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# Stem Cell Therapy Enriched Fat Grafting for the Reconstruction of Craniofacial Deficits

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**Background:** Fat grafting is an effective treatment for craniofacial deformities. Stromal vascular fraction (SVF) is a concentrated form of adipose derived stem cells that can be isolated from fat. The aim of this clinical trial was to assess the impact of SVF enrichment on craniofacial fat grafting.
**Methods:** Twelve subjects with at least two regions of craniofacial volume deficit were enrolled, and they underwent fat grafting with SVF-enriched or standard fat grafting to each area. All patients had bilateral malar regions injected with SVF-enriched graft on one side and control standard fat grafting to the contralateral side. Outcome assessments included demographic information, volume retention determined by CT scans, SVF cell populations assessed by flow cytometry, SVF cell viability, complications, and appearance ratings. Follow-up was 9 months.
**Results:** All patients had improvement in appearance. There were no serious adverse events. There was no significant difference in volume retention between the SVF-enriched and control regions overall (50.3% versus 57.3%, $P = 0.269$) or comparing malar regions (51.4% versus 56.7%, $P = 0.494$). Patient age, smoking status, obesity, and diagnosis of diabetes did not impact volume retention. Cell viability was 77.4% ± 7.3%. Cellular subpopulations were 60.1% ± 11.2% adipose derived stem cells, 12.2 ± 7.0% endothelial cells, and 9.2% ± 4.4% pericytes. A strong positive correlation was found between CD146+ CD31-pericytes and volume retention ($R = 0.863$, $P = 0.027$).
**Conclusions:** Autologous fat transfer for reconstruction of craniofacial defects is effective and safe, leading to reliable volume retention. However, SVF enrichment does not significantly impact volume retention. *(Plast Reconstr Surg Glob Open 2023; 11:e5056; doi: 10.1097/GOX.0000000000005056; Published online 19 June 2023.)*

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## INTRODUCTION

Acquired craniofacial deformities significantly impair social functioning and result in profound adverse psychosocial sequela, including anxiety, depression, social anxiety, and social avoidance.[1–3] Reconstructive procedures aim to return normal facial appearance and improve functionality. Traditional reconstructive options include flap and implant procedures. Autologous fat transfer (AFT) is emerging as a versatile and powerful modality for soft tissue reconstruction and sculpting in many regions of the body and may have applications in craniofacial reconstruction.[4] It is minimally invasive with an excellent safety profile, minimal (if any) donor site morbidity, and short recovery time compared with traditional reconstructive methods. Fat grafting has been shown to not only improve soft tissue volume, but also improve vascularity, skin quality and pliability in regions of fibrosis, and poor skin quality.[5] The main drawback of AFT has remained the unpredictability of volume retention ranging from 20% to 80%.[6–9] Inadequate volume retention compels patients to undergo multiple procedures to obtain a satisfactory result. The implications of this include added cost, additional exposure to the risk of surgery and anesthesia, and

Disclosure statements are at the end of this article, following the correspondence information.

additional recovery time and pain. For these reasons, there is great interest in developing methods to improve fat graft volume retention.

Enrichment of fat graft with adipose derived stem cells (ASC) may be a viable method to improve graft volume retention. Lipoaspirate has a low concentration of adipose-derived stem cells compared with whole fat.[10] Processing lipoaspirate through a collagenase digestion procedure can produce a stromal vascular fraction (SVF) that contains a concentrated source of ASCs and vascular endothelial progenitor cells, pericytes, and macrophages.[11] This rich reservoir of regenerative precursor cells may improve angiogenesis and promote the survival and division of adipose cells.[12]

Previous studies assessing the impact SVF enrichment of AFT for the treatment of cosmetic and congenital facial soft tissue deficits have demonstrated promising results.[13–16] Traumatic and surgical defects differ from cosmetic and congenital soft tissue deficits due to scarring of the recipient bed. This creates a hostile environment for receiving grafted tissue due to limited vascularity and compliance. This is the first prospective clinical trial assessing efficacy of SVF-enriched fat grafting for the treatment of traumatic craniofacial defects. Furthermore, this study was designed to allow each patient to serve as their own control, thus limiting confounding variables.

