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Meta-analysis of the effectiveness of fat grafting in treating patients with skin scarring

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Abstract: *In this paper, Meta-analysis was adopted to evaluate the effectiveness of fat grafting to prevent and treat scarring in patients. PubMed, Embase, Cochrane Library, China Knowledge Network, Wanfang Data Knowledge Service Platform, and VIP databases were searched for relevant literature on fat grafting for scar prevention and treatment. Meta-analysis of the data was performed using Stata 16.0 software. Ultimately, 5 literature articles were included in this study, enrolling 428 patients with 428 scars. The Meta-analysis finally yielded the following results: the thickness, softness, pruritus, pain and color of the scars were significantly improved by fat grafting for scar treatment; there was no significant difference in the VSS scale scores of the scars. We eventually found that fat grafting was more effective in improving scar thickness, softness, pruritus, pain and color.*

Keywords: *Fat grafting; scar; Proliferative scarring; Effectiveness; Meta-analysis*

1. Introduction

Scarring is a normal product of trauma repair, and wounds and traumas that reach the appropriate depth will leave a scar [1]. Pathological keloid scars generally include proliferative keloid scars and keloids [2]. Scarring is often associated with pain, itching and even dysfunction, seriously affecting the patient's appearance and quality of life [3]. Researchers continue to explore measures to combat scarring, and in 1893 Neuber first proposed the application of autologous fat grafting to fill depressed tissue[4]. Since then, studies on autologous fat grafting in the skin have gradually increased, and most studies now agree that autologous fat grafting can increase skin thickness, but the effect of autologous fat grafting on other aspects of scar improvement is still controversial.[3, 5, 6]. Therefore, this study evaluated the effectiveness of fat grafting against scarring by means of Meta-analysis, aiming to provide an evidence-based basis for clinical practice.

2. Data and methods

2.1. Literature inclusion and exclusion criteria Inclusion criteria

Inclusion Criteria:(1) study population: patients with pathological scarring, with no restrictions on scar type and patient gender, age, or nationality; (2) study type: randomized controlled trial (RCT) studies or class of experimental studies on fat grafting for pathological scarring; (3) outcome indicators: studies containing at least one of the following outcome indicators: the Vancouver Scar Assessment Scale (VSS); scar thickness; scar softness; scar color; scar pain level; scar pruritus level;

Exclusion Criteria:(1) duplicate publications (articles by the same author published in different languages); (2) incomplete data; (3) non-English and Chinese literature; (4) qualitative studies, animal studies, reviews, conferences, case reports; (5) literature that is not available in full text by various means, etc.

2.2. Literature search strategy

A combination of subject terms and free words was used for literature search, using the search formula: ((Cicatrix[Mesh]) OR (Scar) OR (Scarring) OR (Scars) OR (Cicatrization) OR (Cicatrix, Hypertrophic[Mesh]) OR (Cicatrices, Hypertrophic) OR (Hypertrophic Cicatrices) OR (Hypertrophic

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Cicatrix) OR (Scars, Hypertrophic) OR (Hypertrophic Scar) OR (Hypertrophic Scars) OR (Scar, Hypertrophic) OR (Atrophic scar) OR (Pathological scar) OR (Keloid[Mesh]) [Title/Abstract])) AND (((autologous fat transfer) OR (autologous fat grafting) OR (fat transfer) OR (fat grafting) OR (Fat filling) OR (Lipofilling) OR (Adipose stem cell transplantation) OR (fat granule injection grafting) OR (AFT) [Title/Abstract]) to search PubMed, Embase, Cochrane Library databases; with keloid, proliferative keloid, keloid hyperplasia, atrophic keloid, atrophic keloid, keloid scar, superfluous keloid, pathological keloid The search terms were autologous fat transfer, autologous fat graft, fat graft, fat filler, fat stem cell graft, fat particle injection graft, and AFT, and the search time frame was from the establishment of the database to March 13, 2023, and the Chinese databases of China Knowledge Network, Wanfang Database and Vipshop.

2.3. Literature screening and data extraction

Two graduate students, independently screened the literature according to the inclusion and exclusion criteria. Duplicate literature was removed using Note Express software, primary screening was performed based on title and abstract, and the full text was read for re-screening to eliminate literature that did not match. For literature with incomplete data or unconvertible data, attempts were made to contact the authors, and those still unavailable were excluded to determine the final included literature. If disagreement was encountered, the decision was discussed by two persons, and if agreement could not be reached through consultation, it was referred to a third investigator for decision. Two investigators used a uniform data extraction form to extract literature information, including: first author, country, year of publication, scar type, sample size, female proportion, age, disease duration, intervention, time of outcome index assessment, and outcome index.

2.4. Quality evaluation of the literature

Two researchers independently evaluated the quality of the included randomized controlled studies and experimental-like studies according to the evaluation criteria of the Australian JBI Centre for Evidence-Based Health Care (2016) for RCT studies and experimental-like studies, respectively.The evaluation of RCT studies included randomization grouping, allocation concealment, baseline, implementation of blinding, follow-up of study subjects, collection and analysis of outcome indicators, and the evaluation of experimental-like studies included randomization grouping, allocation concealment, baseline, implementation of blinding, follow-up of study subjects, collection and The evaluation of RCT studies included causality of study variables, baseline, control, outcome measures and data analysis, etc. The investigator made "yes", "no", "unclear" and "not applicable" responses to the evaluation items. ", "not applicable". If the literature included in the study fully satisfied the above indicators, the quality grade was A; if partially satisfied, the quality grade was B; if not satisfied at all, the quality grade was C. After the evaluation was completed, two researchers performed cross-review, and in case of disagreement in the evaluation, a third researcher arbitrated and jointly discussed and determined the final quality of the literature.

