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Adipose-derived stromal vascular fraction (SVF) cells in the treatment of rheumatoid arthritis of the hand

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Abstract

Objective: **Rheumatoid arthritis of the hand is debilitating and difficult to manage, with medical therapies having many side effects. Control of inflammation using autologous stromal vascular fraction (SVF) cells offers a possible alternative to drug therapy. The autoimmune process of RA involves the production of inflammatory cytokines from Th1/Th17 cells. SVF contains adipose-derived stem cells (ADSCs). Via their release of paracrine factors, ADSCs reduce inflammation and enhance Treg cell function in collagen-induced arthritis. Specific inhibition of Th1/Th17 cells by ADSCs has been shown. Local infiltration of SVF is a rational strategy for treatment of the hand. We aimed at demonstrating safety and efficacy of autologous SVF in controlling symptoms of small joint RA of the hands.**

Patients and Methods: **Five female patients with chronic RA of five+ years duration and no steroid use were chosen. Lipoaspirate was processed to produce SVF with $238x10^5$ and $895x10^5$ viable cells. 1 cc of suspension was injected intra- and peri-articularly to all 15 joints with 10 cc to the dorsum. Serial measurements were performed in a 6 months follow-up: functional hand score (FHS: pain, stiffness and activities); visual analog score (VAS: pain intensity); and dynamometry (grip strength).**

Results: **Percentage change from baseline at six months for FHS score and VAS score was 91.3% and 91% respectively showing almost complete remission of osteoarthritic pain. The average grip strength increased 59%. Cell dose was not age-related but did vary with disease chronicity. The degree of improvement was not dose-related.**

Conclusions: **This first-in-man use of fresh, non-fractionated, non-expanded SVF shows that intra-articular injection is safe. Minimal dose/hand should exceed 3x106 cells. Data are strongly suggestive of significant therapeutic effect for small joint arthritis.**

Introduction

Rheumatoid arthritis (RA) is a chronic disease that affects multiple joints, causing pain, loss of function, and disability. Approximately 1% of the population is afflicted at an average age of 56 years for men and 54 years for women, with females being more frequently affected at a ratio of 3:1.[1] RA typically attacks small diarthrodial joints. It is particularly devastating for the hand, causing painful flexion and opposition, affecting multiple functions critical for daily activities. Medical management strategies for rheumatoid arthritis of the hand continue to be problematic, each regimen being associated with significant side effects[2]. The pathology of RA is biphasic, beginning with the development of autoimmunity to collagen in the joints, followed by inflammation and tissue destruction. Primary actors in this process are Th1 and Th17 cells which produce inflammatory chemokines and mediators, which