## METHODS

This is an IRB approved (PRO12010078, PRO10100293, PRO12030255), nationally registered (NCT01924364, NCT01633892) prospective cohort study designed to assess clinical outcomes after SVF-enriched fat grafting compared with standard fat grafting of the craniofacial region. Twelve patients with disfiguring craniofacial defects secondary to trauma or surgical procedures were enrolled. Inclusion criteria comprised age of at least 18 years, history of injury (this could be from trauma or surgery as both would result in a scarred soft tissue deficit) resulting in at least two treatable craniofacial defects with a volume of 3-100 cm$^3$, intact skin covering the treated regions, no communication between the treated regions and the oral cavity or open sinus, and at least 3 months since the inciting injury or last surgery. Exclusion criteria included an inability to provide informed consent, active infection, cancer diagnosis within the last 12 months or current chemotherapy or radiation treatment, axis I DSM-IV diagnosis or known substance abuse, systemic disease that would render a surgical procedure and associated anesthesia unsafe, life expectancy of less than 9 months, coagulopathy, pregnancy, and allergy to collagenase. Follow-up was 9 months.

Demographic data and medical history were collected. All patients had more than one area of volume loss requiring AFT. This allowed each patient to serve as their own control and have discrete areas treated with either SVF-enriched or standard fat grafting. Additionally, each subject underwent fat grafting into bilateral malar eminences, which was a well vascularized, favorable recipient bed in all patients, with enriched fat on one side and nonenriched on the contralateral side. All regions that would undergo AFT were numbered in a standardized pattern. Either even or odd numbered regions were picked by a random number generator (GraphPad Software, Inc, La Jolla, Calif.) for treatment with SVF-enriched graft. The remaining sites were treated with nonenriched, standard fat grafting.

### Takeaways

**Question:** The aim of this study was to compare stem cell enriched versus standard fat grafting for the treatment of traumatic craniofacial defects.

**Findings:** Standard and stem-cell–enriched fat grafting are both safe and effective treatments for traumatic craniofacial deformities. Stem cell enrichment does not impact volume retention.

**Meaning:** Standard fat grafting can be used to safely and effectively treat patients with traumatic craniofacial defects. Stem cell enrichment does not improve outcomes, and is therefore not recommended, as it adds additional cost and time to the procedure.

### Surgical Technique

Fat was harvested using manual liposuction from the abdomen and/or flanks and divided into two equal aliquots. One half was used for isolation via collagenase digestion to produce the SVF.[11] The remaining lipoaspirate was processed by centrifugation (3 minutes at 1200*g*) to separate the aqueous and oil layers. The aqueous layer was then decanted by gravity and the oil layer was absorbed using surgical patties. SVF was manually mixed with half of the fat prepared for engraftment. An 18-gauge needle was used to perform focal scar release in areas of significant scarring and tethering. Both enriched and nonenriched fat was transferred to 1 mL syringes for injection. All areas were injected with enriched or nonenriched fat as determined by the random number generator (Fig. 1). A small-gauge, blunt injection cannula with a single hole at the distal end was used for graft placement. Fat was deposited via multiple points around the depression in small aliquots upon withdrawal of the cannula in a radial fan pattern at all levels to disperse the graft as evenly as possible. Fat was grafted until the desired volume was achieved or compliance and size of the recipient bed would not allow further transfer of fat. Patients went home the day of surgery.

### Cellular Characteristic Analysis

Flow cytometry was performed to assess the cellular subpopulations within the SVF. Cell isolates were suspended in 5 μL of neat mouse serum to prevent nonspecific antibody binding. Two microliters of monoclonal mouse antihuman flourochrome conjugated antibodies, including CD3-FITC, CD146-PE, CD34-ECD, CD90-PE-Cy5, CD117-PE-Cy7, CD31-APC, and CD45-APC-Cy7, were used to simultaneously stain the isolate. Cell viability was determined based on 4′,6-diamidino-2-phenylindole (DAPI) exclusion. Eight-color, 14-parameter data files were acquired on a three-laser Gallios Flow Cytometer

