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Autologous fat graft assisted by stromal vascular fraction improves facial skin quality: A randomized controlled trial

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KEYWORDS
Adipose-derived SVF;
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Summary *Background:* Cell-assisted lipotransfer (CAL) promotes the survival of fat grafts with high vascular density and improves skin quality by increasing collagen content. However, no study has quantified the changes on the skin surface, and rigorous methodological evaluations are still lacking.
Design: Fifty patients were recruited and randomly divided into two groups: an experimental group ($n=25$) that underwent a stromal vascular fraction (SVF)-assisted fat graft and a control group ($n=25$) that underwent fat graft only.
Methods: The SVF cells were counted, tested in terms of viability, and characterized. The volumes of whole faces were determined by using a 3D scanner and Geomagic software preoperation, immediately after surgery, and 6 months postoperation. Facial skin qualities, including spots, wrinkles, texture, pores, UV spots, brown spots, red areas, and porphyrins, were detected by a VISIA skin detector preoperation and 6 months postoperation. A visual analog scale was used for clinical evaluation.
Results: The cell pellet contained 1-3 $\times 10^7$/mL of fresh SVF cells. The cell viability exceeded 98%. The immunophenotyping characteristics and stemness were consistent with the features of adipose- derived stem cells (ADSCs). The survival rate of SVF-enriched fat grafts was significantly higher than that of control grafts: 77.6%±11.6% versus 56.2%±9.5% ($p<0.001$). The VISIA values of wrinkles (19.3 ± 6.6 versus 10.9 ± 5.5, $p<0.001$) and texture (15.8 ± 7.0 versus 10.3 ± 5.0, $p<0.01$) were significantly higher in SVF-enriched group than in control group at 6 months postoperation. During long-term follow-up, the majority of patients in both groups were satisfied with the final facial esthetic results.

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Conclusions: Our results demonstrated the positive outcomes of autologous SVF-assisted fat graft in improving facial skin quality and its promising application potential in clinical settings. This study is registered at www. ClinicalTrials.gov, number NCT02923219.

Introduction

During aging, degenerative processes affect the skin and deep structures of the face, such as changes in collagen bundle structure, subcutaneous tissue relaxation, wrinkles, pigmentation, and uneven texture.[1] Autologous fat grafting is widely utilized for reconstructive and esthetic purposes, such as increasing the quality of skin, softening scar tissue, filling a soft-tissue defect, and increasing the projection of body parts,[2,3] because it is easily available, biocompatible, natural looking, and non-immunogenic.[4] However, the major obstacle of using fat grafts is the unpredictable and often low graft survival rate, which represents a significant burden for patients, surgeons, and healthcare systems, leading to multiple supplemental surgeries and increased treatment-associated costs.[5]

Inadequate tissue vascularization is the main cause of low graft survival.[6] Flacco et al.[7] demonstrated that deferoxamine preconditioning improves perfusion and fat graft retention. Okyay et al.[8] proved that treatment of fat grafts with the selective beta-1-blocker metoprolol resulted in a good quality graft. Moreover, cell-based strategies can enhance the survival rate of fat grafts by enriching them with additional adipose-derived stromal cells.[9]

Stromal vascular fraction (SVF) comprises multipotent elements, including adipose-derived stem cells (ADSCs), endothelial cells, fibroblasts, pericytes, and immune cells, that are easily extracted from adipose tissues.[10] SVF has been applied for the treatment of scar-related conditions, given its regenerative potential, including the release of growth factors and activation of dermal angiogenesis.[11] Koh et al.[12] postulated that enriching the vascular supply with co-implantation of SVF might improve the microenvironment and survival of the graft. In addition, the survival rates of autologous fat grafts range from 24% to 51.4%, whereas those of fat grafts enriched with a freshly isolated SVF are higher (63% to 90.4%) than those of traditional lipofilling at 12–19 months of follow-up.[13–15]

Animal studies have shown that subcutaneous ADSCs injections increase dermal thickness and collagen density in aged mice and reduce wrinkles induced by UVB irradiation.[16] Clinical studies have shown that grafting fat tissue in an irradiated area can improve skin quality.[17] In clinical practice, plastic surgeons have found that the skin qualities of patients who received facial fat grafts improved postoperatively. However, no study has quantified the changes on the skin surface, and rigorous methodological evaluations are still lacking. Thus, given the potential ability of SVF application to improve facial skin quality, this study aimed to quantify the rejuvenating effects of the SVF enrichment of fat grafts. Results were shown in terms of fat graft survival and facial skin quality.