attract polymorphonuclear leukocytes and macrophages into the joint. The ensuing cascade of inflammatory factors (cytokines and free radicals) is tissue destructive. Stromal and vascular fraction nucleated cells (SVF) are readily obtained via liposuction and processing using enzymatic digestion and centrifugation of adipose lipoaspirate[3]. SVF is a heterogeneous population of mono-nucleated cells that include adipose-derived stem cells (ADSCs) of mesenchymal phenotype, endothelial progenitor cells (EPCs), and pericytes[4-6]. After processing, SVF can be transplanted into the target tissue via local injection. Mesenchymal stem cells (MSCs), when implanted, exert many local effects including tissue regeneration, neovascularization, anti-inflammation, and the control of fibrosis. The principal mechanism of action is via paracrine elaboration of multiple growth factors and cytokines[7]. The safety and efficacy of *culture-expanded* ADSCs derived from SVF for the treatment of chronic limb ischemia (CLI) has been documented[8,9]. Carstens et al[10] reported the use of *non-culture-expanded*, non-fractionated SVF administered at the point-of-care for CLI for the induction of in-situ angiogenesis and wound-healing. The antifibrotic effects of SVF in the treatment of subcutaneous fibrosis after burn injuries and skin graft donor sites have been documented as well[11-13]. Reports documenting the treatment of osteoarthritis with bone marrow stem cells, BMSCs, and adipose-derived stem cells, ADSCs[14,15], support the concept that such therapy, when applied for hand arthritis, has the potential for pain relief and perhaps the regeneration of articular cartilage[16,17]. The effects of SVF on rheumatoid arthritis have not been previously documented in humans. ADSCs have been shown *in vitro* to reduce inflammation and enhance Treg cells in rheumatoid arthritis[18-20]. Strategies for the treatment of rheumatoid arthritis have been tested in the murine model of collagen-induced arthritis (CIA). This condition is produced by subcutaneous injection of avian (chicken) type II collagen into mice. The rationale for this treatment is predicated on: (1) the inhibition of inflammatory autoimmune responses; (2) enhancing the immunosuppressive function of Treg cells[21,22]. Allogenic BMSCs induced a clone of Treg cells and suppressed the development of CIA[23]. ASCs have also been shown to induce a different clone of Treg cells that decreased the expansion of antigen-specific Th1 and Th17 cells and produced the inhibitory immunoregulator IL-10. Given these results and given the safety profile of SVF cells administered intra-articularly and subcutaneously, a decision was taken to carry out an open label, non-randomized study. The objective of this study was to assess the safety and feasibility of non-culture-expanded, adipose-derived SVF cells administered intra-articularly and peri-articularly in five patients with symptomatic rheumatoid arthritis of the hands. The study was performed at the teaching hospital HEODRA of the National Autonomous University of Nicaragua in León. Our results demonstrate a significant therapeutic effect in the reduction of osteoarthritis pain in the small joints of the thumb and fingers.

Materials and Methods

Ethics statement

This study was approved by the Medical Ethics Committee of UNAN-Leon and by the Ministry of Health of Nicaragua (MINSA). The procedures followed were in accordance with the Ethical Standards of the Responsible Committee on Human Experimentation (Institutional and National, Universidad Nacional Autónoma de Nicaragua - Leon) and the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all participants in accordance with standards of MINSA and the World Health Organization, and included consent to publish this study in all formats.

Study design and patient selection

Five female patients with symptomatic rheumatoid arthritis of the hands were admitted to the study. The criteria for inclusion were: documented rheumatoid arthritis affecting both hands for more than one year. Criteria for exclusion were: use of steroids, unstable cardiovascular disease at the moment of enrollment, smoking and/or the presence of chronic pulmonary disease, ongoing infection and/or sepsis, and uncontrolled diabetes.

Procedures: SVF processing, and implantation

Collection and processing of SVF

The lipoaspirate was collected into a sterile tissue-processing canister (GID SVF-1, Louisville,

CO, USA) for tissue dissociation and processing under closed conditions at all times, following the manufacturer's instructions. It was first washed three times with sterile Lactated Ringer's solution (at 39°C) to remove erythrocytes, leukocytes, and oils. It was then dissociated with GMP-grade collagenase (GIDzyme, GID, Louisville, CO, USA) with an additional 125 ml of additional Lactated Ringer's solution, at a concentration of 200 CDU/ml of total volume was added to the adipose tissue with collagenase enzyme (Worthington CLS-1, Lakewood, NJ, USA) at a concentration of 200 CDU/ml of total volume. The collagenase was injected into the cannister via a sterile 0.22 micron filter (Millex-MP, Millipore, Billerica, MA, USA). The mixture was dissociated for 40 minutes by placing on an incubated benchtop orbital shaker table (MaxQ 4450, Fischer Scientific, Waltham, MA, USA) at 37°C and 150 RPM. After dissociation, human albumin solution (Baxter HealthCare, Deerfield, IL, USA) was added to achieve a concentration of 2.5% then centrifuged for 10 minutes at 800 g. The resulting SVF cell pellet at the bottom of the device was removed using a 6-inch needle (Abbocath-T, Hospira, Sligo, Ireland) connected to a 20 cc syringe with 15 ml Hartmann solution. 10 microliters of SVF were taken from the final suspension and submitted for differential staining. Two samples were then passed through an image cytometer (ADAM MC, Portsmouth, NH, USA) for counting of nucleated cells and to assess cell viability.

