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Use of Autologous Adipose-Derived Stromal Vascular Fraction to Treat Osteoarthritis of the Knee: A Feasibility and Safety Study

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Abstract

Objective: Autologous adipose-derived stromal vascular fraction (SVF) was used to treat ten osteoarthritic knees of grades II or III (K-L scale) under an IRB-approved protocol in a feasibility and safety study. The primary objective of this study was to determine if adipose-derived SVF can be safely used for intra-articular injection of the knee. The secondary objective of this study was to evaluate the feasibility of an intra-articular injection of adipose-derived SVF for pain relief in osteoarthritic knees.

Methods: 10 knees in 6 patients were treated with an intra-articular injection of adipose-derived SVF; patient ages ranged from 52-69 years with a mean of 59 years. Adverse events were monitored for indication of safety. Patient pain data was obtained at 2, 4, 6, and 12 weeks follow up using the PROMIS questionnaire and a pain and mobility questionnaire. The t-test for paired data (2-tailed) was used to assess statistical significance of the PROMIS data and Wilcoxon Ranked Sums nonparametric testing was used to access statistical significance for the pain and mobility questionnaire. Stromal vascular fraction was obtained through disaggregation of lipoaspirate and resuspension of the cell pellet in 3 ml of Lactated Ringer's Solution, with a mean of 48 million nucleated SVF cells and a mean viability of 78%, injected per knee. Cell suspension was injected into the intra-articular space using ultrasound guidance.

Results: (1) No infections, acute pain flares, or other adverse events were reported related to an intra-articular injection of adipose-derived SVF in the knee. (2) At 12 weeks post-op all 10 knees showed decreased pain and increased mobility (α=0.01). Nine of ten knees reported either maximum possible or very significant decrease in pain.

Conclusions: Use of autologous adipose-derived SVF in the knee is a promising cell-based therapy that addresses a significant clinical need with no known regenerative solution. A larger clinical efficacy study is needed that includes a control arm and extended follow-up data at time points including six months and one year.

Level of evidence: Level II

Keywords: Stem cell; Regeneration; Amyotrophic lateral sclerosis

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Introduction

Regenerative cell therapy, using a patient's own cells to treat osteoarthritis (OA) is a promising new paradigm where the anti-inflammatory and healing properties of the cells directly address the inflamed and painful condition of OA. Recent investigations have shown that infrapatellar fat pad derived mesenchymal stem cell (MSC) therapy with intra-articular injections was safe, and provided assistance in reducing pain and improving mobility in patients with knee OA [1]. These results have been confirmed by other authors in similar studies using mesenchymal cultured cells [2,3]. Recent studies on animal and human subjects have shown the efficacy of adipose-derived stem/stromal vascular fraction cells to decrease inflammation and pain and to increase the range of motion and ambulation [4-6]. OA is a disease process that results from degeneration of the tissues of the knee joint [7]. Also known as degenerative arthritis, OA is the most common form of the different types of arthritis and the most common musculoskeletal disorder [8]. Over 20 million people in the United States are affected by OA and people of all ages and races appear to be equally affected. OA is typically diagnosed by plain x-ray and/or MRI. Correlations or causes of OA include aging, heredity, obesity, and iatrogenic injury from surgery, trauma, or disease. Next to aging, obesity is the most common risk factor for knee OA. The negative impact of OA on society is expected to increase exponentially as the world population ages and obesity continues to increase [9].

The most common symptom of OA is joint pain. It is a complex condition of broad pathology with loss of, or damage to, articular cartilage and accompanied by changes to the subchondral bone and synovium [10,11]. The immune system is involved in disrupting joint homeostasis by producing local inflammatory reactions, with production of pro-inflammatory cytokines and metalloproteinases [11]. The loss of cartilage results in friction between the bones of the knee that leads to pain and limitation of joint mobility. Inflammation within the joint can also stimulate new bone outgrowth producing bone spurs. The healing process is slow, and where repair of the damaged tissues cannot occur, secondary fibrosis sets in [12].

