Outcome of Conventional Adipose Tissue Grafting for Contour Deformities of Face and Role of Ex Vivo Expanded Adipose Tissue-Derived Stem Cells in Treatment of Such Deformities

Muhammad Mustehsan Bashir, FCPS (Plastic Surgery), FCPS (Surgery),[*] Muhammad Sohail, FCPS (Plastic Surgery), FCPS (Surgery),[*] Afzaal Bashir, FCPS (Plastic Surgery),[*] Farid Ahmad Khan, FCPS (Plastic Surgery), FRCS (Ed),[†] Sadia Nosheen Jan, FRCS (Surgery), FCPS (Plastic Surgery),[*] Muhammad Imran, MBBS,[‡] Fridoon Jawad Ahmad, PhD,[§] and Mahmood S. Choudhery, PhD[||]

Objectives: To evaluate the outcomes of conventional fat grafting for facial contour deformities and to describe clinical outcome of a patient with contour deformity of face treated with ex vivo expanded adipose tissue-derived mesenchymal stem cells (ASCs) enriched fat graft.

Place and Duration of Study: The Department of Plastic Surgery and Tissue Engineering and Regenerative Medicine Laboratory, King Edward Medical University/Mayo Hospital, Lahore, from September 2015 to September 2017.

Methods: Patients with contour deformities of face requiring soft tissue augmentation were included. Fat was harvested, processed, and injected following a standard protocol. Both subjective and objective assessments were performed and complications were also noted.

Results: Twenty-five patients underwent 51 fat-grafting sessions over a period of 24 months. Eighteen (72%) patients underwent multiple fat-grafting sessions. Mean (standard deviation) soft tissue thickness after 72 hours and 6 months of first fat graft session was 18.62 (7.2) and 12.88 (6.21) mm, respectively, which corresponds to 30.77 (13)% reduction of transplanted fat. Physician and patient assessment scores were 3.42 (0.92) and 4 (1.04), respectively. Few minor complications were observed. In the patient undergoing ex vivo expanded ASCs enriched fat graft, there was minimal decrease in soft tissue thickness of treated area (44 mm vs 42 mm) 6 months postoperatively and patient was highly satisfied with the outcome after the single session.

Conclusion: Conventional fat grafting is safe for correction of facial contour deformities. However, procedure needs to be repeated multiple times to produce satisfactory results. Beneficial effects of ex vivo expanded ASCs enriched fat grafting have a potential to alter the current treatment paradigm of fat grafting for soft tissue reconstruction.

Key Words: Adipose tissue-derived stem cells, contour deformities, fat graft

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Facial contour deformities requiring soft tissue augmentation often result from conditions such as congenital or developmental disorders, acquired diseases, and trauma.[1,2] Significant contour deformity of face causes both functional as well as esthetic problems for the patient. Recently, autologous fat grafting has gained pervasive acceptance for the management of contour deformities of the face. Fat being an autologous tissue source is considered an ideal soft-tissue filler because it is abundant, readily available, inexpensive, host compatible, and can be harvested easily and repeatedly.[3–6] However, 1 major concern in using conventional autologous fat graft is the lack of consistency of final clinical outcome due to significant absorption (40% to 80%) of transplanted fat. Thus, it is desirable to use innovative techniques to address this issue. The role of fat auto-transplantation in plastic surgery has evolved from a controversial technique designed for simple volume augmentation to the foundation for the innovative and burgeoning field of regenerative medicine. This is based on the fact that adipose tissue contains adipocytes and the stromal vascular fraction (SVF) consisting of multiple cell types. Adipocytes account for 20% or fewer of the total number of cells in adipose tissue whereas there are only 3% adipose tissue-derived mesenchymal stem cells (ASCs) in SVF of adipose tissue.[7] Although this percentage is relatively low, ASCs have been shown to enhance angiogenesis, decrease apoptosis, and modify the local inflammatory response owing to their immunosuppressive and immunomodulatory properties.[8] By combining traditional fat graft with ASCs, graft viability and survival may be improved. Recent animal studies have suggested that expanded ASCs could help in preserving transplanted fat and improving overall outcome.[9–11] The rationale of current study was to prospectively evaluate the clinical outcomes of conventional fat grafting for the treatment of contour deformities of the face requiring

