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Safety, Efficacy and Short-Term Results with Intra-Articular Bone Marrow Concentrate for Arthritic Knee Pain

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Abstract

Objective: Bone marrow concentrate cell procedures have been used frequently over the last decade in the setting of osteoarthritic knee pain and catabolic knee pain syndrome. In this study, safety and therapeutic benefit were assessed for treating knee osteoarthritis using Bone Marrow Concentrate (BMC) with an intra-articular approach. We sought to determine the short-term outcomes of patients treated with this modality over an average ten month follow up period (range 3-36 months) using validated and accurate outcomes assessments including the SF-12, IKDC, LEFS and the visual analogy score for pain. On average, there was improvement in all outcomes analyses over the time period studied. Study patients were uniformly pleased with their outcome and only one patient had gone on to have a total knee replacement during the study period at two years. Two patients with recurrent effusion and pain underwent a Platelet Rich Plasma (PRP) procedure within three months of their BMC procedure. Bone marrow concentrates can provide short-term pain relief in the setting of knee osteoarthritis even when only an intra-articular injection is used. We have modified our treatment algorithm to its seventh generation since 2006 and now include a subchondral injection in addition to intra-articular injection in nearly all patients. In general, those results have been superior to patients receiving intra-articular injection alone.

Methods: 94 patients with unicompartmental varus gonarthrosis were treated prospectively. Patients elected to undergo a clinical procedure with intra-articular autologous bone marrow concentrate in the setting of varus gonarthrosis and catabolic osteoarthritic pain syndrome. Patients all failed multimodality conservative treatments before being offered orthopedic immunobiologic treatment with bone marrow concentrate injection. All patients were treated by one surgeon at one facility using the same technique for harvest and injection. Patient related outcome measures (PROMs) were obtained in the pre-operative and post-operative setting at defined time points and included the SF-12, IKDC, LEFS and VAS score for pain. PROMs were compared to determine if there was meaningful improvement in mean clinical outcome metrics from baseline prior to treatment. The frequency and type of adverse events were also examined.

Results: No serious adverse events were reported with treatment in any patient. There was meaningful improvement in mean clinical outcome metrics from baseline in all patients during the time period studied. Mean change in visual analog scale exceeded the published minimum clinically important difference of 2.5 (3.4). The Lower Extremity Functional Scale mean change was +20 which exceeds a published 9 point minimum clinically important difference. The IKDC score mean change was +17 which exceeds a published 8 point minimum clinically important difference. Differences from baseline to follow up in the SF-12 demonstrated improvement in both the physical component (+9) and to a lesser degree the mental component (+2). The mean change in the physical component of the SF-12 exceeded the published minimally clinically important difference of 3.77.

Conclusion: Safety was demonstrated for bone marrow aspiration and concentration from the anterior gluteal pillar followed by a bone marrow concentrate procedure via an intra-articular route of administration in patients with isolated, unicompartmental varus gonarthrosis with Kellgren-Lawrence 2-3 knee osteoarthritis. Mean changes at 10 months showed substantial improvement from baseline in the clinical outcome metrics with VAS, IKDC, LEFS and SF-12 all exceeding published minimal clinical important difference values. Patients were satisfied with a bone marrow concentrate procedure for osteoarthritic knee pain during this short term follow up period.

Keywords: Autologous Bone Marrow Concentrates; Knee Osteoarthritis; Knee Pain; Cell Therapy

Introduction

Osteoarthritis is a progressive, whole-joint disease rather than a pure cartilage disorder [1]. The catabolic mechanisms underlying knee osteoarthritic pathways are becoming better understood and new, disease-modifying systemic drugs are being developed for the treatment of OA [2, 3]. These molecules target the molecular pathways that lead to joint destruction, potentially limiting the progression of OA. Bone Marrow Concentrates (BMC) are a natural source of small molecules that direct anti-inflammatory and immunomodulatory responses at the molecular level. Autologous cell therapy treatments consist of a cellular component and a plasma protein component that play distinct roles in combatting catabolic joint osteoarthritis and auto-inflammation [4]. Nucleated signaling cells from the harvested bone marrow function through cell receptor mediated signaling mechanisms that often involve a second messenger to activate anti-inflammatory and immunomodulatory pro-anabolic genes favorable to joint health [5]. Hyaluronic acid complexed platelet poor plasma concentrates can be filtered through size exclusion using 55 kD nanopore filaments to eliminate pro-inflammatory molecules and water, and retain anti-inflammatory and immunomodulatory molecules like TSG-6, TGF-B, IRAP and A2M (Minnetech®, Minneapolis, MN). A growth factor concentrate (GFC) matrix can be elaborated from the platelet poor plasma to function as nucleated bone marrow concentrate cell scaffolding for knee osteoarthritis when mixed with autologous thrombin to activate platelet dense granules [6].