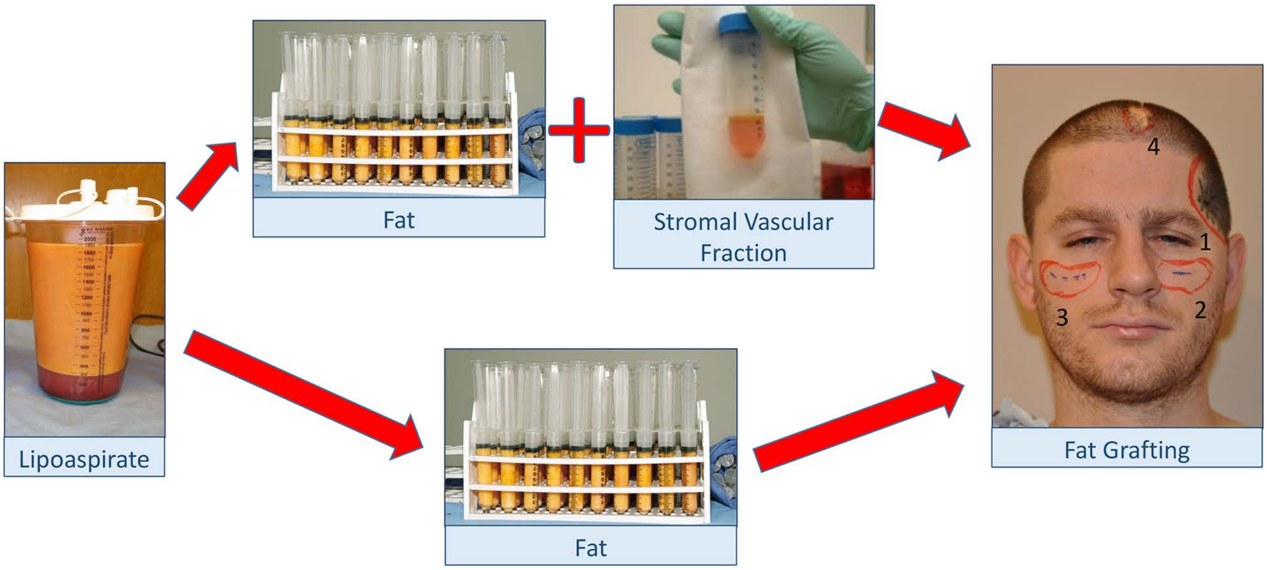


**Fig. 1.** Fat was harvested by liposuction and split, so that half was enriched with SVF and the other half was treated by standard processing. Areas of soft tissue deficit are marked and numbered in a clockwise direction. Even or odd regions were chosen at random to be enriched with SVF, and the other regions were treated with standard fat grafting. In all patients, the right and left cheek/malar regions served as a control: one side was treated with SVF-enriched fat graft and the other with standard fat graft.

(Beckman Coulter), and cell sorting was performed on a Beckman-Coulter MoFlo sorter. Cell yield per gram of tissue was calculated and cell dose, expressed as cell number added per gram of grafted tissue, was also calculated.

### Volume Retention Analysis

Graft volume retention was assessed by CT scan. High-resolution CT was performed on a 64-channel scanner prior to surgery and at 1, 3, and 9 months after surgery. All scans were analyzed by a dedicated head and neck radiologist with 20 years of experience. Manual tracing of the area of injected fat was performed on each axial slice and summed to create the volume measurement for each scan. Three-dimensional surface renderings were created to demonstrate contour abnormalities (Fig. 2). The volume difference from baseline

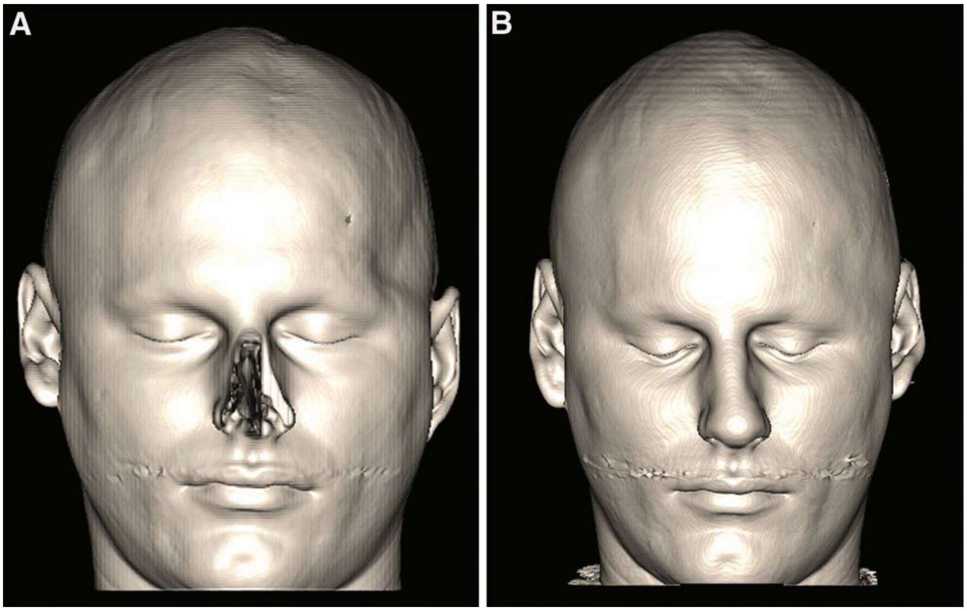


**Fig. 2.** Fat graft volume was assessed by CT scan. A, Preoperative CT scan. Note the volume deficit in the left temple and along a horizontal scar of the mid-vertex. B, Postoperative CT scan. Improved soft tissue volume in the left temple, mid-vertex and bilateral malar regions.

to 1 month postprocedure was used to calculate the volume of fat grafted because at one month the majority of operative edema would have subsided and minimal graft resorption would be expected. The volume remaining at 9 months was compared with this to determine the degree of fat resorption. The 3-month scan was used to ensure reliability of the measurements and stability of the degree of resorption.

