Platelet rich in growth factors or hyaluronate in the management of osteochondral lesions of the talus

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Abstract:

Background: Conservative options for osteochondral lesions (OCL) of the talar dome are limited, and currently there is a lack of scientific evidence to guide management.

Purpose: To evaluate the short term efficacy and safety of Platelets Rich Plasma (PRP) compared with Hyaluronic Acid (HA) in reducing pain and disability caused by OCL of the ankle.

Study design: Prospective, quasi-randomized trial (Level 1).

Methods: Thirty two subjects aged 18 to 60 were allocated to a treatment by intra-articular injections of either HA (group 1) or PRP (PRGF technique, group 2), for OCL of the talus. 30 osteochondral lesions, 15 per arm, received 3 consecutive intra-articular therapeutic injections and were followed for 28 weeks. The efficacy of the injections in reducing pain and improving function was assessed at each visit using the AOFAS Ankle-Hindfoot Scale (AHFS), the Visual Analog Scale (VAS) for pain, stiffness and function and the subjective global function score.

Results: The majority of subjects were male (79%, 23). AHFS improved from 66 and 68, to 78 and 92, (groups 1 and 2, respectively) from baseline to week 28 ($P<0.0001$) favoring PRP ($P<0.05$). Mean VAS scores, (1- Asymptomatic, 10- Severe symptoms) decreased for Pain (5.6 to 3.1 group 1, 4.1 to 0.9 group 2), stiffness (5.1 to 2.9 group 1, 5.0 to 0.8 group 2), and function (5.8 to 3.5 group 1, 4.7 to 0.8 group 2), from baseline to week 28, ($P<0.0001$) favoring PRP ($P<0.05$ for stiffness, $P<0.01$ for function, $P>0.05$ for pain). Subjective global function scores, reported on a scale from 0 to 100 (with 100 representing healthy, pre-injury function), improved from 56 and 58 at baseline to 73 and 91 by week 28 (group 1 and 2 respectively, $P<0.01$ in favor of PRP).

Conclusion: OCL of the ankle treated with intra-articular injections of PRP and HA resulted in a decrease in pain scores and increase in function for at least 6 months, with minimal adverse events. PRP treatment led to a significantly better outcome than HA.

Key Terms: Osteochondritis Dissecans, Osteochondral lesion, Ankle, PRP, Hyaluronic Acid

Introduction:

Osteochondral lesions (OCL) of the talus are relatively uncommon, and involve injury to cartilage and subchondral bone[41]. OCL occur most frequently in the knee, elbow and the ankle, are more likely to affect males, and occur most commonly in the young population[37,42]. The cause of OCL of the talus may include trauma, ischemia, abnormal ossification or genetic predisposition[12,41]. Although trauma is probably the most likely cause of OCL of the ankle, repetitive microtrauma may also be a contributing factor[19]. Sports-related injuries causing inversion, forced dorsiflexion, plantar flexion or lateral rotation of the tibia may lead to traumatic lesions[10]. These lesions may either heal spontaneously or progress to give chronic symptoms of deep joint pain, worse on weight bearing and exercise[42]. Lesions may also develop subchondral cystic change or detach, forming intra-articular loose bodies[41,42]. Catching, stiffness and joint swelling may also be reported. Since articular cartilage is aneural, the pain is thought to arise from the subchondral bone beneath the OCL defect and may be caused by high fluid pressure during weightbearing[41].

The prognosis for OCL of the talus varies according to a patient's age at the time of lesion development. Lesions identified during childhood and adolescence tend to heal spontaneously while older individuals often have poorer results[37]. A variety of treatments exists for OCL of the talus, with options being dependent upon the stage of the lesion[6,15] commonly determined by CT classification. Ferkel has graded lesions from 1 to 4: grade 1 lesions include cystic lesions with intact walls; grade 2 lesions (2a, 2b) include cystic lesions communicating with the talar dome or a full-thickness lesion with an overlaid fragment; grade 3 stands for undisplaced lesions with lucency; grade 4 lesions are free loose fragments[15].

Goals of treatment are the improvement of joint function, the reduction of pain and the prevention of early joint degeneration. The conservative treatment options are limited[43], tend to be reserved for grade 1 and 2 lesions, and include immobilization, restriction of weight bearing and physiotherapy. Surgical intervention is recommended if non-operative treatment is unsuccessful or for initial treatment of grade 3 and 4 lesions[15,23]. This features curettage and microfracture, retro and antegrade drilling, fragment removal, fragment refixation, abrasion arthroplasty and bone or cartilage transplantation [8,17,24,39,42].

Hyaluronic acid (HA) may be used as a conservative treatment option for knee and ankle osteoarthritis[29,34] and recently for talar OCD[27]. Intra-articular injection of HA reduced pain and associated inflammation, and supplement endogenous joint fluid. Moreover, some

studies have suggested that HA treatments act to facilitate a biological activation based on the lasting benefits of HA treatment long after the presence of HA after injection[1].

Platelet Rich Plasma (PRP) has been proposed as a novel treatment modality for the management of articular cartilage injuries of the knee, hip and ankle, with reduced pain and improved function following intra-articular injection[13]. PRP application improves the quality of synovial fluid by inducing, amongst other, the endogenous secretion of hyaluronic acid[3,35]. PRP administration also leads to improved outcome for low grade cartilage degeneration in the knees of young males[21].

We performed a quasi-randomized study to test the null hypothesis that PRP and HA injections in patients with talar OCL are equally effective to reduce pain and improve function in the short term.