From the *Department of Plastic Surgery, King Edward Medical University, Mayo Hospital; †Department of Plastic Surgery, Principal, Chairman and Dean, Shaikh Zayed Medical Complex; ‡King Edward Medical University, Mayo Hospital; §Tissue Engineering Laboratory Pediatric Surgery, King Edward Medical University; and ||Tissue Engineering and Regenerative Medicine Laboratory, Department of Biomedical Sciences, King Edward Medical University, Lahore, Pakistan.
Received October 24, 2017.
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Address correspondence and reprint requests to Dr Mahmood S. Choudhery, PhD, Assistant Professor, Tissue Engineering and Regenerative Medicine Laboratory, Department of Biomedical Sciences, King Edward Medical University, Lahore, Pakistan;
E-mail: drmahmood@kemu.edu.pk
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soft tissue augmentation in terms of patient and surgeon satisfaction, percentage reduction in fat graft volume, and complications. Moreover, clinical outcome of a patient with contour deformity of face treated with fat graft enriched with ex vivo expanded ASCs is also described for the first time.

METHODOLOGY

In the current study, 25 patients with congenital or acquired contour deformities of face requiring soft tissue augmentation were included. Patients with contour deformities in skin grafted areas and where skin was adherent to facial skeleton were excluded from study. Patients were consecutively enrolled from September 2015 to September 2017. After informed consent, demographic, clinical (site and etiology of the deformity), and laboratory data of patients were collected. Patients taking aspirin, alcohol, and herbal medications were advised to stop their use 1 week before the surgery. All the study protocols were approved by Institutional Review Board of King Edward Medical University, Lahore, Pakistan.

The study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Preoperative photographs were taken under standard conditions of light, distance, views, and camera make.

Intervention

Fat harvesting, preparation, and transfer were performed using a standardized protocol. Fat was harvested either from abdomen or lateral side of the thigh using the technique described by Pasquale et al.[6] The syringes containing the aspirated fat were allowed to stand vertically for 5 to 10 minutes to separate fat from liquid portion. The bottom layer of tumescent fluid and blood was drained out. Remaining layer of fat in the syringes was filtered using a strainer to separate fat from oil and debris. Normal saline was used to wash and purify the fat. The purified fat was then transferred to 1 mL syringes.[2] The fat was injected to areas requiring augmentation following the principles of structural fat grafting as described by Coleman et al.[5] End point of lipo-filling was achieved by visual clinical symmetry with the opposite side.[5]

Ultrasonography

All patients were subjected to ultrasonography of treated area using a B-mode ultrasound device and linear 12 MH high frequency probe (Sonoace X4; Samsung Medison, Seoul, South Korea). The sonographer measured the thickness of the subcutaneous tissue in millimeters. Measurements were made as triplicate, and the mean of 3 data points was used for analysis. First, measurement of soft tissue thickness was taken 72 hours after the fat grafting. In order to have a reproducible measurement in subsequent examinations, the operator noted down and marked precise anatomic landmark points with an indelible marker, saving a digital image for future reference. Measurements of soft tissue thickness were repeated at 6 months by same sonographer[12] (Fig. 1E, F, K, L, P, Q, U, V, X, Z, and Z1).

After 6 months, the need for regrafting of fat in the affected area was also assessed. Fat-grafting sessions were repeated in patients where symmetry was not achieved. Patients were photographed on each visit.