The goal of treatment in OA is to reduce joint pain and inflammation while improving and maintaining joint function. Treatment of OA includes weight reduction and avoidance of injurious activities, physical therapy, and mechanical support devices. Medications are used to treat OA pain. They can be used topically, orally, or injected into the joints (corticosteroids) to decrease joint inflammation and pain. Currently for recalcitrant pain of moderate to severe OA of the knee that does not respond to the aforementioned treatments, injections of hyaluronic acid, such as Synvisc-One (Genzyme Biosurgery, Cambridge MA) or Orthovisc (Anika Therapeutics, Inc., Bedford MA) into the joint can often times alleviate pain and inflammation [13]. More recently the use of Platelet Rich Plasma (PRP) and Prolotherapy are being evaluated to relieve the pain of OA [14-17]. Thus, clinical interventions to date are primarily symptomatic, not regenerative. They have little impact on the degenerative nature of the disease [10]. Surgical knee replacement is reserved for end stage chronic OA disease. Although it provides excellent pain relief and joint motion, knee replacement has a limited lifespan [18]. Recent studies on animal and human subjects have

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shown the efficacy of adipose-derived stem/stromal vascular fraction cells to decrease inflammation and pain and to increase the range of motion and ambulation [4-6].

Stromal vascular fraction (SVF) cells derived from adipose tissue include renewable reparative cell populations and thus are potentially important to multiple disease processes and therapeutic applications for the repair and regeneration of acute and chronically damaged tissues [19-22]. The adipose derived SVF cells appear to not only provide protective and rejuvenating properties, but are abundant in supply and easily obtained from human lipoaspirate samples. The stromal vascular fraction obtained from adipose tissue is a heterogeneous cell population that contains, among others, a MSC (6.7%) compartment, an endothelial precursor cell compartment (2%), and a monocyte/macrophage compartment (10%) [23]. Freshly isolated SVF cells have been characterized by flow cytometry in several studies [24,25]. However, the authors report differences regarding the relative abundance of the different cell populations comprising the SVF. Differences result from use of different isolation techniques, different cell surface markers, and/or different gating strategies for the flow cytometer. The SVF does not include any mature adipocytes (floating cells), structural debris, connective tissue, or red blood cells. For accurate counting the counting method used to assay the SVF needs to specifically count mono-nucleated cells and be capable of accurately excluding RBC's and other nonviable small debris fragments, RBCs, or oil droplets.

In this paper we describe the use of autologous adipose-derived SVF to treat grades II and III OA (K-L scale) in ten knees in six patients. Our primary objective was to evaluate the safety of SVF injection for OA of the knee. Our secondary objective was to evaluate the feasibility of an intra-articular injection of adipose-derived SVF for relief of pain in osteoarthritic knees. Clinical comparison to other therapeutic options for the treatment of OA such as corticosteroids or viscosupplementation was not part of this study. This clinical study was submitted for IRB review, and approved by an accredited IRB (IntegReview, Austin, TX, USA). The study is listed on the clinicaltrials.gov website (NCT02276833).

Methods

Study design and ethics

This was a prospective interventional study monitoring adverse events and comparing pain before and after intra-articular injection in the knee of adipose-derived SVF from 10 knees in 6 patients with osteoarthritic knees. Patients were followed for 12 weeks with follow-up visits at 2, 4, 6 and 12 weeks. Study participants voluntarily provided written Informed Consent to participate in the study and signed the Health Insurance Portability and Accountability Act (HIPAA) authorization before any study procedures were performed.

Study inclusion/exclusion criteria

Inclusion criteria were ages 20-70, male or female with grades II-III (K-L scale) radiologically documented OA of one or both knees, ASA class I-II and a BMI less than 35, knee pain graded as greater than 4 out of 10 on screening questionnaire, and able to speak, read and understand English. Exclusion criteria were any patient parameters falling outside of the inclusion criteria parameters, any current oral or parenteral steroid or blood thinner use, any hyaluronic acid-based injection to the affected knee joint within the previous six months, or any corticosteroid injection to the affected knee joint within the previous three months. End stage (Grade IV) OA was excluded.