Administration of autologous SVF cells

The total volume of the SVF suspension was determined based on the number of joints involved, these being per hand: 15 interphalangeal and metacarpophalangeal joints, with the wrist joint space considered as a single confluent space. Using a 23-gauge needle, the cell suspension was then administered into and around the following joints: thumb carpometacarpal (CMC), metacarpals (MPs), proximal interphalangeal (PIP), and distal interphalangeal (DIP). The intra-articular dosing was 0.25 cc. Periarticular dosing consisted of 0.25 cc on either side of the joint.

Methods of assessment

Each patient was examined and completed an assessment sheet for each hand before surgery, at 3 months postop and at 6 months postop.

- Visual Analog Scale (VAS) was used to measure pain, full-scale range from 0 to 10.
- Functional hand score (FHS) was used to measure three subscales: pain, stiffness, and difficulty with activities. The FHS had a total of 12 individual questions, each one scored from 1 (no symptoms) to 5 (extreme symptoms), with a minimum score of 12 and a maximum score of 60. The raw score was adjusted to a full-scale value of 100 points by multiplying by 1.66. The functional hand score assessment is shown in Figure 1.
- Grip strength for each hand was measured using a dynamometer, with the best result chosen from five consecutive attempts and recorded in kg (Figure 2).

Statistical considerations

The evaluation was a within-groups comparison of six-month scores relative to baseline measurements using a 2-tailed paired *t*-test. 95% confidence intervals and Cohen's d test were used to assess the size of the effect. No control group was used.

Results

Patient characteristics

Five female patients were enrolled with ages ranging from 38 years to 72 years. All were right-handed and ambulatory.

Safety

All liposuctions and SVF injections were well tolerated and uneventful. No complications attributed to the procedures were observed either short- or long-term, including excessive pain/discomfort, allergic/immune reactions, bleeding or infection (local or systemic). In particular, despite the injection of fluid beneath the scars, no skin necrosis occurred. The procedural data (cell yields, and viability) is presented in Table 1.

Patient demographics and cell data

The patients ranged in age from 39 to 72 years. All were right-handed. Two patients had concomitant arthritis of the shoulder with a significant limitation of motion in all planes. The biologic

GID

Adipose-derived SVF for Treatment of the Hand

Pain, Stiffness & Function of the Hand

Adipose-derived SVF

Site ID: _____ Visit: ☐Pre-Op ☐Surg ☐Day 2

Subject ID: _____ ☐6 wks ☐3 mos ☐6 mos

Left or Right hand: L R (circle letter) Date: __ __ / __ __ / 2016

1. In the last week think about the pain you had in your hand joints. Mark the level of pain on the line below.

No Pain — Moderate Pain — Unbearable Pain

0 1 2 3 4 5 6 7 8 9 10

Think of how your hand has felt in the last week. Circle the number that best answers the following questions with regard to that hand:

			None	Mild	Moderate	Severe	Extreme
PAIN – how much pain have you had in the last week …							
Pain	2	when opening a screw-top container or jar?	1	2	3	4	5
	3	when writing?	1	2	3	4	5
	4	when lying in bed at night (pain that disturbs your sleep)?	1	2	3	4	5
	5	when turning a key or turning a door knob?	1	2	3	4	5
	6	when grasping a handle to pull open a heavy door or car door?	1	2	3	4	5
STIFFNESS is the sensation of decreased ease in moving your hand. In the last week …							
Stiffness	7	How severe has the stiffness in your hand joints been right after waking up in the morning?	1	2	3	4	5
	8	How severe has the stiffness in your hand joints been later in the day, near the time you go to sleep?	1	2	3	4	5
DIFFICULTY – how difficult has it been to perform these daily activities in the last week …							
Function	9	when carrying a heavy object with a handle such as a heavy purse, briefcase, bucket, or shopping bag?	1	2	3	4	5
	10	when using scissors or tools that use a squeezing motion?	1	2	3	4	5
	11	when cutting your food with a knife?	1	2	3	4	5
	12	When buttoning a shirt or blouse?	1	2	3	4	5
	13	When tying shoes or tying a knot?	1	2	3	4	5

