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ORIGINAL ARTICLE

Evaluation of Aesthetic Outcome of Combined Micro-needling And External Nano Fat Application in Treatment of Old Scars

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ABSTRACT

Background: Microneedling and nanofat application have each demonstrated efficacy in scar remodeling through complementary mechanisms microneedling induces controlled dermal injury to stimulate neocollagenesis, while nanofat delivers adipose-derived stem cells and growth factors to enhance tissue regeneration. This study aimed to evaluate the aesthetic outcome of combining microneedling with external application of nanofat in the management of old scars.

Methods*:* This prospective case series included 24 patients (79.2% males, mean age 24.8 ± 5.44 years) with scars older than six months of various etiologies. All underwent external nanofat application combined with microneedling. Donor fat was harvested (most commonly from the abdomen) and processed into nanofat for topical application during microneedling. Outcomes were assessed preoperatively and at 3–6 months postoperatively using POSAS (observer and patient components).

Results*:* The overall mean POSAS score improved significantly from 57.3±2.79 pre-treatment to 40.9±2.79 post-treatment ($P < 0.01$), reflecting a 28.6% improvement. Observer scores showed marked reductions in vascularity (−21.08%), pigmentation (−27.42%), thickness (−24.27%), pliability (−25.21%), and total score (−24.09%). Patient-reported scores improved in pain (−34.25%), itching (−26.87%), stiffness (−44.98%), and total score (−31.80%). Minor complications included transient ecchymosis/bruising (54.2%), hypopigmentation (20.8%), hyperpigmentation (16.7%), and superficial wound infection (8.3%), all managed conservatively. No severe adverse events occurred.

Conclusion: The combination of external nanofat application with microneedling is a safe, well-tolerated, and effective minimally invasive approach for improving the aesthetic quality of old scars. The significant improvements across both observer and patient POSAS scores support its inclusion as a valuable modality in modern scar management protocols.

Keywords: Nanofat, microneedling, POSAS, regenerative medicine

INTRODUCTION

Microneedling has evolved continuously since its introduction in the early twentieth century. This minimally invasive technique is based on controlled, non-pathogenic puncturing of the skin using micro-sized needles, which stimulates dermal cells to release growth factors key mediators in tissue repair and to increase collagen production [1,2].

Also referred to as percutaneous collagen induction therapy, microneedling has been shown to improve the appearance of cutaneous scarring by promoting collagen and elastin synthesis, collagen remodeling, and thickening of both the epidermis and dermis. The fine needle punctures also create transient micro-channels that enhance the transdermal absorption of topically applied agents, thereby augmenting their therapeutic effects [3,4].

Due to its simplicity, safety profile, and non-ablative nature, microneedling has been investigated extensively for its efficacy in the treatment of atrophic scars [5]. Clinical

applications extend beyond scar management to include acne vulgaris, facial rejuvenation, abnormal pigmentation, alopecia, and transdermal drug delivery [6].

In parallel, there has been growing interest in the regenerative properties of autologous fat grafting. Multiple studies have demonstrated its effectiveness in enhancing wound healing, improving scar pliability, and restoring tissue quality. These regenerative effects are largely attributed to the presence of adipose-derived stem cells (ADSCs) and associated growth factors within the graft [7].

Nanofat, an ultra-purified derivative of adipose tissue, is devoid of mature adipocytes yet retains a rich population of ADSCs, microvascular fragments, and regenerative cytokines [8]. Clinical evidence supports its use in improving atrophic scars, wrinkles, and skin dyschromia. While its effects on pigmentation and vascularity are modest, nanofat has been shown to significantly enhance the texture, elasticity, and pliability of scar tissue.

Given the delivery-enhancing capabilities of microneedling and the potent regenerative profile of nanofat, combining these two modalities may offer synergistic benefits, potentially leading to superior aesthetic outcomes in scar management.