Adipose harvest

Using no oral or parenteral sedation, standard wetting solution (1 liter Lactated Ringer's, 50 milliliters of 1% lidocaine, and 1 cubic centimeter of 1 : 1000 epinephrine) was infused through small incisions created with the tip of a #11 scalpel blade in the abdomen or flank using a standard multi-hole infusion cannula. A super-wet plus technique (2 volumes of wetting solution to 1 volume of proposed fat aspirate) was used to infuse the solution into the deep and superficial fat compartments. Twenty minutes was allowed for maximum vasoconstrictive effect of the epinephrine. Fat was harvested using standard suctioned-assisted liposuction (SAL) method with a 3 mm cannula at approximately 0.5-0.7 atmosphere of vacuum, aspirating approximately 200-300 cubic centimeters of lipoaspirate into a sterile tissue processing container (GID SVF-1, Louisville, CO) for each knee to be treated.

Adipose-derived SVF preparation

Lipoaspirate was harvested and processed all the way to the generation of the SVF within a single GID SVF-1 sterile disposable device. The GID SVF-1 unit contains the washing agitation mechanism, the mesh filter, and the ability to be used in a centrifuge all in the same device. After harvest the lipoaspirate was washed three times with 37 degree centigrade Lactated Ringer's solution containing 20 milligrams Cipro and 5000 units heparin per liter and the fluid portion was removed through the mesh filter system using standard operating room suction apparatus, leaving adipose tissue, sans washing fluid (termed dry adipose tissue) inside the canister. The washing process removes red blood cells and free oils from the adipose harvest tissue. The canister was weighed to determine the amount of dry adipose available for further processing. The dry washed adipose was dissociated using Type I collagenase (Worthington, Lakewood, NJ) at a concentration of 200 CDU/milliliter of total catalytic volume. Where total catalytic volume is the volume of the adipose tissue plus an equal volume of 37 degrees centigrade Lactated Ringer's solution. The collagenase was injected into the canister through a sterile 0.22 micron filter (Millex-MP, Millipore, Cork, Ireland). The device with adipose tissue, Lactated Ringer's solution, and collagenase was then placed into an incubated shaker for 40 minutes at 38 degrees centigrade at 150 RPM (Figure 1). After disaggregation human albumin solution was added to achieve a concentration of 2.5% and reduce further collagenase activity. The device was then centrifuged at 800 g for 10 min. The supernatant, including all floating cells and debris and the aqueous phase, was removed using a port on the top of the device and discarded. The SVF pellet at the bottom was resuspended in 10 mL of sterile Lactated Ringer's solution, accessed via the central port on the device using a 14G 5.5 inch spinal needle (Abbocath-T, Hospira, Sligo, Ireland). A sample of 0.5 milliliters of the resuspension was collected in a 1.5 cubic centimeter Eppendorf tube to be used for cell counting and assay. The resuspended SVF cells were concentrated into a 3 milliliter dose using a sterile 15 milliliter Falcon tube at 400 g for 4 minutes. No RBC lysing solution was used. The SVF output using this device and method have been characterized using flow cytometry on 23 independent patient samples using 16 different antibodies, showing the CD45-/CD31-/CD34+ fraction (adipose-derived stromal/stem cells) at 16.26 ± 14.94%. The detailed methods and results of this analysis and comparison to other published results have been submitted for publication [26].

SVF counting method

The SVF cell count and viability was assessed using an ADAMMC

image cytometry system (Bulldog Bio, Portsmouth, NH) for automated cell counting. The ADAMMC uses propidium iodide staining to count viable and nonviable nucleated cells. A 100 µL aliquot of the assay sample was diluted with a 1:5 ratio (1 part sample to 5 parts sterile Lactated Ringers solution) to adjust the sample within the operating limits of the ADAMMC. The differential stains were applied and aliquots loaded into the disposable cassette that is utilized with the ADAM device. The results from the ADAM counting device provide the concentration of SVF cells in the resuspension syringe and the percentage viability. The total volume of the resuspension in the syringe was multiplied by the concentration to give the total number of resuspended mononucleated cells (no adipose cells, no RBCs, and no fragments included in the counting process).