Methods

Study Design:

Twenty nine patients with 30 symptomatic osteochondral lesions of the talus, who failed to respond to previous treatment modalities, were included in the study and treated in our University medical center between 2008 and 2010. The study was approved by the institutional review board of the medical center.

Patients were given a full verbal and written explanation of the study, objectives and treatment. After obtaining written informed consent, screening and demographic questionaires were completed. All patients had completed previous non-operative therapy consisting of temporary immobilization, the use of analgesics and anti-inflammmatories, partial weight bearing and orthotic provision. Non-ambulating patients, those with osteoarthritic changes at imaging, patients with suspected previous joint infection, hypersensitivity/allergy to hyaluronic acid, pregnant or lactating women, patients with concomitant systemic disease, open wounds or skin ulcers and those taking anticoagulants or having a prolonged bleeding time were excluded. Patients who had undergone lower limb intra-articular injection or surgery within the previous 6 months were also excluded.

A clinical examination was performed, recording range of movement and the presence of tenderness and ankle effusion. The most recent CT scan was evaluated, and lesions were classified separately by two examiners according to location, grade and size. The presence of loose bodies, osteoarthritic changes, impingement spurs or other pathologies which could impair assessment also led to exclusion.

Patients received either HA (group 1) or PRP (group 2), (Figure 1). Patients received either HA (group 1) or PRP (group 2). Because the treatment was not blinded and the time intervals between HA and PRP injections were different (1 week interval for HA injections, and 2 week intervals for PRGF injections), treatment was randomly allocated to each block of patients. Once a group of 5 lesions was accumulated, treatment was initiated. Treatment was randomized according to presentation. In this way, we were able to schedule the injections and follow up visits at the same time intervals for few patients at a time, making the process easier to manage logistically. Group 1 received one weekly injection of 2 mL, 1% (20 mg) Sodium Hyaluronate solution (Euflexxa, Ferring Pharmaceuticals, Inc). Costs range between US$ 200 and 250 for three 2 mL injections over two weeks for a total of three injections (day 0, day 7, day 14). Group two received one injection of 2 mL of PRP (PRGF System II, BTI,

Vitoria, Spain), at a cost of around US$ 30 per injection once the equipment is in place, every two weeks, over four weeks for a total of three injections (day 0, day 14, day 28). We have previously found optimal efficacy with PRGF injections separated by a two week period for knee and ankle cartilage related injuries.

PRGF was prepared as described by Sánchez et al[35,36]. 18 mL of peripheral blood was collected into 2 9 mL tubes containing 3.8% (wt/vol) sodium citrate. Tubes were centrifuged at 640 g for 8 min. the 1 mL plasma fraction located just above the buffy coat was aspirated, from each tube, and dispensed into an empty tube under vertical air flow conditions. Seconds prior to the infiltration, calcium chloride was added to a final concentration of 22.8 mM. The activated concentrate was then injected into the ankle joint, before coagulation, and so the fibrin scaffold containing the platelet aggregates would directly form within the joint capsule[35,36]. The platelets concentration in this type of PRP is 2-3 times blood platelets count which considered to be moderately elevated. Moderately elevated platelet concentrations seem to induce optimal biological benefit, with lower platelet concentrations leading to suboptimal effects, and higher platelet concentrations to inhibitory effects[4,18,25,26,35]

The injection process was performed under strictly sterile conditions via a medial approach to the ankle joint. No local anasthetic was used for group 2 (PRP) in order to prevent a possible negative interaction[26]. For group 1, superficial local anaesthetic infiltration was used only at the patients request. The activated PRGF concentrate was injected before coagulation and so the fibrin scaffold containing the platelet aggregates was directly formed within the joint capsule[35].

Immediately after each injection, the patient's ankle was moved passively throughout its full range of motion to disseminate the injected fluid throughout the joint. Patients were advised to avoid unnecessary walking for 24 hours.

Acetaminophen (Paracetamol) was recommended as an analgesic, if needed, but patients were instructed to avoid non-steroidal anti-inflammatory medications for two weeks after the last injection given the possible negative interaction with PRP[13,26]. Patients were also instructed to avoid sports activity or heavy physical work for 2-3 days post injection.

Efficacy measurements:

Function, range of motion and adverse events were assessed at the time of enrollment and at weeks 4, 12 and 28 post-injection. Swelling, tenderness, joint subjective pressure and local pain during motion and while at rest were also recorded. Primary efficacy measures

were determined using the modified Ankle Hind-Foot Score[20] (AHFS) and the Visual Analogue Scale[11] (VAS), completed by the subjects at each visit. Subjects were also requested to assess their subjective global function and disability (ranging 1-100%). Specifically, each subject was asked to assess their function during activities of daily living and subjective well being compared to prior function. Comparisons were determined as a percentage of the subject's previous functional capability and "well being", prior to developing ankle symptoms. The VAS validated questionnaire consisted of a series of questions each with a score that ranged from 1 to 10. In this study we have been using the 'Q scale', where 10 equals 'perfect health' as the anchor point. The questionnaire evaluated the degree of pain while standing, sitting or lying in bed during the day, walking on flat surface, climbing stairs and night pain. Additional information included the degree of joint stiffness experienced in the morning and throughout the day. Finally, the VAS was applied to functional activities, evaluating the subjective patient performance while climbing up and down the stairs, walking on flat surface, going out for a long walk, or performing household work.

At each follow-up visit, physical exam also assessed possible swelling of the affected joint, tenderness, subjective pressure and local pain during motion and while at rest.

The primary endpoint was a reduction in pain and improved function as translated to the AHFS or VAS scales, without reintervention during the study follow up time period.