METHODS

Study Design and Ethical Approval

This prospective case series study was conducted at the Department of Plastic and Reconstructive Surgery, Zagazig University Hospitals, Egypt, over a 12-month period from May 2024 to May 2025. A total of 24 patients presenting with old scars were recruited, provided they fulfilled the eligibility criteria. Approval was taken from the research ethical commitee and the institutional review board (IRB# 183/19-May-2024) of Faculty of Medicine, Zagazig University. Consent from all patient on participating in the study. The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Eligibility Criteria

Eligible participants were male or female, aged between 18 and 40 years, and had scars older than six months following complete wound healing. The included scars encompassed a range of etiologies such as post-burn, post-traumatic, post-surgical, and acne-related lesions. Only patients free from chronic systemic illnesses that could contraindicate the planned procedure were considered for inclusion. Patients were excluded if they were elderly with significant comorbidities, specifically those classified as ASA Grade III or IV, or if they declined participation, follow-up, or consent for photography. Additional exclusion criteria comprised the presence of keloid or hypertrophic scars, active acne, current corticosteroid or retinol therapy, and psychological conditions such as needle phobia or intolerance to exposure to blood. Individuals meeting any of these criteria were not enrolled in the study.

Operational Design:

All selected patients underwent a standardized preoperative assessment protocol. A complete medical history was obtained, including personal data, presenting complaint, and relevant present, past, and family history. A thorough clinical examination was performed, consisting of both general assessment to detect any associated injuries and detailed local examination of the scar. Scar evaluation included documentation of its length, width, thickness, type of healing, pigmentation abnormalities, and any history of previous revision attempts.

Routine laboratory investigations were performed for all patients, including complete blood count (CBC), coagulation profile, and liver and kidney function tests. To minimize the risk of perioperative infection, a single preoperative dose of prophylactic antibiotic (ceftriaxone 1 g, intravenous) was administered following a negative skin sensitivity test.

The study population comprised 24 patients with variable types of facial and body scars. Sixteen patients underwent the procedure under local anesthesia alone, while eight patients required local anesthesia combined with sedation to ensure optimal comfort during the intervention.

Nano-fat Preparation

The lower abdomen and thighs were selected as the primary donor sites for fat harvesting. After aseptic preparation, tumescent anaesthesia comprising 500 mL of 0.9% saline

solution, half an ampoule of adrenaline (1 mg/mL), 10–15 mL of 2% lidocaine hydrochloride, and sodium bicarbonate ($NaHCO_3$) at 10 mEq/L was infiltrated into the donor site through a 2-mm incision created with a no. 11 blade (Fig. 1A). Using a 20-mL Luer Lock syringe attached to a 2.5-mm × 15-cm harvesting cannula, approximately 80–120 mL of mixed fat and tumescent solution was manually aspirated from the subcutaneous fat layer (Fig. 1B).

To enhance patient comfort and cooperation during the procedure, mild to moderate sedation was administered. This allowed patients to maintain spontaneous respiration and verbal responsiveness while minimizing procedural discomfort. Sedation was achieved using agents such as midazolam, fentanyl, or propofol, with drug choice and dosage individualized according to patient age, body weight, medical history, and anxiety level. Continuous monitoring of heart rate, blood pressure, oxygen saturation, and respiratory rate was performed throughout the procedure, in accordance with standard safety protocols.

The harvested material was allowed to decant vertically in the syringe for 3–5 minutes to facilitate natural separation of layers. The yellow adipose grafts settled in the middle layer, with the lipid layer floating on top and infranatant fluid at the bottom (Fig. 1C). Typically, 1.5 mL of microfat was obtained from every 5 mL of aspirate, yielding approximately 30–40 mL of microfat from 100 mL of macrofat. The lipid layer was removed, and a single wash with Ringer's solution was performed to eliminate residual anaesthetic solution and red blood cells (Fig. 1D). The donor site was then dressed with a sterile compression dressing to minimize postoperative bruising.

The cleaned microfat was mechanically emulsified by transferring the content back and forth 30 times between two 20-mL syringes connected by a 2.4-mm connector, followed by another 30 passes through a 1.4-mm connector, and finally 30 passes through a 1.2-mm connector, until a fully liquefied and whitish, homogeneous consistency was achieved (Fig. 1E).

For nanofat preparation, the emulsified fat was passed once through a nano-transfer block containing a double filter (400µm and 600 µm single-use cartridge net) and collected into a 20-mL syringe. The processed nanofat was then transferred into 1-mL Luer Lock insulin syringes, ready for injection (Fig. 1F).

