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ORIGINAL ARTICLE

Autologus bone marrow stem cells in atrophic acne scars: A pilot study

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Abstract

Background: Acne scar is a very distressing and difficult problem for physicians and patients. Management of cutaneous scarring from acne can be challenging and confusing. The available modalities may be effective, having considerable morbidity and long downtime. Besides, they may not have the same efficacy in different skin types or acne scar types.
Objective: To evaluate the short-term safety and efficacy of autologous bone marrow (BM) stem cells (SCs) in treating atrophic acne scars.
Methods: Fourteen patients with moderate to severe atrophic acne scars were included. All patients were subjected to single session of autologous BMSCs therapy. Each patient received 5 μg/kg/day granulocyte colony-stimulating factor (G-CSF) as a single subcutaneous dose for 2 successive days before BM aspiration. The SC-containing solution was injected under each scar intradermally. The scars of the patients were clinically assessed both qualitatively and quantitatively before and after 6 months. The patients were given a preformed questionnaire Cardiff acne disability index (CADI) before and after treatment.
Results: After 6 months of the injection, there was significant improvement in the qualitative grading, quantitative grading and CADI scores. All types of scars showed significant improvement. No significant adverse effects were reported in any patient.
Conclusion: Autologous BMSCs seem to be a safe and effective treatment option for the management of all types of atrophic facial acne scars.

Keywords

Acne, atropic scars, injection, stem cell

History

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Introduction

Acne affects over 80% of the population at some point in their lives, yet not all people with acne develop scars. It is currently not possible to predict which patient may have scar and which may not. Facial acne scarring is a psychologically devastating condition (1,2). Acne scars may be atrophic or hypertrophic. The former type is usually classified into rolling, ice pick and boxcar (3).

Different treatment modalities have been used to ameliorate atrophic scars with varying degrees of success. These include chemical peels, subcision, surgical excision, punch grafting, dermabrasion, ablative and nonablative laser resurfacing as well as tissue augmentation with a variety of fillers (4). The majority of traditional treatment options suffer from the limitation of either being marginally effective or having considerable morbidity. Treatment options like laser resurfacing or dermabrasion that offer significant improvement in facial scars are invariably associated with considerable morbidity and long downtime and interfere with the daily activities of the patient in the post-treatment period. On the other hand, treatments like microdermabrasion and nonablative resurfacing with lasers that are associated with minimal or no downtime do not show the same level of efficacy as the traditional, ablative resurfacing techniques (5).

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Stem cells (SCs) are the self-renewing progenitors of specialized body tissues, undifferentiated SCs have the capacity to generate one or more specialized tissues and they are responsible for the ability of an organism to heal certain types of injury. These cells can be isolated from a variety of sources including embryos, umbilical cord blood (UCB) and adult tissues (6). The use of adult SCs as mesenchymal stem cells (MSCs) is becoming more realistic in skin and scar repair. MSCs can be isolated from bone marrow (BM) and other tissues such as adipose tissue, UCB and skin tissue (7). SCs have the properties of self-renewal and multipotency. BM-MSCs can differentiate into multiple skin cell types, such as keratinocytes and fibroblasts that contribute to skin repair and improvement of scar healing (8).

The aim of this work was to evaluate the short-term safety and therapeutic effect of the autologous BMSCs in treating atrophic acne scars.

Patients and methods

This study was carried out on 14 patients (10 males and 4 females) suffering from moderate to severe atrophic acne scars. They didn't receive any treatment for acne scars for 1 year before enrollment in the study. All patients had acne scars with no active acne lesions in the last year. Patients underwent previous treatments varied from dermabrasion (six patients), chemical peel (five patients) or Erbium fractional laser resurfacing (three patients). The age of the patients ranged from 29 to 42 years (mean 34.8 ± 6.29). The majority of the patients were in the third decade of their life. All patients were of African Egyptian race.

They were selected from the Outpatient Clinic of Dermatology and Venereology Department, Tanta University Hospital. This study was done in cooperation of four departments: Dermatology, Clinical Pathology, Internal Medicine, and Anesthesia and Intensive Care. The study protocol and the consent were approved by the local ethics committee. After taking an informed consent from the patients, they were subjected to complete history taking, thorough general and dermatological examination, routine laboratory investigations including bleeding, prothrombin and coagulation time test, to exclude any hematologic diseases. Chest X-ray and abdominal ultrasound were done to exclude any systemic illness. Each patient received granulocyte colony-stimulating factor (G-CSF) (Neubogen) for 2 successive days before BM collection, by a dose of 5 μg/kg/day by subcutaneous route till white blood cells reach 17 000/μl. Then, BM samples were collected under complete aseptic conditions.

