

Open Label Trial of Autologous Adipose-Derived Stromal Vascular Fraction Cell Injections to Treat Diabetic Peripheral Neuropathy: Safety and Clinical Improvement

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Abstract

Background

Diabetic peripheral neuropathy (DPN) is a serious complication of diabetes mellitus that can result in chronic pain and contribute to the development of diabetic foot ulcers (DFU). Patient reports from clinical trials using adipose-derived (AD) stromal vascular fraction cells (SVF) to treat DFU suggested concurrent improvement in DPN.

Methods

This was an open-label, pilot clinical trial to study the safety and potential clinical benefit of autologous ADSVF administered by local injection to treat DPN. Nine subjects with documented complete loss of protective levels of light touch sensation and vibration were treated. Sensory perception threshold levels (SPT) were measured by Semmes-Weinstein monofilaments while vibration perception threshold levels (VPT) were documented using a Horwell neuroesthesiometer. Eight of the nine subjects also had unilateral non-healing diabetic foot ulcers (DFU) despite standard local wound care for ≥ 3 months. Photos and ulcer size measurements were taken of the DFU. Subjects underwent a limited volume liposuction and then the lipoaspirate underwent enzymatic digestion to generate the autologous SVF cells. Forty million SVF cells (in 60 cc Ringer's Lactate) were implanted along the pedal arteries, into the dorsum of the foot and into the deep plantar space. Subjects were followed at 4, 12, 24, and 48 weeks for safety, changes in neuropathy, and wound healing.

Results

There were no severe adverse events related to SVF-treatment during the 48-week follow-up. However, one subject who entered the study with an ischemic toe lesion had progression of ischemia at 4 weeks resulting in extensive loss of plantar surface skin requiring digital amputations. One subject was lost to follow-up after 4 weeks. Perception thresholds improved in all available (7) subjects by 12 weeks. At the end of the study (48 weeks), 3 subjects regained normal levels of SPT, and 6 subjects had regained normal levels of VPT. In addition, wounds up to 32 cm² healed after local SVF treatment.

Conclusions

Local implantation of autologous SVF cells in this small subject population was safe and demonstrated potential clinical benefit for treating DPN. Larger clinical trials are needed to further document ADSVF safety and DPN efficacy.

Trial Registration

The trial was retrospectively registered in [clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT07553468) [NCT07553468].

Background

Diabetes mellitus (DM) is a challenge to global health systems, affecting an estimated 589 million (M) people and consuming at least \$1 trillion US dollars in expenditures [1 IDF]. Sequelae are common in the distal extremity, with peripheral neuropathy (DPN) affecting up to 50% of patients within the first 10 years of the disease. [2 Sun]. Underlying mechanisms suggested for DPN include glycation of proteins needed for neural function (advanced glycation end-products – AGEs), decreased expression of neurotrophic factors, production of reactive oxygen species (ROS), and microvascular disease with impaired blood circulation in diabetic nerves, among others [3 Javid]. Elevated glucose levels result in the release of excess ROS and upregulate transcription factors causing inflammation [3 Javid]. Studies in diabetic rats have linked ROS to the development of neuropathy and microvascular pathology. Oxidative stress-related deficits affect both nerve blood flow and nerve conduction velocity (NCV), as well as damage to neurons. Pro-inflammatory cytokines, interleukin (IL)-6, IL-1-beta, and tumor necrosis factor (TNF)-alpha, have been linked with reduced NCV and neuropathic pain in humans and animals [4 Doupis] with higher blood levels of IL-6, TNF-alpha, and C-reactive protein (CRP) reported in DPN patients compared to healthy controls. Therapies to modulate the pro-inflammatory state in DPN have been reported and appear promising. Neutralizing antibodies against these pro-inflammatory cytokines have been shown to have a beneficial effect on NCV and pain in animal models [5 Bonhof]. Additionally, the anti-inflammatory cytokines IL-4 and IL-10 seem to have DPN protective effects [6 Mulligan, 7 Clark].

DPN follows a progressive course in over 50% of patients, characterized initially by loss of pedal sensation, predisposing to failure to perceive traumatic injuries predisposes to ulceration [diabetic foot ulcers (DFU)], and the threat of limb loss [8 Bolton, 9 Volmer-Thole]. Current treatments for DPN are directed toward glycemic control and amelioration of neuropathic pain, when present. Neither of these strategies have been shown to reliably address neuronal damage [10 Chang]. DFU occur in 25% of all DM patients with resulting pain, infections, disability, and amputations.

In the United States the total medical cost for the management of diabetic foot disease adds \$9 to \$13 billion to the cost for management of DM alone [11 Armstrong]. DPN and DFU are particularly burdensome for resource-poor health systems, such as Nicaragua, where patient outcomes options are reduced to chronic pain, infection, or amputation. Given the role of DPN as the causative factor for pain and DFU, new strategies for its management are urgently needed.