Methods trial design

The authors adhered to CONSORT (Consolidated Standards of Reporting Trials) guidelines to report this randomized clinical trial. A single-center, parallel, prospective, randomized controlled trial designed to assess the therapeutic effects of SVF-enriched fat grafts on facial skin quality was undertaken at the Department of Plastic Surgery, Xuzhou Medical University's affiliated hospital from September 2016 to January 2019. The study protocol complied with the Declaration of Helsinki and was approved by the ethics committee of the Affiliated Hospital of Xuzhou Medical University (No. XYFY2016-KL020-02). All patients provided written informed consent. The study is registered at www. ClinicalTrials.gov (number NCT02923219).

Participants

Fifty participants from Xuzhou and surrounding cities were included in accordance with the following inclusion criteria: healthy females, aged 20–55 years old, body mass index (BMI) range of 18.5–24 kg/m^2, and requiring autologous fat graft. Patients were excluded in accordance with the following exclusion criteria: known chronic diseases (e.g., hypertension, diabetes, and cardiopathy), psychosis, genetic diseases, infectious diseases, smoking, pregnancy or planned pregnancy within a year after the procedure, breastfeeding, allergy to the drugs used for general anesthesia, non-native or planned emigration within a year after the procedure, strong treatment preferences, and consequent refusal to undergo randomization. All eligible participants were assessed by two experts in plastic surgery and informed about both treatments.

Interventions

The participants underwent facial autologous fat transfer with or without SVF. Fat tissue was harvested from the inferior abdomen under general anesthesia via standard sterile liposuction techniques as described by Coleman.[18] In the experimental group, 200–240 mL of fat tissue was harvested per person. A quarter of the aspirated fat was reserved as a cell scaffold. Three quarters of the aspirated fat was sent for SVF isolation. In the control group, 50–60 mL of fat tissue was harvested per person via the same method.

All of the SVF samples were processed with the same laboratory technique as previously described[19] in a good manufacturing practice (GMP)-grade laboratory (Figure S1). All reagents and biological samples were sub-

jected to standard microbiological identification to detect microorganisms. The SVF-fat complex was prepared within 1.5 h.

The two groups were subjected to the same steps which have been widely used for successful fat transplantation.[18] The procedure was performed by the same plastic surgeon. Local graft doses were adjusted during the procedure in accordance with the following esthetic conditions: mainly 8-12 mL in the forehead, 5-10 mL in the bilateral temporal, 6-10 mL in the bilateral cheek, 3-6 mL in the bilateral nasolabial groove, and 2-4 mL in the bilateral zygomatic. The total amounts of fat injected in each patient were recorded.

The patients were tracked systematically. Oral antibiotics and detumescence drugs were administered within 3 days after surgery. The patients were advised to avoid rubbing and pressing their faces. The dressing was changed 2 days after the surgery. The suture was removed 7 days after the surgery. The regular follow-up was conducted. The patients were photographed preoperation and 6 months postoperation for clinical evaluation.

Outcomes

In the laboratory, the SVF cells were counted, tested in terms of viability, and characterized.

The primary outcome was 3D facial volumetry done using Artec's handheld 3D scanner (Artec, USA). A 3D scanner was used to scan the whole face preoperation, immediately after surgery, and 6 months postoperation. Geomagic software was utilized to calculate the volume changes at different time intervals on the basis of which one was best fitting (Figure S2). The participants were scanned by a well-trained technician in the 3D Digitization Center of our hospital.

