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A Prospective Safety Study of Autologous Adipose-Derived Stromal Vascular Fraction Using a Specialized Surgical Processing System

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Abstract

Autologous adipose-derived stromal vascular fraction (SVF) has been proposed as a remedy for a number of inflammatory, autoimmune, and degenerative conditions. This procedure had mainly been evaluated in veterinary medicine and outside the United States when this study was initiated. This study looks at adverse events to evaluate safety as its primary objective and secondarily follows efficacy of SVF as deployed through intra-articular injections and intravenous infusions for a variety of orthopedic and non-orthopedic conditions. We hypothesized that autologous SVF deployment using a specialized surgical processing system (the CSN Time Machine® system, trademark name for the MediKhan Lipokit/Maxstem system; MediKhan, Los Angeles, California) was safe (ie, minimally acceptable adverse events) and that clinical efficacy could be demonstrated. This was a prospective case series. After institutional review board approval, 1698 SVF deployment procedures were performed between 2011 and 2016 by us and other affiliates with our same system trained by us as a nearly closed sterile surgical lipotransfer procedure on 1524 patients with various degenerative, inflammatory, and autoimmune conditions with a majority involving the musculoskeletal system. All outcome test data were collected in an online database over a 5-year period. Our study shows a very low number of reported adverse events and a reduction in pain ratings after 6 months or more across a variety of musculoskeletal diseases and improvements in a variety of other degenerative conditions. Our system for producing adipose-derived SVF therapy for our patients was safe and benefits could be measured for a long time after SVF deployment. Further controlled long-term studies for specific disease conditions with large patient populations are necessary to further investigate the benefits observed.

Keywords

fat transplant, liposuction, new technology, stem cells, stromal vascular fraction

Introduction

For a number of years, medical groups throughout the United States have been treating patients with bone marrow–derived stem cells. One organization, the International Cell Medicine Society, has organized registries and institutional review boards to follow and evaluate various programs related to stem cell therapy. Of particular note, they have found no significant evidence of adverse events directly related to treatments with bone marrow–derived mesenchymal stem cells (MSCs) that generally require an expansion process through cell culture techniques.[1]

Through technologic advances, we are currently able to isolate adult stromal vascular fraction (SVF) from adipose tissue in a sterile, nearly closed system in a relatively quick (1 hour) time frame. The SVF separated from lipo-aspirate by enzymatically digesting the collagen-binding matrix contains a heterogeneous population of cells. Among these are adipose-derived stem cells (ADSCs), similar in morphology to adult MSCs, hematopoetic stem cells (HSCs), endothelial progenitor cells, macrophages, red blood cells, platelets, growth factors, and T-regulatory cells.[2,3]

Plastic and cosmetic surgeons have been using SVF in conjunction with fat as a way to fortify the graft material for improved uptake, particularly in breast augmentation procedures. Yoshimura has been particularly significant in advancing this concept in Japan and coined the term the *CAL* procedure—cell-assisted lipotransfer—in an article from

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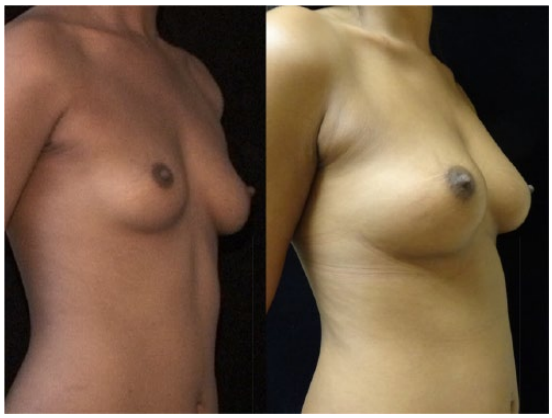

Figure 1. Berman patient before and 9 months following CAL breast augmentation.
Note. CAL = cell-assisted lipotransfer.

2008.[4] In April 2010, Berman had the opportunity to visit Dr Yoshimura and Dr Kamakura on 2 separate days and observe each doctor perform CAL breast augmentation using 2 different systems. Dr Kamakura used 2 Cytori devices that produced SVF through an automated system whereas Dr Yoshimura used the same system as the authors. Although cosmetic and plastic procedures can certainly benefit from SVF-enhanced fat transfers (see Berman's before and after breast augmentation with the CAL procedure; Figure 1), SVF, through its stem cell potential, could conceivably be used to affect positive changes in a far more vast array of therapeutic conditions. All injuries and diseases negatively affect our "cells" and thus a stem cell should be the logical choice to advance cellular (and thus, tissue) repair.

There is a plethora of anecdotal and more recently, evidence-based information to suggest that MSCs may have significant beneficial use for a large variety of inflammatory, autoimmune, and degenerative conditions.[5-11] A large number of treatments have been successfully conducted on animals as accepted practices of veterinary medicine.[12] Much work with these cells has been done in the laboratory, whereas fewer evidence-based studies have been aimed at therapeutic outcomes. Two recent reviews by Nguyen and Guo et al discuss the current concepts and evidence of SVF efficacy in the literature.[13,14] More recently, Michalek, from the Czech Republic, reported excellent safety data and very favorable outcomes using intra-articular SVF on 1128 patients evaluated for arthritic conditions.[15]

One of the common criticisms to investigating or treating patients with SVF is the concern for potential risks. Although several safety studies appear in the literature,[10,11,15-20] we felt compelled to evaluate a larger number of patients and follow their safety as well as clinical responses. We chose to look at safety as our primary objective with clinical outcomes being a secondary objective. Furthermore, we not only evaluated intra-articular delivery but intravenous infusion as well.

Material and Methods

Patients

After institutional review board (IRB) approval, patients who met criteria for selection (see clinicaltrials.gov CSN111) that included a variety of degenerative, inflammatory, or autoimmune conditions were included in this study and treated with autologous adipose-derived SVF. Between 2011 and 2016, a total of 1698 procedures were performed on 1524 patients (eg, 1 patient might have had multiple procedures over time or multiple deployment sites within 1 procedure). Of these patients we received 1698 acute and 526 long-term follow-up reports regarding adverse events. For paired 6-month outcome analysis, records were analyzed for several treated conditions.

Patients met with a variety of consultants, most frequently with specialists from disciplines that generally oversaw their respective conditions, to ascertain appropriateness for the procedure. Specific IRB-approved deployment methods for each condition were used (see Table 1). Patients were educated and no guarantees were made nor were patients coerced to undergo treatments. Contraindications to inclusion in the study included age less than 18, pregnancy, severe coagulopathy, significant active infections, particularly systemic and especially dental infections, and metastatic or uncontrolled cancer. Patients on anti-coagulation therapies for various heart or other embolic conditions were, however, treated within this study without discontinuing their anti-coagulation medications. Most patients received intravenous (IV) therapy (anecdotally it appears complimentary) in addition to their regional targeted deployments (intra-articular in most orthopedic patients). Patients signed IRB-approved informed consents emphasizing the investigational nature of their SVF deployments and underwent an additional brief history and physical exams prior to their procedures.

Patients were followed for adverse events related to lipoharvesting and SVF deployment. Short-term and long-term complications were followed as well as mild, moderate, or serious adverse events. An online Health Insurance Portability and Accountability Act of 1996 (or HIPAA)–compliant database was used to track patients for safety data as well as outcome data. In most cases, patients reported any adverse outcomes directly to the database to mitigate the Hawthorne effect (ie, observer effect) as they were not under direct observation that might have swayed their responses. Severe adverse events were to be reported to the IRB. The study was conducted through the offices of California Stem Cell Treatment Center and several other locations (research affiliates of the Cell Surgical Network; Table 2) that participated in our study. All affiliate research sites were trained by the authors and used the same devices, techniques, and

Table 1. List of Current IRB Numbers.