Statistical analysis:

Statistical analyses were blinded and performed according to the intention-to-treat principle. Baseline values between groups of age and the time each patient suffered from OCL of the ankle and of baseline scores of the 5 response variables (AHFS, Pain, stiffness, and function - based on a VAS and global function score), were compared using t-Test. The effect of gender, age, grade and previous arthroscopic surgery, were evaluated using Pearson Chi-Square or Fisher's Exact Test.

The effect of the substance injected over time, for each group, on each of the 5 response variables, was assessed using ANOVA with repeated measures analysis. The questions concerning pain, stiffness and function using the VAS scale were averaged, creating pain, stiffness and function scales. The scales were computed for each time point (baseline, weeks 4, 12, and 28).

All statistical tests with p values were two-sided, and the selected level of significance for all variables was alpha = 0.05. SPSS statistical software version 12.0 (SPSS Inc, Chicago, IL) was used for data analysis.

Results

From 2008 to 2010, a total of 32 eligible patients with 33 symptomatic OCL lesions of the talus met the inclusion criteria and were randomized into two treatment groups. 29 patients (30 OCL) completed the treatment protocol and subsequent assessments. Three patients were excluded from the study. Two patients (one from each group) decided not to continue to participate in the study as they had both received additional medical opinions suggesting alternative treatment. The third patient relocated overseas and was lost to follow up. Group 1 included 15 OCL (15 patients) and Group 2 included 15 OCL (14 patients). One patient had symptomatic lesions affecting both ankles, and, according to our quasi-randomization process, received PRP injections in both ankles. Identical results were obtained including and excluding the second ankle in Group 2. Both groups had similar demographic data and base line symptom scores, duration and lesion classification (Table 1).

The mean AHFS scores for all patients significantly improved ($P<0.0001$) from baseline to weeks 4, 12 and 28, however, group 2 patients (PRP) had a significantly greater improvement ($P<0.05$) than those treated with Group 1 (HA), (Table 2, Figure 2). The mean VAS for pain, stiffness and function scores were also all significantly improved ($P<0.0001$) from baseline at weeks 4, 12 and 28, for both groups (Table 2). A statistically significant difference was noted for Group 2 (PRP) over Group 1 (HA) for VAS stiffness ($p<0.05$) and VAS function ($p<0.01$) but not for VAS pain (Table 2).

Mean subjective global function scores increased over time (Table 2). This was evidenced for both groups, but the PRP treated patients yield a higher level of improvement ($P<0.01$). Overall, the patterns of the AHFS, the subjective global function and three VAS scores showed a consistent rapid improvement from baseline through week 12th and remained low, or kept on improving (for group 2) throughout the study to the final visit at week 28th.

A large proportion of subjects (10/15 in group 1 and 12/15 for group 2) reported having constant or daily pain at presentation. Beginning from week 4 onwards patients reported decreased pain, with increasing numbers of patients reporting only intermittent rather than constant pain. Also, by week 12, no subjects reported constant pain. Four subjects from Group 2 developed a new onset of mild symptoms of plantar fasciitis following the treatment, and one subject developed mild Achilles tendinopathy at their last follow up assessment. Two of the four patients with plantar fasciitis had decreased sub-talar motion at initial evaluation,

and the patient with Achilles tendinopathy had pes planus. These symptoms did not influence their outcome scores.

Regarding complications, there were 90 injections performed with no reported superficial or deep infections. Two subjects described mild pain within a few hours following one injection in Group 1 (2 of 45 total injections). This resolved spontaneously within a day. One patient from Group 2 reported on acute mild pain following all three injections. These resolved spontaneously within 3 weeks. As would be expected, localized minor discomfort and mechanical pressure was a common report at the injection site in the 1-2 days following each injection, in both groups.

Discussion

In this quasi randomized controlled trial, both HA and PRP (PRGF) were effective in improving subjective well-being and pain, stiffness, and function associated with Grades 1 to 3 OCL of the talus, who failed previous treatment modalities. PRP produced a significantly greater improvement than HA. Both treatments caused only minimal discomfort related to the injections and no complications. The main improvement occurred during the first 12 weeks post treatment, followed by a lesser improvement with PRP or plateau with HA until the end of the study follow up time period, at 28 weeks. AHFS, VAS and subjective function scores significantly improved with either treatment and the proportion of subjects experiencing constant pain decreased over time. The use of both HA and PRP appears to offer a viable treatment option for patients with ankle OCL, with a significantly better outcome attributed to PRP treatment.

These findings suggest that these treatment methods should be considered as an effective first line for management of OCL of the talus, unless there are definite indications for surgery e.g. intra-articular loose body or mechanical recurrent locking.

As articular cartilage injuries cause high morbidity, there has been increased interest in new therapeutic modalities. PRP injection has been recently proposed as a novel treatment modality for the management of articular cartilage injuries of the knee, hip and ankle[13]. Even though clinical evidence is lacking, basic research supports the use of PRP derived growth factors to improve cartilage healing[28] and clinical data supports its use in meniscal and hip labral repair and augmentation[5,30,31,35].

Clinical studies on the use of PRP in cartilage related pathologies have been reported. A retrospective cohort study[35] reported decreased pain and enhanced function, as assessed using the WOMAC scale, after three intra-articular injections of PRGF compared to HA for knee OA. PRGF was significantly superior to HA, although both have showed positive short term effects. Another pilot study of 100 patients with osteoarthritis of the knee receiving three intra-articular PRP injections found favorable results with reduced pain and improved function[16]. Statistically significant improvement was observed at 2, 6, 12 and 24 months follow up and these results were significantly better in younger patients and lower degrees of cartilage degeneration. These beneficial effects were reduced by 12 and 24 months follow-up with a median duration of 9 months benefit[16]. The present study followed patients for six months after injections. This relatively short time period can be considered a limitation, although

similar to most conservative treatment evaluation studies[7,22,38]. Nevertheless, further follow up is still being conducted.