Mesenchymal stromal/stem cells

The finding that multipotent stem/stromal cells (now called MSCs) derived from bone marrow (BM) could differentiate *in vitro* into various cell types raised the possibility that these cultured (manufactured) MSCs could be used to treat multiple diseases [12 Caplan]. MSCs from multiple sources (placenta, umbilical cord, adipose tissue, among others) have been shown to recognize sites of injury, “sense” the environment, and selectively respond through multiple pathways to support the remodeling/repair of injured tissues. *In vitro* expanded MSCs has shown great promise based on their ability to produce signaling molecules useful for regeneration. Many of these factors are proangiogenic (e.g., VEGF) and help induce the formation of new blood vessels, while other factors help in the repair process of injured

tissues [13 Caplan 2006]. Cell contact and paracrine factor secretion appear to be more relevant to tissue repair than the initial proposed mechanism of MSC differentiation [14 Caplan 2014].

There is abundant evidence from animal studies that MSC might have a role in the treatment of DPN. DM-related nerve damage in rats and mice has multiple components, including vascular insufficiency, hypoxia, oxidative stress, and a chronic heightened pro-inflammatory state [15 Vojttassek]. When human MSCs cultured from varying sources have been injected into animal DPN model systems, there is evidence of nerve regeneration and neuroprotection and an improvement in peripheral nerve function [16 Alizadeh]. The improvements in nerve function are considered to be secondary to the MSC secreted proteins to include angiogenic factors (e.g. VEGF) and various anti-inflammatory factors (e.g. IL-10) [17 Dama].

Only a few trials using MSC to treat DPN in humans have been reported. These have been recently reviewed using a meta-analysis of 7 methodologically-sound clinical trials (totaling 400 subjects) [18]. The clinical trials to date have used either BM mononuclear cells (which contain an MSC fraction) or umbilical cord MSC. Generally, the cells were injected intramuscularly in the index leg using a large total dose ($10^8 - 10^9$ cells). Follow-up periods ranged from 3–12 months. Cell therapy was considered safe with only mild – moderate swelling and pain at the injection sites which resolved over a few days. The studies reported benefits of improved nerve conduction velocities in both motor and sensory nerves, improved vibration perception testing (VPT), and in Toronto Clinical Scoring System scores. The review authors concluded that further studies using cellular therapy (to include different MSC types) in larger studies for longer follow-up periods should be conducted.

Disadvantages to the use of cultured or mobilized MSCs, regardless of tissue origin, include the time of harvest, mobilization, or Good Manufacturing Practice culture/manufacturing; the cost of the harvest, mobilization, or culture; and the potential for allergic reactions if the cell product comes from an allogeneic source [19 Mastrolia, 20 Gentile, 21 Elzenberger]. An autologous, adipose-derived (AD)-MSC containing product, termed AD stromal vascular fraction (SVF) represents an alternative treatment strategy that can be obtained and delivered as a point-of-care intervention.

Using an enzymatic processing approach, Brown et al. describe a closed-system method to harvest and process cells from adipose tissue that involves a limited lipo-aspiration procedure (100 cc); followed by washing to remove blood cells and debris; treatment with type I collagenase for collagen digestion; centrifugation, and then filtration of the cell suspension through a 400-micron mesh. The resulting cell pellet is collected, and the supernatant is discarded. The cell pellet is a heterogeneous mixture of fibroblasts, smooth muscle cells, stromal progenitor cells, endothelial precursor cells, tissue-resident macrophages, pericytes and preadipocytes [22 Bolton]. The lipo-aspirate harvest, SVF isolation and separation procedures can be conducted in less than 3 hours using a sterile disposable device, SVF-2 (GID BIO, Louisville, CO, USA) as a point of care procedure [23 Garza].

ADSVF and cultured AD-MSC are different cell products [24 Gentile Calabrese 2019]. Both work through cell-contact and secretory (paracrine) pathways; both have been shown to decrease inflammation,

decrease fibrosis and increase micro-capillary networks [25 Nguyen]. ADSVF has been shown to secrete numerous growth factors and cytokines, including vascular endothelial growth factor, transforming growth factor-1, hepatocyte growth factor, IL-10 and interferon-gamma [26 Guo]. In addition, SVF has been shown to induce M2 macrophages, further driving an anti-inflammatory environment [27 Zhu]. ADSVF has been used in multiple clinical trials by this study team and others to treat diseases to include: peripheral vascular disease [28 Carstens], DFU [29 Carstens], burn injuries [30 Fakiha], and systemic sclerosis [31]. SVF has been used in the United States under a Food and Drug Administration (FDA) investigational device exemption (IDE) to treat knee osteoarthritis (safe and with evidence of potential efficacy) [23 Garza] and has recently completed a pivotal clinical trial (> 150 subjects) for that indication.

This is the first report of the safety of autologous ADSVF cells delivered by injection to the lower leg to treat patients with DPN. In addition, the potential for DPN clinical benefit from SVF treatment was evaluated in this small, non-placebo-controlled, point-of-care clinical trial.