Trial name	Approval no
SVF Combined With Vaccinia in Patients With Advanced Solid Tumors	ICSS-2016-001
Cells on Ice (COI) Program: The Use of Frozen/Thawed and/or Expanded Cells via Cell Banking	ICSS-2016-002
Lumbar Puncture for Deployment of SVF Informed Consent	ICSS-2016-003
General Patient Consent Form Including Spanish Version	ICSS-2016-004
Patient Consent for IV Mannitol	ICSS-2016-005
Consent for Low Intensity Shock Wave Treatment of the Penis	ICSS-2016-006 (Conditional)
Ophthalmology Consent Form	ICSS-2016-007
Repeated Informed Consent Form	ICSS-2016-008
Deployment of SVF for Backs	ICSS-2016-009
Deployment of SVF for COPD	ICSS-2016-010
Deployment of SVF for Hips	ICSS-2016-011
Deployment of SVF for Neurologic Conditions	ICSS-2016-012
Deployment of SVF for Shoulders	ICSS-2016-013
Deployment of SVF for Urologic Conditions	ICSS-2016-014
Clinical Intervention Study: Deployment of Stromal Vascular Fraction in Autoimmune Conditions	ICSS-2016-015
Intraventricular Deployment of SVF Using Ommaya Reservoir	ICSS-2016-016
Secondary Evaluation for Adverse Events Related to the Deployment of SVF	ICSS-2016-017
Deployment of SVF for Cardiac Conditions	ICSS-2016-019 (Conditional)
Deployment of SVF for Knees	ICSS-2016-020 (Conditional)
Deployment of SVF for Ophthalmology	ICSS-2016-021 (Conditional)

Note. COPD = chronic obstructive pulmonary disease; IRB = institutional review board; SVF = stromal vascular fraction.

IRB-approved protocols to isolate and deploy SVF and follow outcomes.

SVF Deployment

Patients underwent instillation of local anesthetic consisting of lidocaine 0.5% with epinephrine 1:400 000 and sodium bicarbonate 8.4%. Using a sub-dermal non-tumescent method, small regions of torso skin (approximately 20 cm^2) were blocked (usually abdominal or posterior flanks).[21] The patients then received sterile prep and drape. The CSN Time Machine® system (USA trade name for the MediKhan Lipokit system; MediKhan, Los Angeles, California; 510 K approved for fat grafting) was used to harvest, centrifuge, incubate, and isolate the product. Within 2 minutes of local anesthetic injection, a mini liposuction was performed through a number 11 blade puncture wound using the negative pressure syringe technique with a TP101 syringe and a 3-mm cannula. Approximately 50 cc of the lipo-aspirate solution was obtained and condensed by centrifugation at 2800 rpm for 3 minutes in the Time Machine® centrifuge. 12.5 Wunsch units of T-MAX® Good Manufacturing Practices (GMP) grade collagenase (private label name for Liberase by Roche, Indiana) in 25 cc of normal saline was added to 25 cc of condensed fat and incubated at 38°C in the Time Machine® incubator for 30 minutes to digest the collagen matrix to procure the SVF in closed Time Machine Syringes (TP-102 syringe by MediKhan) in the operating room. The product was washed with D5LR sequentially (3 times) and then the SVF concentrate was isolated. SVF was filtered through a Food and Drug Administration (FDA)–approved 100-μm nylon filter (BD Falcon cell strainer; Becton Dickinson, Franklin Lakes, New Jersey). Photomicrography using the Invitrogen by Countess (Invitrogen, ThermoFisher Scientific, Waltham, Massachusetts) was used to document lack of aggregation, allow for a basic cell count, and measure cell viability using 0.4% trypan blue. Cell viability, measured by the Countess, demonstrated that our final SVF product reliably ranged from 65% to 95%. SVF was then deployed in various different ways depending on the condition under consideration for treatment. SVF deployments in most patients were IV, intra-articular, and/or into soft tissue in some orthopedic cases. Other routes for non-orthopedic cases were intra-thecal, intra-peritoneal, and nebulized.

To provide enhanced cell characterization, 25 different patient samples were sent for flow cytometry to a reference laboratory at University of California, San Diego, USA.

Questionnaires

To evaluate subjective outcomes, we utilized standard questionnaires and scores to follow up with our patients. Details about which questionnaires were used can be found in Table 3.

Database

All patients were treated in clinics and by doctors of the Cell Surgical Network using approved deployment protocols. Data were collected via e-mail and telephone and entered into a customized TrackVia (Denver, Colorado) database. All responses were voluntary and patients did not receive compensation to participate.

Statistics

Data were analyzed with IBM SPSS statistics (Version 23; IBM Inc, Armonk, New York). We performed descriptive statistics and analyzed the data with Student's *t* test, paired sample *t* tests, and one-way analysis of variance (ANOVA). Data are presented as means ± standard errors of the mean (SEMs). *P* values were assumed significant, when $\alpha < .05$.

Table 2. List of Cell Surgical Network Treating Physicians Who Contributed Data.

Stem cell treatment center	Physicians					
Arizona Stem Cell Treatment Center	Robert Dryden, MD					
Atlanta Stem Cell Treatment Center	Edmond Griffin, MD	Ashley Curtis, MD				
Bienville Stem Cell Treatment Center	Bob Terrell, MD	Daniel Wittersheim, MD	Jeff Noblin, MD	John Drake, MD	Yekaterina Karpitskaya, MD	
California Stem Cell Treatment Center	Elliot Lander, MD	Mark Berman, MD	Jackie See, MD	David Milstein, MD	John Feller, MD	Jonathon Braslow, MD
California Stem Cell Treatment Center cont.	Stuart May, MD	Christopher Duma, MD	Roland Reinhardt, MD	Thomas Grogan, MD	Walter O'Brien, MD	
Cell Surgical Network of Florida	David Heekin, MD	Lewis J. Obi, MD	Orlando Florete, MD			
Chicago Stem Cell Treatment Center	Daniel Ritacca, MD	Jay Joshi, MD	Kathleen Morno, MD	Howard Freedberg, MD		
Cleveland Stem Cell Treatment Center	Mark A. Foglietti, DO					
Colorado Stem Cell Treatment Center	Greta McLaren, MD	Ken Oleszek, MD	Renald Bernard, MD	Michael Otte, MD		
Columbus Stem Cell Treatment Center	David Garcia, DO					
Singapore Stem Cell Team	Z Teo, MD					
Europe Stem Cell Treatment Center Team	Josie Muscat, MD	Jaroslav Michalek, MD				
Indiana Stem Cell Treatment Center	Robert Jackson, MD	Chris Lowery, MD				
Innovations Stem Cell Treatment Center	Bill Johnson, MD					
Irvine Stem Cell Treatment Center	Thomas Gionis, MD					
Kansas Regenerative Medical Center	Andrew Pope, MD	Frank C. Lyons, MD	Steven Pelpquin, MD			
Las Vegas Stem Cell Treatment Center	Julio Garcia, MD					
Little Rock Stem Cell Treatment Center	Richard D'Anna, MD	James Rudder, MD	Ken Martin, MD			
Longevity Stem Cell Treatment Center	Gurney F. Pearsall Jr, MD					
Manhattan Stem Cell Treatment Center	Basil Pakeman, MD					
Miami Stem Cell Treatment Center	Nia Smyrniotis, MD					
Michigan Stem Cell Treatment Center	Charles Mok, MD	Andrew Georgeson, MD				
Midwest Stem Cell Treatment Center	Gregory Chernoff, MD	Kevin Macadaeg, MD				
Mississippi Stem Cell Treatment Center	Hazem Barmada, MD					
Morrow Stem Cell Treatment Center	David Morrow, MD					
New Jersey Stem Cell Treatment Center	Erica Song, MD					
Newport Beach Stem Cell Treatment Center	Michael Elam, MD	Julian Whitaker, MD				
New York Stem Cell Treatment Center	Adam Schaffner, MD	Jeffrey D. Gross, MD	Kamau Kokayi, MD			
New York Stem Cell Treatment Center at Manhattan	David Borenstein, MD					
New Zealand Stem Cell Treatment Center Team	Peter Chapman-Smith, MD					