External Nanofat Application with Microneedling

Twenty minutes prior to microneedling, topical lidocaine 5% cream was applied to the scar area to minimize patient discomfort during the procedure. The dermapen device was prepared and the needle depth was adjusted between 1.0 mm and 2.5 mm, according to the patient's skin type and the anatomical site of the scar. The prepared nanofat was then applied externally while simultaneously performing microneedling with the dermapen. The device was moved across the scar in vertical, horizontal, and diagonal passes in both directions to ensure uniform coverage and penetration (Fig. 2A).

Nanofat Cream Preparation

No portion of the harvested nanofat was discarded. Following completion of injection and external application, the remaining nanofat was combined with a water-based gentamicin (Garamycin) cream inside a syringe. Mixing was performed using a three-way connector to ensure thorough homogenization of the components (Fig. 2B). The resulting nanofat–gentamicin cream was dispensed to the patient for early postoperative scar care, with instructions to store it under refrigeration at 4–8 °C, preferably in the refrigerator door compartment.

Postoperative Scar Care

Starting from the third postoperative day, patients were advised to keep the treated scars exposed and to apply the nanofat–gentamicin cream twice daily, massaging gently after washing the area with warm water. The postoperative medication regimen included oral antibiotics (ampicillin/sulbactam, 1 g every 12 hours), oral anti-edema therapy (α-chymotrypsin tablets, three times daily before meals), and oral analgesics (paracetamol 500 mg, three times daily after meals). This regimen was maintained for one week postoperatively to support healing and optimize treatment outcomes.

Follow up:

Patients were evaluated at 3 and 6 months postoperatively to assess the aesthetic outcome of the treated scars. Assessment was performed using the Patient and Observer Scar Assessment Scale (POSAS) (Fig. 2C), which evaluates scar characteristics from both the patient's and the clinician's perspectives. Standardized digital photographs were obtained at each follow-up visit to enable direct comparison between preoperative and postoperative appearances, ensuring consistent documentation of treatment results.

Statistical analysis:

Data were collected, reviewed, coded, and analyzed using the Statistical Package for the Social Sciences (IBM SPSS, version 27). Quantitative variables were presented as mean, standard deviation (SD), and range for parametric data, and as median with interquartile range (IQR) for non-parametric data, while qualitative variables were expressed as frequencies and percentages. The one-sample Kolmogorov–Smirnov test was applied to assess the normality of quantitative data distribution, and Spearman's correlation coefficient was used to evaluate the relationship between two quantitative parameters within the same group. A 95% confidence interval (CI) was adopted with an accepted margin of error of 5%, and statistical significance was interpreted as follows: P-value > 0.05 was considered non-significant (NS), P-value < 0.05 was considered significant (S), and P-value < 0.01 was considered highly significant (HS).

RESULTS

Table (1) showed that most of cases in this study were males (19 (79.2%)). The commonly affected age was the young age group (18-40 years) with overall age Means (24.8±5.44).

Table (2) showed the Clinical data related to scars of patients of the study, most common cause of scars in this study was post traumatic (19 cases (79.2%)), Most patients were presented after one year of injury (71% >12 months) with cheek representing the most commonly affected site (41.7%). About (58.4%) of scars (14 cases) were ≤ 5cm in length, The atrophic type had the highest incidence in the study (50%). Also, about (45.9%) of cases were hypopigmented.

Table (3) showed surgery related data of the studied patients, The most commonly used type of anesthesia was the use of local infiltration (66.7%). Most cases in this study were operated within 30 - 60 minutes, The time of Derma-pen use in most cases (16 cases) was ≤ 5 minutes, while the time of Nanofat preparation estimated for majority of cases in this study (62.5%) was 30-60 minutes. The most common appropriate amount of blood loss in the whole operation in this study (amount in lipoaspirates +blood loss after Derma-pen) was ≤50 ml.

Table (4) showed nanofat harvesting and processing data of the studied patients. The most common site of fat harvesting was the abdomen in 19 cases (79.2%), In most cases (54.2%) we needed less than 60 CC of fat harvesting that yielded almost 5 CC of nanofat.

Table (5) showed postoperative complications. Although we had 11 cases with hypopigmentations (pre-operative), the only remaining hypopigmented scares were only 5 cases. Regarding hyperpigmentation 4 out of the 5 cases that had pre-operative hyperpigmented scars were still having such a problem, although they reported some slight improvement. Patients who had seroma (3 cases), Aspiration done under local anesthesia. Patients who had ecchymosis & bruising (13 cases), ice packing and anti-edematous treatment help to improve. Patients who had superficial wound infection (2 cases), antibiotics and daily dressing help to improve.