Administrator's Signature: _____ Date: _____

Hand Pain, Stiffness, & Function CRF Ver 1.0 Page 1 of 1

Figure 1. SVF intake form for hand study. Form allows for recording of visual anlog score (VAS) and the muti-dimensional functional hand score (FHS).

Figure 2. Dynamometer. Hand held instrument measures grip strength in kilograms and pounds. We used the average of five attempts per hand. Motivation and fatigue are factors requiring clinical support during testing to elicit maximum performance.

Table 1. Procedural data.

Age	Volume	Viability	Viable cells	Viable cells/gm	Comment
39	341 cc	87%	286,000,000	838,000	
42	408 cc	75%	129,000,000	316,000	childhood RA
58	458 cc	95%	410,000,000	895,000	
63	259 cc	84%	61,800,000	238,000	lupus, shoulders
72	330 cc	91%	261,000,000	790,000	shoulders

Note: Cell counts (Most common results: 400,000 – 600,000 cells/gm)
- 100,000 cells/gm of adipose à terrible, worst case, cold fluids, bad patient, messed up processing
- 200,000 cells/gm: low yield, bad patient, poor processing
- 400,000 cells/gm: common yield, decent processing
- 600,000 cells/gm: good yield, good processing, good patient
- 800,000 cells/gm: upper end of good yields
- 1,000,000 cells/gm: excellent processing on very good patients, but rare

productivity of three patients, as measured by the number of viable cells per gram of dry russue was within the expected range (500,000 to 1,000,000). This included our oldest patient, age 72 (Figure 3). As in our previous studies, the SVF cell count is not age-related, although in functionality the SVF cells may behave differently. Two of the patients, both with a significant medical background, had a low yield of viable SVF cells. Patient 2 had been in with ill since childhood and patient 4 had a history of active lupus.

Outcomes

Three assessment methods were used. The results are summarized in Table 2.

Functional hand score (FHS)

FHS was measured in three categories: pain, stiffness, and quality of function. Individual parameters were: night pain, pain with writing, pain on opening a jar, pain on turning a key, pain on opening a heavy (car) door, morning stiffness, evening stiffness, buttoning and unbuttoning a shirt, tying a not (as in shoes), using scissors, and holding a bag in the air (Figure 4).

- FHS is scored 0-100.
- All patients (100%) showed decreased arthritis pain in both hands as measure by the FHS. The mean preop FHS score was 50.1 and was reduced to a mean 6-month value of 4.4, for a reduction of 92%. No relapse occurred.
- The FHS revealed that the effects took place very rapidly. Patients uniformly confirmed sig-

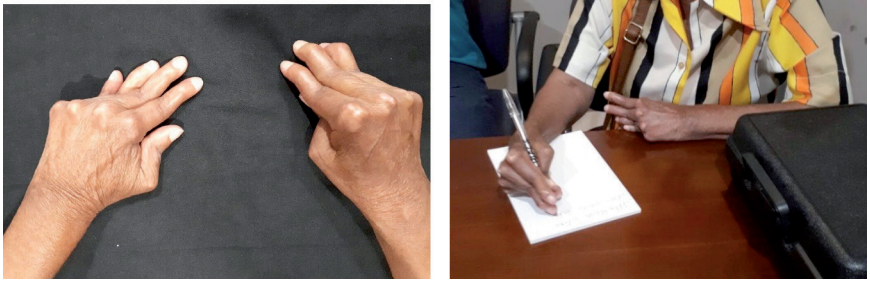

Figure 3. Key pinch restored. 72 your old woman with rheumatoid arthritic hand deformities. Was unable to write. At 3 months she recovered pinch and was able to write legibly. Although unable to use the dynamometer to assess grip strength she demonstrated ability to hold heavy objects in the air. Photos taken at 6 months.