As a secondary method of subjective volume assessment, a facial volume scale was completed by the surgeon preoperatively and at 3-week, 3-month, and 9-month follow-up visits. Photographs from prior visits were used for comparison so that the physician did not have to rely entirely on memory of each patient's appearance at the prior visit. This assessment is a three-point scale: (1) obvious contour defect consistent with baseline appearance, (2) significant improvement in contour from baseline but still noticeably different from the preinjury appearance or contralateral side, (3) normal appearance and/or close approximation to the uninjured contralateral side.

### Psychosocial Assessment

Quality of life was assessed at baseline as well as at 3-, 6-, and 9-month follow-up visits. Assessments included the Satisfaction with Appearance (SWAP) questionnaire,[17] satisfaction with medical/health services (Client Satisfaction Questionnaire, CSQ-8),[18] and global quality of life and general functioning (RAND SF-36).[19]

### Statistical Analysis

A priori power analysis using standard conventions of alpha = 0.5 and beta = 0.8 indicated that enrollment of five patients should provide sufficient power to detect clinically meaningful differences in volume of soft tissue and impact on quality of life between groups. All data were analyzed using IBM SPSS for Mac Version 20.0 (IBM Corp., Armonk, N.Y.). Descriptive statistics were used to compare demographics, surgical details, volume retention, cellular characteristics and psychological data among groups and were recorded as frequencies and percentages for categorical variables and as means and standard deviations for numerical variables. Student $t$ test was used to compare the volume retention between the two groups. Pearson and Spearman rank correlation coefficients were used to study relationships between continuous variables or nonnormally distributed data, with $R$ defined as the correlation coefficient value. Statistical significance was considered to be a value of $P$ less than 0.05.

## RESULTS

Twelve subjects were enrolled. All patients underwent AFT to the traumatic craniofacial defectcs and bilateral malar regions with either SVF-enriched of standard fat grafting as determined by a random number generator. Follow-up was 9 months. The mean age was 46.7 ± 14.1 years, and the average BMI was 26.9. Two patients (16.7%) were obese with a BMI greater than 35. There was no significant change in patient BMI during the study period. No patients carried a diagnosis of diabetes mellitus. Five patients (41.7%) were active smokers at the time of the intervention, and two (16.7%) had a history of smoking. Obesity, age, and smoking status did not significantly impact graft volume retention. Detailed demographic information is presented in Table 1.

Surgery lasted 253.8 ± 40.3 minutes and SVF processing took 99.8 ± 14.2 minutes. The mean volume grafted per reconstructed site was 10.4 ± 7.3 mL, whereas the overall mean volume grafted per patient was 37.1 ± 14.6 mL. All patients went home the day of surgery. There were no significant complications. The most commonly reported adverse events were pain, ecchymosis, erythema, swelling, and itching at the site of fat harvest, which is consistent with the expected postoperative recovery following liposuction and resolved with a short course of oral pain medication. SVF from four patients (33.3%) grew skin flora on culture; however, no patients demonstrated clinical signs of infection. All patients had an objective improvement from their preoperative compared with postoperative appearance at each time point as measured by the facial volume scale (Fig. 3). There was no statistically significant difference in the facial volume scale between regions treated by standard versus enriched fat graft.