(continued)

Table 2. (continued)

Stem cell treatment center	Physicians						
North Carolina Stem Cell Treatment Center	Payton Fennell, DO	Krishna Bhat, MD	James Stevens, MD				
Northern California Regenerative Cell Treatment Center	William Chen, MD						
Northern California Stem Cell Treatment Center	Andrew Solkovitz, MD	Bob Ghelfi, MD	Leonard Soloniuk, MD	Tony Chang, MD	William Heyerman, MD		
OC Wellness Rejuvenation and Stem Cell Center	Michael Grossman, MD						
Orange County Regenerative Medicine	Michael Arata, MD						
Palm Beach Stem Cell Treatment Center	Daniela Dadurian, MD						
Park Avenue Stem Cell Treatment Center	Joel Singer, MD						
Pennsylvania Stem Cell Treatment Center	Thomas Young, MD						
Phoenix Stem Cell Treatment Center	Steven Gitt, MD					Steven Gitt, MD	
Regenerative Medicine Specialists	Joseph Cabaret, MD						
San Diego Stem Cell Treatment Center	Barzan Mohedin, MD	Craig Salt, MD	Jim Amsberry, MD	Marty Bastuba, MD	Pete Hanson, MD	Robert Scott, MD	Scott Hacker, MD
San Diego Stem Cell Treatment Center	Tal David, MD						
San Francisco Stem Cell Treatment Center	Ahvie Herskowitz, MD						
Scottsdale Stem Cell Treatment Center	Marin Borsand, MD						
Seattle Stem Cell Treatment Center	Don Wortham, MD						
Silicon Valley Stem Cell Treatment Center	Yung Chen, MD						
South Africa Stem Cell Treatment Center	Barlodien Kotze, MD	Tommie Van Wyk, MD					
South Florida Stem Cell Treatment Center	Michael Sinclair, MD						
Stem Cell Center of Georgia	Alexander Kessler, MD	Jamie Walraven, MD					
Stem Cell Center of Texas	James Davis, MD						
Tennessee Stem Cell Treatment Center	Lawrence Schrader, MD						
The Center for Regenerative Cell Medicine	Todd Malan, MD						
Vancouver Stem Cell Treatment Center Team	Martin Braun, MD						
Vero Beach Stem Cell Treatment Center Team	David Tran, MD	John Sarbak, MD	Paul Hatten Jr, MD	Richard Steinfeld, MD	Joanne Wernicki, MD	Leslie Huszar, MD	Michele Maholtz, MD
Vero Beach Stem Cell Treatment Center Team cont.	David Griffin, MD						
Visalia Stem Cell Treatment Center	Talaksoon Khademi, DO						
Vitality Stem Cell Treatment Center of Palm Desert	Mark Foster, MD						
Waxahatchie Stem Cell Treatment Center	Marc Roux, MD						

Table 3. Questionnaires Used for Various Treated Conditions.

Condition		Questionnaire used			
Knee	VAS	Knee Injury and Osteoarthritis Outcome Score (KOOS)–Physical Function Short Form (KOOS-PS)	WOMAC	Knee NAS (TrackVia Version)	The AQoL-4D Instrument
Hips	VAS	Hip Injury and Osteoarthritis Outcome Score (HOOS)–Physical Function Short Form (HOOS-PS)		Hip NAS (TrackVia Version)	The AQoL-4D Instrument
Shoulders	VAS	DASH		Shoulder NAS (TrackVia Version)	The AQoL-4D Instrument
Ankle	VAS	Foot and Ankle outcomes Questionnaire		Joint NAS (TrackVia Version)	The AQoL-4D Instrument
Elbow	VAS	DASH		Joint NAS (TrackVia Version)	The AQoL-4D Instrument
Back	VAS	Oswestry Questionnaire		Back-Neck NAS (TrackVia Version)	The AQoL-4D Instrument
Neck	VAS	Neck Disability Index		Back-Neck NAS (TrackVia Version)	The AQoL-4D Instrument
Cardiac		Minnesota Living With Heart Failure Questionnaire		Cardiac Follow-up (TrackVia Version)	The AQoL-4D Instrument
Lung				Pulmonary Questionnaire (TrackVia Version)	The AQoL-4D Instrument
Peyronie's	IIEF	EHGS	PDQ	Peyronie's Disease Follow-up (TrackVia Version)	The AQoL-4D Instrument
Erectile dysfunction	IIEF	EHGS		Erectile Dysfunction Follow-up (TrackVia Version)	The AQoL-4D Instrument
Incontinence	IIQ-7	UDI-6		Incontinence Follow-up (TrackVia Version)	The AQoL-4D Instrument
IC	VAS	IC Symptom and Problem Questionnaire	Pelvic Pain and Urgency/ Frequency Patient Symptom Scale	IC Follow-up (TrackVia Version)	The AQoL-4D Instrument
Lichen sclerosis	VAS				The AQoL-4D Instrument
Autoimmune	VAS			Autoimmune Follow-up (TrackVia Version)	The AQoL-4D Instrument

Note. VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Index of Osteoarthritis; NAS = Numeric Analog Scale Left/ Right; AQoL-4D = Assessment of Quality of Life; DASH = Disabilities of the Arm, Shoulder, and Hand; IIEF = The International Index of Erectile Function Questionnaire; EHGS = Erectile Hardness Grading Scale; PDQ = Peyronie's Disease Questionnaire; IIQ-7 = Incontinence Impact Questionnaire; UDI-6 = Urogenital Distress Inventory Short Form; IC = interstitial cystitis.

Results

Conditions Examined

A total of 1698 procedures were performed on a total of 1524 patients and some patients had multiple procedures at different time points or multiple deployment sites at 1 procedure, or both. We investigated a variety of musculoskeletal conditions as well as urogenital, autoimmune, neurological, cardio-pulmonary, and other conditions.

Cell Characterization

Flow cytometry was utilized to examine 27 different random samples of SVF using the FACSCalibur flow cytometer (BD Biosciences, Franklin Lakes, New Jersey). All tested SVF samples displayed both hematopoietic and mesenchymal cell lineages. We characterized and enumerated surface markers of freshly isolated ADSCs. As there is no unique single marker for ADCSs, a combination of markers was used to identify and separate ADCSs from other cell subsets in SVF. Although ADSCs were detected to be uniformly expressing same characteristic markers ($CD45^{low}$ $CD34^{+}$ $CD31^{-}$ $CD90^{+}$), their absolute numbers varied substantially from one patient to another. The other cell subsets in SVF were characterized as follows: HSCs with a phenotype $CD45^{+}$ $CD34^{low}$ $CD14^{+}$ $CD31^{-}$ $CD206^{+}$, M1 macrophages $CD45^{+}$ $CD34^{-}$ $CD14^{+}$ $CD206^{-}$ as well as pericytes $CD45^{-}$ $CD34^{-}$ $CD31^{-}$ $CD146^{+}$, and CD3+ T-cells. As expected, no 2 SVF samples were identical in cell composition.

Table 4. Documented and Reported Post-procedural Adverse Events From All Cases.