Table 2. Hand score, visual analog pain score (VAS), and grip strength

Subject	Pre FHS	Post FHS	% change from baseline	Pre VAS	Post VAS	% change from baseline	Pre Grip (units)	Post Grip (units)	% change from baseline
1	41.6	2.1		7	0		21.0	28.1	
2	43.7	0.0		8	0		8.0	17.0	
3	79.0	12.5		3	1		17.5	36.0	
4	99.8	10.4		10	0				
5	33.3	4.2		5	1		24.0	34.0	
6	22.9	0.0		4	0		20.0	27.0	
7	12.5	0.0		5	1		0.0	17.0	
8	91.5	2.1		9	1		17.0	25.0	
9	85.3	10.4		8	0				
10	31.2	2.1		8	2		24.0	25.0	
N	10	10		10	10		88		
mean	50.1	4.4	91.3%	6.7	0.6	91.0%	16.4	26.1	59.0%
SD	31.7	4.8		2.3	0.7		8.4	6.9	

nificant improvement in the first two weeks postop. These trends were quantified at 12 weeks. For almost all parameters there was no significant change after 12 weeks. Fine motor skills did continue to improve in two patients and stiffness (both morning and evening) was progressively improved in two others.

Visual analog scale (VAS)

VAS uses universal diagrams of the face to represent pain states (Haefeli) (Figure 5).

- The VAS is a 0-10 ordinal scale.
- All patients (100%) demonstrated decreased arthritic pain in both hands.
- In 4/5 the final score achieved level 1. The remaining patient dropped her scores to level 2 per hand.

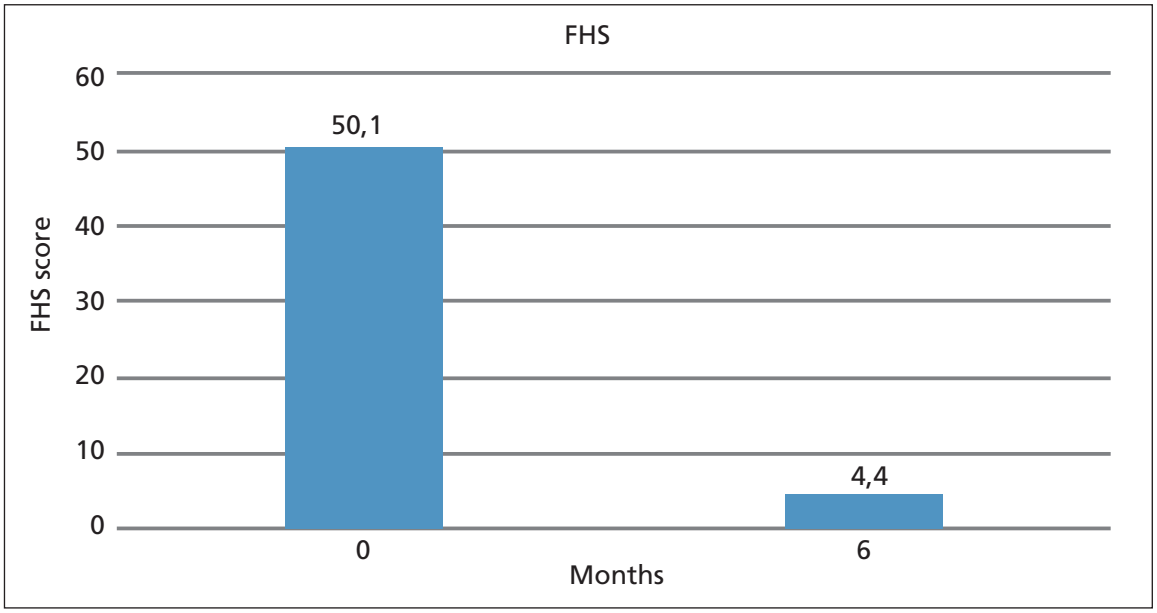

Figure 4. Functional hand score (FHS). The percentage decrease from baseline is 91.3%.

