Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders

CASE REPORT

Regenerative Injection Therapy with Whole Bone Marrow Aspirate for Degenerative Joint Disease: A Case Series

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Abstract: Regenerative therapeutic strategies for joint diseases usually employ either enriched concentrates of bone marrow-derived stem cells, chondrogenic preparations such as platelet-rich plasma, or irritant solutions such as hyperosmotic dextrose. In this case series, we describe our experience with a simple, cost-effective regenerative treatment using direct injection of unfractionated whole bone marrow (WBM) into osteoarthritic joints in combination with hyperosmotic dextrose. Seven patients with hip, knee or ankle osteoarthritis (OA) received two to seven treatments over a period of two to twelve months. Patient-reported assessments were collected in interviews and by questionnaire. All patients reported improvements with respect to pain, as well as gains in functionality and quality of life. Three patients, including two whose progress under other therapy had plateaued or reversed, achieved complete or near-complete symptomatic relief, and two additional patients achieved resumption of vigorous exercise. These preliminary findings suggest that OA treatment with WBM injection merits further investigation.

Keywords: osteoarthritis, bone marrow aspirate, prolotherapy, case series, chronic pain

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Introduction

Degenerative joint disease represents a major and growing cause of disability and health care resource consumption. Osteoarthritis (OA), the most common joint disease, affects 12% of U.S. adults[1] and generates an estimated economic burden of more than $15 billion.[2] A major goal of therapy is the stimulation of regenerative processes in the joint that will facilitate the restoration of degenerated cartilage to a healthy state. The development of percutaneous interventions that potentially enhance regenerative processes has improved the prospect for non-surgical treatments that may produce durable improvement in pain and function.[3] One approach to regenerative therapy is to supply affected joints with either autologous chondrocytes or chondrogenic bone marrow-derived mesenchymal stem cells (BMSC), prepared as a buffy coat fraction of bone marrow with or without ex vivo expansion. Recent preliminary studies support the investigation of these therapies for OA.[4–7]

An alternative approach to regenerative therapy is the injection of substances or cells that may support chondrogenesis by enhancing the availability of prochondrogenic microenvironmental factors. One such therapy is prolotherapy, in which the joint is injected with an irritant substance such as hyperosmolar dextrose or sodium morrhuate that may act as a proliferant via the induction of local inflammatory and wound healing cascades. Randomized controlled trials have shown the effectiveness of dextrose prolotherapy for OA[8,9] and for chronic tendinopathies[10,11] as well as, with less consistency, for lower back pain.[12,13] A recent single-arm prospective study supported the effectiveness of this treatment for OA.[14] Another therapeutic strategy of this type is the injection of an autologous preparation of enriched platelets which are expected to release chondrogenic growth factors following the activation of clotting pathways. Several studies support the efficacy of platelet-rich plasma for OA.[15,16]

While treatments based on either stem cells or supportive chondrogenic stimulation show efficacy as single therapies for OA, treatments that combine these modalities may be especially promising. This was suggested by a recent study in which the combination of BMSC with the growth factor TGF-beta-1 resulted in enhanced restoration of cartilage defects in an animal model.[17] Cartilage growth has been reported for a patient receiving combined treatment with platelet-rich plasma and BMSC for degenerative joint disease.[7] The clinical utility of such approaches may, however, be limited by their complexity and cost as well as the need for specialized laboratory services.

Here we report our observations using intra-articular injection of whole tibial bone marrow, a simple and inexpensive procedure, to treat a series of patients displaying degenerative joint ailments. Whole bone marrow (WBM) injection potentially captures elements of several regenerative strategies. In contrast to prior BMSC therapies, marrow is not fractionated, and therefore potentially supportive chondrogenic components in marrow plasma are retained in addition to BMSC. An additional potential benefit is that tibial marrow represents a rich source of marrow adipocytes. Marrow adipocytes share properties[18] with brown fat adipocytes that have been linked to endochondral bone formation via a mechanism thought to involve adipocyte-dependent generation of a chondrogenic microenvironment.[19] WBM injection therefore represents a novel modification of regenerative therapy for degenerative joint disease. We used WBM injection both as monotherapy and, for most patients, in combination with dextrose prolotherapy, which has been frequently utilized as monotherapy for OA patients in our clinic.