Outcome

Mean (standard deviation, SD) of volume of fat injected per procedure was measured in cm^3 (mL). The number of fat-grafting sessions and total volume of fat injected to achieve clinical symmetry per patient was also noted. Subjective physician assessment was performed for clinical symmetry (comparing the affected side to the unaffected side) and overall appearance. It was done by clinical examination and comparing preoperative and 6 months postoperative (after final fat graft session) photographs. Two plastic surgeons, independently, rated postoperative appearance using a 5-point scale as (1) very unsatisfied; (2) unsatisfied; (3) neither satisfied nor unsatisfied; (4) satisfied; and (5) extremely satisfied. Subjective patient satisfaction assessment was also performed at 6 months after final session using same 5-point scale. Objective assessment of soft tissue thickness of treated area was performed using a B-mode ultrasound device. The difference in mean of 3 measurements taken at 72 hours postoperatively and at 6 months after the first fat-graft session was noted down as percentage reduction in fat graft volume.

Frequencies and percentages of both recipient and donor sites complications such as swelling, bruising, hematoma, seroma, and contour irregularities were noted.

Statistical Analysis

Data were analyzed using SPSS version 16. Qualitative variables like gender, etiology, fat harvesting site, number of sessions, and complications of the procedure were expressed as proportions. Quantitative variables like age, patient and physician assessment scores, volume of fat injected in 1 procedure, total volume of fat injected per patient, and percentage reduction in fat graft volume were expressed as mean (SD). Paired sample t test was used to compare the soft tissue thickness means measured at 72 hours and at 6 months after first graft session. P value ≤ 0.05 was considered significant.

RESULTS

A total of 25 patients underwent 51 fat-grafting sessions over a period of 24 months. The mean (SD) age of patients was 21 (5) years with 20 (80%) females. Most common indication for fat grafting was idiopathic hemifacial atrophy in 14 (56%) patients followed by congenital craniofacial microsomia in 5 (20%), post-traumatic deformity in 4 (16%), and postinfective deformity in 2 (8%) patients. Fat was harvested from the abdomen in 17 (68%) and lateral thighs in 8 (32%) patients.

Areas and Volume Augmentation

Three patients (12%) had augmentation of multiple areas at the same time. Eighteen (72%) patients underwent multiple fat-grafting sessions. Mean preoperative soft tissue thickness, mean soft tissue thickness 72 hours and 6 months after first fat graft session and mean percentage reduction in soft tissue thickness are detailed in Table 1. Mean (SD) volume injected in 1 session was 25 (14) mL (range 6–45 mL). Number of fat-grafting sessions per patient required to achieve clinical symmetry and mean volume of fat transferred in each patient are also detailed in Table 1.

Patient and Physician Satisfaction

Six months after final graft session, mean (SD) of subjective physician, and patient assessment scores using 5-point Likert scale were 3.42 (0.92) and 4 (1.04), respectively.

Complications

None of our patients had serious complications like loss of vision. However, minor postoperative complications were noted such as swelling in 51/51 (100%) procedures and bruising in 39/51 (76%) procedures. These minor complications were resolved in 2 to 4 weeks without any treatment. Four patients had recipient site cellulitis. It settled at 2 weeks with oral antibiotics in 3 patients and in 1 patient it progressed to discharge of pus from injection site that required IV clarithromycin for 1 month based on culture report.