Injection and image guidance method

The patient was placed in a supine position and the area over the lateral suprapatellar region of the knee was prepared in the usual sterile fashion using an iodine prep solution (1% Iodophor) followed by a 70% isopropyl Alcohol solution. This location was used due to ease of access into the intra-articular space and to avoid injecting into the fat pad of the knee. No sedation or pain medication was administered to the patient. An ethyl chloride topical anesthetic was sprayed on the lateral knee until the skin color changed to white. 1% Lidocaine local anesthetic was injected using a 25 gauge needle to numb the skin and subcutaneous tissues. Using an M-Turbo Sonosite ultrasound system, the joint space was identified and under live ultrasound guidance the knee was aspirated using an 18 gauge/1.5 inch needle, if fluids were available for aspiration. Then, all the 3 cubic centimeters of buffered solution of SVF was slowly injected into the intra-articular space through the same 18 gauge/1.5 inch needle. The needle was then removed and direct pressure over the injection site was placed for approximately ten (10) seconds. Hemostasis after injection was confirmed, and the injection site was cleaned with an alcohol wipe and covered with a sterile Band-Aid. The patient was given crutches and asked to be non-weight-bearing on the injected knee for two (2) days. The patient was allowed to bend and flex the knee as long as non-weight-bearing condition is maintained.

Pain and mobility assessment methods

Assessment of knee pain was done using the Patient Reported Outcomes Measurement Information System (PROMIS) pain instruments, a validated pain scale system developed under funding by the NIH. PROMIS is a system for measurements of patient reported health status for physical, mental, and social well–being, including three measurements of pain [27]. The PROMIS Pain Intensity instrument (3a) assesses how much a person hurts. The PROMIS Pain Behavior instrument (Bank 1.0) measures behaviors that indicate to others that an individual is experiencing pain. The PROMIS Pain Interference instrument (Bank 1.0) measures the consequences of pain on relevant aspects of one's life. Patient responses are converted to numeric values in a validated scale. Responses to each question in a pain instrument range from 1 to 5 (1=not at all, 2=a little bit, 3=somewhat, 4=quite a bit, 5=very much), and are summed over the number of questions in the bank to create a raw score. The raw score is converted to a standardized score using an iterative response method with a mean of 50 and SD of 10, based on a large sample of the general population of the United States. The validated PROMIS pain scales provide interval data and allows calculation of the mean and SD, and use of *t* tests of significance. Data were recorded preoperatively (time 0), and at follow-up points at 2 weeks, 4 weeks, 6 weeks, and 12 weeks. The *t*-test for paired data (2-tailed) was used to assess statistical significance of the PROMIS data.

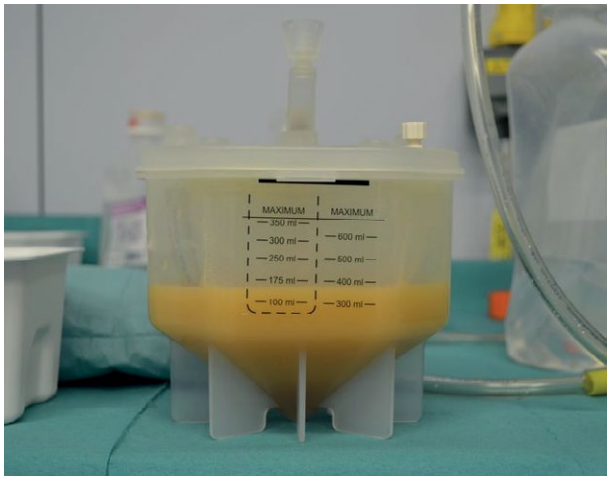

Figure 1: Disaggregated adipose tissue in the GID SVF-1 device, prior to centrifugation.

Additionally patients were asked to respond to a pain and mobility questionnaire with one question on pain and one question on mobility. The questionnaire asked the patient to compare their increase/decrease in pain and mobility relative to before surgery using a ± 1-5 scale (Figure 2). On this scale negative numbers correspond to decreasing pain/mobility, and positive numbers correspond to increasing pain/mobility. This questionnaire provides ordinal data and allows calculation of the median and significance using Wilcoxon Ranked Sums nonparametric testing.

Results

Patient data and dose characterization data, for 10 total knees of 6 patients, are shown in Table 1. No adverse events related to the knee injection were reported, including no acute pain flares, no inflammation, and no infection. One case of patellar tendonitis was reported at week three that resolved spontaneously. No infections or interventions related to the lipoplasty sites were recorded. One lipoplasty patient had an adverse reaction to Latex in the compression garment which resolved spontaneously with replacement of the garment.