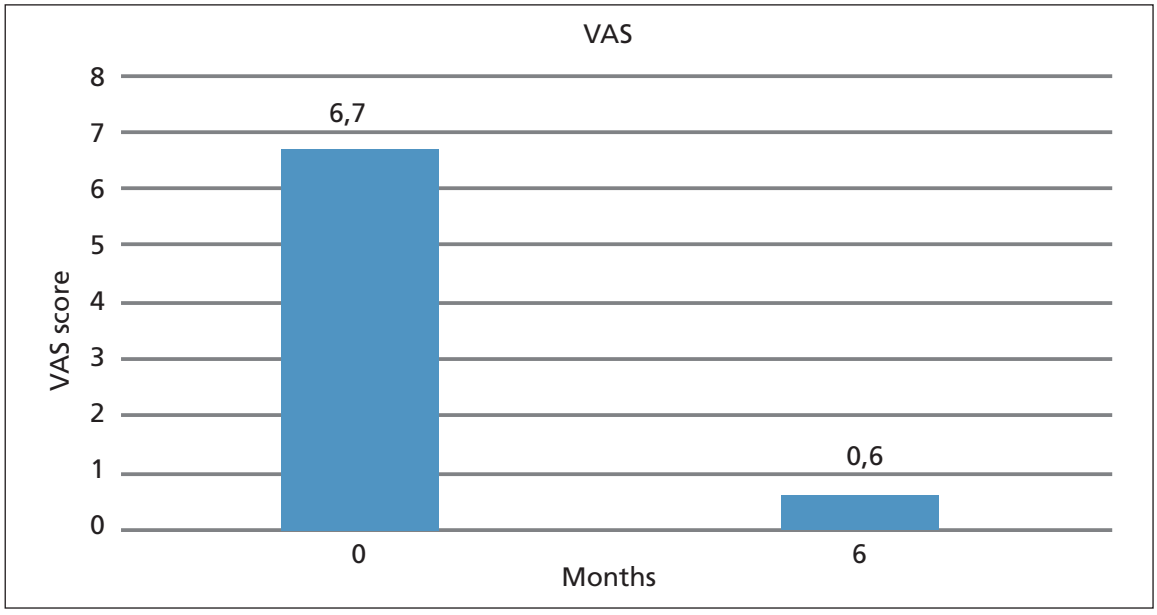

Figure 5. Visual analog score (VAS). The percentage decrease from baseline is 91%

- VAS is scored 0-10. The mean preop VAS score was 6.7 and was reduced to a mean 6-month value of 0.6, for a reduction of 91%. No instances of relapse occurred.

Grip strength (kg)

Grip strength was measured in each of 8 hands. Five attempts were made with each hand and the results summarized (Figure 6).

- All subjects capable of using the dynamometer 8/8 hands (100%) showed an increase in grip strength. One of the five patients could not perform this test due to deformity of her MP joints and fingers that prevented her from grasping the instrument.
- The mean preop value of 16.4 kg increased to a 6-month value of 26.1 kg, for an increase of 59%.