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FIGURE 1. Patient 1: (A) Preoperative view of patient of idiopathic hemifacial atrophy with significant contour deformity of left side of face. (B) Intraoperative view showing marking of recipient site. (C) Postoperative view 6 months after 1st autologous conventional fat grafting session. (D) Postoperative view 6 months after 2nd autologous fat grafting session. (E, F) Ultrasonic measurement of soft tissue thickness, taken 72 hours and 6 months after 1st session (patient 2). (G, I) Preoperative frontal and lateral views of patient with posttraumatic contour deformity of left side of lower lip, left commisure, and chin. (H, J) Postoperative frontal and lateral views 6 months after conventional autologous fat grafting. (K, L) Ultrasonic measurement of soft tissue thickness, taken 72 hours and 6 months after session. Patient 3: (M) Preoperative view of patient with idiopathic hemifacial atrophy with significant contour deformity of right side of whole face. (N) Postoperative view 6 months after 1st autologous fat grafting session. (O) Postoperative view 6 months after 2nd autologous fat grafting session. (P, Q) Ultrasonic measurement of soft tissue thickness, taken 72 hours and 6 months after 1st session. Patient 4: (R) Preoperative view of patient with idiopathic hemifacial atrophy with significant contour deformity of left side of chin and mandibular area. (S) Postoperative view 6 months after 1st autologous fat grafting session. (T) Postoperative view 6 months after 2nd autologous fat grafting session. (U, V) Ultrasonic measurement of soft tissue thickness, taken 72 hours and 6 month after 1st session. Patient 5: (W) Preoperative view of patient with idiopathic hemifacial atrophy with significant contour deformity of right side of face. (X) Postoperative view showing marked anatomic landmark points with an indelible marker. (Y) Postoperative view 6 months after treatment with ex vivo expanded adipose tissue-derived mesenchymal stem cells enriched fat graft (z, z_1) Ultrasonic measurement of soft tissue thickness, taken 72 h and 6 months after session.

Clinical Report

A 30-year-old woman presented with idiopathic hemifacial atrophy involving right cheek. Disease was static for 3 years. Patient consented for treating the contour deformity with expanded adipose tissue-derived mesenchymal stem cell-enriched fat graft (Fig. 1W, X, Y, Z, Z1). Fat tissue was harvested under local anesthesia from only one side of the abdomen. In total, 30 mL of fat tissue was harvested by standard sterile syringe aspiration as described above. The ASCs were isolated and culture expanded in a certified laboratory approved by the Institutional Review Board. Standard protocols of the international society for cellular therapy were adopted for isolation and culture expansion of ASCs.[13] However, instead of fetal bovine serum, patient's serum was used to neutralize the enzymatic activity. Medium used to culture the cells also contained 5% autologous serum. After 2 weeks, the patient again underwent fat harvest. The prepared fat (50 mL) was enriched with ex vivo expanded ASCs and was transferred to recipient site. Ultrasonic measurements of soft tissue thickness were done at 72 hours and then at 6 months after the surgery by same sonographer. There was minimal decrease in soft tissue thickness of treated area 6 months after the surgery (44 mm vs 42 mm), and patient was highly satisfied with the outcome with the single session of the ex vivo expanded ASCs enriched fat graft.

TABLE 1. Fat Grafting

No of Sessions	Number		Age, %		P
Single session	7		28		
Two sessions	10		40		
Three sessions	8		32		
Volume Injected	**Mean**	**SD**	**Minimum**	**Maximum**	
Volume injected in 1 session, mL	25	14	6	45	
Volume injected per patient, mL	73	27	15	125	
Assessment	**Mean**	**SD**	**Minimum**	**Maximum**	
Preoperative soft tissue thickness, mm	4.67	2.43	1.60	11.1	
Postoperative soft tissue thickness 72 h after 1st fat grafting session, mm	18.62	7.8	5.70	34.20	0.00
Postoperative soft tissue thickness 6 months after 1st fat grafting session, mm	12.88	6.21	4.3	28.20	
Percentage reduction in soft tissue thickness 6 months after 1st fat graft session	30.77	13.08	12.16	66.23	

SD, standard deviation.

DISCUSSION

We prospectively evaluated the clinical outcomes of conventional fat grafting for the treatment of contour deformities of the face. Moreover to our knowledge, this is the first clinical report of use of ex vivo expanded ASCs enriched fat graft in a patient of contour deformity of face. The results of our study show that autologous fat grafting is safe and effective technique for restoring volume in contour deformities of face. However, the study found high rate of graft resorption as shown by decrease in soft tissue thickness of treated area 6 months after the first fat graft session. Although majority of the patients were happy with their postoperative facial appearance but they required more than 1 fat-grafting session to achieve satisfactory results. Contrary to it, patient undergoing ex vivo expanded ASCs enriched fat graft was highly satisfied with the single session (Fig. 1).