Another primary outcome was the facial skin qualities of individuals, which were recorded preoperation and 6 months postoperation by using a VISIA skin detector (Canfield, USA).[20] The instrument is used for the quantitative analysis of the pathological features, including spots, wrinkles, texture, pores, UV spots, brown spots, red areas, and porphyrins of the facial skin. Percentile refers to the ranking of skin levels among people of the same age, gender, and race. The higher the percentile is, the better the skin level will be. The average of the three perspectives obtained from the left, center, and right sides was used as the data for the next statistical analysis. VISIA value is equal to the difference in percentiles preoperation and 6 months postoperation. A 3D viewer system in VISIA displays the patient's skin texture. Red represents bulges, and blue indicates dents.

As a tertiary outcome, a visual analog scale with five possibilities (i.e., very unsatisfied, unsatisfied, neither unsatisfied nor satisfied, satisfied, and very satisfied) was used for clinical evaluation. Patients from both groups were instructed to answer the satisfaction questionnaire during their follow-up 6 months postoperation.

Sample size

Fifty patients would be needed to detect a difference between groups.

Randomization

Research coordinators at each center randomly assigned eligible participants using an interactive voice response (IVR) system. The blinding of allocation was guaranteed by using opaque sealed envelopes containing assignments. Patients and clinical efficacy evaluators, including 3D scanning and skin-quality-detecting technicians, were blinded before and after the assignment to interventions.

Statistical analysis

Data were statistically analyzed using SPSS 20 (IBM, Chicago, IL, USA), and graphs were generated using Prism 6 (GraphPad Software, La Jolla, CA, USA). Student's *t*-test, paired-sample *t*-test, or one-way ANOVA was used for comparisons. Two-sided $p<0.05$ was considered statistically significant.

Results

Study population

Figure 1 illustrates the flow diagram of the study. No adverse events were observed during the liposuction, lipofilling, and long-term follow-up of patients in both groups. Thus, no participant was excluded or withdrawn. The patient demographics are presented in Table S1. The participants in the SVF-enriched and control groups were 35.5 ± 8.2 (range: 22-50 years old) and 35.3 ± 8.1 years old (range: 20-51 years old) with no significant differences ($p = 0.917$), respectively. The BMI of the participants in the SVF-enriched and control groups was 21.2 ± 1.8 and 21.6 ± 1.9 Kg/m^2 with no significant differences ($p = 0.487$), respectively.

Cell identification

The cell pellet contained $1\text{-}3 \times 10^7$/mL of fresh SVF cells. The cell viability by trypan blue exclusion consistently exceeded 98%. The P3 cells after culture expansion presented a typical fibroblast-like morphology. The immunophenotyping characteristics and stemness were consistent with the features of ADSCs (Figure S3).

Survival rate of grafted fat

The measured graft volume of all patients' grafts was 56.7 ± 3.7 mL, and the actual graft volume of all grafts was 56.0 ± 3.8 mL ($p = 0.270$, Table 1, Figure S4A). The initial facial volumes of the SVF- enriched and control groups were 1206.4 ± 146.5 and 1231.8 ± 146.3 mL ($p = 0.542$), respectively. On day 180, the residual volumes of the SVF-enriched and control groups were 1249.3 ± 146.9 and 1263.5 ± 145.8 mL, respectively ($p = 0.734$, Table 2, Figure S4B), corresponding to 42.9 ± 5.6 and 31.7 ± 5.2 mL of the volume differences 6 months postoperation ($p<0.001$). The volumes of fat transferred in the SVF-enriched and control groups were 55.6 ± 3.8 and 56.5 ± 3.8 mL without statistical difference ($p = 0.419$, Table 2, Figure 2A). The volumetric

Table 1 Face volume of all patients preoperation and immediately after surgery.

	Measured value ($n=50$)	True value ($n=50$)	t- value	p- value
Face volume preoperation (mL)	1219.1 ± 145.5	/	/	/
Face volume immediately after surgery (mL)	1275.8 ± 145.5	/	107.452	<0.001*
Volume difference(mL)	56.7 ± 3.7	56.0 ± 3.8	1.116	0.270**

* Face volume preoperation vs. Face volume immediately after surgery.
** Volume difference Measured value vs. True value n = patient number.

Table 2 3D volumetry of fat graft in both groups.