	None	Mild	Moderate	Severe	Missing	Total
Question	n (valid %)				n (% of total)	
Liposuction issues: Problem with surgical prep?	1575 (93.9)	79 (4.7)	21 (1.3)	2 (0.1)	21 (1.2)	1698 (100.0)
Pain from local anesthesia?	1311 (78.1)	314 (18.7)	48 (2.9)	5 (0.3)	20 (1.2)	
Pain from liposuction procedure?	834 (49.7)	599 (35.7)	211 (13.2)	24 (1.4)	20 (1.2)	
Pain at liposuction site after 1 week?	975 (59.2)	526 (32.0)	135 (8.2)	10 (0.6)	52 (3.1)	
Infection at liposuction site?	1657 (99.5)	8 (0.5)			33 (1.9)	
Any unusual/allergic reaction to procedure?	1029 (98.8)	13 (1.2)			656 (38.6)	
Pain at deployment site?	1168 (70.1)	384 (23.0)	80 (4.8)	33 (2.0)	33 1.9)	
Pain after 1 week at deployment site?	1347 (82.3)	218 (13.3)	59 (3.6)	12 (0.8)	32 (1.9)	
Infection at deployment site?	1650 (99.7)	5 (0.3)			43 (2.5)	
Bleeding at deployment site?	1552 (93.1)	107 (6.4)	7 (0.4)	1 (0.1)	31 (1.8)	
Hematoma?	1657 (99.8)	2 (0.2)			37 (2.2)	
Infection with fever?	1651 (99.8)	4 (0.2)			43 (2.5)	

Table 5. Long-Term Follow-Up Questionnaire, With Descriptive Statistic for Follow-Up Time and Answers to Questions.

	Mean ± SEM	Median	Minimum	Maximum
	22.13 ± 0.44	19.5	12.0	64.0
	No	Yes	Missing	Total
Follow-up time (months)	n (valid %)		n (% of total)	
Did you experience any adverse events that you believe are related to stem cell therapies?	515 (98.1)	10 (1.9)	1 (0.1)	526 (100.0)
After your SVF procedure, have you been diagnosed with a tumor or cancer?	499 (98.0)	10 (2.0)[a]	17 (3.2)	

Note. SVF = stromal vascular fraction.
[a]A total of 10 self-reported and 1 more reported via telephone interview for a total of 11 cancer patients.

No Major Adverse Events Were Seen Associated With IV Deployment

Most (97%) of the deployment protocols used included IV deployment as part of the treatment and 1477 IV SVF deployments were performed. Some IV SVF infusions were primary modalities of SVF delivery and some IV infusions were supplementary to the primary deployment such as intra-articular or intra-thecal. The final double filtering of SVF down to 100 µm was designed to prevent risk of any embolic events.

No Major Adverse Events Were Seen in the Immediate Context Related to SVF Therapy

The data in Table 4 are descriptive and shown as number of procedures, validation of response, and total numbers and percentages. Table 4 shows answers to questions for all procedures. Although 7 out of 12 questions had patients reporting a severe reaction (the worst category), this was a very low rate and only accounted for 0.1% to 2.0% of all responses. Also this was mostly related to pain during the liposuction procedure. Only 1 problem with the surgical prep was reported. Patients reported 8 mild infections at the liposuction site and 5 mild infections at the deployment site; 1 severe, 7 moderate, and 107 mild bleedings, and 4 mild blood clots (superficial hematomas) at the deployment site were reported. No severe infections, allergic reactions, pulmonary emboli, or deep vein thromboses were reported.

In addition, in an effort to confirm the sterility of the SVF product, 25 consecutive SVF samples from 25 different patients were sent to LabCorp, Burlington, North Carolina, for culture testing to evaluate for any possible contaminant. There were no organisms seen or cultured in any of the specimens.

No Major Adverse Events Were Seen in a Follow-Up Questionnaire

The data from our long-term follow-up of a total of 526 responses to our questionnaires were received and are presented in Table 5. The mean ± SEM follow-up time was

Table 6. Patient Self-Reported Adverse Events.

Treated condition	Patient reports
Knee	SVF therapy takes too much energy
Knee	Indirect related negative experience with Demerol injection
Knee	Dental abscess
Knee	Baker's cyst 1 year after therapy
Knee	Bursitis, leg swelling
MS	MS flare-up after SVF therapy
MS	Extensive bruising and rejection of the HBO therapy afterward
Stroke/cardiac	Irregular heartbeats, patient passed away
Gout	Pain at site plus severe neck pain
Macular degeneration—dry	Eye condition got worse

Note. SVF = stromal vascular fraction; HBO = hyperbaric oxygen; MS = multiple sclerosis.

22.13 ± 0.44 months; the median was 19.5 months with a minimum of 12.0 and a maximum of 64.0 months (Table 5). Regarding the question of occurrence of adverse events that are attributed by the patient to the therapy, 515 (98.1%) answered with "No" and 10 (1.9%) patients answered with "Yes." The patient reports and physician's notes for these events are reported in Tables 6 and 7. Finally, there were 12 (0.72%) reported diagnoses of cancer in 11 out of 1524 patients. The patient reports and doctor's notes for these cases are presented in Table 8.

Pain and Assessment of Quality of Life (AQoL) Is Decreased After Treatment in Orthopedic Conditions and Knee

In the group of patients with orthopedic diseases, the age of female (n = 175; 66.35 ± 0.75) and male (n = 228; 64.83 ± 0.76) patients was not significantly different from each other, $t(531) = 1.37$; $P = .17$ (Figure 2A), whereas male (n = 230; 29.72 ± 0.45) patients had a significantly higher body mass index, $t(403) = -3.81$; $P < .001$, as analyzed by unpaired Student's t test compared with female patients (n = 175; 27.16 ± 0.50; Figure 2B). Time had an overall significant effect on pain (Figure 2C), $F(3, 156) = 19.47$; $P < .001$, and AQoL (Figure 2D), $F(3, 111) = 4.38$; $P < .006$, as analyzed by one-way ANOVA, whereas the post hoc Bonferroni comparison revealed a significant reduction in pain compared with baseline (5.68 ± 0.29; $P < .001$) after 1 (3.75 ± 0.29; $P < .001$), 3 (3.31 ± 0.31; $P < .001$), and 6 months (3.35 ± 0.33; $P < .001$), and for AQoL compared with control (6.47 ± 0.55) after 1 (5.10 ± 0.59; $P = .007$) and 6 (5.06 ± 0.55; $P = .04$) months.

Separated for knee and shoulder procedures, knee patients had significantly lower pain ratings (baseline vs 6 months, 4.87 ± 0.32 vs 2.96 ± 0.29; Figure 3A), $t(48) = 5.01$; $P < .001$; lower Knee Injury and Osteoarthritis Outcome Score (baseline vs 6 months, 33.89 ± 2.54 vs 21.72 ± 2.04; Figure 3B), $t(60) = 4.91$; $P < .001$; and lower AQoL (baseline vs 6 months, 5.33 ± 0.46 vs 3.98 ± 0.48; Figure 3C), $t(56) = 3.54$; $P = .001$, 6 months after the procedure. In the group of patients with shoulder procedures, pain ratings (baseline vs 6 months, 5.50 ± 0.40 vs 2.76 ± 0.49; Figure 3D), $t(20) = 5.95$; $P < .001$, and Disabilities of the Arm, Shoulder, and Hand scores (baseline vs 6 months, 34.53 ± 3.21 vs 21.34 ± 4.02; Figure 3E), $t(20) = 3.35$; $P = .003$, were significantly lower at 6 months compared with baseline. Table 9 furthermore shows the 6-month outcome for all conditions where a paired data set of at least 3 patients was available. Here some significant improvements after 6 months were found for some urogenital conditions with a specific focus on interstitial cystitis, erectile dysfunction, and Peyronie's disease. Details about these comparisons are shown in Table 10.

Discussion

SVF and ADSCs have shown tremendous promise as a regenerative therapy. Their use in cosmetic/plastic surgery has been well documented, particularly for CAL in cases of breast augmentation, reconstruction, and a variety of other areas.[4] SVF and ADSCs have demonstrated the ability to not only differentiate along mesenchymal lines but into many other cells and tissues as well.[22(p103)] The cells have been frequently used for chondrogenesis and other orthopedic applications, particularly in veterinary medicine, making it one of the most common areas for clinical applications. Early empiric success with positive responses to SVF deployments for orthopedic conditions encouraged us to continue our work in the form of an IRB-approved investigation to collect data to establish safety while continuing to observe for clinical trends in therapeutic cases. When this study was first initiated, the predominant concern about SVF deployments centered on the paucity of safety data and the insufficient proof of efficacy for lack of evidence-based analysis. We chose to look at safety as our primary objective with clinical outcomes being a secondary objective. Our study is the first to show safety data using both IV and regional deployments of SVF for a high number of treated patients for several conditions in the degenerative, inflammatory, and autoimmune spectrum. Safety in our series appears to have been adequately demonstrated in the lack of adverse events directly related to SVF deployment. Certainly, the minimal and occasional complaints about the liposuction or the occasional delayed healing at the liposuction site should not be considered of any real consequence. Indeed, many of our patients are in the ASA III category and frequently continued their anticoagulants because of the high risk of discontinuing them. Even they had minimal bleeding and no serious problems secondary to the liposuction portion of the procedure.