Total procedure time, from start of injection of wetting solution to the finish of the injection of the cell resuspension into the knee, ranged from 90 to 120 min, becoming shorter with experience. Total cell processing time, from finish of lipoaspiration to cell resuspension for injection, averaged 55-60 min. Conclusion of the lipoplasty phase and preparation of the knee for injection was completed during the 55-60 min required for the cell processing. Table 2 provides the pre-op and 12-week post-op scores and the statistical calculations for all three measures of pain in the PROMIS system. All 3 pain measures were statistically significant at α=0.01.

PROMIS data magnitude of effect

For the Pain Intensity scale 7 of 10 knees recorded the lowest possible score by week 12. For the Pain Interference and Pain Behavior

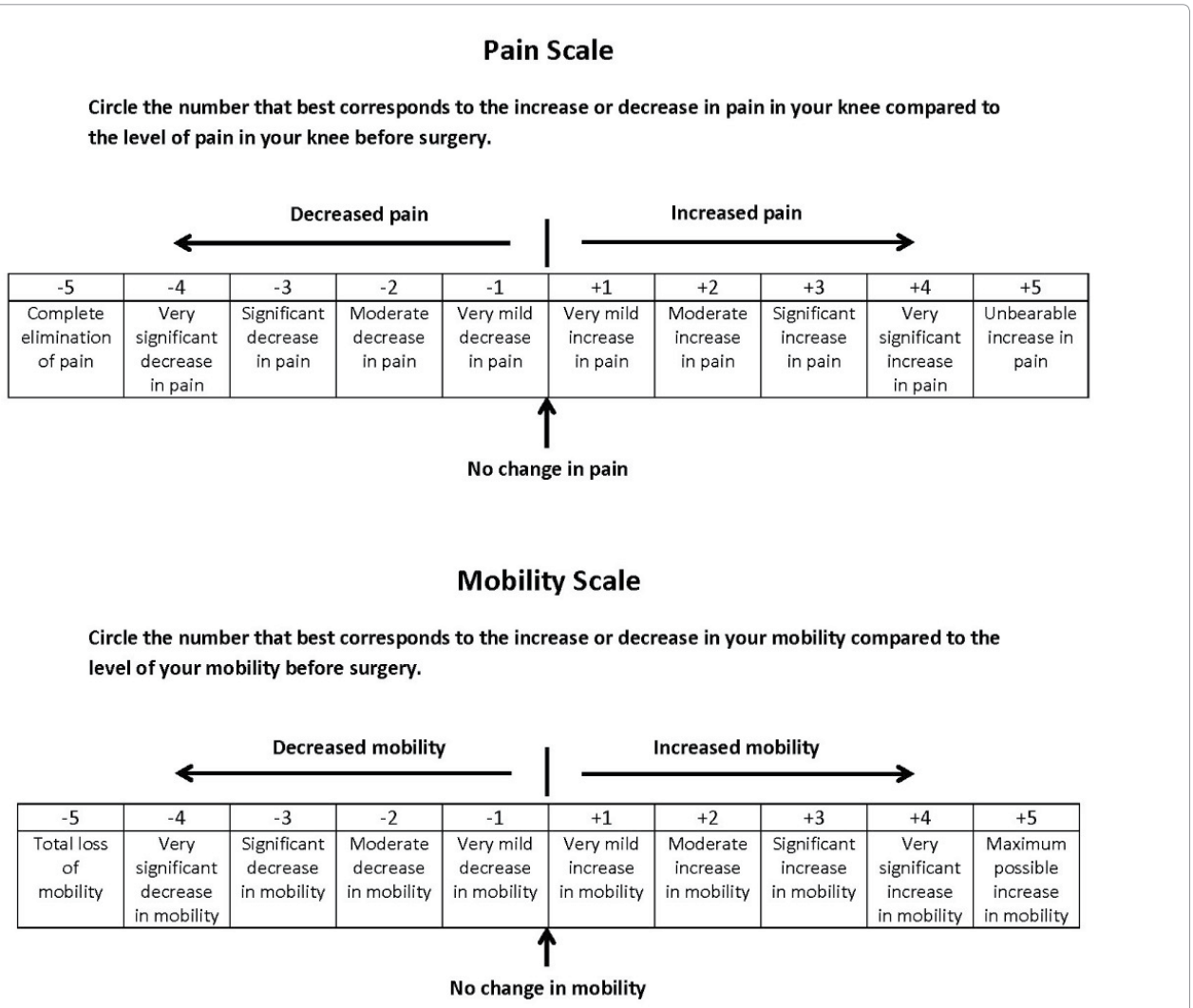

Figure 2: Pain and Mobility Questionnaire.