Bone marrow aspiration

Assay procedure

The patients were given inhalational anesthesia. Fifty milliliters of the BM was harvested from the upper iliac crest by using an aspirate needle under complete aseptic conditions. The aspirated BM was collected in a sterile conical tube, which contained 4 ml of anticoagulant (heparin). Isolation of mononuclear cells from the BM aspirates by density gradient centrifugation was done; only fresh BM was used; freezing and thawing of BM cells was avoided. All steps were performed under complete aseptic conditions.

The aspirated BM was diluted at a ratio of 7:1 with buffer. Cells were passed through a 100-μm filter to remove bone fragments and cell clumps. Thirty milliliters of diluted cell suspension was carefully layered over 15 ml of ficoll-paque in a 50-ml conical tube. Centrifugation at 2000 rpm for 20 minutes at 20 °C in a swinging bucket rotor without brake was done. The BM-MNCs were carefully transferred at the interphase to a new 50-ml conical tube. Cells were washed twice by adding up to 40 ml of buffer, mixed gently and centrifuged at 1500 rpm for 10–15 minutes at 20 °C. The supernatant was carefully removed completely. For removal of platelets, the cell pellet was resuspended in 50 ml of buffer and centrifugation at 1500 rpm for 10 minutes at 20 °C was done. Then the supernatant was carefully removed completely. The cell pellet was resuspended in appropriate amount of buffer for downstream applications.

Evaluation of the patients

The patients were photographed by using a canon camera 14 mega pixels at the start of the study and monthly for the next 6 months (Figures 1 and 2). All patients were assessed clinically at the time of enrolment and at the end of the study by the qualitative grading score (Table 1) (9). The appearance and grading of scars were then compared with those in the pretreatment period. On the objective lines, an improvement of scarring by two grades or more was labeled as excellent response, whereas a good response meant an improvement by a single grade only. Any invisible change in the facial scarring response was labeled as poor (5). Quantitative assessment of acne scar improvement was done by counting the