Methods

Study Design and Ethical Approval

The primary objective of this prospective, open-label, clinical study was to determine the safety of locally-injected autologous AD SVF cells in the treatment of DPN. The secondary objective was to document possible DPN treatment clinical benefit as measured by changes in sensory perception threshold (SPT) and/or vibration perception threshold (VPT). In addition, the effect of SVF treatment on non-healing DFU was measured (degree of wound closure over time). As all subjects were to undergo a surgical procedure (liposuction), the Nicaragua Ministry of Health (MINSa) requires that all subjects receive active treatment, that is, no untreated or placebo control subjects. Subjects were treated with a single dose of locally injected SVF cells and then followed out to 48 weeks.

The study was conducted within the National Health Care system at the academic hospital for the Universidad Nacional Autónoma: Hospital Escuela Oscar Danilo Rosales Argüello (HEODRA) in León. All clinical procedures were in accordance with the ethical standards of the Committee on Human Experimentation (Universidad Nacional Autónoma de Nicaragua - León) and the Helsinki Declaration of 1975, as revised in 2024. The study was approved February 22, 2022 by the MINSa Institutional Review Board [number DGD-NVSQ-197-02-22]. Informed consent (including data/images for publication) was obtained from all study participants. The trial was registered in clinicaltrials.gov [NCT07553468].

Subject Population

Patients with Type 2 DM and complaints of DPN were identified from community health centers of the Leon region, Nicaragua, and subsequently referred to the orthopedic service at the Leon University teaching hospital where they were screened for eligibility by the study orthopedic surgeon.

Inclusion criteria were: (1) male or female; (2) 30–70 years; (3) clinically stable diabetes; (3) presence of DPN as documented reductions in sensory perception threshold (SPT) and/or vibration perception threshold below protective levels; and (4) capacity to understand and provide informed consent. Existence of a unilateral chronic DFU was allowed.

Exclusion criteria were (1) presence of a disease prohibitive of surgical intervention, (2) smoking and/or substance abuse within 3 months of the onset of the study; (3) inability to fulfill the objectives and responsibilities of the study.

Nine patients were enrolled (convenience sample) and treated. Eight subjects had been previously hospitalized for non-healing wounds and discharged. The wounds had remained open for at least three months at the time of study enrollment despite standard of care treatment in Nicaragua which consisted of wet-to-dry dressings changes and encouragement to avoid weight bearing. Three subjects were considered candidates for amputation at the time of enrollment. Subject characteristics are listed in Table 1 (Results).

Baseline Studies

Subject intake consisted of informed consent, and history (with medications recorded) and physical exam. Baseline peripheral nerve measurements (described below) were conducted with two types of sensation representing two separate pathways being assessed in each patient – fine touch (anterior columns) and vibration (posterior columns). DFUs, when present, were measured and photographed. All baseline studies were conducted by the study orthopedic surgeon.

Sensory perception threshold. SPT reflects small nerve fiber integrity; alterations in this metric reflect the clinical severity of DPN. SPT is commonly measured with the Semmes-Weinstein monofilament method consisting of plastic fibers of decreasing diameters representing different degrees of force (grams) required to cause flexion of the fiber, thus documenting the threshold of sensation [32 Jeng]. Plantar innervation demonstrates a distal-proximal gradient of increasing thresholds, the smallest being those of the toes, followed by the metatarsal heads and then the heel [33 Hennig]. On this basis, a simplified system of SPT measurement was used, using 3 successive measurements on the heel. A diminished protective sensation at the heel occurs with a target force of 4–8 grams while loss of protective sensation is present at a target force of greater than or equal to 10 grams. [34 Nakamoto]

Vibration perception threshold. VPT is a measure of large nerve fiber integrity and is important in the assessment of DPN. VPT was assessed using the Horwell neuroesthesiometer (Algeos, Liverpool, UK) [37 Young, 38 Young]. An electric current mode varying from 0 to 50 volts (v) is converted into vibrations of 50 Hz and transmitted to the patient using a vibrating stylus which is applied perpendicular to the skin at defined points. In this study, baseline and sequential measurements of VPT were focused on the calcaneus. VPT responses were graded as normal (< 15v); or mild (15-20v), moderate (20-25v), or severe

(> 25v) vibration perception dysfunction [39 Azzopardi]. A diagnosis of DPN is supported by voltages $\geq$ 15.

Procedures

Acquisition and processing of SVF cells. For clarity, SVF cells are not a manufactured 'stem cell' product; no cell culturing or expansion are required. The technique of SVF harvest and processing has been described by Brown, et al [22 Brown]. Approximately 80–120 ml of abdominal fat was aspirated and collected into a sterile, closed-system, SVF-2 tissue container (GID BIO, Louisville, CO, USA). The lipoaspirate was washed to reduce erythrocyte and leukocyte cell load and then enzymatically treated to disaggregate the tissue. Adipocytes (in the supernatant) were separated from the nucleated stromal and vascular cells (in the cell pellet) using centrifugation. The SVF was isolated and separated at the point-of-care in less than 2 hours. The total nucleated cell count and SVF cell viability was determined using a fluorescence cytometer (LunaStem® Logos Biosystems, Annandale, VA). SVF from all subjects had a minimum of 80% cell viability. All subject lipoaspirates generated more than 40M SVF cells except for subject #2 whose lipoaspirate (for unexplained reasons) only yielded 20M SVF cells despite having an adequate lipoaspirate volume.