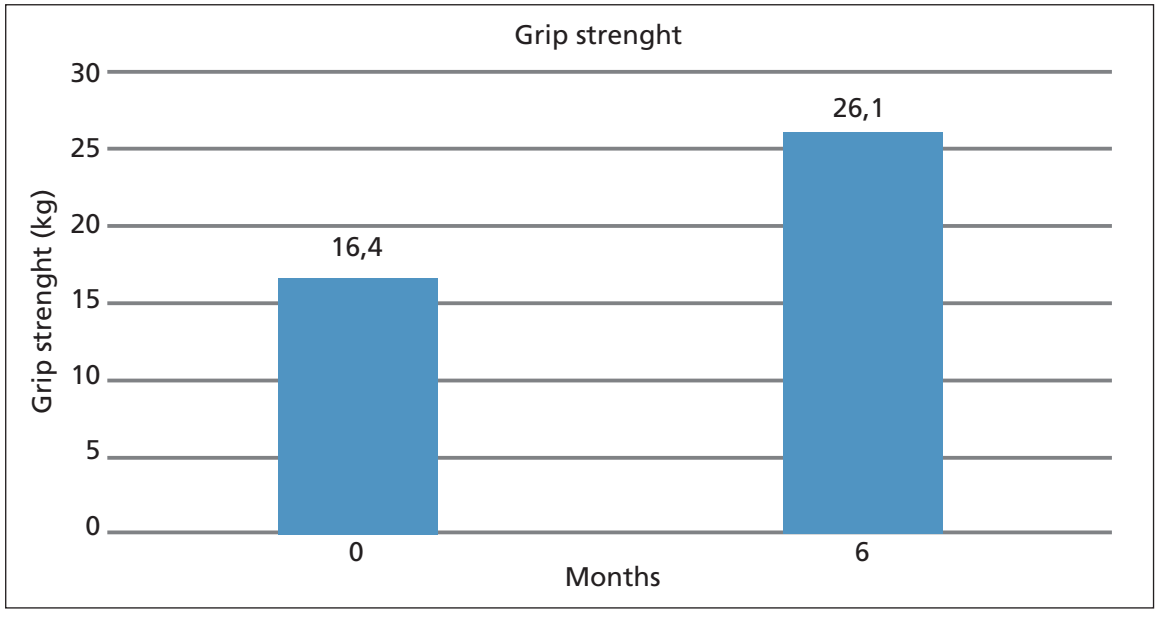

Figure 6. Grip strength. The percentage increase from baseline is 59%

Table 3. Statistical results for within-group comparison.

	Hand score	VAS	Grip strength
p-value (2-tailed)	<.001	<.001	.003
95% CI	29.5-69.9	4.3-7.9	5.0-14.4
Cohen's d	2.0	36	1.3

- Grip strength continued to improve over time for 4/5 patients, the fifth patient 's hands being too deformed to hold the dynamometer. Although this test is very quantitative, it is effort dependent and, by using five serial measurements per hand per session, some artifact may exist due to patient fatigue.

All three metrics showed strong statistical significance comparing 6-month scores relative to baseline scores (Table 3). The lower bound of the 95% confidence intervals for the difference score for each scale is greater than zero, showing superiority of the 6-month scores relative to the baseline scores. The effect size (Cohen's d) for both the FHS and the VAS is huge, and the effect size for the grip strength is very large, using Cohen's d-scale for effect size (Table 4).

In sum, the percentage change from baseline for the hand score and the VAS scores were 91.3% and 91%, respectively, indicating an almost complete remission of osteoarthritic pain at 6 months. The average grip strength change from baseline was an increase of 59% over baseline. All subjects (100%) showed decreased osteoarthritic pain in both the hand score and the VAS score. All subjects (100%) showed an increase in grip strength. One subject was not able to grasp the grip dynamometer (both left and right hands).

Chuck pinch restored

Video at 6 months demonstrating increase chuck pinch to turn the key to open a door handle **(**https://youtu.be/_jUcaM3GrSY**)**

Statistical Analysis

The study evaluates the change in pain scores relative to baseline measurements. No control group was used. Statistical evaluation is a within-groups comparison of the 6-month scores relative to the baseline as measured by the 2-tailed paired *t*-test. Table 3 shows the results of the within-groups testing for these three metrics. 95% confidence intervals are shown for the difference scores for each group. Table 4 explains how Cohn's d test is used to assess the size of the effect. All three metrics above showed strong statistical significance comparing 6-month scores relative to baseline scores. The lower bound of the 95% confidence intervals showed a 95% confidence that the means of the 6-month scores are less than the means of the baseline scores for both PSQ and VAS. There is a 95% confidence that the mean of the 6-month grip strength is greater than the mean of the baseline grip strength. By Cohen's definition, the effect size for PSQ and VAS strength is huge and for grip strength is very large.