Table 1: Patient and Procedural Data.

Knee No.	Age/Sex	OA Grade	Total SVF cells injected per knee	Viability %	Dry adipose harvest per knee (ml)	SVF cells per ml dry adipose
1	54/M	II	59.5e6	82	92	647,000
2	54/M	II	59.5e6		92	647,000
3	69/M	II	50.4e6	73	105	480,000
4	52/M	II	27.3e6	85	60	458,000
5	52/M	II	27.3e6		60	458,000
6	63/F	II	36.9e6	79	90	410,000
7	63/F	II	36.9e6		90	410,000
8	53/F	II	43.2e6	77	136	377,000
9	64/F	II	70.5e6	72	93	760,000
10	64/F	III	70.5e6		93	760,000
Mean	58.8		48.2e6	78	91.1	540,700

scales the lowest possible score at week 12 was achieved by 9 of 10 and 7 of 10 knees, respectively. Cohen's *d* was used to estimate the effect size – the effect of the independent variable on the scores of the dependent variable. A large effect is a value of *d* greater than 0.80, which was obtained for each of the three pain metrics.

The PROMIS scale ranges (minimum to maximum) for each assessment scale are shown in Table 2. These ranges can be linearly transformed to a 0-100 point scale range used by common orthopedic validated scales such as WOMAC and KOOS. The transformation is: *100 point score=(PROMIS raw score – PROMIS lowest possible score)/(range of PROMIS score)*100.*

The values for the scores for each knee for each PROMIS assessment

Table 2: Pre-operative and 12-Week PROMIS Pain Scores.

	Pain Intensity 3a		Pain Interference Bank 1.0		Pain Behavior Bank 1.0	
Knee No.	**Week 0**	**Week 12**	**Week 0**	**Week 12**	**Week 0**	**Week 12**
1	53.7	30.7	65.3	38.6	60.3	35.3
2	43.8	30.7	53.7	38.6	55.2	35.3
3	48.4	30.7	53.5	38.6	57.4	35.3
4	43.8	40.5	52.8	38.6	53.8	51.2
5	30.7	30.7	46.6	38.6	50.9	35.3
6	42.6	30.7	51.1	38.6	43.8	35.3
7	42.6	30.7	52.8	38.6	53.8	35.3
8	51.3	43.8	61.5	44.8	57.6	51.3
9	45.7	40.5	52.6	38.6	56.5	49.7
10	35.8	30.7	46.6	38.6	46.8	35.3
Mean	43.84	33.97	53.65	39.22	53.61	39.93
Change in Mean		9.87		14.43		13.68
STD DEV	6.81	5.34	5.83	1.96	5.12	7.74
SEM	2.15	1.69	1.84	0.62	1.62	2.36
95% Conf. Int.	39.62-48.06	30.66-37.28	50.04-57.26	38.00-40.44	50.44-56.78	35.30-44.56
T-test (*p*)		0.0016		0.0001		0.0003
Effect size (*d*)		1.70		3.50		2.25
Scale range	30.7 (none) – 71.8 (maximum)		38.6 (none) – 83.8 (maximum)		35.3 (none) – 77.9 (maximum)	
Assessment questions	3		12		12	
Mean transformed to 0-100 point scale	32	8	33	1	43	11