Autologous fat grafting reported by Neuber in 1893 has now become the most widely practiced plastic surgery procedure for soft-tissue augmentation/reconstruction and rejuvenation.[4] A large number of technical details of autologous fat grafting had been described

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claiming superiority of one over the other, in providing greater number of viable and better functioning adipocytes in fat graft.[14,15] A lack of consensus still exists regarding ideal donor site; however, majority of studies found no difference in number of adipocytes in fat harvested from abdomen, thigh, and flank or around knee.[8,16] Studies comparing harvesting method with Coleman technique (Syringe aspiration) versus pump aspiration have mentioned that Coleman technique is superior to pump aspiration as regard number of viable adipocytes.[5,9] Similarly many studies comparing processing of fat graft by gravity and filtration followed by washing versus centrifugation showed no effect on cellular viability.[16]

In the current study, we processed the samples with a rationalized approach to autologous fat grafting discussed in much of the current scientific studies. Harvesting of fat grafts was performed with less traumatic syringe aspiration method to gain maximum number of viable cells. Harvested fat was minimally handled and quickly processed with gravity and filtration. Small aliquots were injected throughout layers of tissue to improve long-term cell survival.

Fat graft outcomes are determined by a multifactorial process with highly variable retention rates as in recent reviews with a range from 32.8% to 94.1% and 20% to 95%, respectively,[16–18] Many refinements were introduced in fat harvesting, processing, and methods of reinjection to improve long-term cell survival and decrease resorption.

Like many other studies, we also found highly variable reduction in soft tissue thickness at 6 months (12% to 66%) after the first fat graft session, though all the procedures were performed by same surgeon using same technique. Unlike many surgeons who performed overcorrection to overcome long-term volume reduction, we limited correction to clinical symmetry in our patients. We believe that if excessive quantities will be injected, the fat grafts will not be vascularized appropriately and will have high rate of complications like fat necrosis and resorption. In support of this, studies have shown that larger and thicker fat grafts undergo relatively more resorption.[19,20] This is based on the fact that nonvascularized fat grafts obtain nutrients and oxygen through plasmatic diffusion from surrounding tissues until vascularization is restored by in-growth and reconnection of capillaries and vessels. The surviving area of the graft is approximately 1.5 ± 0.5 mm from the edge. As proposed previously, we believe that transferred fat may act as a natural scaffold and temporary filler to restore the volume immediately while ASCs will start participating in multiple parameters of tissue regeneration. This model supports the "host replacement theory" that has been put forward to describe how fat grafts survive after they are transplanted.[21]

Adipose tissue contains fibroblasts, endothelial cells, pericytes, preadipocytes, and various immune cells, in addition to ASCs. Furthermore, the exact proportion/quality of ASCs present in fat graft varies between individual patients. This is an important consideration in noncell-assisted lipotransfer, as Philips et al[22] have shown a correlation between graft retention and the number of ASCs present within a patient's adipose tissue.

Based on this belief, several studies have assessed the effects of cell-assisted lipo-transfer. As it stands, the current body of literature consists of a mixture of 2 different cell-assisted lipo-transfer techniques: supplementation of fat with autologous SVF cells, and supplementation with in vitro-expanded ASCs. In the first procedure, fat grafts are enriched with a freshly isolated SVF containing a mixed cell population that includes a minor fraction of ASCs. However, the reported results were not substantially better than those obtained with traditional lipofilling.[23–26] By contrast, recent animal studies have shown that fat grafts enriched with ex vivo expanded ASCs markedly improved residual graft volume and histologic appearance.[9,27,28] In a randomized placebo-controlled trial, effect of expanded ASCs on fat graft retention was studied on volunteers. Compared with controls, the ASC-enriched grafts displayed higher amounts of adipose tissue and newly formed connective tissue and less necrotic tissue after 121 days.[10] The results of our clinical report also favor the belief that the most important cell population determining the survival of fat graft is ASCs. The beneficial effect of ASCs on graft survival is thought to be because of improved early vascularization, either as the result of ASC differentiation into endothelial cells or as the result of the immunomodulatory and trophic effects of ASCs.[9,27,29,30]

Though the overall results of conventional fat grafting were acceptable but most of the patients where surgeon and patient satisfaction scores were high and had undergone multiple fat-grafting sessions. Thus, 1 cannot be certain about predictability of conventional fat graft retention for individual patient.