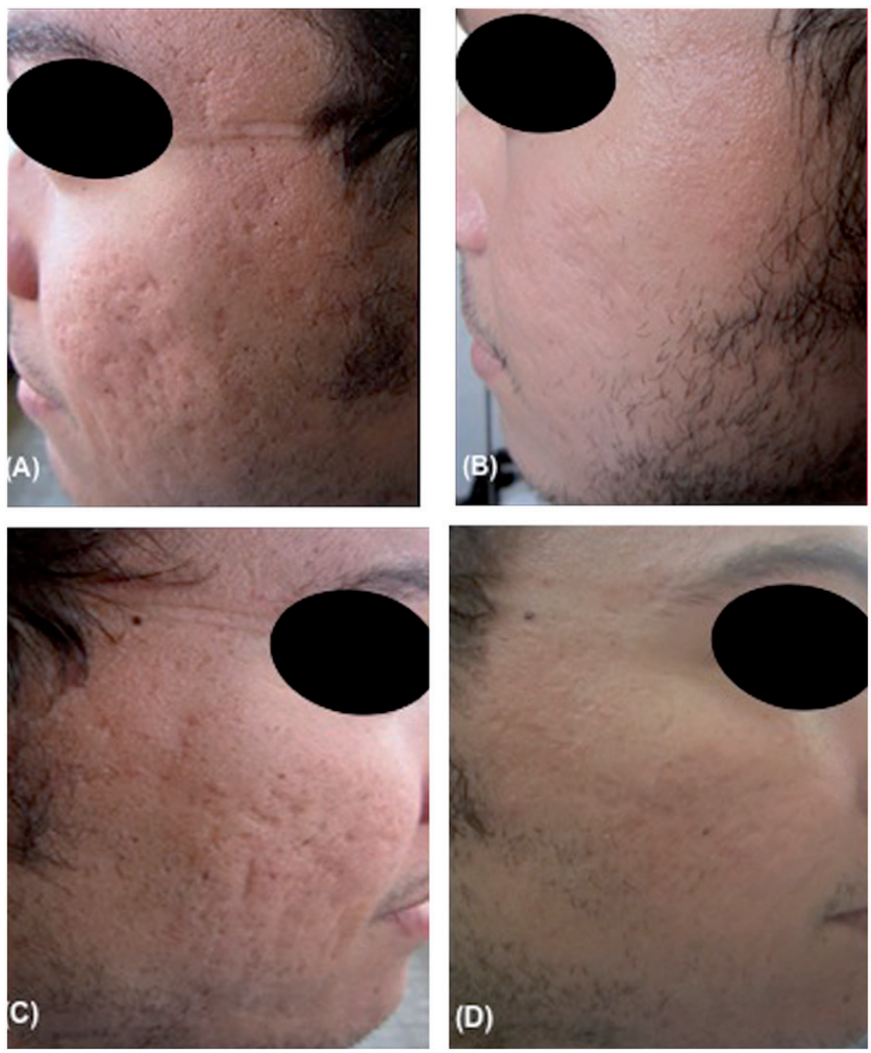

Figure 1. A patient showing excellent response (A): left side before treatment. (B): Left side after treatment. (C): Right side before treatment. (D): Right side after treatment.

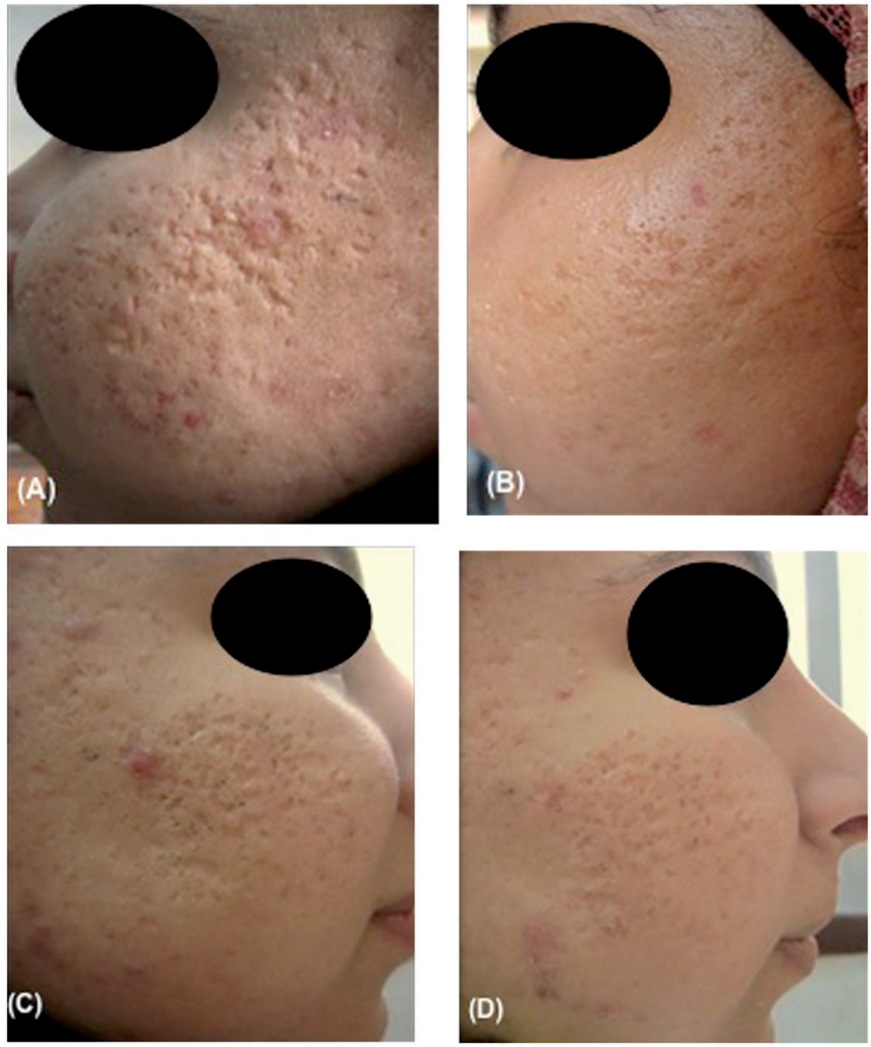

Figure 2. A patient showing good response (A): left side before treatment. (B): Left side after treatment. (C): Right side before treatment. (D): Right side after treatment.

Table 1. Qualitative scarring grading system.