Previous laboratory investigations done in conjunction with Roche Laboratories utilizing the Cedex Hi-Res System demonstrated that collagenase was effectively diluted to

Table 7. Doctor Notes Regarding Acute and Long-Term Follow-Up Adverse Events.

1. Three patients with knee injections sustained an unusual swelling post-deployment. All resolved with oral steroids or NSAIDs. These symptoms lasted about 24 to 72 hours and then spontaneously resolved. Two were aspirated within the first week by our orthopedic surgeon showing no bacteria and very low to no glucose. Patients went on to have successful outcomes. The swelling occurred in 1 knee while both knees had received SVF.
2. Four patients had flu-like symptoms including mild myalgias and fatigue that occurred 1 or more days post-deployment. Symptoms resolved in 24 hours.
3. A 49-year-old female patient received IV SVF and nebulized cells for pulmonary fibrosis. One week post-liposuction and deployment she presented to her local hospital with abdominal distention. She was treated conservatively for several days. Apparently, she had developed a bowel obstruction that went undiagnosed and she became septic and subsequently expired. There was no evidence of any injury from liposuction or relation to SVF deployment as a cause of her bowel strangulation.
4. A very sick, frail, 86-year-old male with end-stage pulmonary fibrosis received intravenous SVF and then 2 weeks after deployment, his family flew him to another country in the hopes of obtaining additional cell-based treatments there. He died in Israel while awaiting cell expansion for more treatments. There was no evidence of SVF involvement with his demise.
5. A 60-year-old male received a back intra-discal injection. Three days post-deployment, he developed pain in the back area. He was hospitalized for a low-grade fever and pain and no local pathology was identified. One of several routine blood cultures revealed an oral pathogen. He was treated and the condition resolved. Subsequently, we revised our pre-operative instructions by noting in "red ink" that should there be any dental infections (eg, periodontal disease or otherwise), then it should be cared for in advance of any invasive procedure.
6. A debilitated 63-year-old male patient with late stage ALS received IV SVF. Eight days, later he was hospitalized with recurrent bout of pneumonia. He then went on to develop DVTs, which were not present on his hospital admission, and then a pulmonary embolism. He had orders to not resuscitate and eventually expired. There was no evidence of relation to SVF deployment. There was no evidence of relation to SVF deployment.
7. A 79-year-old female patient with COPD developed pulmonary congestion shortly after IV and nebulized SVF deployment. She was hospitalized in the ICU overnight. X-ray examinations revealed diffuse congestion without heart enlargement. She received diuretic therapy and close monitoring. By the next morning, not only did her congestion clear up, as did X-ray examinations, but her COPD dramatically improved as well and she was breathing easier than she had in years. She was subsequently discharged.
8. Localized infection at liposuction site: One patient reported an infection; however, he was applying "lip balm" to the area and it was resolved without intervention.

Note. COPD = chronic obstructive pulmonary disease; SVF = stromal vascular fraction; NSAID = nonsteroidal anti-inflammatory drug; ALS = amyotrophic lateral sclerosis; DVT = deep vein thrombosis; IV = intravenous.

Table 8. Twelve Malignancies as Reported by 11 Patients After SVF Deployment Over a 5-Year Follow-Up.

Patient	Date Tx	Center	Diagnosis	How SVF was deployed	Cancer type
74, male	10/29/2013	Calif SCTC	Crohn's	IV	Prostate-focal
54, female	6/20/2012	Calif SCTC	Wrist DJD	IV/intra-artic	SCC skin distal arm
74, male	5/2/2012	Calif SCTC	Shoulder DJD	Intra-artic	Superfic vocal cord
77, male	4/25/2012	Calif SCTC	Knees DJD	Intra-artic	Breast cancer
54, female	5/22/2013	Calif SCTC	IC	IV and bladder	DCIS breast cancer
54, female	5/22/2013	Calif SCTC	IC	IV and bladder	SCC skin clavicle
68, male	3/16/2011	Calif SCTC	ED	Intracorporal	Basal cell carcinoma nose
85, female	2/6/2013	Calif SCTC	Asthma	IV	Basal cell carcinoma
76, male	4/21/2014	Carolina SCTC	Knees DJD/Parkinson	IV and intra-artic	Non-Hodgkin's lymphoma lower spine and sternum
76, male	4/9/2015	Michigan SCTC	RA/knee arthritis	IV and intra-artic	Skin carcinoma left wrist
50, female	1/22/2013	Newport SCTC	Renal failure	IV	DCIS breast cancer
77, male	9/17/2013	Newport SCTC	Back/arthritis	IV	Skin cancer

Note. SVF = stromal vascular fraction; SCTC = Stem Cell Treatment Center; DJD = degenerative joint disease; SCC = squamous cell carcinoma; ED = erectile dysfunction; DCIS = ductal carcinoma in situ; IC = interstitial cystitis.

insignificant quantities (less than control) after 2 rinses (dilutions) and we routinely perform a third wash as part of our standard protocol (Figure 4). Although collagenase has already been FDA approved for direct injections into soft tissue for certain conditions (eg, Peyronie's and Dupytren's) and thus has minimal systemic ramifications, we considered it important to document that patients did not receive any significantly measurable collagenase in their SVF. Nonetheless, there is no evidence that any harm comes from the cells treated with a GMP non-mammalian collagenase

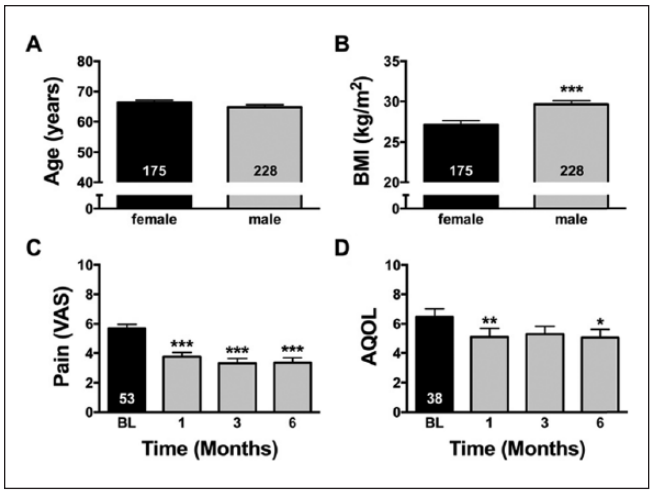

Figure 2. Baseline data, pain, and AQoL.
Note. In the group of patients with orthopedic diseases, (A) the age of female and male patients was not significantly different from each other, (B) whereas male patients had a significantly higher BMI as analyzed by unpaired Student's *t* test. Time had an overall significant effect on (C) pain ($P < .001$) and (D) AQoL after 1 and 6 months. Data are presented as means ± standard errors of mean and were assumed significant when $P < .05$. AQoL = Assessment of Quality of Life; BMI = body mass index; VAS = Visual Analog Scale.