### Volume Retention Analysis

Overall volume retention was 66.7 ± 17.9% at 3 months and decreased to 54.2 ± 19.0% at 9 months. There was no significant difference in volume retention at 9 months

**Table 1. Patient Demographic Data**

| Subject | Age | Gender | Smoking Status | BMI | Mechanism of Injury | Volume Grafted (cc) |
|---|---|---|---|---|---|---|
| 1 | 59 | Man | Never | 25.7 | Intracranial hemorrhage | 34.0 |
| 2 | 52 | Man | Never | 25.5 | Assault | 47.7 |
| 3 | 30 | Man | Quit | 25.8 | Fall | 46.7 |
| 4 | 53 | Man | Quit | 36 | Motorcycle crash | 22.0 |
| 5 | 31 | Man | Current | 17.9 | Gunshot wound | 33.3 |
| 6 | 23 | Man | Never | 24.1 | Blast injury | 58.0 |
| 7 | 45 | Woman | Never | 35.3 | Meningioma resection | 62.6 |
| 8 | 44 | Man | Current | 26.6 | Gunshot wound | 42.5 |
| 9 | 69 | Man | Current | 21.2 | Motor vehicle accident | 34.8 |
| 10 | 56 | Man | Never | 34.3 | Motor vehicle accident | 22.5 |
| 11 | 61 | Man | Current | 25.4 | Assault | 19.8 |
| 12 | 37 | Man | Current | 25.4 | Assault | 21.0 |

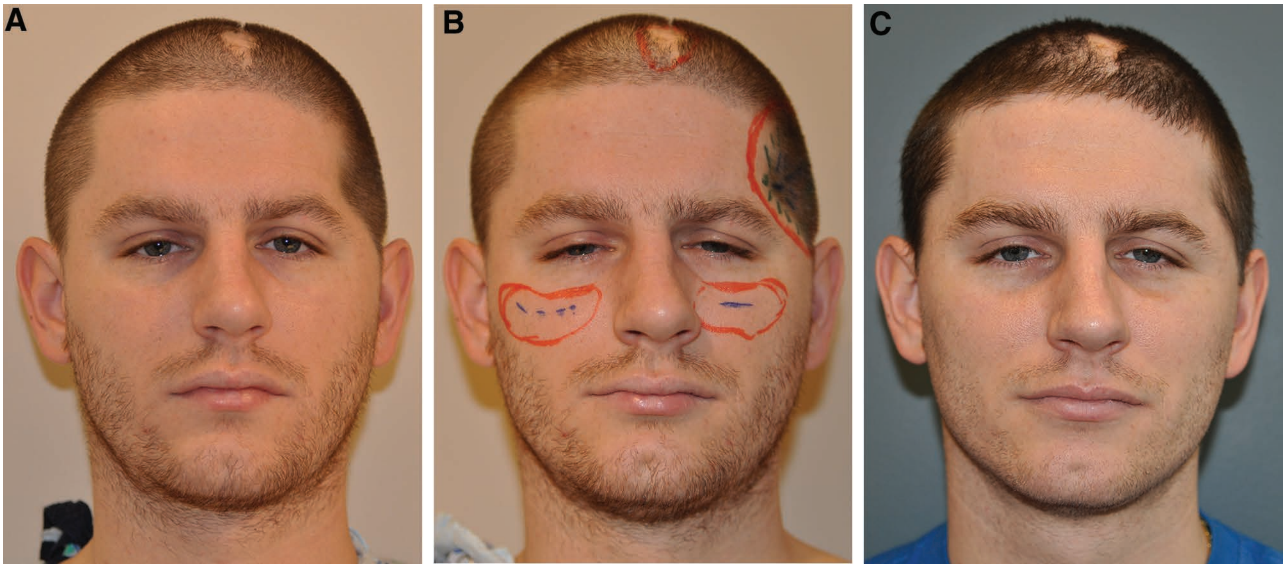


**Fig. 3.** A 25-year-old man who sustained a blast injury while serving in Iraq, requiring left craniotomy. A, Preoperative appearance. Note soft tissue deficits most pronounced in the left temple. B, Soft tissue deficits are marked and numbered in order following a clockwise pattern. Either even or odd numbers are assigned enrichment with SVF at random. Malar regions serve as a control, as one side is enriched and the other is treated with standard fat grafting. C, Postoperative appearance. Note improvement in the left temple hollowing as well as other regions of volume enhancement.

between the SVF-enriched and control regions when comparing all treated areas (50.3% versus 57.3%, $P = 0.269$). Similarly, there was no significant difference comparing the SVF-enriched and standard fat-grafted malar regions within each patient (51.4% versus 56.7%, $P = 0.494$) (Figs. 4 and 5). Pearson and Spearmen's rank correlation coefficients failed to find a correlation between volume retention at 9 months and age ($R = -.002$, $P = 0.994$), history of smoking or current smoking ($R = -0.775$, $P = 0.225$), and obesity ($R = 0.15$, $P = 0.66$).