Table 6; showed that the Comparison between preoperative and postoperative Observer Assessment Score. There was marked improvement in the parameters of the score both individually + in the final total score. P-value are found to be highly significant in all of them (P<0.01).

Table 7; showed the Comparison between preoperative and postoperative patient Assessment Score. There is marked improvement in the parameters of the score both individually in the final total score. P-value are found to be highly significant in all of them (P<0.01).

Table 8; showed that the Comparison between overall preoperative and postoperative POSAS scores. Evidently, there is marked improvement in the parameters of the score

both individually. P-value are found to be highly significant in all of them (P<0.01).

Cases Presentation

Case 1 :A 25-year-old male patient presented to the outpatient clinic at Zagazig University Hospitals with an old scar over the right temple and forehead, persisting for 1.5 years following post-traumatic injury. The patient underwent external nanofat application combined with microneedling using a dermapen under local anesthesia. The operative time was approximately 40 minutes. Fat harvesting was performed from the abdomen, yielding 40 mL of macrofat, which was processed to obtain 4.5 mL of nanofat.

Preoperative assessment using the Patient and Observer Scar Assessment Scale (POSAS) revealed a total score of 50, which improved to 36 at the postoperative follow-up.

Case (2): A 19-year-old male patient presented to the outpatient clinic at Zagazig University Hospitals with an old post-traumatic scar on the left cheek, persisting for eight months following a cut wound. The surgical intervention consisted of external nano-fat application combined with dermapen therapy. The procedure was performed under local anesthesia with sedation and lasted approximately 40 minutes. Autologous fat was harvested from the abdomen, yielding 30 mL of macro-fat and 5 mL of nano-fat for injection. The Patient and Observer Scar Assessment Scale (POSAS) score improved from a preoperative value of 52 to a postoperative value of 37, indicating a marked improvement in scar quality.

Table (1): Demographic data of studied cases.

Item	No.	%	Mean	SD
Age				
(18 – 40)	**24**	**100.0%**	**24.8**	**5.44**
(40 – 60)	**–**	**–**		
Sex				
Male	**19**	**79.2%**	**–**	**–**
Female	**5**	**21.8%**		

Table (2): Clinical data related to scars of patients of the study.

Item		No. (%)	%
Cause of scar	**Post traumatic**	**19**	**(79.2%)**
	Surgical	**4**	**(16.6%)**
	Post burn	**1**	**(4.2%)**
Duration	**6-12 month**	**7**	**(29.2%)**
	More than 12 months	**17**	**(70.8%)**
Site	**Cheek**	**10**	**(41.7%)**
	Forehead	**7**	**(29.2 %)**
	Abdomen	**2**	**(8.3 %)**
	Combined	**5**	**(20.8%)**
Scar Length	**≤ 5 cm**	**14**	**(58.4%)**
	5 - 10 cm	**8**	**(33.3%)**
	> 10 cm	**2**	**(8.3%)**
Type of scar	**Atrophic**	**12**	**(50%)**
	Broad	**3**	**(12.5%)**
	Regular	**3**	**(12.5%)**
	Irregular	**6**	**(25%)**
Color of scar	**Normal**	**8**	**(33.3%)**
	Hypopigmentation	**11**	**(45.9%)**
	Hyperpigmentation	**5**	**(20.8%)**

Table (3): Surgery related data of the studied patients:

		Total no.= 24
Type of anesthesia	**Local**	**16 (66.7%)**
	local + sedation	**8 (33.3%)**
Time of surgery groups (min)	**30 - 60 min**	**19 (79.2%)**
	60 - 90 min	**5 (20.8%)**
Time of Dermapen use	**≤5 min**	**16 (66.7%)**
	5-10 min	**8 (33.3%)**
Time of Nanofat preparation	**≤30 min**	**6 (25%)**
	30 -60 min	**15 (62.5%)**
	>60 min	**3 (12.5%)**
Approximate amount of blood loss	**≤50 ml**	**13 (54.2%)**
	50 -100 ml	**10 (41.6)**
	>100 ml	**1 (4.2%)**

Table (4): Nanofat harvesting and processing data of the studied patients:

		Total no.= 24
Site of harvested fat	**Abdomen**	**19 (79.2%)**
	Inner thigh	**4 (16.6%)**
	Buttocks	**1(4.2%)**
Amount of harvested fat (cc)	**≤ 60 CC**	**13 (54.2%)**
	60 - 100 CC	**10 (41.6%)**
	>100 CC	**1 (4.2%)**
Amount of nanofat obtained	**≤ 5 ml**	**13(54.2%)**
	5 - 10 ml	**10 (41.6%)**
	> 10 ml	**1 (4.2%)**

Table (5): Postoperative complications of the studied intervention.