SVF cell injection. A volume of the autologous SVF suspension containing a dose of 40 million (M) SVF cells was suspended to a total of 60 cc Lactated Ringer's (LR) solution. In the 8 subjects with DFU, administration to the DFU / ankle was performed at four injection sites: (1) 20 cc into the dorsum of the foot (and dorsal wound bed), (2) 20 cc subcutaneously around the perimeter of the wound, (3) 10 cc along the tibialis posterior pathway at the ankle prior to entry into the plantar surface, and (4) 10 cc along the tibialis anterior / dorsalis pedis pathway from the ankle to the dorsum of the foot. The location sites of injection are presented in the Graphical Abstract. Subject #2 received 20M SVF in the same locations in a ratio of the above. In the one subject without a DFU, 15 cc of cells were placed dorsally, 25 cc to the plantar space, 10 cc along the tibialis posterior and 10 cc along the tibialis anterior/dorsalis pedis. All SVF cells were injected in a point-of-care setting within 30 mins of completing lipoaspirate acquisition and processing.

Postsurgical care. Lipoaspirate site and DFU (if present) were covered with gauze bandages. Patients were observed overnight in the hospital with vital signs and clinical observation for any potential (serious) adverse events [(S)AE] with emphasis on post-operative pain, bleeding and swelling.

Study Follow-up.

Post-intervention safety assessment. After hospital discharge, patients were followed for (S)AE by weekly telephone call for three weeks, and then with in-person visits at 4, 12, 24, and 48 weeks after treatment. (S)AEs were categorized and graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 [38].

Clinical benefit assessment. Subjects were evaluated with in-person visits at 4, 12, 24, and 48 weeks. Clinical benefit evaluations included history, physical exam, SPT and VPT (neuropathy), and wound healing (as described for Baseline Studies). Subject reports of time to wound healing (closed wound with no drainage) were tracked and confirmed at the next in-person visit.

Statistical Analysis

Primary Objective – Safety. The incidence of (S)AE were recorded and relationships between any (S)AE and the intervention were determined.

Clinical Benefit Objective. Subjects served as their own controls, i.e., baseline status versus outcomes at 48 weeks with regards to: (1) degree of DPN (SPT/ VPT). (2) DFU healing. The Wilcoxon Signed Rank Test was used to evaluate group response at each follow-up time point versus baseline SPT and VPT values. Wound healing (closed wound surface without drainage) was documented via measurements and photographic comparisons.

Results

Patient demographics, wound size and wound healing at 48 weeks

Nine patients with documented DPN, ages 43 to 56 years, were enrolled in this study with eight completing follow-up to 48 weeks as shown in Table 1. Subject #4 had an ulcer that penetrated from the dorsal surface through to the plantar surface. Subject #8 had a progressive ischemic insult to the foot at week 4, resulting in plantar surface skin sloughing (a wound of 112 cm²) and serial amputation of all digits. Only baseline SPT and VPT scores could be obtained for this subject. The subject was followed out to 48 weeks for treatment safety and DFU healing. Subject #9 was lost to follow-up after 4 weeks; data for this subject is included up to the time of lost to follow-up.

Table 1
Subject characteristics; wound size; wound closure.

ID	Age	Sex	Wound (cm ²) size Time of enrollment	Wound status - Subject reported time of closure
01	43	F	Neuropathy only	Not applicable
02	56	M	24	12 weeks
03	50	M	32	8 weeks
04	47	M	8 dorsal / 8 plantar; with wound core extending between the 2 surfaces	Dorsal surface – closed at 24 weeks Plantar surface - granulating at 48 weeks Wound (core) connecting the two surfaces – closed at 48 weeks
05	58	M	30	28 weeks
06	54	F	12	16 weeks
07	50	F	30	32 weeks
08	43	F	9	Progressive ischemia ◊ DFU increased to a total plantar surface area of 112 cm ² . Granulation tissue at 48 weeks.
09	56	F	20	Lost to follow-up

Safety

The surgical procedure was well tolerated by all patients. Patients were followed in the hospital for 24 hours with monitoring for potential (S)AE related to the SVF cell harvest procedure (bleeding) or any untoward reaction in the wound itself. Adverse events were limited to localized grade 1–2 post-operative swelling and pain. Symptoms resolved within 2–3 days.

After discharge, patients were contacted by telephone weekly for three weeks to assess for (S)AE and then seen in-person in the orthopedic clinic at the times indicated. At the 4-week follow-up, subject #2 was noted to have developed progressive ischemia of the (index) SVF-treated foot. The subject's foot ischemic injury progressed to extensive plantar surface skin sloughing (112 cm) and ischemic digits requiring serial amputations (Grade 4 SAE). The study physician did not consider the progressive ischemia and resulting damage to be SVF-treatment related but rather a result of progressive DM-related vascular disease. Subject #7 developed a new lateral surface first digit ulcer on the index foot after 24 weeks (Grade 3 SAE), while the index plantar DFU was healing. Based upon the location of the new lesion, the lesion was considered to be due to a new pressure surface and not a treatment-related SAE. There were no other skin events, infections, or amputations.