	Experimental group ($n=25$)	Control group ($n=25$)	t-value	p-value*
Face volume preoperation (mL)	1206.4 ± 146.5	1231.8 ± 146.3	-0.614	0.542
Face volume immediately after surgery (mL)	1263.3 ± 147.5	1288.2 ± 145.4	-0.602	0.550
Face volume 6 months postoperation (mL)	1249.3 ± 146.9	1263.5 ± 145.8	-0.342	0.734
True graft volume (mL)	55.6 ± 3.8	56.5 ± 3.8	-0.816	0.419
Measured graft volume (mL)	56.9 ± 3.7	56.4 ± 3.8	0.485	0.630
Volume difference 6 months postoperation (mL)	42.9 ± 5.6	31.7 ± 5.2	7.405	<0.001
Volumetric persistence (%)#	77.6 ± 11.6	56.2 ± 9.5	7.127	<0.001

* Experimental group vs. Control group.
# Volumetric persistence = Volume difference 6 months postoperation / True graft volume n = patient number.

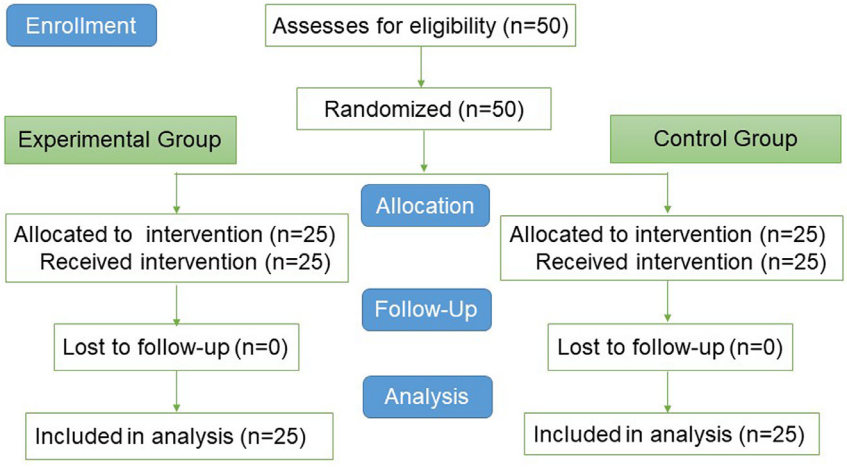

Figure 1 CONSORT flow diagram.

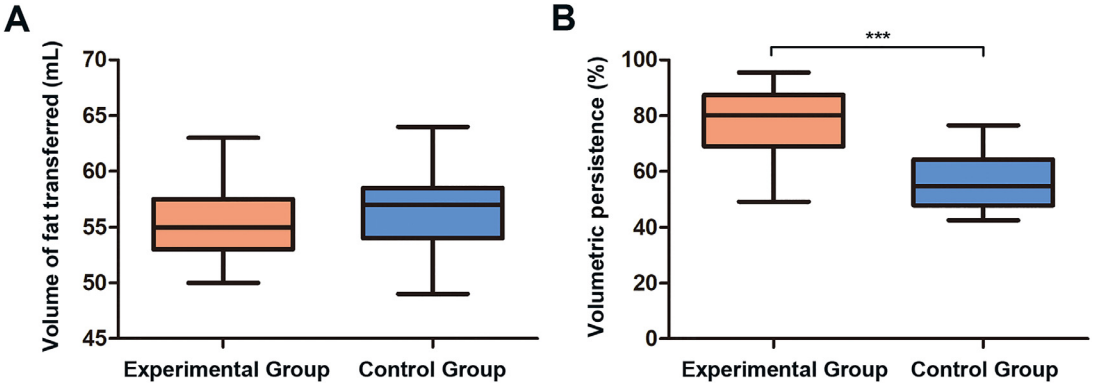

Figure 2 A. The volumes of fat transferred in the experimental and control groups. B. The volumetric persistence values in the experimental and control groups. ***$P<0.001$.

Table 3 VISIA values of the therapeutic effect on facial skin quality in both groups.

