Guided Mesenchymal Stem Cell Layering Technique for Treatment of Osteoarthritis of the Knee

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ABSTRACT

Current treatments for osteoarthritis consist of weight reduction, rest, exercise, non-steroidal anti-inflammatory drugs (NSAIDS, both oral as well as topical), intra-articular glucocorticoid injections, viscosupplements, physical therapy, and bracing. [1-3]

Though effective for symptom relief in many cases, these therapies are palliative only. While there is encouraging evidence that weight reduction might modify disease, there is little evidence that any current treatments can restore articular cartilage.[4]

Multiple anecdotal reports in the literature have described the use of autologous stem cells for the treatment of osteoarthritis.[5-6] However, no series from a rheumatology practice has been published.

There have been credible scientific investigations indicating autologous mesenchymal stem cells may have therapeutic value for the treatment of osteoarthritis.[7]

We report our experience employing an ultrasound-guided procedure using autologous mesenchymal stem cells, growth factors, and fat matrix. We term this a guided mesenchymal stem cell layering procedure (GMSCL).

INTRODUCTION

Our working hypothesis has been that autologous stem cells from bone marrow can be stimulated to grow cartilage if provided with a proper scaffold, autologous growth stimulating factors, and followed by a strict

program of limited weight-bearing.

MATERIALS AND METHODS

Between June 2008 and May 2010, we performed a guided mesenchymal stem cell layering procedure on 23 patients. They ranged in age from 36-83 years. The gender distribution was 17 men and 6 women. Body mass index ranged from 21-36.[1]

Radiographs of the knee were performed on all patients. Kellgren Lawrence class distribution was 6 Kellgren-Lawrence Grade 2, 10 Kellgren-Lawrence Class 3, and 7 Kellgren-Lawrence Class 4.

In preparation for the procedure, patients were advised to take no non-steroidal anti-inflammatory drugs, either oral or topical, for 1week prior to and 1 month following the procedure. Dietary fish oil was also proscribed for the same length of time. Patients were permitted to continue prophylactic baby aspirin. They were advised to take no intra-articular injections for at least 1 month prior to the stem cell procedure.

All patients underwent informed consent outlining the investigational/ experimental nature of the procedure.

Prior to the actual operation, patients underwent identification of landmarks using ultrasound (Logic E, General Electric, Madison, WI). Anatomic sites chosen included the posterior iliac crest for procurement of bone marrow, flank or buttock for fat harvesting, and knee. Specifically, most patients with osteoarthritis of the knee have stereotypical pain located at the joint line, medial patellar facet, and adductor tubercle. Each of these sites was identified and marked.

Patients then underwent phlebotomy of sixty cc's of whole blood for creation of platelet-rich plasma concentrate. Ten mg of oral diazepam were also given to patients at this time. The patients were then escorted to the ambulatory surgical suite.

They were placed in a prone position and the entire low back and buttocks were prepped with Betadine and alcohol. The skin and subcutaneous tissue overlying the posterior iliac crest were anesthetized with 1% lidocaine. A small longitudinal skin nick was made using a number eleven scalpel blade. A two mm Jamshidi biopsy needle was then advanced through bone into marrow. Sixty cc's of marrow were then harvested using heparinized syringes.

The marrow was then processed into 5 ccs of stem cell concentrate using a proprietary centrifuge system (Harvest Technologies, Cambridge, MA; Arteriocyte, Hopkinton, MA). In addition, a site at the flank or buttock was chosen for fat harvest. Subcutaneous fat was obtained using local lidocaine anesthesia and a "stirring" technique. A small longitudinal skin nick was made using a number 11 scalpel blade. Ten cc's of fat were then retrieved using a fenestrated two mm Veress needle.

The patient was then repositioned in the supine position. The entire lower extremity was prepped with Betadine scrub and then draped using a sterile stockinette, elastic wrap, and a fenestrated drape. Most patients then underwent local anesthetic injection of the area using 1% lidocaine. In later cases, a femoral nerve block was used in order to achieve better anesthesia.

A small longitudinal skin nick was made at the center of a triangle formed by the medial joint line, the medial patellar facet, and adductor tubercle.

A 2.9 blunt wrist arthroscopy cannula and trochar were then introduced. The trochar was removed, but the cannula was kept in place to use as a guide. A 2 mm sharp trochar was then introduced and used to fenestrate the medial patellar facet, the medial joint line, and the adductor tubercle. Any osteophytes were removed, or at least reduced in size, using the trochar. In addition, patients who had meniscal pathology also underwent fenestration of the diseased meniscus using an 18-gauge spinal needle. All fenestration was accomplished using direct ultrasound guidance.

After fenestration was completed, small amounts of stem cell concentrate and platelet-rich plasma were injected at the various

sites. The balance of the stem cell concentrate, platelet-rich plasma, and fat were injected into the joint. This was followed by 2.5 cc's of a mixture of calcium chloride and human recombinant thrombin (Recothromb, ZymoGenetics, Seattle, WA), in order to convert the mixture into a gel.

Patients were then advised to go at strict non weight-bearing for two weeks. Those patients with either a valgus or varus angulation were given prescriptions for braces to unload the narrowed compartment. Physical therapy was initiated two weeks following the procedure. Limited weight-bearing was begun at that time.

RESULTS

Data was available for twelve patients at six months and ten patients at one year.

There were four treatment failures, defined as patients who did not have significant clinical improvement by three months. In addition, one patient passed away from an unrelated problem and one patient lived too far away to make the return trips needed for follow up.

Five patients had not hit the six month mark.

The following subjective data was collected:

Western Ontario and McMaster University Arthritis Index (WOMAC), Patient Visual Analogue Scale, Patient Global Assessment, Patient 50 Foot Walk Pain, and Physician Global Assessment. Standard Deviation and Standard Errors of the Mean were all calculated for.