The use of WBM injection was initiated in our chronic pain clinic in February 2011. Treatment series have been completed for four new patients with OA of the hip, knee, or ankle, presented here as a consecutive case series. In addition, three OA patients previously treated at our clinic with regenerative injection monotherapies switched to WBM injection therapy during this period. We observe a strong trend of patient-reported improvement in pain, functionality, and quality of life, suggesting that this treatment merits further investigation.

Case Descriptions

Patients

All of the patients whose case presentations are described in this report initiated WBM injection therapy at our chronic pain clinic between February and June 2011. All patients were diagnosed with OA of the hip, knee, or toe. Patient-centered treatment decisions were made on an individual basis; no attempt was made

to algorithmically assign patients to WBM injection or other regenerative therapies in use at the clinic. The decision to treat with WBM injection included a positive assessment by the treating physician with respect to patient willingness to complete a series of treatments, comply with a prescribed exercise program and participate in this case series. WBM injection was not selected for patients with narcotic use, non-OA joint pain, systemic conditions, or age under 18. The case series presented here includes all of the seven OA patients whose treatment at our clinic was either with combined WBM/dextrose therapy exclusively or those who switched to WBM or WBM/dextrose treatment following prior treatment with other regenerative injection monotherapy (dextrose prolotherapy or platelet-rich plasma), and who completed an interview following final WBM treatment. Initially, WBM injection was used as a monotherapy (Case 5), and subsequently in combination with dextrose prolotherapy. Characteristics of the seven patients are reported in Table 1. This report was prepared in accordance with the guidelines of the Declaration of Helsinki.

Interventions

All WBM injections were with tibial marrow, except in Case 4 in which both tibial and iliac marrow were employed. For tibial bone marrow aspiration, the area to be harvested was prepped with hydrogen peroxide and Chloraprep and anesthetized with 5% Lidocaine cream. With the patient in a supine position, 4 cc of 1%–2% procaine was administered intradermally, subcutaneously, and on the periosteum around the aspiration site, approximately 2 cm distal to the tibial plateau. Bone marrow access was obtained using an EZ-IO intraosseous access system with a heparinized 45 mm needle. After the periosteum was pierced, the drive and stylet were removed and a 12 cc syringe containing heparin (2000 U in 1 cc) was used to aspirate 8 cc of bone marrow. The syringe was gently agitated for mixing and the contents injected into the joint, which had been anesthetized with 1 cc 8% procaine prior to injection.

One patient (Case 4) with modest improvement after tibial WBM treatment was switched to WBM treatment using iliac marrow. For iliac aspiration, the area of the left posterior iliac was prepped and anesthetized as for the tibial procedure. Bone marrow access was obtained using an OnControl aspiration system with a heparinized 102 mm needle (11 g). 10 cc syringes containing heparin (3000 U in 3 cc) were used to aspirate up to 60 cc of bone marrow, as required. Each treated joint, anesthetized

Table 1. Summary of outcomes.

Case	1	2	3	4	5	6	7
Age	59	69	76	56	56	69	63
Sex	F	M	F	F	M	F	M
Involved joints	R ankle	R, L knee	R, L hip	R, L knee R hip	R, L hip	R, L knee	R, L hip
Duration[a]	3 yr	4 yr	3–4 yr	6 mo–3 yr	>6 yr	>8 yr	>5 mo
Comorbidities	Suspected scleroderma			Labral tear			
Prior therapy	Cortisone	Dex			Dex, PRP	Surgery Dex	Dex
Tx no.[b]	4	5	7	6[c]	3[d]	2	2
Tx period	8 mo	8 mo	12 mo	10 mo	5 mo	5 mo	2 mo
Notable outcomes							
IN	WDP: 30 ft	PI 7 PF 90[e]	PI 6 PF 60	SI Poor ET	PI 4 PF 100	PI 4 PF 20	PI 6 PF 30 Limp, cane
FN	WDP: 2 mi	Symptom-free	PI 4 PF 20	SI resolved Resumed biking	PI 2 PF 30	No pain	PI 1 PT 10 Normal gait No cane

Notes: [a]Duration of pain prior to initial WBM treatment; [b]number of WBM injections; [c]includes tibial and iliac WBM injections; [d]WBM monotherapy. All others received WBM in combination with dextrose prolotherapy; [e]PI and PF for the more severe (right) knee only. Other patients reported identical PI and PF for all joints.

Abbreviations: Dex, Dextrose prolotherapy; ET, exercise tolerance; FN, final interview; IN, presentation at initial WBM treatment; PF, pain frequency; PI, pain intensity; PRP, platelet-rich plasma; SI, sleep interruption; WDP, walking distance without pain.

with procaine, was injected with 10 cc of marrow. For hip joints, a second 10 cc aliquot was injected using an anterior approach.