### Cellular Characteristic Analysis

Cellular subpopulations were 60.1 ± 11.2% CD34+ CD146- CD31- ASCs, 12.2 ± 7.9% CD31+ endothelial cells, and 9.2 ± 4.4% CD146+ CD31- pericytes. Although Pearson rank correlation coefficients failed to find a correlation between percentage of adipose derived stem cells or endothelial cells and volume retention, a strong positive correlation was found between CD146+ CD31- pericytes and volume retention ($R = 0.863$, $P = 0.027$). Cell viability was 77.4 ± 7.3%. There was no significant correlation between cell viability and volume retention at 9 months ($R = 0.356$, $P = 0.283$). Cell yield ranged from $6.8 \times 10^4$ to $1.3 \times 10^6$ with a mean of $5.1 \times 10^5 \pm 3.4 \times 10^5$ cells per gram of fat. The average cell dose administered was $5.1 \times 10^5 \pm 3.4 \times 10^5$ cells added to each gram of fat. There was no significant correlation between cell yield and volume retention at nine months ($R = -0.474$, $P = 0.14$).

### Psychosocial Assessment

Patients reported an early postsurgery increase in satisfaction with overall appearance (SWAP total score) from presurgery (baseline) to 3 months postsurgery (t = 2.18; df = 11; $P = 0.052$); and sustained increased satisfaction (from baseline) to 6 months postsurgery (t = 2.53; df = 11; $P = 0.028$); and (from baseline) to 9 months postsurgery (t = 2.29; df = 11; $P = 0.043$). With regard to satisfaction with facial appearance (SWAP), patients also reported early postsurgical increase in satisfaction with facial appearance from baseline to 3 months postsurgery (t = 3.56; df = 11; $P = 0.004$); and sustained increase (baseline to 6 months postsurgery) (t = 2.45; df = =11; $P = 0.032$); followed by a nonsignificant trend for increased satisfaction from baseline to 9 months postsurgery (t = 2.14; df = 11; $P = 0.058$). In contrast, patients reported no significant changes in general health or social or emotional well-being (on the RAND SF-36) from presurgery baseline to any postsurgery follow-up assessment (at 3-, 6-, or 9-months follow-up).

Patients reported high levels of satisfaction with care (CSQ-8) at all time points, with a significant increase from presurgical baseline (27.0 ± 3.3) to 3 months (29.6 ± 2.5) ($P = 0.013$); mean satisfaction scores remained high (≥29.0 out of 32) at all postsurgery time points.

## DISCUSSION

Acquired craniofacial deformities create significant morbidity and can be challenging to treat. Fat grafting has emerged as an effective and safe reconstructive technique for the treatment of these defects. It creates minimal donor site morbidity (in fact many patients consider liposuction of the abdomen and flanks to be an added benefit of the procedure) and has a relatively short recovery period compared with traditional flap and graft reconstructive procedures. Accurate placement of small fat aliquots for precise contouring provides optimal versatility to reconstruct the complex craniofacial anatomy. The main limitation of