Neurologic response

The baseline neuropathy evaluations (SPT and VPT) in the 9 patients and respective changes over 48 weeks following SVF treatment are shown in Table 2. The seven evaluable subjects showed a change from significant impairment of SPT and VPT (baseline non-protective levels) to improved/normal protective levels of SPT and VPT as early as 12 weeks ($P = 0.018$ and $P = 0.022$, respectively, Wilcoxon Signed Rank Test) after autologous AD SVF treatment. as shown by. Furthermore, patients' SPT and VPT levels remained improved at the last follow-up point at 48 weeks ($P = 0.020$ and $P = 0.016$, respectively, Wilcoxon Signed Rank Test).

Table 2
Neurologic response, longitudinal SPT and VPT post-SVF treatment

Subject Number	0 weeks		4 weeks		12 weeks		24 weeks		48 weeks	
	SPT	VPT	SPT	VPT	SPT	VPT	SPT	VPT	SPT	VPT
01	300	50	10	35	4	15	4	10	4	10
02	300	50	10	40	2	10	2	10	2	10
03	300	50	300	45	10	35	4	10	4	10
04	300	50	300	50	10	45	2	15	2	10
05	300	50	300	10	10	40	2	10	2	10
06	300	50	10	50	10	40	10	15	10	15
07	300	37	300	35	10	30	4	10	4	10
08	300	50	ND	ND	ND	ND	ND	ND	ND	ND
09	300	50	300	50	ND	ND	ND	ND	ND	ND

SPT - measured in grams. Scores ≥ 10 grams indicate complete loss of protective sensation

VPT - measured in volts. Scores ≥ 25 volts indicate complete loss of protective vibration sense.

ND – not done. Subject #2 had progressive ischemia to the index foot. Subject #9 was lost to follow-up.

At entry, nine subjects had no protective sensation perception (light touch) as defined by the Semmes-Weinstein scale ≥ 10 grams. SPT was improved by Semmes-Weinstein monofiber testing at 12 weeks after SVF treatment in the seven available subjects. At 48 weeks, three subjects had achieved normal protective levels of light touch (2 grams) and four other subjects maintained their improved SPT. See Fig. 2.

Initial VPT likewise exceeded the protective vibration perception in all patients at baseline (scores ≥ 15 volts). By 12 weeks after SVF treatment, VPT scores were improved in the available subjects. Normal protective levels of vibration sense (10 volts) were achieved in four subjects by 24 weeks. By 48 weeks,

full protective levels were achieved in five of seven subjects with partial protection maintained in an additional subject. One subject did not achieve any level of protective vibration perception. See Fig. 3.

DFU healing response

All subject-reported wound closures and wound-closure time were confirmed at the next in-person follow-up visit (Table 1). Wound closure was achieved by 48 weeks in 7/7 patients (see Supplement for representative clinical cases). However, marked differences in the course of three subjects' DFU warrants further discussion.

- Subject #4 had a penetrating through and through plantar-dorsal wound at time of enrollment. The wound achieved full dorsal closure with stable plantar granulation at 48 weeks and a closed interior wound. He, unfortunately, developed a new progressive ulcer at 1 year (having completed the established study timeline of 48 weeks), complicated by infection, and at 14 months required an amputation.
- Subject #7 developed a new ulceration lateral to the original wound during the study period. The original ulcer closed at 32 weeks and the new ulcer site was covered with granulating tissue at the time of study closure.
- Subject #8, whose initial DFU was considered ischemic in origin, developed further ischemia in the foot which progressed within the first month resulting in subsequent skin slough involving entire plantar surface and requiring serial digital amputations. Despite these extensive wounds, the plantar surface of the foot achieved granulation skin coverage by 48 weeks. The study orthopedic surgeon considered these events to be a result of the natural DM foot disease course and not SVF-treatment related.

Discussion

Two clinical trials have been reported in PubMed (*English language*) examining the safety and efficacy of injected MSC for the treatment of DPN. Mao, et al, treated 168 subjects with DPN with intramuscular injections of autologous, G-CSF mobilized, BM mononuclear cells (which contain a MSC population) obtained by BM aspiration [39 Mao]. The BM mononuclear cells were isolated from the aspirate via Ficoll-Hypaque centrifugation. The harvested cells (dose not specified) were then injected into both thighs and legs (50 sites). All subjects were treated. All subjects had a neurologic exam and multiple nerve evaluations to include symptoms, light touch, vibration and nerve conduction studies (NCS). The study reported only mild swelling and pain at the injection sites as treatment-related AEs. The subjects reported symptom and peripheral stimulation improvement within one month of treatment and NCS velocity improved at the 3-month evaluation. NCS velocity remained significantly improved out to the last evaluation at 12 months, while symptoms and peripheral stimulation were significantly improved out to the 36-month (last) evaluation.