Grades of acne scarring	Level of disease	Clinical features
1	Macular	These scars can be erythematous, hyper- or hypopigmented flat marks
2	Mild	Mild atrophy scars not obvious at social distances of >50 cm or easily covered by facial makeup or beard hair
3	Moderate	Moderate atrophy obvious at social distances of >50 cm; not easily covered by makeup or beard hair, but able to be flattened by manual stretching
4	Severe	Severe atrophic scarring that is evident at social distances greater than 50 cm and is not covered easily by makeup or the normal shadow of shaved beard hair and is not able to be flattened by manual stretching of the skin

total and the differential number of acne scars on both sides of the face before and after 6 months of BMSCs injection, and the percentage of improvement was calculated. The patients were also given a preformed questionnaire called Cardiff acne disability index (CADI) before and after treatment. The line of the questionnaire is made up of five quality-of-life questions graded on a scale of 0–3, with 0 being no impairment and 3 being greatest impairment. The CADI score is calculated by summing the score of each question, resulting in a possible maximum of 15 and a minimum of 0. The higher the score, the more the quality of life is impaired (10).

Intradermal injection

Local anesthesia was applied to the face for 30 minutes before injection. The face was cleansed using local antiseptic solution (alcohol 70%), and SC-containing solution was injected using a 26-gauge needle. Under each scar 0.1–0.3 cc was injected intradermally. Slight compression using cold compresses was done without massage. The patients were kept under observation in the hospital for 1 day and instructed to use sunscreen with SPF50 before going outdoors and topical antibiotic for 2–3 days. The patients were specifically asked about the immediate post-treatment sequel and whether there was any interference with their daily activities in the post-treatment period. Adverse effects of the treatment were reported.

Statistical methods

The analysis was done using SPSS version 11.5 (SPSS Inc., Chicago, IL) for windows statistics software package. Data were expressed as mean ± standard deviation (SD). p Values <0.05 were considered significant. Parametric tests such as t-test were applied for data that followed a normal distribution. Nonparametric tests such as Mann–Whitney U test, Wilcoxon-signed ranks test and Chi-squared test were applied for data that did not follow a normal distribution. Correlations were done using Kendall's tau-b correlation.

Table 2. Differential count of acne scar type's assessment before and after bone marrow stem cell injection.

Acne scar count	Before treatment	After treatment	Z	p
Icepick scars				
Range	7–33	2–16	2.375	0.018*
Mean ± SD	23.57 ± 9.71	8.57 ± 4.61		
Rolling scars				
Range	11–33	4–12	2.366	0.018*
Mean ± SD	19.29 ± 8.22	7.57 ± 3.10		
Boxcar scars				
Range	12–60	6–35	2.366	0.018*
Mean ± SD	41.28 ± 17.16	16.43 ± 11.44		

Z = value for Mann–Whitney test; *statistically significant at $p \leq 0.05$.

Table 3. Acne scar qualitative grading, quantitative grading and CADI scores.

Assessment parameters	Before treatment Mean ± SD ($n = 14$)	After treatment Mean ± SD ($n = 14$)	p value
Qualitative grading score	3.6 ± 0.5	1.9 ± 0.9	<0.01*
Quantitative grading score	83 ± 21.5	34.6 ± 15.6	<0.01*
CADI score	12 ± 3.1	4.6 ± 2.9	<0.01*

*Statistically significant at $p \leq 0.05$.

Results

The patients showed gradual variable progressive improvement of the lesions started at the end of the first month up to the sixth month. In the present study, after intradermal BMSCs injection, the patients started to observe some improvement at the end of the first month to the second month. The skin showed marked changes in hydration, skin tightening and texture improvement (Figures 1 and 2). Follow-up of the patients for 6 months revealed persistent progressive improvement. The effectiveness of BMSCs in all patients was variable irrespective of the previous treatment received.

All scores including qualitative grading, quantitative grading and CADI scores were significantly improved at the sixth month after BMSCs injection. Qualitative grading significantly improved from a mean of 3.6 ± 0.5 to a mean of 1.9 ± 0.9 ($p < 0.01$). Eight patients had an excellent response (Figure 1), five patients had a good response (Figure 2) and one patient had a poor response. The mean percentage of improvement was 46.4 ± 23.9. The quantitative grading significantly improved from a mean of 83 ± 21.5 to a mean of 34.6 ± 15.6 ($p < 0.01$). The mean percentage of improvement was 58.1 ± 19.4. All types of acne scars were counted in each patient before and 6 months after the injection and showed significant ($p < 0.01$) improvement, with no significant difference between different types of scars ($p = 0.072$) (Table 2). CADI score significantly improved from a mean of 12 ± 3.1 to a mean of 4.6 ± 2.9 ($p < 0.01$). The mean percentage of improvement was 61.5 ± 29.7 (Table 3 and Figure 3).