In the osteoarthritic joint, catabolic complexes dominate the synovial fluid [7]. Pro-inflammatory protein molecules found in

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catabolic knee pain syndrome include interleukin one, tumor necrosis factor alpha, interleukin 6, interleukin 8, interleukin 17, interleukin 18, leukemia inhibitory factor, oncostatin M, Matrix Metalloproteinase 13 (MMP-13), ADAMTS and some prostaglandins [8, 9]. These molecules lead to cartilage matrix and cellular degradation from mechanical overload of the knee joint compartment affected [10]. Inflammatory cells make up approximately fifteen to twenty percent of the synovial lining of the knee joint and include immune signaling cells that function through adaptive autocrine and paracrine signaling mechanisms [11]. Other nucleated cells that play a role in osteoarthritis include hematopoetic and mesenchymal stem cells, endothelial cells and pericytes working together [12].

Bone marrow concentrates include anti-inflammatory molecules that may convert the catabolic joint to favour an anabolic environment thereby alleviating joint pain in patients. Anti-inflammatory molecules found in bone marrow concentrate include tumor necrosis factor alpha receptor antagonist, interleukin 4, interleukin 10, interleukin 13, interleukin one receptor antagonist protein (IRAP), alpha two macroglobulin (A2M) and tumor necrosis factor-inducible gene 6 protein (TSG-6). TSG-6 is induced by a number of pro-inflammatory signaling molecules including TNF-a and IL-1. TSG-6 is correlated with proteoglycan synthesis and aggregation and modulates macrophage plasticity, signaling the transition of macrophages from a pro to an anti-inflammatory phenotype [13]. Recently, French surgeons have suggested that subchondral bone injections of bone marrow concentrate are superior to intra-articular injection and better postpone total knee arthroplasty even at long term follow up of fifteen years compared to intra-articular injection of BMC alone [14]. Other authors have reported successful clinical outcomes and safety of a combined autologous bone marrow concentrate intraosseous and intra-articular injection for knee arthritis at twelve months [15]. We currently favour the combined approach as well. BMC has inherent advantages over other treatments commonly used for various knee pathologies because it is a point-of-care immunobiologic product that uniquely and simultaneously delivers growth factors, anti-inflammatory proteins, and mesenchymal stem cells in addition to other nucleated immunomodulatory bone marrow cells. There is increasing evidence for the use of BMC for repair of focal cartilage defects and for the treatment of generalized knee pain [16-19].

Methods

This study is a prospective, non-randomized study conducted at a single site with a single investigator (SAYIII). The purpose of the study was to evaluate the safety, efficacy and potential benefit of treating moderate knee osteoarthritis with an intra-articular injection of autologous bone marrow concentrate harvested from the anterior gluteal pillar. We evaluated 94 patients who consented to participate with the study and who were treated with point of care autologous bone marrow cell therapy for knee arthritis over a three-year period from February 2016 until February 2019. Each patient received 4 ml bone marrow concentrate admixed with 4 mL growth factor concentrate and 2 ml autologous thrombin for platelet activation using our method for bone marrow cell concentration. Patients were recruited from the clinic of the lead investigator. Patients with unilateral or bilateral symptomatic unicompartmental varus knee arthritis having Kellgren-Lawrence 2-3 changes on radiographs were included in the study. Primary clinical endpoints were SF-12, IKDC, LEFS with secondary endpoint of VAS (10-point scale). The endpoints of the study were assessed prior to treatment and at 2 weeks, 6 weeks, 12 weeks, 6 months, one year and yearly thereafter.