Majority of studies had measured outcome after facial fat graft subjectively through visual assessment or photometric evaluation (2- and 3-dimensional photography). Some studies performed 3-dimensional volumetric assessment using imaging modalities like ultrasonography, magnetic resonance imaging, computed tomography, or laser scanning. The acceptance of various imaging technologies to assess fat graft retention shows the nonexistence of a gold-standard outcome measure. In this study, we performed both photometric evaluation and volumetric assessment using B-mode ultrasonography. In our study, we had to measure the soft tissue thickness of treated areas multiple times. We were able to do this using ultrasound technology, which is noninvasive, cost effective, and easily available at our institution and avoids radiation exposure. Although use of ultrasound in facial fat graft studies is not wide spread, but considering its increasing use in soft tissue thickness measurements in breast and gluteal lipo-filling, we consider that it should be used more frequently in future studies involving facial fat grafting.[31]

In our study, frequencies of postoperative complications were comparable to those described in literature. Swelling was observed in all patients, which settled in 3 to 4 weeks. Infection was managed conservatively. Unlike few authors who reported development of acne in some of their patients after facial fat grafting, we did not encounter this complication.

It is still debated whether transplanted fat grafts survive or replaced by native fatty tissue, or an influx of fat stem cells. Researchers are continuously investigating best methods for maximizing outcomes, that is, increase the retention of the transplanted fat graft and minimizing morbidity. Advancements in pre-expansion devices, addition of platelet-rich plasma or adjuvant therapy such as SVF and ASCs, enhancing angiogenesis by addition of growth factors, or use of biochemical cell-stimulating factors, such as insulin or erythropoietin were reported to enhance graft survival.[32,33] Encouraged with our experience of treating contour deformity of face with fat graft enriched with ex vivo expanded ASCs, we have used this technique in a series of patients.

Our study has several limitations. This is a single center study limiting its generalizability. Furthermore, patients were not selected randomly with possibility of selection bias. Another limitation was small sample size of our study and short follow-up of 6 months. Although we were unable to determine long-term fate of transferred fat but previous studies have shown progressive reduction of the soft-tissue thickness within the first 3 months after initial operations with stabilization of these rates from 3 to 6 months postoperatively. The suggested superiority of ex vivo expanded ASCs enriched lipo-transfer over traditional lipo-filling should be investigated further.

CONCLUSION

Conventional fat grafting an effective technique for correction of facial contour deformities. However, the procedure needs to be repeated due to unpredictable resorption of the graft. Beneficial

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effects of ex vivo expanded ASCs on decreasing the absorption of fat graft, if confirmed in future randomized-controlled trials, have a potential to alter the current treatment paradigm of fat grafting for soft tissue reconstruction.

SUMMARY

Significant contour deformity of face causes both functional as well as esthetic problems for the patient. Conventionally, such problems are treated by allogenic fillers and major flap surgery. However, allogenic fillers absorb rapidly and are expensive. They also can produce allergic reactions. Similarly, flap surgery produces considerable donor site morbidity. Recently, autologous fat grafting has gained pervasive acceptance for the management of contour deformities of the face. Fat being an autologous tissue source is considered an ideal soft-tissue filler because it is abundant, readily available, inexpensive, host compatible, and can be harvested easily and repeatedly. We prospectively evaluated the clinical outcomes of conventional fat grafting for the treatment of contour deformities of the face. We concluded that autologous fat grafting is safe and effective technique for correction of facial contour deformities producing dramatic visible change and is without higher adverse effects. However, the procedure needs to be repeated due to significant resorption. Moreover to our knowledge, this is the first clinical report of use of ex vivo expanded ASCs enriched fat graft in a patient of contour deformity of face.

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