For dextrose prolotherapy, the area to be treated was anesthetized with 5% Lidocaine cream and cleaned with hydrogen peroxide and Chloraprep. The injectant contained 15% Dextrose, 0.1% Procaine, 10% Sarapin, and 2 IU human growth hormone. Knee joints were injected with a total of 40 cc at 30 locations in the anterior knee, including medial and lateral collateral ligaments, patellar ligament, vastus medialis, iliotibial tract, and pes anserinus. Hip joints were injected with a total of 50 cc at 38 locations around the hip, including the greater trochanter, intertrochanteric crest, neck of femur, and dorsal ischium. Injected areas included the bony attachments of the ischiofemoral and iliofemoral ligaments, tensor fascia lata, gluteus medius, piriformis, gemellus superior, quadratus femoris, obturator internus, gemellus inferior, and vastus lateralis.

For treatment with platelet-rich plasma, 60 cc autologous blood, anticoagulated with ACD, was separated in a platelet-rich plasma centrifuge for 15 minutes. Platelet-poor plasma was drawn off and 12 cc platelet-rich plasma collected for injection into joints that had been anesthetized with 3 cc of 0.8% procaine.

Clinical outcomes

During the treatment period, information gathered in patient interviews included a rating scale (1–10) for pain intensity as well as percentage rating scales to describe pain frequency (percent of time with pain), pain relief, and overall improvement. At least six weeks after completion of WBM/dextrose treatments, a questionnaire was administered in which patients used a rating scale to assess pre-treatment and post-treatment pain intensity (at rest, during normal activity, and during exercise), stiffness, range of motion, crepitus, and ability to exercise.

Case presentations: cases treated exclusively with WBM/dextrose combined therapy

Case 1

A 59-year-old female presented with a history of three years of right ankle pain following a lateral sprain. The patient was unable to walk more than 30 feet without severe ankle pain and had ceased all weight-bearing recreational activities. Cortisone therapy had been unsuccessful and ankle fusion had been recommended. Based on X-ray and MRI findings, the patient was diagnosed with OA, avascular necrosis of the talus, and synovitis. Serologic tests were suggestive of scleroderma. The patient received four WBM/dextrose treatments over a period of eight months. At second treatment, the patient reported the ability to stand for long periods and walk for half a mile without pain. At third treatment, she reported improved range of motion, less frequent pain, and ability to take two mile walks on hilly, uneven ground, although steep climbs still induced pain. These gains were maintained throughout the treatment period.

Case 2

A 69-year-old male presented with bilateral knee pain, 4/10 on the left (30% frequency) and 7/10 on the right (90% frequency). Pain had begun years earlier while playing rugby and had been more severe for the four years prior to presentation. Pain resulted in frequent sleep interruption and limitation of exercise. Slight flexion limitation was noted. The patient had received prolotherapy from another physician for the previous two years but felt that improvement had ceased. The patient was diagnosed with OA and received five bilateral WBM/dextrose treatments at two month intervals. In an interview conducted two months after the final treatment, the patient reported that he was completely free of pain or stiffness in both knees, had regained full range of motion, no longer suffered sleep interruption, and was no longer limited in exercise or daily life activities.

Case 3

A 76-year-old female presented with a history of 3–4 years of bilateral hip pain, worse on the left side. She was unable to walk more than a mile without significant pain. The patient had received a recommendation for joint replacement. X-rays revealed moderate to severe bilateral degenerative changes in the hips, including osteophyte formation, subchondral sclerosis, and joint space narrowing, with the left side more affected than the right. Degenerative changes of the lower lumbar spine were also noted. At first visit, pain intensity was 6/10 and pain frequency 60%. The patient received seven WBM/dextrose treatments to each hip

over a period of 12 months and adhered to a program of daily bicycle exercise. She reported incremental improvements in pain and function at each visit. At the final visit the patient reported pain intensity of 4/10 and pain frequency of 20%, and described significant gains since the onset of treatment with respect to range of motion, resumption of exercise, reduced crepitus, and reduction of pain medication use by two thirds. She reported her overall improvement as 90%.