Procedure

Procedural pre-medication was accomplished with 5 mg oxycodone and 0.5 mg Xanax taken orally 1 hour before the procedure. Bone marrow concentrate aspiration was accomplished from the anterior gluteal pillar under local anaesthesia with 10 mL of lidocaine 2% with epinephrine and 0.25% Marcaine plain mixed 1:1 to anesthetize the skin, subcutaneous tissue and periosteum. Bone marrow harvest was accomplished percutaneously with a Jamshidi® needle for aspiration. Patients were treated with an iliac crest bone marrow aspiration concentrate that was harvested at the point-of-care in each case from the anterior gluteal pillar using local anaesthetic in an office procedure room. Each aspiration consisted of a 10 ml bone marrow aspirate with care taken to reposition the tip of the Jamshidi after each harvest. Following the harvest, isopycnic centrifugation was used to separate the bone marrow aspirate into three components: red blood cells, nucleated marrow cells and plasma. The red blood cells were discarded. The nucleated cells were aspirated into a syringe and the plasma was passed repeatedly through a nonfilter with 55 kD pores to eliminate pro-inflammatory molecules after the addition of hyaluronic acid to capture TSG-6, which is typically lost through size exclusion otherwise. Hyaluronate is the activator of TSG-6 and the complex is thought to play a chondroprotective role in attenuating the catabolic pain syndrome noted in the setting of osteoarthritis (OA). Pro-inflammatory molecules are typically 30 kD in size, whereas anti-inflammatory molecules are far larger (HA is 2400-3600 kD), providing the basis for size exclusion. The cellular and the plasma components were then mixed into a single syringe and complexed with autologous thrombin to open the dense granules of the platelets contained in the concentrate. This additional step makes the growth factors present in the platelets bioavailable with the addition of thrombin further activating the product and preventing loss of the injectate from the target site. This step is extraordinarily valuable when intraosseous subchondroplasty is contemplated in the treatment setting.

Once the product was obtained, injection was accomplished through a lateral parapatellar approach under meticulous sterile conditions, taking full sterile precautions, and confirmed in each case using ultrasound. Patients were fit with a medial Ossur® cartilage rebound unloader brace (Ossur®, Foothill Ranch, CA) and lateral heel wedge orthotics worn for three weeks prior to the intervention and for a total of 12 weeks after the procedure. Patients were instructed to avoid impact activities for the first two weeks and to wear the unloader brace and Heel-Wedge Orthotics (HWO) at all times while ambulatory for the first six weeks post treatment and then with impact activities including long walks for an additional six weeks. HW orthotics are worn at least two years from the date of the procedure and lifetime wear is encouraged to keep the affected tibial subchondral bone in the medial compartment unloaded and prone to remodeling back to a more normal modulus of elasticity.

Outcomes Assessments

All patients were treated uneventfully and there were no complications reported during the study period. All patients completed a structured six-week physical therapy outpatient program for balance, ROM and strengthening that likely contributed to the success of their treatment. Patients were administered outcomes assessments at time intervals consistent with their post-procedure follow up appointments at two weeks, six weeks, twelve weeks, six months, one year and yearly thereafter until five years.

All patients completed the Short Form-12, visual analog score for pain, International Knee Documentation Committee Outcomes analysis and the Lower Extremity Functional Scale analysis at each time point during the follow up period. We compared changes in PROMs from baseline to most recent follow up to determine if our findings exceeded the published minimally clinically important differences.

Results

In the study group there were 94 patients with an average age of 70 (range 49-90). In the group, there were 34 right knee procedures and 37 left knee procedures. There were 23 patients who had bilateral bone marrow concentrate procedures for knee arthritis through intra-articular injection. All patients had failed multimodality conservative measures prior to being considered candidates for a bone marrow concentrate procedure. Conservative treatments included physical therapy with home exercise and lifestyle modification, topical and oral NSAIDs, corticosteroid injections and hyaluronic acid or platelet rich plasma injection (PRP). No patient had received prior BMC therapy.

Patients improved on all outcomes assessments at all time points included in the study. One female patient had worsening range of motion and continued pain and went on to have a total knee replacement within two years during the study period. No serious adverse events were reported with the procedure in any patient. There was meaningful improvement in mean clinical outcome metrics from baseline in all patients during the time period studied. The visual analog score for pain improved from 5.9 to 2.56. Mean change in visual analog scale exceeded the published minimum clinically important difference of 2.5 (3.4). The average LEFS score improved from 57.7 to 77.5. The LEFS mean change was +20 which exceeds a published 9 point minimum clinically important difference. The average IKDC score improved from 45.4 to 62.6. The IKDC score mean change was +17 which exceeds a published 8 point minimum clinically important difference. Differences from baseline to follow up in the SF-12 demonstrated improvement in both the physical component (+9) and to a lesser degree the mental component (+2) with scores improving from 35 to 43 for the physical component and from 55 to 57 for the mental component. The mean change in the physical component of the SF-12 exceeded the published minimally clinically important difference of 3.77.