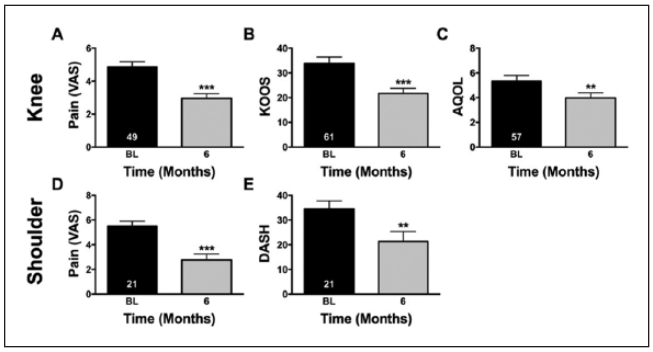

Figure 3. The 6-month outcome for knee and shoulder patients.
Note. Six months after the procedure, knee patients had (A) significantly lower pain ratings ($P < .001$), (B) lower KOOS ($P < .001$), (C) lower AQoL ($P < .005$). In the group of patients with shoulder procedures, (D) pain rating ($P < .001$), and (E) DASH scores ($P < .005$) were significantly lower at 6 months compared with baseline. Data were analyzed with paired Student's *t* test. Data are presented as means ± standard errors of mean and were assumed significant when $P < .05$. VAS = Visual Analog Scale; KOOS = Knee Injury and Osteoarthritis Outcome Score; AQoL = Assessment of Quality of Life; DASH = Disabilities of the Arm, Shoulder, and Hand.
*$P < .05$. **$P < .005$. ***$P < .001$.

that has been effectively diluted to insignificant amounts remaining in the final SVF product.

Perhaps most interesting was the number of positive efficacy results we found in our patient series. Not only did we experience a number of positive results, our affiliates at all other Cell Surgical Network research sites have been able to recapitulate our efficacy results with little inter-observer variability. The majority of our patients fell into the orthopedic category and they also had the most overall benefit from treatments.

From the very start, we saw significant improvements in patients treated. Our first patient, Berman's nurse anesthetist, had painful knee arthritis following a ski injury. She had been on nonsteroidal anti-inflammatory drugs (NSAIDs), had arthroscopy, corticosteroid injections, and could no longer enjoy skiing because of the pain. Her knee had marked crepitus. Within several weeks following SVF direct injection to the knee joint, she was able to return to skiing and no longer had any crepitus in the joint. The next patient was Berman's wife who experienced 3½ years of left hip pain following years of 6 mile a day running. She too had a positive response following SVF direct injection. Neither of these patients has had a return of pain over 6 years following their procedures. Our third patient was scheduled for a total knee replacement. Six years later, she too, still enjoys pain-free walking and has avoided the knee replacement surgery. These were our first 3 patients and though we, and the rest of our affiliates, have not "healed" all of our patients, we have routinely (over 85%) witnessed similar results in our other orthopedic cases. As with any "new" technology, when starting out, you tend to see the worse cases and not always the ones that will most optimally respond. We consider orthopedic conditions the "low hanging fruit" for SVF deployment, but if someone is truly "bone on bone," meaning there is not any significant cartilage "signal" to prompt cartilage differentiation from SVF "stem cells," then one will not experience chondrogenesis or any physical improvement.

Although none of our initial patients were subjected to placebo testing, it may be worth noting the following, particularly as related to the orthopedic conditions: The vast majority of our orthopedic patients had already had multiple interventions. For example, the typical knee patient had already been on a variety of NSAIDs and supplements (eg, glucosamine chondroitin), had corticosteroid injections, hyaluronic acid injections, and frequently arthroscopic interventions. Yet, in spite of all of these interventions, they did not see sustained reduction of pain and improvement in function. With each intervention, a patient may actually sense improvement from a placebo effect and not necessarily the intervention. However, arguably, if the patients do not get improvement from the intervention, then they clearly did not receive any placebo benefit either. If our patients improved from SVF, then it would be rather illogical to assume they improved from a placebo effect in light of the fact that they failed a variety of placebo opportunities in the past. Furthermore, many of our patients had been treated at no cost thus mitigating the idea that by paying for the procedure, they would be likely to respond in the positive. Indeed, many of these patients were family, friends, and professional associates—most likely they would not respond positively unless they actually felt better. Still, we recognize and understand the difference between this observation and real blinded

Table 9. The 6-Month Outcome Data From Available Paired Observations.

	Baseline	6 months			
	Mean ± SEM		N	*t*(*df*)	*P* value
Orthopedic					
Hip					
Pain	5.13 ± 0.64	3.47 ± 0.80	15	*t*(14) = 1.82	.09
HOOS	28.18 ± 3.76	21.20 ± 4.30	15	*t*(14) = 1.48	.16
AQoL	5.27 ± 0.89	3.53 ± 0.60	15	*t*(14) = 2.02	.06
Back					
Pain	6.18 ± 0.63	4.53 ± 0.66	15	*t*(14) = 1.81	.09
Oswestry score	9.73 ± 2.22	10.95 ± 1.65	20	*t*(19) = −0.56	.58
AQoL	7.30 ± 1.32	6.53 ± 0.95	20	*t*(19) = 0.78	.45
Foot and ankle					
Pain	5.25 ± 0.59	4.63 ± 0.76	8	*t*(7) = 0.65	.54
Foot and Ankle Outcome score	64.94 ± 6.45	52.44 ± 8.70	9	*t*(8) = 2.02	.08
Neck and back					
Arthritis	7.00 ± 0.41	3.50 ± 1.55	4	*t*(3) = 2.05	.13
Oswestry score	15.96 ± 4.07	15.00 ± 8.40	4	*t*(3) = 0.17	.88
AQoL	5.71 ± 2.79	6.25 ± 3.75	4	*t*(3) = −0.31	.78
Elbow and hand					
Pain	7.50 ± 1.33	2.67 ± 0.88	3	*t*(2) = 2.31	.15
DASH	17.11 ± 12.35	0.09 ± 4.89	4	*t*(3) = 1.87	.16
AQoL	2.00 ± 0.71	0.25 ± 0.25	4	*t*(3) = 2.33	.1

Note. HOOS = Hip Injury and Osteoarthritis Outcome Score; AQoL = Assessment of Quality of Life; DASH = Disabilities of the Arm, Shoulder, and Hand.

studies that will ultimately be needed to validate our observations. Still, we felt compelled to show enough evidence for safety and a sense of positive empiric outcomes before subjecting patients to placebo trials. Certain trends developed that have helped us gain a greater understanding of efficacy of SVF deployment. In the area of orthopedics, many of the conditions involved arthritic joints with cartilage deterioration. It appeared that as long as there was some cartilage present in the joint, SVF deployment could be effective. In a few cases where cartilage had been completely missing, for example, cases following arthroscopy and Marcaine injection where complete cartilage deterioration resulted,[18] SVF proved ineffective. Nonetheless, SVF effectively reversed most orthopedic conditions involving inflammation or tissue degradation as long as some structure was present. Patients who were missing complete ligaments or had had multiple surgeries were less likely to show a positive response. Despite large numbers of intra-articular deployments, no joint infections were reported. There were 3 cases of immediate post-deployment reactive (culture negative) inflammatory synovitis in knees that were self-limited and responded well to intra-articular steroid administration.

It should further be noted that though some of our patients had deployment with platelet rich plasma (PRP) added to the SVF because it has commonly been suggested that this was necessary for growth factors or other mechanical properties that they possessed, the vast majority of our patients were simply treated with adipose-derived SVF alone and clinically did well. Our study found no evidence suggesting an additional benefit to adding PRP to intra-articular injections. The suggestion is clear—that the inflamed or damaged tissue probably provides sufficient cytokine signals to direct the stem cells in SVF to initiate healing or in addition the SVF has adequate growth factors contained within.