The improvement in qualitative grading was correlated with the improvement of both the quantitative grading and CADI score ($p < 0.01$). The Kendal's tau correlation coefficients were 0.803 and 0.655, respectively. The improvement in quantitative grading was correlated with that of CADI score as well ($p < 0.01$). The Kendal's tau correlation coefficient was 0.671.

All patients tolerated the procedure well except four patients complained of bone ache after the BM harvesting (28.6%), which was relieved by analgesics within 2–3 days. Mild erythema was observed on the face after injection that persisted for 1 day in the four patients (28.6%). Two patients (14.3%) complained of acniform eruption after the procedure but improved by using topical clindamycin (Table 4). The patients were able to perform their daily activities on the same day or the next day after intradermal SC injection.

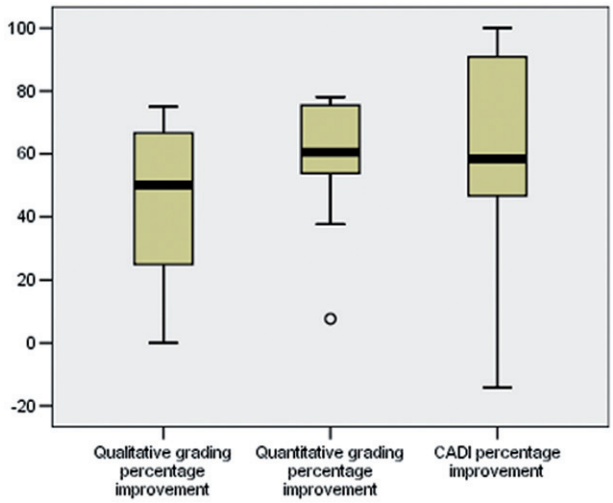

Figure 3. Boxplots of the percentage improvement of the qualitative grading, quantitative grading and CADI scores.

Table 4. Side effects after autologous bone marrow stem cell injection.

Side effects	Number of patients	Percentage (%)
Bleeding at the site of bone marrow aspiration	–	0
Bone ache after bone marrow harvesting	4	28.6
Erythema	4	28.6
Bruises	–	0
Acne form eruption	2	14.3
Post-inflammatory hyperpigmentation	–	0
Interference in the patient's daily activities	–	0

Discussion

The use of adult SCs is becoming more realistic in both skin and scar repair. SCs can be isolated from BM and other tissues such as adipose tissue, umbilical cord and skin tissue. BMSCs may contribute to tissue repair or regeneration of many tissues including myocardium, blood vessels, damaged bone, tendon, cartilage, and skin (11,12). It is clear that normal skin contains BMSCs that are involved in host defense and inflammatory processes and regulate genesis of the epidermis (13). There is a great interest to look for autologous agent as dermal filler used to fill scars and wrinkles (14). This study was carried out on 14 patients with moderate to severe atrophic acne scars. These patients were given G-CSF for 2 successive days before BM aspiration to increase the number of SCs in the BM as the G-CSF receptors are present on precursor cells in the BM leading to their proliferation (15).

Up to our knowledge, this is the first pilot study providing that the BMSC intradermal injection was effective in the treatment of moderate and severe acne scars. The improvement in acne scars in this study was evaluated by three different methods: the quantitative grading system, the quantitative grading system and patient satisfaction score (CADI). BMSC treatment was successful in improving all the three grading scales significantly.

In our study, gradual persistent improvement started by the end of the first month and reached its maximum in 6 months with marked improvement in skin hydration, tightening and texture.

This suggests that such acne scar improvement is expected to be permanent. Long-term results will be reported in the due time.

Interestingly, BMSCs gave such significant improvement in qualitative grading, quantitative grading and CADI scores even in severe acne scars with only one session in short time. Literature review on acne scars recorded that Q-switched and fractional CO_2 laser are required to produce an improvement in mild to moderate acne scars in multiple sessions (16–18).

Correlating the response with the type of acne scars after BMSC therapy showed that there was significant improvement in all types of acne scars. Review of literature revealed that it is difficult to find a single modality effective in all types of acne scars. It is reported that Nd-YAG laser is most effective in superficial boxcar and rolling scars (19). Furthermore, Er-YAG is most effective in ice pick scars (20), whereas the dual mode is effective in rolling and deep boxcar scars (21,22). Therefore, SC therapy in acne scars could be superior to other lines of therapy since it is effective in all types of acne scars after one session.