PRGF is a form of PRP[36], and is a biological delivery systems of a complex mixture of bioactive proteins essential to natural repair, including anabolic and protective factors for cartilage, such as transforming growth factor-**β** 1 (TGF-**β** 1), platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF-I)[35]. In the past decade several crucial roles of growth factors have been identified in joint repair [35]. For example, TGF-β1 is essential for cartilage integrity and a powerful tool to prevent or repair cartilage damage[9]. This growth factor is in its latent form while in the platelets, and is activated by TSP-1 (Thrombospondin), which is also released from platelets alpha-granules found in PRGF. As a result, intra-articular administration of PRGF could retard or prevent progression of degeneration of the joint's cartilage. PRGF levels for TGF-**β** 1 are 29.15±12.88 ng/cc and for PDGF-AB are 17.41±9.66 ng/cc, which is 10 and 20 times the levels found in platelet poor plasma, respectively[35]. PRGF will also provide an exogenous source of TIMPs, natural endoproteinase inhibitors that can inhibit metalloproteinase activity (MMP-1, -3, -13 which degrade collagen) in addition to preventing the breakdown of cartilage aggrecan[40]. PRP also improves the quality of synovial fluid by inducing the endogenous secretion of HA by synovial cells[3]. As a result, PRP exerts an anti inflammatory action, augmenting the flow of synovial fluid and normalizing its synthesis, inhibiting the degradation of endogenous hyaluronic acid, and relieving joint pain[33].

Although non-operative treatments have previously been found to be inferior to surgery for OCL[42], they are usually considered as a first line treatment[15,42]. Ferkel et al[15] reported the long-term results of patients operated for chronic OCL of the talus who underwent a trial of at least 4 months of non-operative management prior to surgical intervention. Conservative treatment traditionally consists of physical therapy, non-steroidal anti-inflammatory medication, orthoses, restriction of weightbearing activities, bracing, and/or cast immobilization. The results of the present investigation are encouraging, and it appears that previous conservative measures are not quite as successful[42] as injections of HA and PRGF. In our hands, PRGF has now become the first line of conservative treatment in these lesions.

Surgery for OCL of the talus aims at regenerating the injured articular cartilage and subchondral bone or fixation of the unstable fragment. The most common operative treatment

involves arthroscopic excision, curettage and bone marrow stimulation (BMS). Although this yields 85% good or excellent results, success rate can vary from 46 to 100%[42].

Autologous chondrocyte implantation (ACI) yields 76% good/excellent results, requires two surgical procedures and is relatively expensive technique. Osteoarticular transfer system (OATS) yields 87% good/excellent results, with donor site morbidity[32,42]. Ferkel et al. reported reduced outcome in the long term with good or excellent results in 64% to 72% of patients at an average follow-up of 71 months[15]. The mean AHFS score following surgery was 84, which is comparable with the outcomes of other studies after arthroscopic treatment of OCL[15]. Angermann and Jensen[2] confirmed that a subpopulation of patients will experience progression of symptoms after surgical treatment and that long-term outcomes deteriorate in 35% of the cases. Fibrocartilage layer lacks the durability of hyaline articular cartilage and this leads to premature deterioration of the repair and a recurrence of symptoms. An additional explanation is the possible preexistent degenerative changes[15].

The outcomes reported in our study (AHFS of 92 at 28 weeks follow up) would suggest that non-operative treatment with PRGF, in our hands, is comparable in efficacy, in the short term, to the reported results following surgical intervention, and should be considered as a valid first line treatment. 87% of our PRGF treated population obtained good results (Final score>95 or 20 point improvement). Future studies will be needed to verify this impression.

When we consider the possible complications and the cost of surgical intervention, intra-articular injection treatment looks even more attractive. Ferkel noted a complication rate of 14%, higher than previously reported for ankle arthroscopy (9%)[14], and 10% of patients required additional surgery. Posterior talus lesions are difficult to reach via anterior arthroscopy, whereas intra-articular injections address lesions wherever they are located within the joint. Prolonged operative time, and/or use of additional portals associated with surgery have also led to increased complications.

Four of our patients reported additional symptoms of plantar fasciitis and Achilles tendinopathy at the final stage of follow up, which later resolved with physical therapy. These new pathologies did not influence outcome scores, and it is possible that the improved in ankle joint function and the resumption of sports, after prolonged reduced activity, led to the development of additional symptoms elsewhere.

Zengerink et al[42] reviewed 52 studies, representing 1361 patients treated for OCL. Our patient population was typical of this cohort. The average patient is a male in his thirties with equal side preponderance. However, Ferkel et al found no correlation between age, gender, side, location or grade of the lesion, length of preoperative treatment (less or more than a year) and clinical outcomes[15].

There are several limitations to this study. One is previous surgery. Five subjects in group 1 and four subjects in group 2 had undergone previous arthroscopy with micro-fracture or drilling to treat the symptomatic OCL. The improvement reported, however, adds strength to the use of PRP injection as a treatment option even for operated osteochondral lesions with unsatisfactory results. The current classification systems to describe postoperative changes in OCL lesions are not very accurate[15]. We acknowledge that there may be discrepancies in the grading of some lesions, but this variation will be present in all series and for all patients.