		Total no.= 24	%
Scar site complications	**Hypopigmentation**	**5**	**20.8%**
	Hyperpigmentation	**4**	**16.7%**
	Superficial Wound infection	**2**	**8.3%**
	Sever bleeding	**0**	**0%**
	Sever pain	**0**	**0%**
Fat donor site complications	**Temporary ecchymosis & bruising**	**13**	**54.2%**
	seroma	**3**	**12.5%**
	Skin irregularity	**0 (0%)**	**0%**
	Wound infection	**0 (0%)**	**0%**

DISCUSSION

The present study evaluated the synergistic effects of external nanofat application combined with microneedling in the treatment of old scars, focusing on dermal remodeling, scar texture, and patient satisfaction using the Patient and Observer Scar Assessment Scale (POSAS) as a validated outcome measure. The findings from our cohort of 24 patients (19 males, 79.2%; 5 females, 20.8%) demonstrated statistically significant improvements across all POSAS parameters, with high patient satisfaction and minimal adverse effects.

The findings indicate that this combined therapy yields promising regenerative outcomes, the scar's appearance showed statistically significant improvement across nearly all evaluated parameters, corroborating previous reports suggesting that both modalities can independently stimulate dermal repair mechanisms and enhance skin quality. However, their combination appears to potentiate these effects beyond what each can achieve alone.

Recent clinical studies support the efficacy of this combined approach. In a prospective cohort of 86 patients, Righesso and colleagues [9] demonstrated significant improvement in skin texture and elasticity using a dual-device method involving nanofat and microneedling. Another case series reported by Qari et al. [10] found that patients with atrophic scars showed marked aesthetic improvement at 3- and 6-month follow-ups when treated with a combination of nanofat, microneedling, PRP, and CO_2 laser. While the multimodal nature of that protocol limits the ability to isolate specific effects, the contribution of nanofat and microneedling was nonetheless highlighted as central to dermal regeneration.

In the present study, improvements in scar appearance were observed in line with these prior findings. Enhanced collagen density, smoother scar texture, and subjective patient satisfaction were evident by the third month, with continued benefits observed through the sixth month. Notably, the non-ablative nature of both treatments ensures a favorable safety profile, with only mild erythema and transient ecchymosis and bruising reported in most patients (54.2%) . These findings align with previously published safety data, which emphasize the low complication rates associated with both microneedling and nanofat procedures [11,12].

Del Papa et al. [13] reported that post-traumatic and surgical scars respond well to nanofat treatment, largely due to the vascular and structural damage these scars often exhibit.

In the current study, we revealed that the clinical data related to scars of patients of the study were most common cause of scars in this study was post traumatic (19 patients (79.2%)),2nd cause Surgical (4 patients (16.6%)), this may be explained by high frequency of males exposure to trauma than females.

Studies evaluating microneedling for post-surgical scars have demonstrated significant reductions in standardized scar assessment scores. A study involving 25 patients with surgical scars found that three microneedling sessions, spaced four weeks apart, led to a 50% decrease in POSAS scores, from 23.7 ± 1.8 before treatment to 11.7 ± 1.0 at 16-week follow-up ($p < 0.001$) [14]. Similarly, an RCT assessing microneedling for post-abdominal surgical scars following deep inferior epigastric perforator (DIEP) flap-reconstruction found that treated scars exhibited a statistically significant improvement in POSAS scores at nine months post-treatment (median 17 vs. 21.4, $p < 0.05$) [15].