	Experimental group ($n=25$,%)	Control group ($n=25$,%)	t-value	p-value*
Spots	9.7 ± 4.2	9.0 ± 5.5	0.465	0.644
Wrinkles	19.3 ± 6.6	10.9 ± 5.5	4.908	<0.001
Texture	15.8 ± 7.0	10.3 ± 5.0	3.189	0.003
Pores	8.8 ± 3.9	6.8 ± 3.7	1.824	0.074
UV spots	7.2 ± 4.0	6.0 ± 4.5	0.954	0.345
Brown spots	6.6 ± 5.5	5.9 ± 4.3	0.545	0.589
Red areas	7.3 ± 4.9	5.7 ± 4.5	1.176	0.245
Porphyrins	1.0 ± 6.9	1.8 ± 9.3	−0.310	0.758

* Experimental group vs. Control group n = patient number.

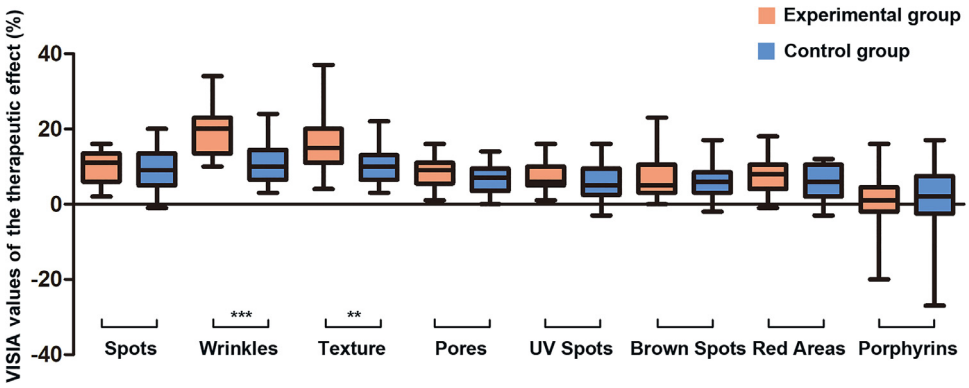

Figure 3 The VISIA values of the therapeutic effect on facial skin quality in experimental and control groups. $^{**}P<0.01$, $^{***}P<0.001$.

persistence values of the SVF- enriched and control groups were 77.6%±11.6% and 56.2%±9.5% ($p<0.001$, Table 2, Figure 2B).

Improvement in facial skin qualities

The baseline VISIA values between groups are presented in Table S2, with no significant differences in terms of spots, wrinkles, texture, pores, UV spots, brown spots, red areas, and porphyrins ($p=0.566$, 0.585, 0.279, 0.211, 0.814, 0.924, 0.806, and 0.946, respectively). The VISIA values of the therapeutic effect on facial skin quality in both groups are shown in Table 3 and Figure 3. The skin qualities of the SVF-enriched and control groups were both improved in terms of spots, wrinkles, texture, pores, UV spots, brown spots, and red areas compared with the preoperative skin qualities. The VISIA values of wrinkles and texture were significantly higher in the SVF-enriched group than in the control group: 19.3 ± 6.6 versus 10.9 ± 5.5 ($p<0.001$) and 15.8 ± 7.0 versus 10.3 ± 5.0 ($p=0.003$), respectively. No significant differences were observed between the experimental and control groups in terms of spots, pores, UV spots, brown spots, and red areas ($p=0.644$, 0.074, 0.345, 0.589, and 0.245, respectively). Porphyrins, which are the bacterial metabolite in the mouth of the hair follicle, were not affected by the study factors.

The representative case photos from the control and experimental groups are shown in Figures S5A and S6A, respectively. After the fat was transplanted, the overall face contour became round because of the increased volume of facial soft tissue. The skin qualities improved significantly; that is, less wrinkles and brighter skin were observed. The changes in skin texture are shown in the 3D viewer (Figures S5B and S6B). The cuticle groove became more even, and the skin became fuller.

Clinical evaluation

Analysis of the satisfaction assessment questionnaire revealed that all patients in both groups were sufficiently informed about the fat grafting procedure, and the majority of participants in both groups were satisfied with the final facial esthetic results during long-term follow-up.