Gibbons, et al, reported on the use of commercial, cultured, allogeneic placenta-derived MSC (PDA-002) to treat DPN in 26 Type-2 DM subjects [40 Gibbons]. Three treatment arms were used: 3 million (M) cells; 30M cells; and placebo (vehicle control) administered as an intramuscular injection on treatment days 1, 29, and 57. Injections were administered in a single leg between the knee and ankle. Subjects were followed for 14 months. While there were multiple (serious) adverse events [(S)AE] in the study population, treatment-emergent (may or may not have been treatment-related) SAEs were limited to: infections (2 subjects), acute kidney injury (2 subjects), myocardial infarction (1 subject); and rotator cuff syndrome (1 subject). No significant differences in (S)AEs occurred between treatment arms. While multiple assays and questionnaires were used to evaluate treatment response, the study found no clinical meaningful changes to neurologic exam scores or symptom scores.

While the subject number in this study is too small to make definitive conclusions regarding, SVF cell treatment of DPN in this point-of-care, nine-subject study was shown to be well-tolerated and without any treatment-related SAE. Minor swelling and pain at the liposuction and injections sites were noted with resolution over the next 2–3 days post-procedure. In this high-risk DM population, one subject was enrolled with what was considered an ischemia-driven DFU. At the four-week follow-up, there was progressive ischemia to the index foot, ultimately requiring amputation of the digits, as presented above. Two subjects developed a new DFU lesion in the index foot after SVF treatment (one after the study end) as described above. The study orthopedic surgeon concluded that the subject's foot SAEs were due to progressive DM-related injury and not SVF treatment.

All subjects had complete absence of protective levels of both sensation and vibration at the time of enrollment. By 48 weeks after autologous SVF treatment, all subjects regained some degree of protective levels of SPT (3 subjects – normal levels) and/or VPT (6 subjects – normal levels). Based upon animal studies, this recovery of nerve function is hypothesized to be due to the secretion of nerve and vascular growth factors, in addition to anti-inflammatory paracrine factors. The combination of these factors support improved blood supply to the nerves, nerve healing, and a decrease in DM-induced pro-inflammation state damage [41 Li, 18 Alizideh].

In a rat model with streptozotocin-induced DM/DPN, a walking track analysis was conducted and compared across four groups of rats (1) non-DM rats; (2) DM-rats (diabetic control); (3) DM-rats subsequently treated with rat ADSVF along the sciatic nerve at 8 weeks after streptozotocin-induction; and (4) DM rats treated with PBS (placebo) along the sciatic nerve also at 8 weeks. The length of the walk footprint remained at baseline for the non-DM rats but became abnormal for all the DM rats at 8 weeks. At 12 weeks after DM-induction, walk footprint was still abnormal in the DM control/placebo rats; however, the walk pattern in the SVF treated rats was significantly improved ($p=.005$). Rats were sacrificed after 12 weeks, and the sciatic nerves were examined. The sciatic nerve was abnormal in the diabetic-control and placebo-control streptozotocin-treated rats with a decrease in the number and diameter of nerve fibers, along with a decrease in the thickness of myelin. In contrast, the SVF-treated rats had a near normal sciatic nerve, suggesting that the SVF may have promoted nerve regeneration. [42 Karatan].

The rate of improvement in SPT/VPT (3 months) after autologous ADSVF treatment in this study is similar to the rate of improvement seen by Mao et al [39 Mao] when using autologous, G-CSF mobilized, BM mononuclear and MSC population. The dose required for maximum benefit is unknown. Gibbons et al used up to 30M cultured placenta-derived stem cells injected three times with no apparent DPN benefit [40 Gibbons]. The choice of 40M SVF cells as a single dose for this study was based on the study team's experience in treating DFU with ADSVF [29 Carstens]. It is of interest to note that Subject #2, who was treated with only 20M cells due to small lipoaspirate cell recovery, was the first to reach normal levels of SPT and VPT at 12 weeks. There is a need for cell dose-ranging studies and potentially multiple injections (and timing thereof) to be part of future trials.

The healing of DFU after treatment with ADSVF was complicated. Based upon previous experience treating DFU with SVF, the progression and new lesion occurrence in this study had not been seen to the same extent [29 Carstens]. That said, the largest DFU at time of enrollment (32 cm²) healed (closed, no drainage) within as short a time as 8 weeks after SVF by subject report. The other uncomplicated wounds healed within 32 weeks. The three subjects with complicated/new lesions unfortunately illustrate the complex nature of DM foot disease, especially in a setting where manual labor is the mainstay of employment and advanced medical interventions (e.g. hyperbaric chambers) are limited.

Improvements in DPN-associated sensory loss are important to improve quality of life and help decrease the development and recurrence of DFU. Current therapies for DPN have been primarily symptomatic in nature. The purpose of the current study was to explore the safety and the potential disease-modifying capability of an autologous, point-of-care, cell-based product, ADSVF. The findings in this study suggest that SVF cells are safe, consistent with multiple other published studies. Further, SVF may reverse diabetes-induced nerve injury that results in neuropathy, presenting a new opportunity for treatment. Indeed, the findings in this study support the ability of SVF to functionally improve DPN in the index foot within 12 weeks of treatment and at a total one-time dose of 40 million cells.