In this study, sites of scars were in cheek, forehead, abdomen or combined and the most common site was cheek (10 patients (41.7%)). Length of scars was less than 5cm, 5-10cm or more than 10cm and the most common was ≤ 5cm. Types of scars was broad scars, regular scars and irregular scars and most common type of scar was (Atrophic). Color of scars was normal scars, hyperpigmentation and most common color of scar was hypopigmentation (11 patients (45.9%)). In agreement with this study, Maione et al. [16] also found hypopigmentation to be the most common discoloration in post-traumatic scars, reflecting similar challenges in pigmentation restoration.

The results revealed a highly significant decrease in both Observer and Patient POSAS scores post-treatment ($P < 0.01$). The overall mean POSAS score dropped from 57.3 ± 2.79

to 40.9 ± 2.79, confirming a marked enhancement in scar appearance, pliability, thickness, and pigmentation. Observer scores specifically improved in vascularity (−21.08%), pigmentation (−27.42%), thickness (−24.27%), pliability (−25.21%), and total score (−24.09%). On the patient side, notable improvements were seen in pain (−34.25%), itching (−26.87%), color (−23.37%), stiffness (−44.98%), and total score (−31.80%).

These improvements are consistent with other studies employing nanofat or microneedling individually or in combination. For example, Kong et al. [17] demonstrated significant POSAS reduction after condensed nanofat and fat grafting for atrophic facial scars, with marked improvements in thickness, pigmentation, and texture. Jan et al. [18] similarly reported enhanced pliability and pigmentation in postburn scars treated with nanofat injection.

This combined technique proved safe and well-tolerated. Only minor complications were observed mainly transient ecchymosis and bruising (54.2%), and isolated cases of seroma (12.5%) at donor sites or hyperpigmentation (16.7%) and superficial skin infection (8.3%) at scar sites. These were managed conservatively. No severe bleeding, pain, or fat necrosis occurred. Notably, the most common donor site was the abdomen (79.2%), and the majority of procedures were performed under local anesthesia (66.7%), reinforcing the approach's feasibility in outpatient settings.

The study of Gentile et al. [19] highlighted the abdomen as an ideal donor site due to its high fat content and accessibility. The processing method yielded small volumes of nanofat (≤5 ml in 70% of cases), consistent with protocols reported in previous studies.

7In this study, the inner thigh of 4 patients (16.6%), the abdomen of 19 patients (79.2%) and the buttocks 1 patient (4.2%) were the primary sites for fat harvesting. Most common amount of harvested fat was (<60cc, 13 patients (54.2%)) and the most amount of nanofat obtained was (≤ 5 ml, 13 patients (54.2%)). This choice aligns with findings from Amr et al. [20], The lower abdomen and thighs were noted as potential donor areas as these sites are richer in SVF, and ADSCs. The most site of harvested fat was Lower abdomen (18 patients, (69.2%)) and inner thigh (8 patients, (30.8%)).

This study showed that there was a positive correlation between both patients and observers assessments. This appears in the non-significant values of P-value in all items of the score + in the total score. Tonnard et al. [8], described a similar agreement in their study, attributing it to the visible and tangible improvements in scar pliability and thickness after nanofat application.

In this study, overall mean value of preoperative POSAS score was (57.3±2.79), Maximum value was 63 and minimum value was 54. The postoperative POSAS score mean value was (40.9±2.79). Maximum value was 60 and minimum value was 45, there is marked improvement in the parameters of the score both individually. P-value are found to be highly significant in all of them (P<0.01).

Verpaele and Tonnard [12] also pioneered the "nanofat needling" technique, emphasizing its dual benefit of collagen induction and regenerative cell delivery.

Our study complements this body of work by demonstrating that external nanofat application without injection till confers therapeutic benefit when combined with microneedling, likely due to enhanced percutaneous delivery.

The comparison between preoperative and postoperative scores highlights the efficacy of external nanofat application combined with microneedling. The total POSAS scores improved significantly from 57.3 to 40.9, representing a marked enhancement in scar quality.

CONCLUSION

In conclusion, external nano-fat application combined with microneedling represents a safe, well-tolerated, and effective treatment modality for old scars, offering measurable improvements in scar quality and patient satisfaction. This technique holds potential as a valuable addition to the armamentarium of scar management strategies, bridging the gap between regenerative medicine and minimally invasive procedures.

Authors' contributions:

In addition to writing and getting the book ready for publication, the writers were in charge of gathering and analyzing the data. The

final version was examined and approved by all authors.

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