Another limitation is the lack of accurate documentation of analgesic use by our patients. Following the injection patients were permitted to use analgesics as required. This may be an influencial factor but we suspect that this would be similar for both groups. Most patients stated that they did not use analgesics upon follow up.

We did not perform a formal power analysis as we planned the choice of the number of patients to enroll in the study according to what we knew our unit could deliver within the time we chose to allocate to the study. Nevertheless, a *post hoc* power analysis was performed based on the Ankle Hind Foot Score (AHFS), which we considered the main outcome measure. We ascertained that the size of our cohorts was sufficient to obtain a 99% chance of detecting a 5% difference in AHFS (the score showed a raise from 68 up to 92.5 points while mean score of 82 would be sufficient to be considered statistically significant, yielding a power > 80%). The *post hoc* analysis supports the results obtained, and the sample size empirically used in the present study.

The need to simplify and reduce the costs of the treatment application induced us to use a quasi-randomized design. However, despite these weaknesses, our selection and recruitment process, our assessment criteria, and our follow-up were performed in strict methodological fashion. Also, with the numbers of patients enrolled, the results of our study are unequivocal.

We succeeded in recruiting 32 patients for this treatment study. Three patients were lost to follow up or left the study prior to treatment for reasons not related with the treatment

itself (as outlined in the Results section). OCL of the talus is not common, and it is relatively hard to recruit patients suffering from this problem. 29 subjects, for a total of 30 OCLs, are a relatively large number for this particular pathology.

In this study, we have used the PRGF (Plasma Rich in Growth Factors) technique to produce PRP [36]. This is one of the first PRP techniques described, and is widely published. PRGF is a cheap and manually prepared concentrate, which results in P-PRP (Pure-PRP with 2-3 times blood platelets count and with no WBC) contrasting with the PRP produced by many commercially available preparation systems. Similarly, the frequency of injections, volumes and activation methods must always be considered when comparing PRP techniques. As a result, we can not extend our study conclusions to all PRP applied techniques or protocols. The influence of PRP on articular cartilage regeneration and synovial fluid composition during the treatment of OCL lesions present future investigational challenges.

Following these encouraging results, we use intra-articular injection of either PRP or Hyaluronic Acid for the first line treatment symptomatic talar OCL patients or as a second line treatment for patients who are symptomatic following surgery. Therapeutic injections should be considered for patients who have symptomatic lesions and yet are not candidates for surgery either due to fitness for anaesthesia or the time constraints associated with surgical recovery, such as professional athletes. In our practice, we recommend PRGF as a first line treatment for OCL of the talus.

Conclusion:

Intraarticular ankle PRGF and HA injections are efficacious in decreasing pain and stiffness and improving function and subjective well being in patient suffering from grade 1-3 OCL of the talus. We recommend that therapeutic intra-articular injections of PRGF should be considered as a first line treatment option. The treatment is safe and provides relief that last at least six months.