There are multiple limitations to this study. The small size of this study limits the safety evaluation of autologous SVF for treating DPN, especially given the disease progression that can be seen with the frequent, concurrent presence of a DFU. In addition, this study was uncontrolled and not blinded for the subjects or the study team and thus, any results for SVF – DPN efficacy are only hypothesis-generating. The addition of serum biomarkers for DPN/inflammation could have been helpful to establish the biologic correlates with DPN improvement. Also, bilateral testing for DPN status would have been helpful to understand a local versus systemic effect of the SVF injections. Future trials would benefit from additional DPN diagnostic tests, serum biomarkers for inflammation, nerve conduction tests, and nerve fiber density studies.

Conclusion

Autologous ADSVF cells are a potential new disease-modifying approach to treat DPN. In this small clinical trial, locally-injected SVF cells were well tolerated; there were no treatment-related SAE when

used to treat patients with DPN. Overall, the clinical benefit in DPN observed in this uncontrolled, pilot study supports continued investigations of SVF to treat DPN.

Declarations

Author contributions

All the authors listed have approved the manuscript that is enclosed. MHC, KAB, and SV drafted the manuscript, MHC, OP, and KAB designed the tables and figures. All authors supervised and revised the work.

Disclaimers

AI was not used in the preparation of this manuscript.

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Ethics approval

The study was approved by the Nicaragua Ministry of Health Institutional Review Board February 22, 2022 [number DGD-NVSQ-197-02-22] as “Pie diabético: tratamiento de las úlceras y de neuropatía con células fracción vascular stromal (FVS/SVF): de tejido adiposo. Un estudio de seguridad y evidencia de respuesta clínica” (Diabetic Foot: treatment of ulcers and neuropathy with stromal vascular fraction cells (SVF). A study of safety and evidence of clinical response. Informed consent (including data/images for publication) was obtained from all study participants. The trial was registered in clinicaltrials.gov [NCT07553468].

Competing interests

Michael Carstens has previously served as a consultant for GID Bio. All other authors declare no competing interests.