Discussion

This first-in-man, small, open-label, non-randomized, no control group safety/ feasibility study describes clinical outcomes obtained when fresh, non- fractionated, not culture-expanded, adipose tissue-derived autologous SVF is administered to treat patients with rheumatoid arthritis of the hand. The rationale for using SVF instead of expanded ADSCs was twofold: first, to test the feasibility of a point-of-care administration of a cell-based therapy approach; and second, to take advantage of the presence of additional regenerative cell populations within the heterogeneous SVF. This study has recognizable limitations. It involves a small number of patients and is non-randomized. In addition, due to logistical difficulties in getting the patients to the center more frequently, the acquisition of intermediate data points was lim-

Table 4. Cohen's d Effect Size

d	0.01	0.2	0,5	0.8	1.2	2.0
Effect size	Very small	Small	Medium	Large	Very large	Huge

ited. Facilities for cell culture that would enable standardization of cell count per cc of injectate were not available. Each patient had a different number of viable cells per gram of dry fat. The oldest patient was 37, so no observations could be made regarding the decline in SVF cell populations with age...although this has been reported in the literature. The number of cells transplanted in each patient varied widely. Another drawback was the lack of standardized SVF dose. Given the natural history of each patient, the study does show that even the lowest dose achieved comparable clinical effects. Thus, although the threshold dose for response is unknown, all patients received an adequate amount of SVF. The cell dose administered (viable cells injected) was not correlated with the degree of clinical improvement, hence a dose-response correlation is difficult to ascertain. These results are comparable to other studies using SVF. Given that no standards currently exist regarding cell dose for small joints the variability of these patients served to perhaps determine a minimum number of cells that would function. All patients, however, responded strongly, indicating that the minimal dosage must involve lesser quantities of cells. SVF dosage for large joints such as knees (unreported data to date) indicates an acceptable clinical response to $15x10^6$ - $30x10^6$ cells. We think that for small joints total dosage of $5x10^6$ cells would be reasonable and could serve as a "floor" for future joint trials. Future studies, involving more rigorous designs, will incorporate such cell product characterization. The duration of the effect must also be determined and, if it proves to be long-term, investigation of the mechanism involved will have to be performed.

Conclusions

This study is, to the best of our knowledge, the first to report the use of fresh, non-fractionated, not culture-expanded, adipose-derived SVF has been used for the treatment of rheumatoid arthritis of the hand. This study demonstrates that:

- SVF harvest, processing and implantation is simple and quick.
- Intra-articular injection of SVF into the small joints of the hand is safe.
- A minimal dose per hand should exceed 30 x 10^6 cells per hand.
- The data are strongly suggestive of a significant therapeutic effect, specifically the reduction of osteoarthritic pain in the finger/thumb joints.

We conclude that implantation of adipose-derived SVF cells represents a biologically rational point-of-care cell-based therapy for symptomatic patients with rheumatoid arthritis of the hand. SVF implantation offers the possibility of relief from pain, while improving stiffness and range of motion. Use of this intervention early in the course of the arthritis could halt or retard the progression of the disease. In addition, it could improve the appearance and function of scars.

Declaration of funding interests

Devices and enzymes for this study were donated by the GID Group

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Conflict of Interest Statement

Michael Carstens consults for the GID Group. The remaining authors declare that they have no competing interests.

Ethical Committee

This study was approved by the Medical Ethics Committee of UNAN-Leon and by the Ministry of Health of Nicaragua (MINSA). The procedures followed were in accordance with the Ethical Standards of the Responsible Committee on Human Experimentation (Institutional and National, Universidad Nacional Autónoma de Nicaragua - Leon) and the Helsinki Declaration of 1975, as revised in 2000.

Informed Consent

Informed consent was obtained from all participants in accordance with standards of MINSA and the World Health Organization, and included consent to publish this study in all formats.

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