The exact mechanism of BMSC intradermal injection in the treatment of atrophic acne scars is still unknown. There are two main branches of SCs in the BM, hematopoietic SCs and MSCs. BM-MSCs are self-renewing, clonal precursors of nonhematopoietic tissues, though they are present as a rare population of cells in the BM (23). BMSCs may contribute to other cells that make up the skin such as keratinocytes and fibroblasts. BMSCs are found to be proliferative in the epidermis and tend to localize to a known SC niche: the CD34 bulge region of mouse hair follicles. BMSCs thus greatly contribute to laying down collagen in the ECM, along with the resident dermal fibroblasts (24). Keratinocyte communication with MSCs in the dermis is essential in maintaining the integumentary structure of the skin (25). These cells are thought to play a role in tissue repair by several mechanisms such as secretion of ECM, antigen presentation, cytokine production, angiogenesis, and wound closure (26). Adult SCs are considered to be the key players in tissue regeneration. They provide daughter cells to repopulate the lost tissues by differentiation and/or by releasing paracrine signaling to do the interaction between keratinocytes and fibroblasts. Keratinocytes release IL-1, which induces fibroblasts to secrete cytokines and growth factors important in skin repair such as keratinocyte growth factor, TGF-β1, FGF, IL-6, G-CSF and HGF. These factors in return promote keratinocyte proliferation and fibroblast remodeling, creating a paracrine loop (27).

Although improvement in wound healing has been demonstrated in many SC treatment reports, we still need to consider several issues when administering SCs to patients. We must consider whether the patients are suitable for SC treatments and which SC population would be the most appropriate. The age of the patients should come into consideration as in older patients the functionality of their SCs decreases even if the quantity does not necessarily decrease. The mode of SC delivery should also be well thought out. The SCs should ideally be able to retain their stemness until delivered and to maintain localization at the scar site.

No major adverse events were detected in this study. All patients tolerated the procedure well. Mild erythema was temporary and faded in the same day. The patients were able to perform their daily activities on the next day. There was no risk of postinflammatory hyperpigmentation, allergic reaction or granuloma formation. Although BM harvesting may have potential side effects as bleeding, infection and persistent pain, no serious side effects were reported in our study as we used autologous and adult SCs. Only bone ache was reported in 28.6% of patients but responded to analgesics in few days and did not interfere with daily activities of the patients. Careful assessment of the patients and proper investigations before the procedure will avoid risk of bleeding. Moreover, complete sterilization and strict aseptic techniques are mandatory. In our study the subject population was quite small, and no complication of anesthesia was reported, but there are published complications of inhalational anesthesia that include nausea, vomiting, hypoxia, pulmonary edema, respiratory insufficiency and temperature changes.

From our point of view, BMSC harvesting may have fast response after one session in comparison to the obstacles of other treatment modalities for acne scars. As microdermabrasion needs multiple frequent sessions, it is effective only in superficial scars. In addition, chemical peeling may potentiate hyperpigmentation in dark skin types and resurfacing by fractional laser is expensive with long downtime. It may be a better option for patients at higher risk of hyperpigmentation and thermal injury when treated with peels and ablative lasers. This has always been a difficult population to treat, and this may provide another good alternative for them. This might be another potential benefit of this treatment. Although the use of filler in the treatment of acne scars does not require preoperative laboratory work or hospitalization, it still has a limited efficacy with short duration results in comparison.

This procedure could be considered expensive as regards multiple investigations and hospitalization and general anesthesia but its effectiveness from first session in severe acne scars types makes the cost–benefit relationship valuable. However, this study is a complicated process, not randomized and not controlled with very small subject population, which may limit its generalization until further studies proved its efficacy and safety.

This is the first study using human BMSC in the treatment of acne scars, so we try to avoid any possible risks to the patients. That is why we made intensive investigations before hospitalization and after treatment. However BM aspiration could be easily done under local anesthesia and no serious complication was found. We are sure that this study is difficult to be generalized, but we hope that in the future there will be a simple technique for isolating SCs from BM or peripheral blood to be used in acne scars.

Conclusion

Autologous BMSC injection is an effective therapy in treating all types of atrophic acne scars. It can be considered safe with minimal side effects and short or no downtime. Limitation of this study was small sample size and short-term follow-up. Furthermore, long-term studies are needed to determine whether these effects are persistent long term beyond 6 months or if the results are temporary compared to the use of a filler. Further studies on large number of patients and using different types of SCs are required to assess the efficacy and safety. Histological and immunohistochemical studies are also required after SC therapy to explore and clarify the underlying mechanism of action.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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