Case 4

A 56-year-old female presented with pain in bilateral knees and right hip. Bilateral knee pain was of approximately three years duration. Pain was severe in the right knee, with frequent crepitus and instability, and had forced the patient to discontinue running. MRI with a previous physician had shown cartilage degeneration. Right hip pain had been intermittent for 16 years, but instability and continuous pain began six months before presentation. The hip pain prevented sleep on the affected side, bicycle exercise had ceased for more than a year, and walking exercise was limited to three miles. MRI with a previous physician showed labral tear. The patient was diagnosed with hip OA and labral tear, and bilateral knee OA. The patient received WBM/dextrose treatment at six visits with 8–10 week intervals. At visits 1 and 2, the right knee and right hip were treated with tibial WBM. At visits 3 and 4, both knees and right hip were treated with tibial WBM. The patient reported modest (20%–35%) overall improvement following these treatments. At the final two visits, bilateral knees and right hip were treated with iliac WBM injection. During the treatment period, the left hip was also treated for pain resulting from a flexor injury incurred following visit 1. Two months after visit 6, the patient reported 65%–95% overall improvement for the three joints. She is able to walk for two hours, no longer has disturbed sleep, and has been able to resume bicycle exercise with minimal discomfort. The patient still experiences intermittent soreness in a small region in the medial aspect of the right patella.

Case presentations: cases with mixed treatment

Case 5

A 56-year-old male presented with bilateral knee pain. The patient is a former competitive weightlifter who continues to do strength training exercise. He complained of instability in both knees during exercise, as well as sleep interruption. The patient received 29 bilateral dextrose prolotherapy treatments over five years. At the final prolotherapy visit, sleep interruption was still present, pain intensity was 4/10, and pain frequency was 100%. Four months later, the patient was treated with platelet-rich plasma. Three months after plasma treatment, the patient began a series of three WBM injection treatments (without dextrose prolotherapy) at 2–3 month intervals. At the time of the second WBM treatment, stability was improved. At the time of the third treatment, pain intensity was 2/10 and pain frequency was 30%. Sleep was no longer affected. These gains were maintained for nine months.

Case 6

A 69-year-old female presented with bilateral knee pain. She had been previously diagnosed with OA, had arthroscopic surgery to both knees eight years earlier, and bilateral medial meniscus repair 15 years earlier. Pain occurred climbing or descending stairs and with standing or walking for two hours. Pain interrupted sleep and limited participation in racquet sports and golf. Pain intensity was 4/10 in the left knee and 5/10 in the right. The patient received six bilateral treatments with dextrose prolotherapy over a ten month period. After the first month of this period, the patient reported uninterrupted sleep, pain intensity of 2/10, resumption of limited golf, and an overall improvement of 50%–55%. One year after the final prolotherapy, pain intensity had returned to 4/10 with a frequency of 20%, and sleep interruption had resumed. At this time, the patient received the first of two WBM/dextrose treatments, five months apart. At the time of the second treatment, pain intensity was 1/10 with a frequency of 20%, sleep interruption was reduced by half, and patient-reported overall improvement was 90%. Eight months following the final WBM/dextrose treatment, the patient reported being free of pain and able to resume full participation in all of her usual athletic activities.

Case 7

A 63-year-old male presented with bilateral hip pain. Pain intensity was 6/10 with a frequency of 50%. The patient received five bilateral treatments with dextrose prolotherapy over a period of 5 months. During this

period, the patient reported overall improvement of 50%; however, this reduced to 30%–40% at the conclusion of the treatment period, at which time pain intensity was 6/10 with a frequency of 30%. Crepitus, previously absent, was now marked. At this point, the patient began a series of two WBM/dextrose treatments two months apart. At the time of the second treatment, pain intensity was 5/10. Crepitus was reduced. Specific pain manifestations previously noted, including ischial tuberosity pain and lateral hip pain, had abated, and the patient reported being able to walk without a cane for the first time in years. Two months after the second WBM/dextrose treatment, pain intensity was 1/10 with a frequency of 10%. Crepitus was absent and the patient reported walking without a limp and no longer needing a cane.

Summary

Treatment and outcome are summarized in Table 1. The period of WBM/dextrose treatment ranged from 2 months (2 injections) to 12 months (7 injections), with a mean period of 7.1 months and a mean treatment number of 4.1. Outcomes reported in Table 1 are selected to highlight notable gains. All patients reported significant gains, and five of seven patients (cases 1, 2, 4, 6, 7) reported either complete relief or strong functional improvement. No adverse events were noted. In questionnaire responses, all patients reported gains for all presenting symptoms, including pain intensity, stiffness, crepitus, and limitation in range of motion and exercise (Table 2).