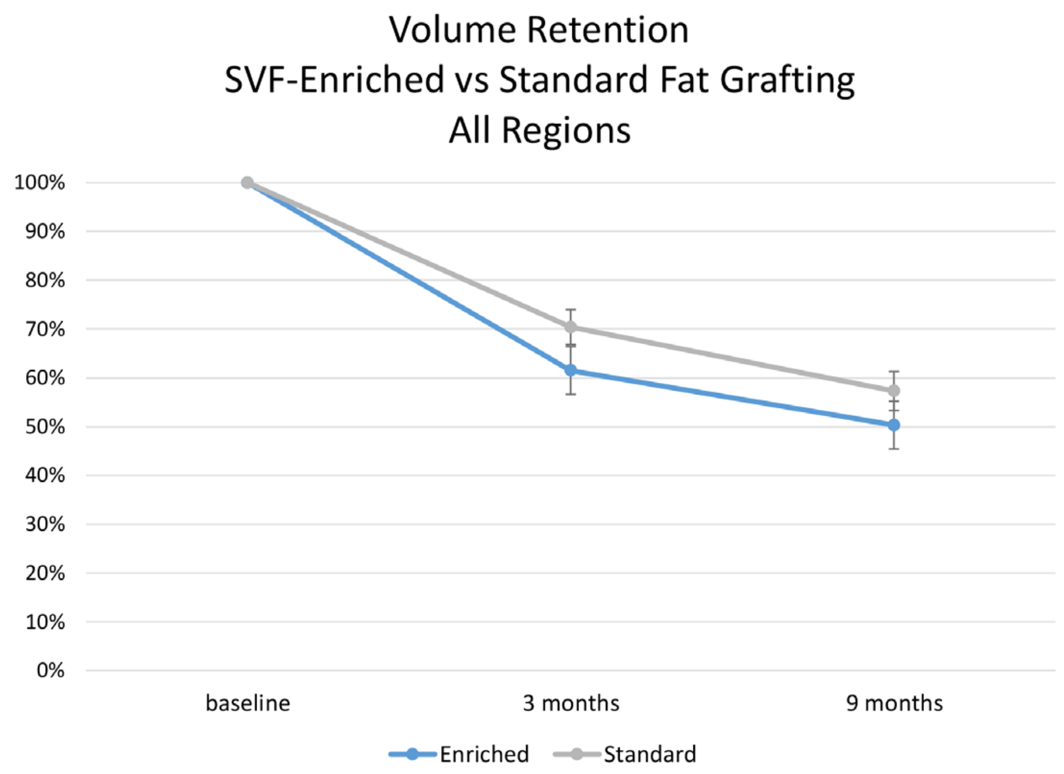


**Fig. 4.** There was no significant difference in volume retention between SVF-enriched and standard fat grafting in all treated regions.

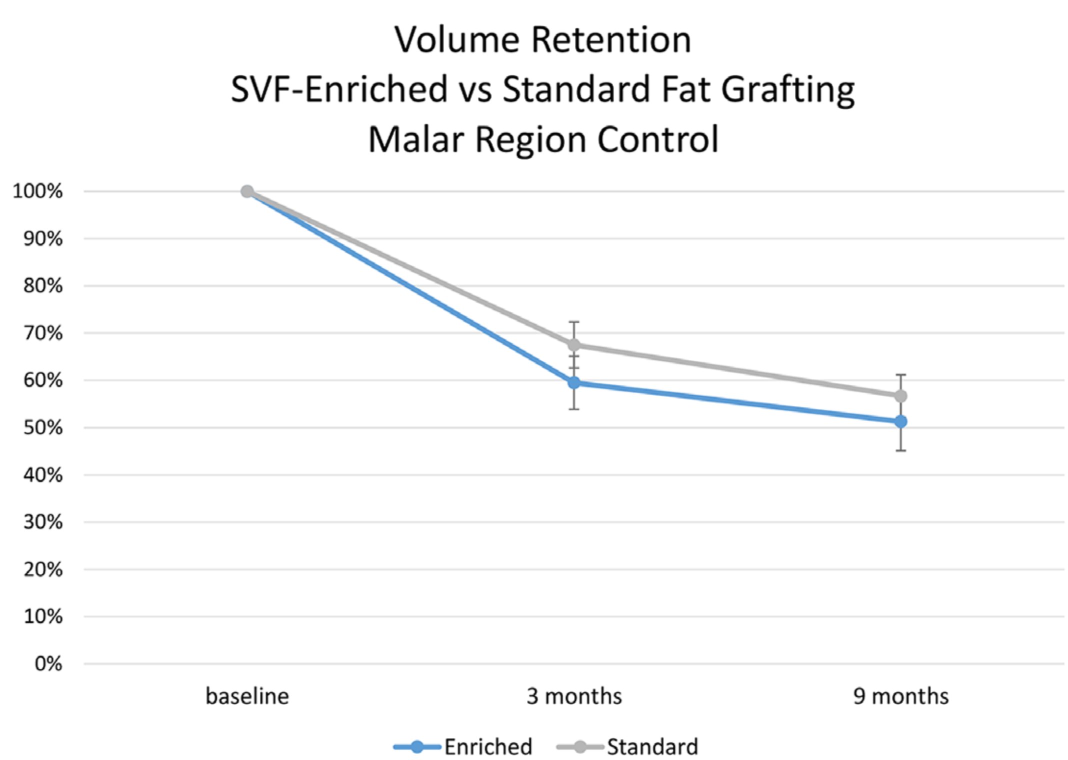


**Fig. 5.** There was no significant difference in volume retention between SVF-enriched and standard fat grafting between left and right malar regions.

this technique continues to be unreliable volume retention. Enrichment of graft with adipose derived stem cell rich stromal vascular fracture has emerged as a potential method to improve retention.