Cost analysis

Table S3 shows the cost analysis of surgeries between groups. Hospital costs were essentially equivalent between the two cohorts except the cost of SVF. Anesthesia time in the SVF-enriched and control groups were approximately 4 and 2.5 h, respectively. The total costs in the SVF-enriched and control groups were approximately $7390 and $6601, respectively.

Discussion

Skin aging is characterized by darkened coloration, increased wrinkles, pigmentation, and sagging. Fat graft can

effectively fix facial soft tissue volume loss and play a good role in filling sunken wrinkles.[21] According to data released by the International Society of Aesthetic Plastic Surgery, autologous fat graft was a common operation for breast and buttock augmentation and facial rejuvenation, accounting for more than 1000,000 procedures performed throughout the world in 2017.[22]

The primary hypothesis of the study was that SVF could improve the survival rate and esthetic purposes of fat graft. However, there is no consensus about how many cells are needed for optimum graft survival and how much fat should be used to isolate the amount of cells in humans so far.[23]

In previous human studies, almost half of the lipoaspirate was used for the isolation of SVF, which increased the ADSCs concentration by 2–5 times compared with non-SVF fat graft.[24] In this study, the proposed method was optimized to produce an enrichment rate (3:1 ratio) that is higher than Yoshimura et al.'s previous principle: CAL (1:1 ratio),[25] which can be simply and conveniently reproduced in an operating theater by other investigators.

Adipose grafts probably turn over rapidly during the first 2–3 months after transplantation because of temporary ischemia followed by reperfusion injury. The selected observation deadline in this study was 6 months postoperation because adipose grafts stabilize 3–6 months after lipoinjection. A huge variability exists in the observations of graft survival by different authors who used different methods.[26] In this study, the measured values correspond well to the true values, indicating the accuracy and credibility of the measurement based on a 3D scanner and Geomagic software. Our results showed that the survival rate of conventional autologous fat grafts was 56.2%±9.5%, which was consistent with Tanikawa's facial lipofilling results.[27] The survival rate of SVF-assisted fat graft was 77.6%±11.6%, which was significantly higher than that of conventional autologous fat graft. With an increment of 20% in graft survival, SVF enrichment could bring about a greater fat transplant volume per session with a higher retention rate, resulting in fewer necessary sessions to achieve satisfactory results.

Autologous fat can improve skin qualities in recipient zones.[28] Our results revealed that all indices except porphyrins in both groups improved significantly after the operation, indicating that the fat grafts with or without SVF were effective in improving the skin quality. However, after lipofilling was conducted, the improvement of wrinkles and texture was significantly greater in the SVF- enriched group than in the control group. This difference cannot be accredited to the increase in survival of grafted fat alone. Some animal experiments have confirmed that the improvement in skin texture by SVF-enriched fat is greater than that by non-enriched fat.[9] Key growth factors (i.e., fibroblast growth factor, vascular epithelial growth factor, and transforming growth factor) are endogenously induced by SVF, resulting in the stimulation of fibroblasts and collagen production within the skin.[29] Furthermore, SVF can provide an enhanced biological framework for adipocytes, thereby favoring adipose tissue survival.[30] These observations indicated that the combination of adipocytes and SVF might be an important factor in improving the efficacy of rejuvenation therapy. Certainly, many researchers also reported a similar positive effect of platelet-rich plasma (PRP) addition as an alternative approach in fat grafting.[31] However, for some patients with fat accumulation, extracting SVF from a large number of excess aspirated fat is better than extracting PRP from blood.

Other variables correlated to autologous fat graft success must also be considered, such as age of the patient, mobile versus less mobile areas of the face, compartments on the face, and impact of recipient site external expansion.[32] In addition, tanning and the rejuvenation affected by theseason were unavoidable, thus we required the patients to maintain the same living habits and places of residence as before, within 6 months after surgery.

In this clinical trial, satisfactory clinical results were generally achieved without any major complications. The overall cosmetic results were generally satisfactory. According to the clinical observation by peers, the facial fat graft assisted by SVF could yield better and lasting improvement effects on gravitational wrinkles and skin texture.