Although the preponderance of outcomes data in this series was orthopedic and those patients (mostly osteoarthritis) responded uniformly well with their inflammatory and degenerative conditions, a number of non-orthopedic conditions were also treated. In the non-orthopedic conditions, we were able to see a number of positive responses in patients with ischemic cardiomyopathy as well as improvement in lung function in many cases of chronic obstructive pulmonary disease. A number of interesting findings occurred in the urologic area with positive responses seen in Peyronie's disease[23] and interstitial cystitis. The area of neurological disorders represents a variety of conditions that appear responsive to SVF treatment. In the area of stroke, traumatic brain injury and cerebral palsy, these all have the similarity of vascular injury resulting in cellular degradation with neurological damage. Some positive clinical responses were seen in all of these categories even in late appearing cases. One might hypothesize that early intervention would be much more effective to prevent scar tissue formation by actually repairing like tissue and blood vessels as soon as

Table 10. The 6-Month Outcome Data From Available Paired Observations.

	Baseline	6 months			
	Mean ± SEM		N	*t*(*df*)	*P* value
Non-orthopedic					
Erectile dysfunction					
Orgasmic	7.17 ± 0.69	7.56 ± 0.82	9	*t*(8) = −0.65	.54
Erection	13.44 ± 2.00	17.00 ± 2.59	9	*t*(8) = −3.83	.005
Sexual desire	8.17 ± 0.67	8.78 ± 0.46	9	*t*(8) = −1.02	.34
Intercourse satisfaction	6.05 ± 1.46	7.89 ± 1.78	9	*t*(8) = −2.19	.06
Overall satisfaction	4.28 ± 0.64	7.00 ± 1.01	9	*t*(8) = −3.54	.008
AQoL	2.06 ± 0.72	0.78 ± 0.32	9	*t*(8) = 1.48	.18
Interstitial cystitis					
Pain	6.70 ± 0.69	3.10 ± 0.86	10	*t*(9) = 4.11	.003
PUF score	22.54 ± 1.93	13.79 ± 1.98	12	*t*(11) = 4.20	.001
O'Leary Sant score	26.54 ± 1.82	12.08 ± 2.01	12	*t*(11) = 6.20	<.001
AQoL	5.03 ± 1.53	3.88 ± 1.29	12	*t*(11) = 1.06	.31
Peyronie's disease					
EHGS	2.33 ± 0.33	3.00 ± 0.00	3	*t*(2) = −2.00	.18
Psychological score	11.93 ± 1.89	8.20 ± 1.20	5	*t*(4) = 3.19	.03
Penile pain	4.37 ± 1.58	2.40 ± 1.03	5	*t*(4) = 1.33	.25
Bother score	7.63 ± 0.90	5.80 ± 1.28	5	*t*(4) = 2.10	.1
PDQ	23.93 ± 2.15	16.40 ± 2.16	5	*t*(4) = 2.55	.06
Neurologic					
AQoL	10.86 ± 1.94	7.91 ± 1.05	21	*t*(20) = 1.99	.06
Autoimmune					
Pain	4.17 ± 1.11	3.67 ± 0.92	6	*t*(5) = 0.32	.77
AQoL	6.73 ± 1.12	5.91 ± 1.38	11	*t*(10) = 0.60	.56
Cardiac					
Minnesota	34.0 ± 15.74	8.0 ± 6.04	4	*t*(3) = 1.27	.29
AQoL	2.25 ± 1.11	1.50 ± 1.19	4	*t*(3) = 0.60	.59
Pulmonary					
AQoL	6.58 ± 0.83	6.67 ± 1.09	12	*t*(11) = −0.09	.93

Note. AQoL = Assessment of Quality of Life; PUF = Pelvic Pain and Urgency/Frequency Patient Symptom Scale; EHGS = Erectile Hardness Grading Scale; PDQ = Peyronie's Disease Questionnaire; Minnesota = Minnesota Living With Heart Failure Questionnaire.

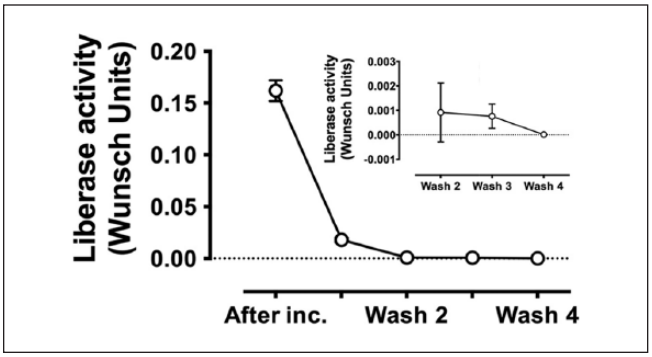

Figure 4. Residual collagenase measured with Cedex Hi-Res System following initial incubation and the 4 serial dilutions in a 50-cc syringe using D5LR.

possible (ie, closer to the acute event). In some cases such as in multiple sclerosis, immune modulation was probably also responsible, as was cell repair or regeneration, for the clinical improvements seen. For the same reason, SVF appeared to improve many of the autoimmune conditions treated in this series. Many of these patients required additional treatments over time. Clearly, this is an area of promise that needs rigorous evaluation. In recent animal (rat model) research conducted by Sean Berman[24] (manuscript in preparation), controlled concussions induced in rats with the D-Actor Shockwave (Storz Medical AG, Tägerwilen, Switzerland) device produced a consistent negative effect on both memory and motor skills. The IV deployment of SVF immediately following these induced concussions showed mitigation of these effects with the best outcomes coming closer to the acute injury. This has been postulated to occur because of an anti-inflammatory effect of SVF on the cytokine cascade and/or from cytokine-induced angiogenesis restoring vascular integrity to the neural system.

The relationship between adult mesenchymal stem cells and cancer has been evaluated and no clear linkage between cell therapy and malignancy in humans has been established.

However, the incidence of teratomas associated with the deployment of induced pluri-potential stem cells as well as embryonic cells has been well described.[25] Eleven patients out of 1524 (age range 18-90+) who received SVF deployment in this study reported development of malignancy at some period in time following their SVF deployment with 5-year follow-up surveillance. One patient was diagnosed with both skin cancer and breast cancer. One patient was diagnosed with skin cancer only 3 days following SVF deployment and therefore it was considered unrelated to cell therapy. One patient developed basal cell carcinoma of the nose 50 months after treatment. All patients either had no therapy (observation of focal prostate cancer) or resection and/or radiation resulting in definitive treatment of the malignancy. No direct correlation between SVF deployment and the incidence of any specific types of malignancy could be identified. The low numbers of cancers detected in this study over 5 years suggests that SVF did not appear to promote malignancy in this patient population. Patients will continue to be monitored on a yearly basis to collect additional information.

Last, it is notable that IV infusion of filtered SVF did not result in additional morbidity. This is the first study of its kind to be published that specifically addresses the safety of IV deployment.

Study Limitations

There was a low follow-up rate, explainable by no paid incentive. One of the limitations of studies evaluating surgical procedures like SVF deployment is the lack of a control arm, but that would require that some patients receive placebo SVF. This has ethical implications as the patients are undergoing a surgical procedure to procure their SVF rather than opening a bottle to receive a drug. Having said that, we have initiated a separate protocol trial for knee treatment using a placebo arm.

Conclusion

On a final note, regardless of any potential controversy surrounding the deployment of adipose-derived SVF, we have developed a nearly closed system following the surgical procurement of lipo-aspirate with an excellent safety profile that appears to provide an abundance of regenerative cells that can potentially mitigate a variety of degenerative conditions. It needs to be noted that regardless of one's actual system for processing cells, there is absolutely no such thing as a completely closed point-of-care system where liposuction is involved. However, in compliance with 21 Code of Federal regulations part 1271 mandating that the FDA prevent the transmission of communicable disease in areas of tissue transfer, aside from the obvious possibility of patient contamination from one's own infectious agents or normal acceptable air (environmental) exposure that occurs with every surgical procedure, there appears to be no additional risk of communicable disease transmission.