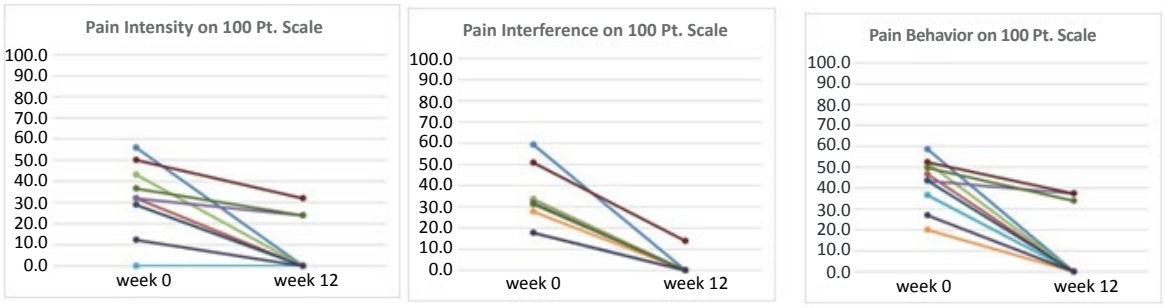

Figure 3: PROMIS pain scale results, showing all 3 metrics transformed to 100-point scale.

scale at time points Week 0 and Week 12, linearly transformed to the 0-100 point scale, are shown in Figure 3.

Ordinal Data Statistical Significance: The Wilcoxon Matched Pairs Signed Ranks *T* test (2-tailed) was used to assess statistical significance of the 2-question questionnaire results. Both decrease in knee pain and increase in mobility were statistically significant at α=0.01. Scores for all ten knees showed decreased pain and increased mobility at the 12-week follow-up. Table 3 provides the preoperative and 12-week post-operative scores and the statistical calculations.

Ordinal data magnitude of effect

At week 12 all 10 knees reported decrease in pain (10/10) and increase in mobility (10/10). Nine of ten knees reported either complete or very significant reduction in pain. The median value of reduction in pain (-4) corresponds to very significant reduction in pain. Nine of ten knees reported either maximum possible or very significant decrease in pain. The median value of decrease in pain (-4) corresponds to very significant decrease in pain. Six of ten knees reported either maximum possible or very significant increase in mtobility. The median value of increase in mobility (+4) corresponds to very significant increase in mobility.

Table 3: Pre-operative and 12-Week Pain and Mobility Scores.

	Pain	Mobility
Knee No.	**Week 12**	**Week 12**
1	-5	5
2	-5	5
3	-4	2
4	-4	4
5	-4	4
6	-5	5
7	-5	5
8	-3	2
9	-4	1
10	-4	1
Median	-4	4
ABS sum + ranks	0	0
ABS sum - ranks	55	55
T for α=0.01 (2-tail)	3	3
T_{obj} (smaller of ranks)	0	0

Significant pain relief and increase in mobility were rapid in onset (2-4 days) for all patients, which was maintained and slowly improved over 12 week follow-up.

Discussion

This was a safety and feasibility study performed to evaluate the use of autologous SVF in application to the knee joint space for treatment of osteoarthritis. No adverse events were reported related to the injection of SVF into the knee joint space. A statistically significant decrease in knee pain and increase in mobility was reported for all patients/knees treated.

The magnitude of the effect on OA pain was the most significant finding. Wang et al. [10] performed a meta-analysis on 18 randomized controlled studies for OA which looked at viscosupplementation (hyaluronic acid, standard of care) *vs* placebo. Seven studies with results reported at ≤ 12 weeks, found a mean peak pain intensity difference of 6.2%, where the peak pain intensity difference was defined as the change in pain intensity divided by the full-scale range of the pain intensity scale. In the present study we found, using the same calculation, a peak pain intensity difference of 24% of full scale (PROMIS Pain Intensity 3a), demonstrating a percentage change 3.8 times greater than the meta-analysis mean change for viscosupplementation.

With evidence of basic safety and feasibility for reduction in pain, the next level of investigation should include a larger number of patients, a control arm, blinding, randomization, and extended follow-up data at six months and one year. Such a study should also include use of objective metrics such as assessment of synovial fluid. If such a study demonstrates the necessary safety and efficacy, then comparison to other known non-regenerative therapies such as injection of corticosteroids or viscosupplementation can reasonably be addressed.

The use of freshly harvested and processed SVF for regenerative therapy eliminates the need for culture expansion mesenchymal stem cells to achieve a clinically therapeutic dose and further eliminates the need for a second surgical procedure required to implant the cultured cells. Use of autologous SVF in the knee is a promising cell-based therapy that addresses a significant clinical need in the treatment of osteoarthritis that to date has no known regenerative solution.

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