The last aspects considered were the effects resulting from the cost-benefit of operation. Hospitals around the world charge different prices. All costs in this clinical trial were calculated in accordance with prices set for 2016 in our hospital. Although the SVF-enriched fat graft took a longer duration of operation (approximately 1.5 h) and had the extra cost of consumables (approximately $789 per session), the patients did not have to accept multiple sessions, resulting in less treatment-associated costs (approximately $6601 per session). Thus, the SVF-enriched fat graft may be considered a cost-effective approach.

Adipose-derived SVF, progenitor, and stem cells have made significant strides as a therapeutic modality in recent years, and they are allowed for clinical use in many countries, such as the USA, the UK, Russia, Italy, France, India, Brazil, Korea, and China.[33] However, significant barriers remain to the safe and efficacious use of stem cell therapies. In the USA, any surgeon who wishes to use ADSCs isolated via collagenase needs to submit an Investigational New Drug application to the FDA and have an approved institutional review board with the referring institution.[34] In Europe, the process of converting protocols, including collagenase-processed ADSCs, into a process that is compliant with the European good manufacturing process (eGMP) requires assays that have carefully considered all the risks and benefits for the patient end user.[35] Given the current culture and the complexity of regulatory issues, expanded ADSCs are only allowed in some registered clinical trials in China. Thus, isolating SVF from large amounts of fat tissues can secure a sufficient number of cells without excessive culture or passage requirements and is a feasible treatment in the current commonly accepted practices.

Finally, our study has some limitations that should be addressed to further improve its implementation in clinical surgery. For example, quantitative analysis of various cell components in SVF and the quantity proportions of SVF cells and adipose cells were not conducted. In addition, the SVF group needed approximately 1.5 h longer than the control group because it could be unwise and unethical to make the patients in the control group wait for the re-injection under anesthesia without any operation for the consistency of OR time between groups.

Overall, autologous adipose-derived SVF-assisted fat graft appeared to be a valid alternative for patients to receive treatment for facial rejuvenation and contour

improvement. In addition, controlled implementation of cell-based therapies is crucial for the appropriate translation of this technology to the clinical setting.

Declaration of Competing Interest

None.

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Participating Center: Affiliated Hospital of Xuzhou Medical University, Department of Plastic Surgery.

Research Coordinators and Research Assistants (2016-2019): Yating Yin MD[1], Jianhua Li MD[1], Hao Wang MD[1], Pingping Wang MD[1], Wanling Zheng MD[1], Jianxia Hao[1], Yanping Guo MD[1], Wenli Liu[1], Hao Xiao[1], Jing Wang[1], Chengwei Zhao[1] and Yixian Shan[1]. The Research Coordinators and Research Assistants screened patients, obtained consent, randomized participants and collected data.

Senior Cell Bank Technologists: Hanxiao Wei MD[1], Yating Yin MD[1], Feifei Chen PhD[2], Xia Zheng PhD[1], Haiyan Ren PhD[1], Chao Lv PhD[1] and Weiyun Ma PhD[1]. The cell bank technologists implemented the study interventions.

Medical Directors, Cell Bank: Dr. Peisheng Jin MD[1], Dr. Aijun Zhang MD[1] and Dr. Qiang Li MD[1]. **Adjudicators:** Dr. Peisheng Jin MD[1], Dr. Changbo Tao MD[1] and Dr. Xueyang Li MD[1]. Primary Outcomes were adjudicated for presence and severity.

DSMB: Dr. Tie Xu MD[1] and Xiaomei Wang MHA[1]. The Data and Safety Monitoring Board reviewed two formal interim analyses and regular reports of our primary composite outcome as well as serious adverse events.

Statisticians: Prof Huashuo Zhao D.Sc.[3], Yating Yin MD[1] and Jianhua Li MD[1]. The statisticians performed quality assurance checks on data and conducted the study analysis.

Data Entry: Jing Wang[1], Chengwei Zhao[1], Caiqi Shen MD[1] and Qichuan Yin MD[1]. Data Entry personnel uploaded Case Report Forms, reconciled data queries and conducted quality assurance checks on the database.

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Data Access and Responsibility: The principal investigator, Peisheng Jin, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2019.11.010.

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