Furthermore, all of us involved in this research network activity of deploying cells and collecting data have been gratified by a large percentage of sincerely appreciative patients. We are confident that the medical and scientific communities will continue to advance cellular therapies and likely find more advanced cell lines or delivery mechanisms. This procedure found its origins in cosmetic/plastic surgery via liposuction. It is exciting that we can use part of our plastic surgical skills working together with a variety of other disciplines to further advance patient care beyond the arena of purely cosmetic or reconstructive surgery. There is no need to limit our surgical skills to purely aesthetic cases. Indeed, many of our affiliates have cosmetic/plastic surgeons as a center of their network of doctors and have found this new aspect of their careers to be incredibly rewarding. We believe we have entered a new era of medicine and the cosmetic/plastic surgeon can play a significant role in advancing cellular therapy.

Although we agree that double-blinded studies would eventually be required to disprove any placebo effect, we believe it is important to demonstrate that there are minimal adverse events associated with SVF treatments and that the risks are acceptable, primarily being related to the method of harvesting and deployment. We can conclude that the deployment of SVF via IV, intra-articular, and into soft tissue is overall safe and well tolerated. In particular, improvement in pain scores and quality of life ratings of treated musculoskeletal conditions served to demonstrate this particularly well. Some conditions had a low follow-up rate making a true treatment effect difficult to evaluate. More stratified data and controlled studies are necessary to investigate treatment outcome for these conditions.

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Declaration of Conflicting Interests

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References

1. Centeno CJ, Al-Sayegh H, Freeman MD, Smith J, Murrell WD, Bubnov R. A multi-center analysis of adverse events among two thousand, three hundred and seventy two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions. *Int Orthop*. 2016;40:1755-1765.
2. Riordan NH, Ichim TE, Min WP, et al. Non-expanded adipose stromal vascular fraction cell therapy for multiple sclerosis. *J Transl Med*. 2009;7:29. doi:10.1186/1479-5876-7-29.
3. Zuk PA, Zhu M, Mizuno H, et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. *Tissue Eng*. 2001;7(2):211-228. doi:10.1089/107632701300062859.
4. Yoshimura K, Sato K, Aoi N, et al. Cell-assisted lipotransfer for cosmetic breast augmentation: supportive use of adipose-derived stem/stromal cells. *Aesthetic Plast Surg*. 2008;32:48-55.
5. Cayci C, Carlsen BT. Osteoarthritis of the wrist. *Plast and Reconstr Surg*. 2014;133(3):605-615. doi:10.1097/01.prs.0000438463.90968.d6.
6. Chang H, Do BR, Che JH, et al. Safety of adipose-derived stem cells and collagenase in fat tissue preparation. *Aesthetic Plast Surg*. 2013;37(4):802-808. doi:10.1007/s00266-013-0156-7.
7. Pak J. Regeneration of human bones in hip osteonecrosis and human cartilage in knee osteoarthritis with autologous adipose-tissue-derived stem cells: a case series. *J Med Case Rep*. 2011;5:296. doi:10.1186/1752-1947-5-296.
8. Pak J, Lee JH, Lee SH. Regenerative repair of damaged meniscus with autologous adipose tissue-derived stem cells. *Biomed Res Int*. 2014;2014:436029. doi:10.1155/2014/436029.
9. Rodriguez JP, Murphy MP, Hong S, et al. Autologous stromal vascular fraction therapy for rheumatoid arthritis: rationale and clinical safety. *Int Arch Med*. 2012;5:5. doi:10.1186/1755-7682-5.
10. Wang ZX, Cao JX, Li D, et al. Clinical efficacy of autologous stem cell transplantation for the treatment of patients with type 2 diabetes mellitus: a meta-analysis. *Cytotherapy*. 2015;17(7):956-968. doi:10.1016/j.jcyt.2015.02.014.
11. Xia P, Wang X, Lin Q, Li X. Efficacy of mesenchymal stem cells injection for the management of knee osteoarthritis: a systematic review and meta-analysis. *Int Orthop*. 2015;39(12):2363-2372. doi:10.1007/s00264-015-2785-8.
12. Black LL, Gaynor J, Gahring D, et al. Effect of adipose-derived mesenchymal stem and regenerative cells on lameness in dogs with chronic osteoarthritis of the coxofemoral joints: a randomized, double-blinded, multicenter, controlled trial. *Vet Ther*. 2007;8(4):272-284.
13. Guo J, Nguyen A, Banyard DA, et al. Stromal vascular fraction: a regenerative reality? part 2: mechanisms of regenerative action. *J Plast Reconstr Aesthet Surg*. 2016;69(2):180-188. doi:10.1016/j.bjps.2015.10.014.
14. Nguyen A, Guo J, Banyard DA, et al. Stromal vascular fraction: a regenerative reality? part 1: current concepts and review of the literature. *J Plast Reconstr Aesthet Surg*. 2016;69(2):170-179. doi:10.1016/j.bjps.2015.10.015.
15. Michalek J, Moster R, Lukac L, et al.Autologous adipose tissue-derived stromal vascular fraction cells application in patients with osteoarthritis [published online ahead of print January 20, 2015]. *Cell Transplant*. doi:10.3727/096368915X686760.
16. Benoit E, O'Donnell TF, Patel AN. Safety and efficacy of autologous cell therapy in critical limb ischemia: a systematic review. *Cell Transplant*. 2013;22(3):545-562. doi:10.3727/096368912x636777.
17. Bhansali A, Asokumar P, Walia R, et al. Efficacy and safety of autologous bone marrow-derived stem cell transplantation in patients with type 2 diabetes mellitus: a randomized placebo-controlled study. *Cell Transplant*. 2014;23(9):1075-1085. doi:10.3727/096368913x665576.
18. Ma XR, Tang YL, Xuan M, Chang Z, Wang XY, Liang XH. Transplantation of autologous mesenchymal stem cells for end-stage liver cirrhosis: a meta-analysis based on seven controlled trials. *Gastroenterol Res Pract*. 2015;2015:908275. doi:10.1155/2015/908275.
19. Sun X, Ying J, Wang Y, et al. Meta-analysis on autologous stem cell transplantation in the treatment of limb ischemic. *Int J Clin Exp Med*. 2015;8(6):8740-8748.
20. Van Pham P. Clinical trials for stem cell transplantation: when are they needed? *Stem Cell Res Ther*. 2016;7:65. doi:10.1186/s13287-016-0325-0.
21. Breu A, Rosenmeier K, Kujat R, Angele P, Zink W. The cytotoxicity of bupivacaine, ropivacaine, and mepivacaine on human chondrocytes and cartilage. *Anesth Analg*. 2013;117(2):514-522. doi:10.1213/ANE.0b013e31829481ed.
22. See JR, Ling D. Addendum. History of adipose derived stromal vascular fraction stem cells. In: Berman M, Lander E, eds. *The Stem Cell Revolution*. Bloomington, IN: AuthorHouse; 2015:103-116.
23. Lander EB, Berman MH, See JR. Stromal vascular fraction combined with shock wave for the treatment of Peyronie's disease. *Plast Reconstr Surg Glob Open*. 2016;4(3):e631.
24. Berman S, et al. Summary of acoustic shock induced concussion treated with SVF in rat model, March 2016. Preclinical study, Celavie Biosciences, LLC California State University, Northridge, CA, October 2015.
25. Riggs JW, Barrilleaux BL, Varlakhanova N, Bush KM, Chan V, Knoepfler PS. Induced pluripotency and oncogenic transformation are related processes. *Stem Cells Dev*. 2013;22(1):37-50. doi:10.1089/scd.2012.0375.

Author Biographies

Mark Berman, MD, FACS, the 2010 president of the AACS, following years of work with adipose transplantation, evolved to using adipose for regenerative cells. Along with Dr Lander, he cofounded the Cell Surgical Network to advance adipose stem cell therapy.

Elliot Lander, MD, FACS, recently voted one of the top 5 physicians in the Palm Springs desert area, a board certified urologic surgeon, began studying safety and efficacy of autologous adipose derived cells with Dr Berman in 2010. The Cell Surgical Network research group that was founded along with Dr Berman has now treated more than 6000 patients around the world.