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Figures

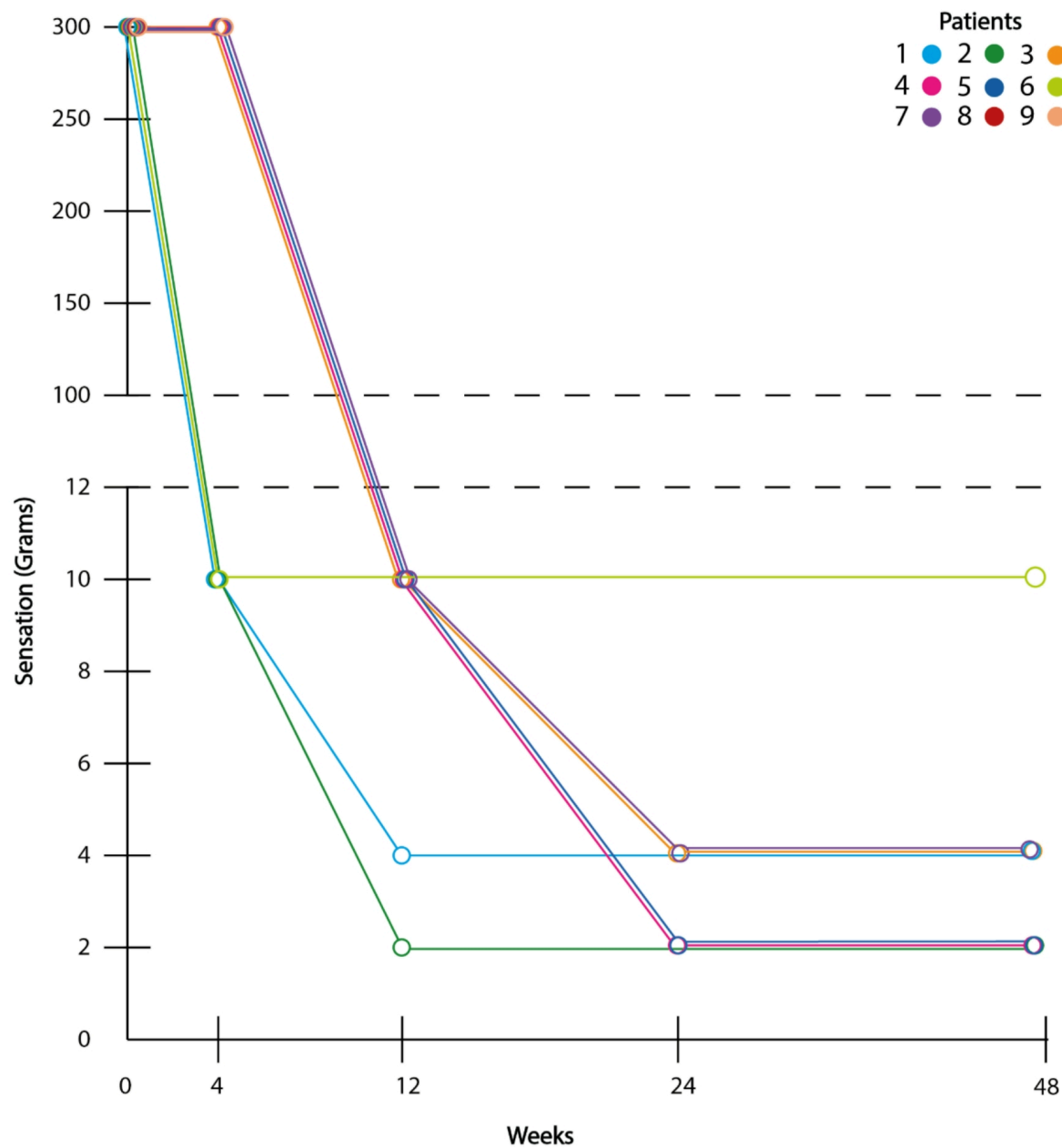


Figure 1

Figure 2. Changes in sensation perception threshold (SPT) over time; subjects 1 – 9. Loss of protective plantar sensation as measured by Semmes-Weinstein is ≥ 10 grams.

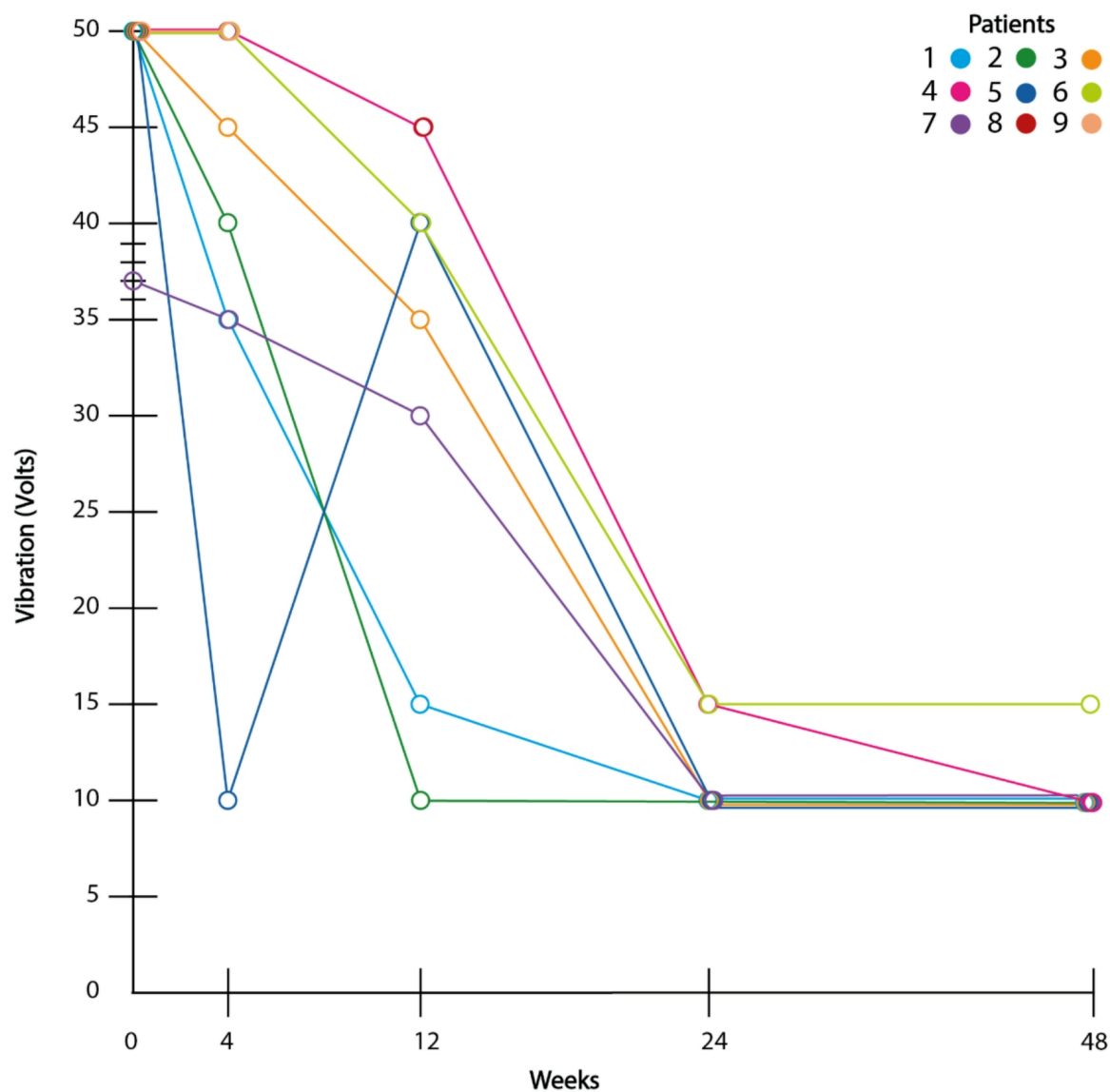


Figure 2

Figure 3. Changes in vibration perception threshold (VPT) over time; subjects 1 – 9. Values were graded as normal/protective (< 15v); or mild (15-20v), moderate (20-25v) or severe (> 25v) vibration perception dysfunction

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