Flow Diagram

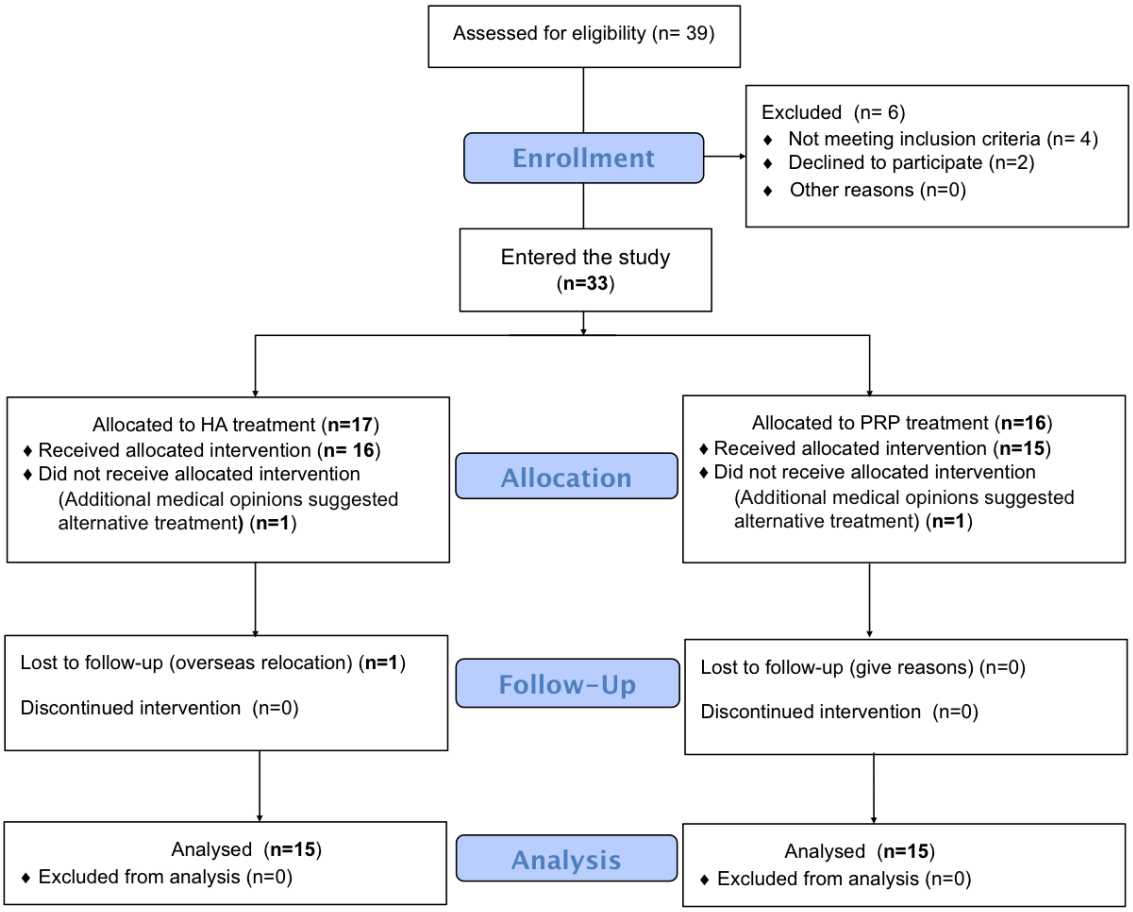

Table 1. Demographic data and Baseline Characteristics

	Group 1 – HA (s.d)	***Group 2 – PRP*** (s.d)
Age, Mean	36.5 (15.2)	42.8 (18.1)
Time suffer	9.2 (6.2)	7.2 (5.5)
Gender, n (%)		
Male	11 (73.0%)	12 (80%)
Female	4 (27.0%)	3 (20%)
Side, n (%)		
Right Ankle	8 (53%)	9 (60%)
Left Ankle	7 (47%)	6 (40%)
Location, n (%)		
Posteromedial \ Medial	13 (87%)	14 (93%)
Anterolateral \ Lateral	2 (13%)	1(7%)
Mean Lesion Size (cm^2)	1.26 (R. 0.46-3.5)	1.41 (R. 0.44-3.2)
Grade (Ferkel), n (%)		
1	2 (13%)	2 (13%)
2a	4 (27%)	5 (33%)
2b or 3	9 (60%)	8 (54%)
Previous Arthroscopy	5 (33%)	4 (27%)
AHFS, Mean	66.4 (15)	68 (14)

Mean demographic data and baseline characteristics showed no significant difference between the groups

Table 2. Outcome Measures - Time by Group Interaction

		Group 1 – HA	*Group 2 – PRP*
	Week	**Mean (SD)**	**Mean (SD)**
AHFS	0	66.4 (15)	68.0 (14)
	4	78.2 (14)	84.3 (7)
	12	81.2 (14)	89.7 (7)
	28	78.3 (14)	92.5 (8)
VAS Pain Score	0	5.6 (1.7)	4.1 (2.1)
	4	3.7 (1.5)	1.6 (1.5)
	12	3.0 (2.1)	0.9 (1.0)
	28	3.1 (2.1)	0.9 (1.4)
VAS Stiffness Score	0	5.1 (2.8)	5.0 (2.3)
	4	3.2 (2.0)	2.5 (1.7)
	12	3.0 (2.4)	1.4 (1.8)
	28	2.9 (2.3)	0.8 (1.2)
VAS Function Score	0	5.8 (1.9)	4.7 (2.1)
	4	4.0 (2.0)	2.2 (1.4)
	12	3.5 (2.5)	1.1 (1.1)
	28	3.5 (2.6)	0.8 (1.2)
Subjective Global Function Score	0	56 (18)	58 (22)
	4	67(18)	79 (14)
	12	71 (21)	90 (9)
	28	73 (20)	91 (10)

