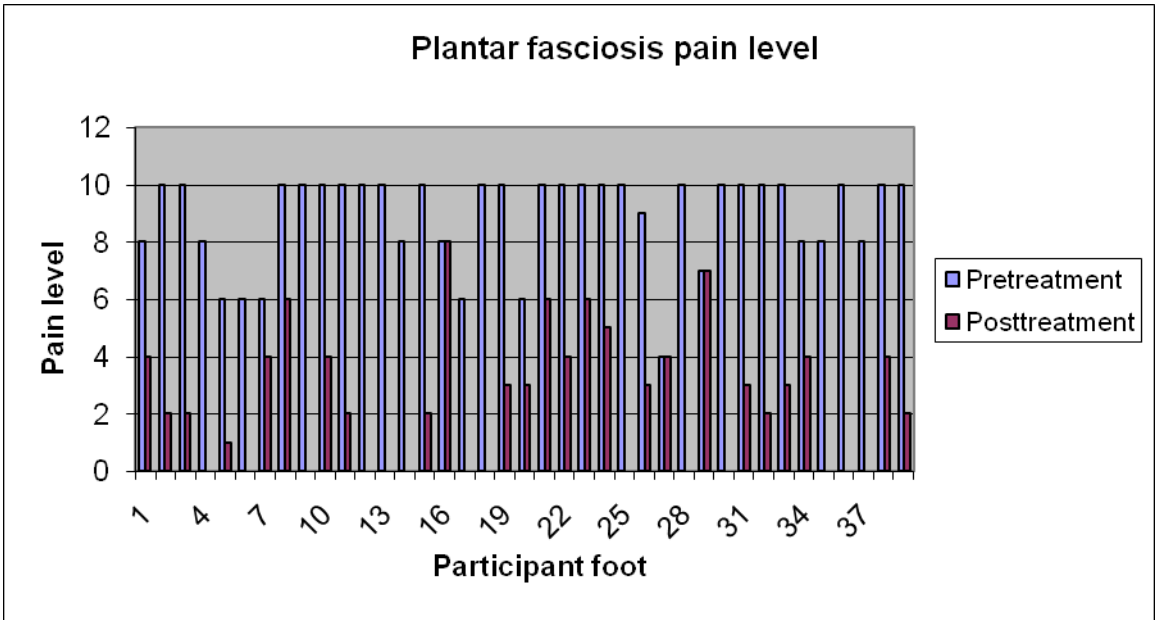


Figure 2

Plantar fasciosis pain level pre and post treatment for 39 feet that received no further treatment. Fourteen feet had no pain after APC treatment as seen by absence of post treatment bar. Three feet had no change in their pain.

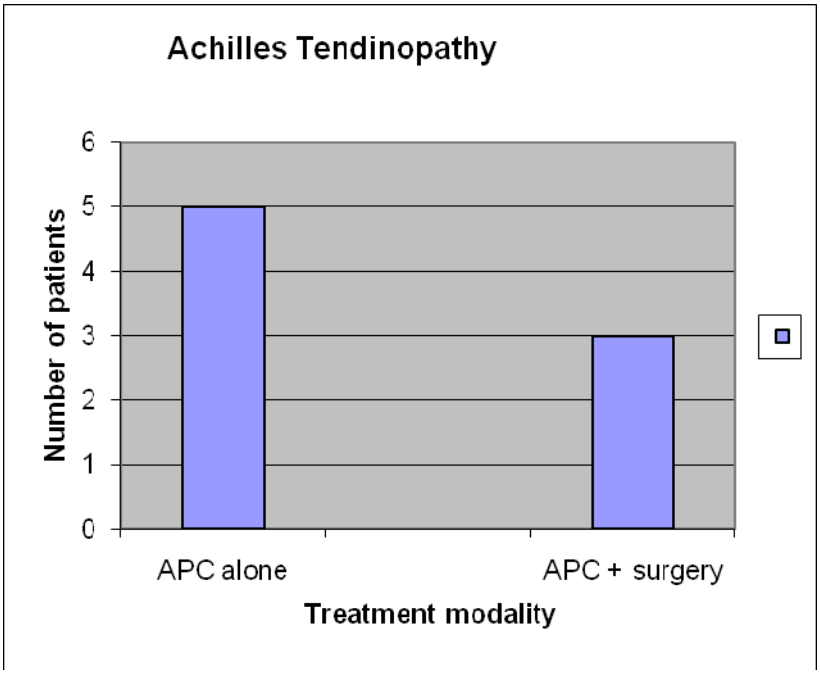


Figure 3

Achilles tendinopathy group: five feet treated with APC alone received no further treatment. Three feet required surgical intervention after APC.

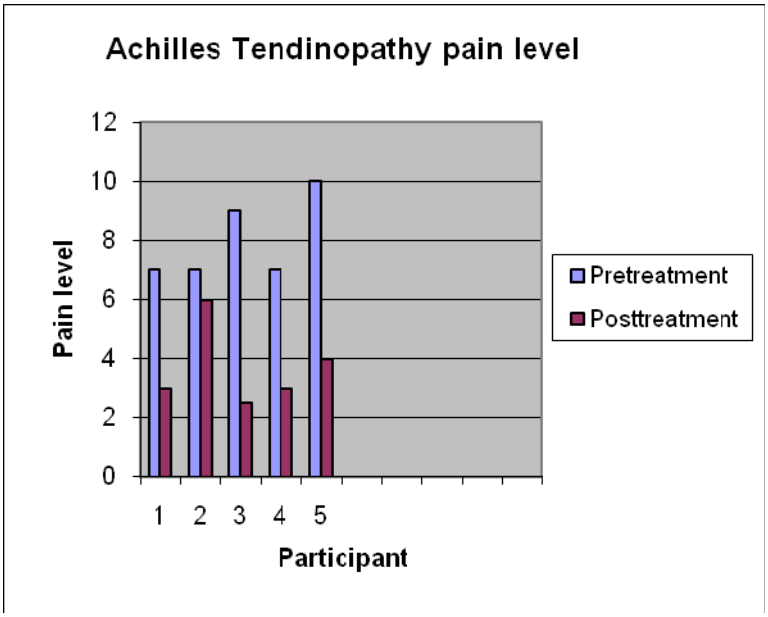


Figure 4

Achilles tendinopathy pre and post treatment pain level for the 5 feet that required no further intervention.