Δ 6 Months= -19.9
Δ 12 Months= -7.9
SD=17.92
SD= 9.97
SEM= 5.67
SEM= 3.15

Patient VAS Pain
Δ 6 Months= -33.7
Δ 12 Months= -25.2
SD= 16.71
SD= 25.94
SEM= 5.57
SEM= 8.20

Patient Global Assessment
Δ 6 Months= -33.0
Δ 12 Months= -33.1
SD= 24.13
SD= 19.04
SEM= 8.05
SEM= 6.35

Patient 50 Foot Walk Pain
Δ 6 Months= -26.3
Δ 12 Months= -16.7
SD= 15.54
SD= 12.05
SEM= 4.91
SEM= 4.01

Physician Global Assessment
Δ 6 Months= -51.2
Δ 12 Months= -53.0
SD= 21.60
SD= 24.15
SEM= 6.83
SEM= 8.54

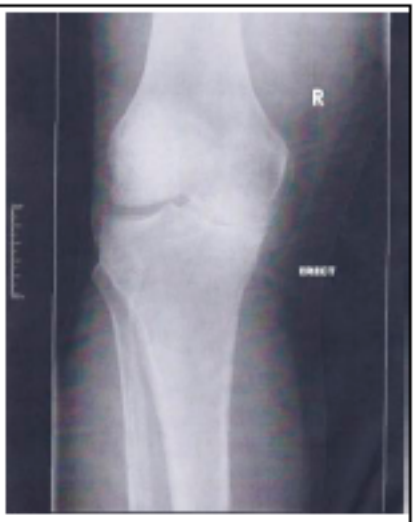
In addition, one objective measurement of patello-femoral cartilage thickness at seven standardized points was performed. This was done by flexing the knee to 90 degrees. Identical sites were matched for accuracy. Five measurements were collected for each point in order to assure reproducibility. The high and low values were dropped and the three middle measurements were averaged.

Ultrasound measurement of patello-femoral cartilage thickness at 7 standardized points:

- Mean improvement from baseline to 6 months (12 pts): 0.4 mm
- Mean improvement from baseline to 12 months (10 pts): 0.8 mm

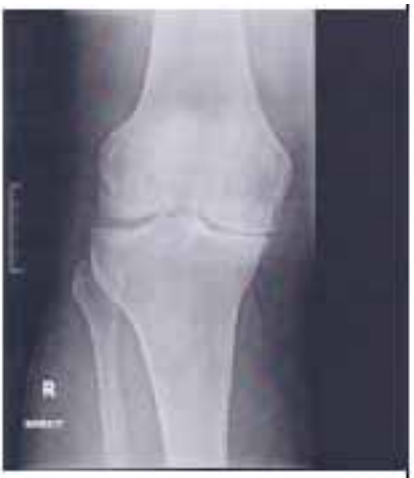
DISCUSSION

One of the first reports of a possible regenerative effect of stem cells in arthritis was presented in a caprine model [8].



January 7, 2009

Figure 1



August 25, 2010

Figure 2

Since then, significant investigations have alluded to the potential of mesenchymal stem cells for cartilage repair [9-11]. However, there have been no studies that have looked at specific measurements of clinical change in a cohort of patients with osteoarthritis of the knee in a rheumatology clinic setting.

There are a few points that need to be emphasized regarding this study. This was not a prospective clinical trial. This was a retrospective analysis of results of a procedure.

Bone marrow was chosen because it represents a ready reservoir of mesenchymal stem cells [12]. The purpose for the fenestration is to stimulate an acute inflammatory response and allow chemattractants to draw stem cells into the area [13]. This is the first step in healing and is the possible catalyst for the induction of stem cell growth and multiplication [14-17].

Since articular cartilage is avascular and aneural, the pain from osteoarthritis does not arise from the wearing away of cartilage per se. It is probably due to a combination of cytokine production as well as local irritation of the joint capsule by osteophytes [18]. By removing or smoothing osteophytes as well as modulating inflammation at the sites of pain, theoretically, new cartilage growth will be accompanied by symptomatic improvement. While our numbers are small, they represent a start in the right direction. Like any study reporting a new technique, the results raise more questions than provide answers.

First, could the results be due to placebo effect? The answer is a resounding yes. However, if an examination of another intervention in osteoarthritis such as the celecoxib trials, the clinical responses in our current evaluation appear to be quite favorable [19].

Other questions that then could be asked are, "Are the results real?" Only further investigation will answer this query. Another question is this… "If the results are real, how long does the effect last?"

And other questions follow such as "What types of controlled trials need to be done next?" "What chondrocyte growth factors are involved?" "What types of stem cells work the best?" "What other methods might work better?" "Is there a genotypic dependence?"

One interesting anecdote highlights the potential of this therapy.

CASE HISTORY

A 61 year old man underwent a stem cell procedure for severe osteoarthritis of the right knee in January 2009. His baseline radiographs showed Kellgren-Lawrence 4 changes in the medial compartment (Figure 1). Several months later, he sent an email to the author…"I just came back from my orthopedist, I had a cortisone injection in my left knee. Not the knee you performed the procedure on. Anyway I asked if he could take an x-ray of my right knee and compare it to my last x-ray done on 1/7/09.

Attached are both x-rays. Can Dr. Wei take a look and give me an opinion? My orthopedist said he sees growth…" (Figure 2).

While the radiographs would both be graded Kellgren'Lawrence 4, it is clear there has been an improvement in joint space in the second film.

CONCLUSION

While it is an uncontrolled study, guided mesenchymal stem cell layering demonstrates some promise as a treatment for OAK. Further study is recommended.

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