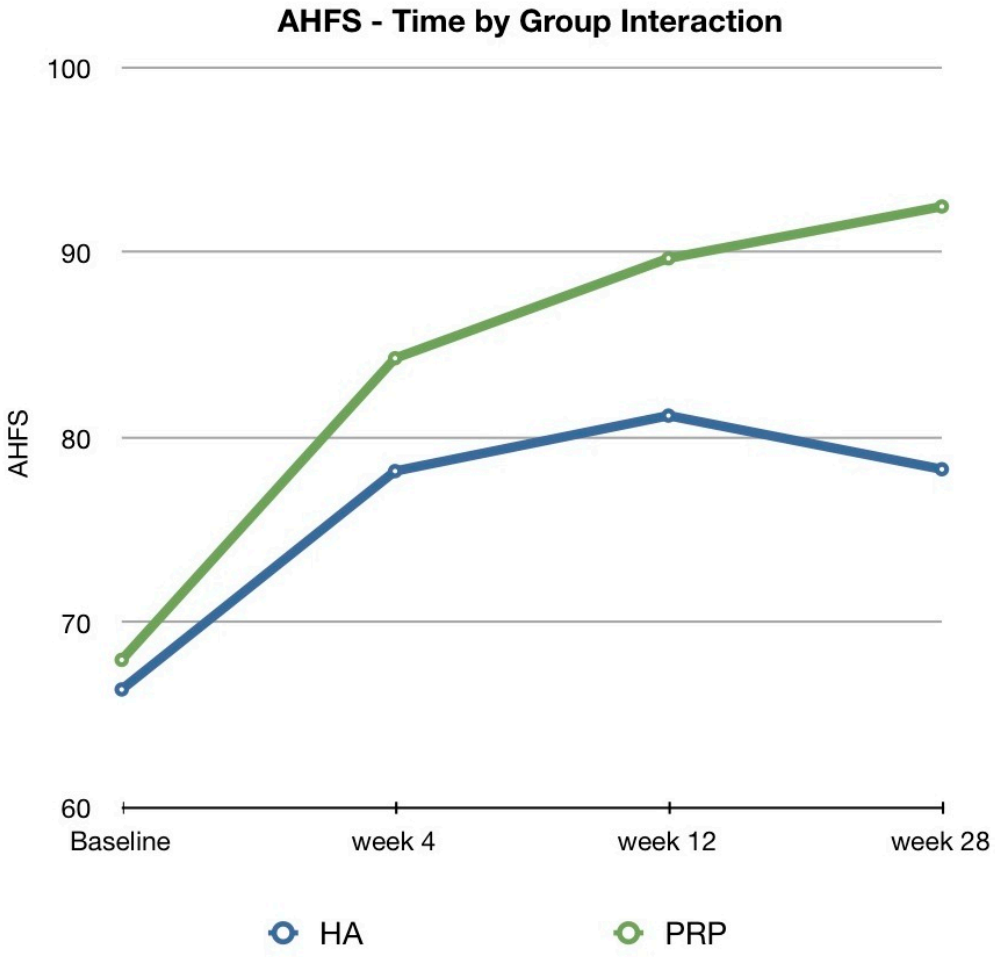

Figure 2: AHFS - Time by group interaction

We can see that while HA influence on AHFS is slightly decreasing between 3rd and 4th follow up evaluations (12th and 28th weeks), the PRP (PRGF) treated patients keep on improving ($P<0.05$).

REFERENCES:

1. Abatangelo G, O'Regan M. Hyaluron: biological role and function in articular joints. *Eur J Rheumatol Inflamm*. 1995;151:9-16.
2. Angermann P, Jensen P. Osteochondritis dissecans of the talus: long- term results of surgical treatment. *Foot Ankle.* 1989;10:161-163.
3. Anitua E, Sánchez M, Nurden AT, et al. Platelet-released growth factors enhance the secretion of hyaluronic acid and induce hepatocyte growth factor production by synovial fibroblasts from arthritic patients. *Rheumatology.* 2007;46(12):1769–1772.
4. Anitua E, Sánchez M, Nurden AT, et al. New insights into and novel applications for platelet-rich fibrin therapies. *Trends Biotechnol.* 2006;24:227–34.
5. Arnoczky SP, Anderson L, Fanelli G, et al. The role of platelet-rich plasma in connective tissue repair. *Orthopedics Today*. 2009;26:29.
6. Baltzer AWA and Arnold JP. Bone-cartilage transplantation from the ipsilateral knee for chondral lesions of the talus. *Arthroscopy.* 2005;4(2):2159-2166.
7. Bannuru RR, Natov NS, Dasi UR, Schmid CH, McAlindon TE.Therapeutic trajectory following intra-articular hyaluronic acid injection in knee osteoarthritis--meta-analysis. *Osteoarthritis Cartilage*. 2011;19(6):611-9.
8. Baums MH, Heidrich G, Schultz W, Steckel H, Kahl E, Klinger HM. Autologous chondrocyte transplantation for treating cartilage defects of the talus. *J Bone Joint Surg Am*. 2006;88(2):303-308.
9. Blaney Davidson EN, van der Kraan PM, van den Berg WB: Review. TGF-β and osteoarthritis. *Osteoarthritis Cartilage.* 2007 Jun;15(6):597-604.
10. Canale ST and Belding RH. Osteochondral lesions of the talus. *J Bone Joint Surg Am*. 1980;62:97-102.
11. Carlsson AM. Assessment of chronic pain. I. Aspect of the reliability and validity of the visual analog scale. *Pain*.1983;16:87-101.
12. Clanton TO and DeLee JC. Osteochondritis dissecans. History, pathophysiology and current treatment concepts. *Clinl Orthop Relat Res*. 1982;167:50-64.
13. Engebretsen L, Steffen K, Alsousou J, Anitua E, Bachl N, Devilee R, Everts P, Hamilton B, Huard J, Jenoure P, Kelberine F, Kon E, Maffulli N, Matheson G, Mei-Dan O, Menetrey J, Philippon M, Randelli P, Schamasch P, Schwellnus M, Vernec A, Verrall G. IOC

consensus paper on the use of platelet-rich plasma in sports medicine. *Br J Sports Med.* 2010;44(15):1072-1081.

14. Ferkel RD. *Arthroscopic Surgery: The Foot and Ankle*. Philadelphia, Pa: JB Lippincott; 1999:145-169.

15. Ferkel RD, Zanotti RM, Komenda GA, Sgaglione NA, Cheng MS, Applegate GR, Dopirak RM. Arthroscopic treatment of chronic osteochondral lesions of the talus: long-term results. *Am J Sports Med*. 2008;36(9):1750-62.

16. Filardo G, Kon E, Buda R, Timoncini A, Di Martino A, Cenacchi A, Fornasari PM, Giannini S, Marcacci M. Platelet-rich plasma intra-articular knee injections for the treatment of degenerative cartilage lesions and osteoarthritis. *Knee Surg Sports Traumatol Arthrosc.* 2011;19(4):528-35.

17. Gobbi A, Francisco RA, Lubowitz JH, Allegra F, Canata G. Osteochondral lesions of the talus: randomized controlled trial comparing chondroplasty, microfracture, and osteochondral autograft transplantation. *Arthroscopy*. 2006;22(10):1085-1092.

18. Graziani F, Ivanovski S, CeiS, et al. The in vitro effect of different PRP concentrations on osteoblasts and fibroblasts. *Clin Oral Implants Res.* 2006;17:212–219.

19. Hixon AL and Gibbs LM. Osteochondritis dissecans: a diagnosis not to miss. *Am Fam Physician*. 2000;61(1):151-156, 158.

20. Kitaoka HB, Alexander IJ, Adelaar RS, Nunley JA, Myerson MS, Sanders M. Clinical rating systems for the ankle-hindfoot, midfoot, hallux and lesser toes. *Foot Ankle Int*. 1994;15(7):349-353.

21. Kon E, Buda R, Filardo G, et al. Platelet-rich plasma: intra-articular knee injections produced favorable results on degenerative cartilage lesions. *Knee Surg Sports Traumatol Arthrosc.* 2010;18:472–479.

22. Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, Fornasari PM, Giannini S, Marcacci M. Platelet-Rich Plasma Intra-Articular Injection Versus Hyaluronic Acid Viscosupplementation as Treatments for Cartilage Pathology: From Early Degeneration to Osteoarthritis. Arthroscopy. 2011 Aug 8. [Epub ahead of print].

23. Kreuz PC, Steinwachs M, Erggelet C, Lahm A, Henle P, Niemeyer P. Mosaicplasty with autogeneous talar autograft for osteochondral lesions of the talus after failed primary arthroscopic management. A prospective study with a 4-year follow-up. *Am J Sports Med*. 2006;34:55-63.

24.Kumai T, Takakura Y, Higahiyma I, Tamai S. Arthroscopic drilling for treatment of osteochondral lesions of the talus. *J Bone Joint Surg Am*. 1999;81(9):1229-1235.

25.Mastrangelo AN, Vavken P, Fleming BC, Harrison SL, Murray MM. Reduced platelet concentration does not harm PRP effectiveness for ACL repair in a porcine in vivo model. *J Orthop Res*. 2011;29(7):1002-1007.

26.Mei-Dan O, Mann G, Maffulli N. Platelet-rich plasma: any substance into it? *Br J Sports Med.* 2010;44(9):618-9.

27.Mei-Dan O, Maoz G, Swartzon M, Onel E, Kish B, Nyska M, Mann G. Treatment of osteochondritis dissecans of the ankle with hyaluronic acid injections: a prospective study. *Foot Ankle Int.* 2008;29(12):1171-1178.

28.Milano G, Sanna Passino E, Deriu L, et al. The effect of platelet rich plasma combined with microfractures on the treatment of chondral defects: an experimental study in a sheep model. *Osteoarthr Cartil.* 2010;18:971–980.

29.Petrella RJ and Petrella M. A prospective, randomized, double-blind, placebo controlled study to evaluate the efficacy of intra-articular hyaluronic acid for osteoarthritis of the knee. *J Rheumatol*. 2006;33(5):951-956.

30.Philippon MJ, Briggs KK, Hay CJ, et al. Arthroscopic labral reconstruction in the hip using iliotibial band autograft: technique and early outcomes. Arthroscopy. 2010;26:750–756.

31.Philippon MJ, Schroder e Souza BG, Briggs KK. Labrum: resection, repair and reconstruction sports medicine and arthroscopy review. *Sports Med Arthrosc.* 2010;18:76–82.

32.Reddy S, Pedowitz DI, Parekh SG, Sennett BJ, Okereke E. The morbidity associated with osteochondral harvest from asymptomatic knees for the treatment of osteochondral lesions of the talus. *Am J Sports Med*. 2007 Jan;35(1):80-85.

33.Rydell N, Balazs EA: Effect of intra-articular injection of hyaluronic acid on the clinical symptoms of osteoarthritis and on granulation tissue formation. *Clin Orthop Relat Res*. 1971; 80:25-32.

34.Salk RS, Chang TJ, D'Costa WF, Soomekh DJ, Grogan KA. Sodium hyaluronate in the treatment of osteoarthritis of the ankle: a controlled, randomized, double-blind pilot study. *J Bone Joint Surg Am.* 2006;88(2):295-302.

35.Sánchez M, Anitua E, Azofra J, Aguirre JJ, Andia I. Intra-articular injection of an autologous preparation rich in growth factors for the treatment of knee OA: a retrospective cohort study. *Clin Exp Rheumatol.* 2008;26(5):910–913.

36.Sánchez M, Anitua E, Azofra J, Andía I, Padilla S, Mujika I. Comparison of surgically repaired Achilles tendon tears using platelet-rich fibrin matrices. *Am J Sports Med*. 2007;35(2):245-51.

37.Schenck RC Jr and Goodnight JM. Current concept review – osteochondritis dissecans. *J Bone Joint Surg Am*. 1996;78:439-456.

38.Shimizu M, Higuchi H, Takagishi K, Shinozaki T, Kobayashi T. Clinical and biochemical characteristics after intra-articular injection for the treatment of osteoarthritis of the knee: prospective randomized study of sodium hyaluronate and corticosteroid. *J Orthop Sci.* 2010;15(1):51-6.

39.Taranow WS, Bisignani GA, Towers JD, Conti SF. Retrograde drilling of osteochondral lesions of the medial talar dome. *Foot Ankle Int*. 1999;20(8):474-480.

40.Tortorella MD, Arner EC, Hills R, Easton A, Korte-Sarfaty J, Fok K, Wittwer AJ, Liu RQ, Malfait AM: Alpha2-macroglobulin is a novel substrate for ADAMTS-4 and ADAMTS-5 and represents an endogenous inhibitor of these enzymes. *J Biol Chem.* 2004;23;279(17):17554-61.

41.Van Dijk CN, Reilingh ML, Zengerink M, van Bergen CJ. Osteochondral defects in the ankle: why painful? *Knee Surg Sports Traumatol Arthrosc.* 2010;18(5):570-580.

42.Zengerink M, Struijs PA, Tol JL, van Dijk CN. Treatment of osteochondral lesions of the talus: a systematic review. *Knee Surg Sports Traumatol Arthrosc.* 2010;18(2):238-46.

43.Zengerink M, Szerb I, Hangody L, Dopirak RM, Ferkel RD, van Dijk CN. Current concepts: treatment of osteochondral ankle defects. *Foot Ankle Clin*. 2006;11(2):331-359.