Patient follow-up averaged 10 months (range 3-36 months) in our series. Further study of this patient cohort will be valuable to determine the endurance of the intra-articular BMC treatment model, particularly in comparison to the subchondral/intra-articular procedure that we favour now.

Discussion

Recent evidence suggests that, rather than simple wear and tear of the articular surface, subchondral bone stiffening and synovial inflammation can lead to the initiation and progression of knee osteoarthritis [20]. Structural instability prompts the release of inflammatory cytokines that disrupt tissue homeostasis pathways and triggers the degenerative process [21].

Gaining a better understanding of these immunomodulatory signaling pathways has led to the development of novel treatment modalities including bone marrow concentrate injections. Several autologous immunobiologic treatments have surfaced over the last ten years and support for clinical application is growing steadily [22-24]. Despite being used off-label and for experimental purposes, intra-articular signaling cell technology has become available and is in high demand for orthopaedic surgical use in the setting of osteoarthritic knee pain syndrome and other clinical conditions [25]. In our experience, patient demand for these treatment modalities has risen steadily over the past decade. Our study confirmed the safety and efficacy in the short term follow up (average follow up 10 months) of patients who underwent intra-articular cell therapy with BMC injection in the setting of knee OA and that is consistent with reports from other authors [26]. In the setting of BMC injection for knee OA, some other authors have reported the recurrence of synovitis with or without pain of the BMC treated knee managed with supplemental conservative treatment or PRP [6]. Two of the 94 patients in our study required PRP supplementation at three months that was accomplished with intra-articular PRP preparations using an A2M filter and that reliably eliminated the pain and recurrent effusion in each case. We have found that the recurrence of effusion is predictably limited in patients undergoing orthopaedic immunobiologic treatments with both PRP and BMC and those effects from cell therapy are consistent with an immunomodulatory and anti-inflammatory rather than a structural mechanism.

Signaling cell treatments are thought to act by an immunomodulatory and anti-inflammatory mechanism that reverses the catabolic cytokine concentration of synovial fluid in the degenerative joint [27]. Cartilage homeostasis is governed by articular chondrocytes via their ability to modulate extracellular matrix production and degradation through cellular signaling pathways [28]. With pathologic impact loading and resultant subchondral stiffening that occurs with Varus or valgus alignment, the articular cartilage loses the ability to maintain ECM in the superficial lamina spending resulting in loss of surface lubricin and chondroprotection. Once the collagen network is mechanically degraded, irreversible cartilage damage proceeds through redundant inflammatory and degenerative pathways [29]. Autologous small molecule reversal of these pathologic signaling pathways has the potential to restore anabolic conditions to the joint and limit the progression of destructive arthritis through the concentration of anti-inflammatory and immunomodulatory molecules like TGF-B, A2M, IRAP and TSG-6 in the bone marrow concentrate product. Cell therapy is thought to act via paracrine and direct cellular communication through exosomes [30].

No serious adverse events were reported with treatment. There was meaningful improvement in mean clinical outcome metrics from baseline in all patients during the time period studied. Mean change in visual analog scale exceeded the published minimum clinically important difference of 2.5 (3.4). The Lower Extremity Functional Scale mean change was +20 which exceeds a published 9 point minimum clinically important difference. The IKDC score mean change was +17 which exceeds a published 8 point minimum clinically important difference. Differences from baseline to follow up in the SF-12 demonstrated improvement in both the physical component (+9) and to a lesser degree the mental component (+2). Improved patient outcome measures were recorded for all validated outcomes assessment instruments during the period studied.

Other authors have reported on the safety and efficacy of intra-articular bone marrow concentrate injections with most studies demonstrating global safety with 60-80% efficacy during the time period studied [31-33].

Conclusion

Our study confirms the safety and efficacy of the signaling cell procedure during a follow up period averaging ten months. Future

studies are necessary to determine the longer term efficacy of this technique and its safety profile and although many studies have been published to date, most are of limited scientific quality.

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