Discussion

We have explored WBM injection in combination with dextrose prolotherapy as a cost-effective approach with potentially broad application for OA in non-specialized settings. Our initial experience has been encouraging, as all patients experienced significant gains in treatment periods of 2–12 months without adverse events. Additionally, five of seven patients experienced strong functional improvement (cases 1, 3 and 7) and/or complete or near-complete pain relief (cases 2, 6 and 7). Patients uniformly expressed satisfaction with outcomes in interviews. Five patients (cases 2–6) reported receiving previous recommendation for joint replacement, and at final interview none believed replacement would be needed. Notably, three patients (cases 5–7) whom we had previously treated with prolotherapy alone, and whose gains appeared to have either stabilized or reversed, achieved substantial gains with 2–5 months of WBM/dextrose combined treatment. Spontaneous improvement in this time frame was unlikely for these patients, arguing against selection bias as the sole cause of our observations. However, selection for susceptibility is possible, since no attempt was made to avoid such selection.

Additional weaknesses in this retrospective report include incompletely structured patient interviews, the use of a post hoc questionnaire, paucity of objective outcome measures, and short follow-up periods (2–9 months). The use of combined treatment weakens the assessment of the novel WBM injection component. Despite these shortcomings, the consistency, strength, and rapidity of improvement suggest that more extensive and more strongly designed prospective observational studies are warranted.

Preclinical and clinical studies of the use of autologous bone marrow for chondrogenic repair have focused on preparations in which MSC are enriched

Table 2. Responses to questionnaire.[a]

Case	1		2		3		4		5		6		7	
	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
Pain intensity[b]	8.7	0.0	4.3	0.0	3.0	0.2	2.1	0.0	10.0	0.0	7.0	0.3	8.0	0.0
Stiffness	9.0	1.0	6.0	0.0	8.0	1.5	0.0	0.0	10.0	0.0	8.0	1.0	8.0	1.5
ROM[c]	9.0	1.0	0.0	0.0	6.5	2.0	1.3	0.0	10.0	0.0	7.0	0.0	7.0	3.5
Crepitus	0.0	0.0	0.0	0.0	1.5	0.0	3.0	0.0	10.0	0.0	6.0	0.0	3.5	0.0
Exercise[c]	5.0	1.0	3.0	1.0	2.5	2.0	2.7	1.7	5.0	1.0	4.0	1.0	4.0	2.0

Notes: [a]Post hoc assessments of condition before first WBM injection (PRE) and >6 weeks following final WBM injection (POST). The mean score for all involved joints is reported for each patient; [b]data represent the mean of scores for pain during rest, activity and exercise; [c]ROM and exercise scores of 10 represent maximum limitation.
Abbreviation: ROM, range of motion.

and expanded, with the assumption that quantity of delivered MSC is critical.[4,6,7,20,21] This assumption, however, remains untested, and recent studies, including the use of MSC in a goat OA model,[22] suggest that the chondrogenic action of MSC may depend more on trophic functions, including the secretion of angiogenic factors such as vascular endothelial growth factor, than on the chondrocytic differentiation and structural incorporation of these cells.[23,24] In this case, delivered MSC concentration may be less important than the microenvironmental context of delivery, and complex preparations, including whole marrow, are potentially advantageous. While a correlation has been observed between marrow MSC concentration and the efficacy of grafted marrow for osteogenic repair of non-unions,[25] early studies demonstrated efficacy of non-union treatment using direct, immediate injection of unprocessed WBM without MSC enrichment.[26,27] These studies, like ours, were motivated by a desire to develop simple, rapid, inexpensive options with low morbidity for use in outpatient settings. Our preliminary findings suggest that WBM injection merits investigation as one such alternative for OA.

Conclusions

Initial observations using WBM injection in conjunction with dextrose prolotherapy for treatment of osteoarthritic joints suggest that the procedure is safe and potentially efficacious. Treatment courses of less than 12 months are associated with substantial gains in pain relief and functionality.

Author Contributions

Analyzed the data: RAH. Wrote the first draft of the manuscript: AO. Contributed to the writing of the manuscript: AO, RAH. Agree with manuscript results and conclusions: AO, RAH. Jointly developed the structure and arguments for the paper: AO, RAH. Made critical revisions and approved final version: AO, RAH. All authors reviewed and approved of the final manuscript.

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Competing Interests

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Disclosures and Ethics

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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