Matsumoto et al first proposed the idea of enriching fat graft with freshly isolated SVF in 2006.[10] This technique was first applied to humans by Yoshimura et al in 2008.[20] There is heterogeneity in the fat survival rate reported across studies in the current literature.[21] Pooled analysis demonstrates higher fat survival in cell-assisted lipotransfer, which includes both SVF as well as cultured adipose derived stem cell enriched procedures, compared with noncell-assisted fat grafting (60% versus 45%, $P = 0.0096$) with subgroup analysis in the face maintaining higher fat survival in the cell-assisted lipotransfer group (71% versus 52%, $P = 0.041$).[22] Published studies assessing patient and surgeon satisfaction and subjective improvement following treatment with either SVF-enriched or standard fat grafting techniques report mixed results of improved satisfaction or no difference in the SVF-enriched patients.[20,23,24] Five published studies aim to assess the impact of SVF enrichment on AFT in the face. Two are retrospective cohort studies of patients with Parry Romberg syndrome or cosmetic concerns who were treated with either SVF-enriched or standard fat grafting techniques. CT scans were used for volume analysis.[15,24] Sasaki et al performed a prospective nonrandomized cohort study comparing standard fat grafting to SVF-enriched, platelet rich plasma enriched, and SVF and platelet rich plasma-enriched fat graft in patients desiring cosmetic soft tissue enhancement in the face. Volume analysis was performed using 3D photography.[14] Tanikawa et al performed a randomized controlled trial in patients with craniofacial macrosomia, where half of the patients were treated with SVF-enriched fat grafting, and the other half with standard AFT. Volume was assessed by CT scan.[16] These studies report improved volume retention in SVF-enriched compared with standard fat grafting in the craniofacial microsomia and cosmetic patient populations. The only study assessing traumatic facial deformities was performed by Gentile et al. This study included both traumatic and burn scars; half of each scar was treated with SVF-enriched fat grafting, and the other half with standard fat transfer. Volume retention was assessed by MRI and ultrasound. They report improved retention in the SVF-enriched compared with the standard fat grafting areas.[25]

Traumatic and surgically created craniofacial deformities present unique challenges that are not encountered in microsomia or cosmetic soft tissue deficits. The graft recipient bed has limited vascularity and compliance inherent in scar tissue. Therefore, studies in this specific patient population are indicated. The only previous study to assess the impact of SVF enrichment on traumatic scars groups burn scars in the analysis.[26] However, burn scar pathophysiology greatly differs from other surgical scars because of the prolonged inflammatory and reparative process, altering wound healing and predisposing the wound to the development of hypertrophic scarring. We aimed to perform the first clinical trial comparing SVF-enriched to standard AFT in patients with traumatic and surgical craniofacial defects.

Clinical trials previously performed at our institution have demonstrated that volume retention is significantly impacted by inherent individual characteristics,[4] therefore we ensured each patient could serve as their own control. All enrolled patients had at least two traumatic or surgical defects, half of which were treated with standard fat graft, and the other half with SVF-enriched fat graft. Additionally, all patients had their right and left malar regions, which were free of traumatic insult or scar tissue, treated with SVF-enriched fat graft on one side and standard fat graft on the contralateral side.

Our results demonstrate that AFT is a safe and effective technique for the treatment of traumatic and surgical craniofacial defects. There were no significant adverse events. Overall volume retention was 54.2 ± 19.0% and there was subjective improvement in appearance.

Fat is gradually resorbed during the first 2 months and stabilizes around 3 months, therefore 9-month follow-up was used to determine volume retention.[14] We hypothesized that the SVF-enriched fat graft would have a higher retention rate compared with standard methods because this has been reported in studies largely focused on treating breast, cosmetic and congenital soft tissue defects. We, therefore, were surprised to find no significant difference between SVF-enriched and standard fat transfer in our patient population. This suggests that traumatized and scarred craniofacial tissue may create an environment that is less impacted by the addition of SVF.

Paik et al report that fat graft retention is optimized at a concentration of 10,000 cells per 200 μL of fat, which is equivalent to $5 \times 10^4$ cells per 1 mL.[27] The mean cell yield in our study was $5.1 \times 10^5$ cells per 1 g, and results did not demonstrate a significant difference in retention based on cell yield in this patient population.

Patient characteristics (including age, smoking status, and obesity) did not significantly impact volume retention. There are likely other inherent biologic characteristics unique to each individual that we have yet to understand that have a greater impact on retention than any of these single factors. Future studies are needed to better understand how to optimize patient characteristics and procedural techniques to improve volume retention and outcomes.

## CONCLUSIONS

SVF-enrichment of fat graft to traumatic craniofacial defects does not improve volume retention. Due to the added time and resources required for processing SVF (a mean of 100 minutes in our facility), we would not recommend enriching fat graft with SVF for this patient population.

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## DISCLOSURES

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## PATIENT CONSENT

*The patient provided written consent for the use of his images.*

## ACKNOWLEDGMENTS

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