2.5. Statistical methods

Stata 16.0 statistical software was used for analysis. The measures were expressed as mean and standard deviation, and weighted mean difference (WMD) or standardized mean difference (SMD) was used as an indicator for effect statistical analysis, and 95% confidence intervals (95% CI) were calculated for effect analysis. The heterogeneity among studies was judged using the χ^2 test and I^2 index, and when I^2< 50% and P>0.1, it indicated that there was no heterogeneity and the fixed-effect model was used for analysis; when $I^2 \geq 50\%$ and $P \leq 0.1$, it indicated that there was heterogeneity and the random-effect model was selected for analysis, and the source of heterogeneity was further determined by subgroup analysis.

3. Results

3.1. Literature search results

A preliminary search obtained 2647 literature, and 2093 remained after eliminating duplicates. 5 papers were finally included after reading the title, abstract and full text [7-11], including 1 in English[7] and 4 in Chinese[8-11], with a total of 428 patients and 428 scars. Details are shown in the screening process Figure 1. The basic characteristics of the included literature are shown in Table 1.

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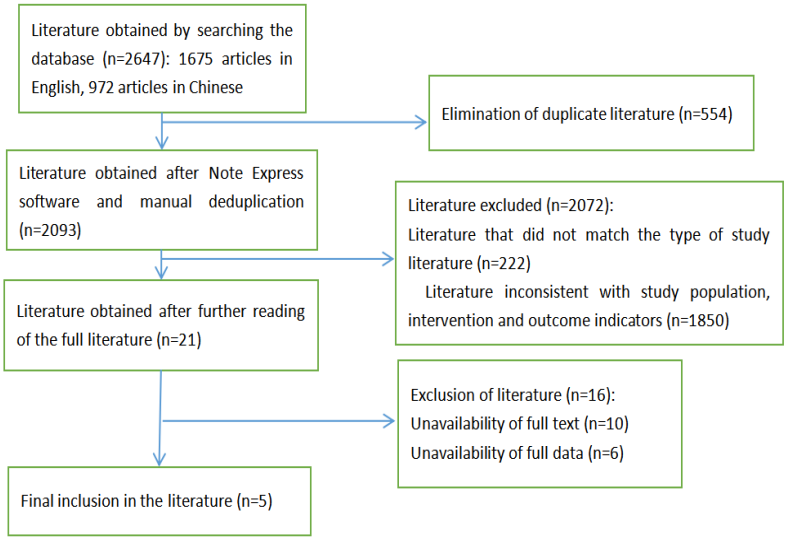

Figure 1: Flow chart of literature screening.

Table 1: Basic characteristics of the included literature.

First author	Country	Year of publication	Types of scarring	Sample size		Percentage of women		Age		Course of disease(day)		Interventions		Ending Rating Time	Ending indicators*
				Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group	Intervention group	Control group		
Hu Junqi[8]	China	2022	Proliferative scarring	50	50	Male26 Female24	Male25 Female25	20-49 33.9±9.08	9-48 33.58±9.33	21-90 59.35±17.46	33-88 60.88±16.33	PDL + Autologous Fat Transfer	PDL	Before treatment After 24 weeks of treatment	②③④⑤⑥
Dai Xiaogang [11]	China	2021	Proliferative scarring	34	34	Male21 Female13	Male19 Female15	20-49 33.89±9.07	18-47 33.57±9.32	30-90 59.34±17.45	32-87 60.87±16.32	PDL + Autologous Fat Transfer	PDL	Before treatment 6 months after treatment	②③④⑤⑥
Zhu Xiyun[10]	China	2022	Post-burn hyperplasia	40	40	Male21 Female19	Male22 Female18	18-60 48.58±10.02	18-60 47.76±10.43	40-90 61.52±15.43	40-90 61.43±15.38	PDL + Autologous Fat Transfer	PDL	Before treatment 24 weeks after treatment	②③④⑤⑥
Liu Jing[9]	China	2022	Proliferative scarring	40	40	Male24 Female16	Male22 Female18	20-50 37.2±11.2	20-50 38.1±10.6	-	-	Autologous Fat Transfer	Fractional Erbium Laser Treatment	Before treatment 1 month after the first treatment 1 month after the last treatment	①
Liu Jing[9]	China	2022	Proliferative scarring	40	40	Male24 Female16	Male25 Female15	20-50 37.2±11.2	20-48 37.4±12.1	-	-	Autologous Fat Transfer	Triamcinolone acetonide intra-scar injection	Before treatment 1 month after the first treatment 1 month after the last treatment	①
Cervelli, V[7]	U K	2012	Depressed scar	20	20	Male10 Female10	Male9 Female11	37±16	38±16	-	-	PRP Autologous Fat Transfer	Laser Treatment	Pre-operative 1st, 2nd, 4th, 8th postoperative week 3rd, 6th month after surgery	③⑥
Cervelli, V[7]	U K	2012	Depressed scar	20	20	Male10 Female10	Male11 Female9	37±16	38±15	-	-	PRP Autologous Fat Transfer	PRP Autologous Fat Transfer+ Laser Treatment	Pre-operative 1st, 2nd, 4th, 8th postoperative week 3rd, 6th month after surgery	③⑥

*Note: ① total VSS score; ② scar thickness; ③ scar softness; ④ degree of scar itching; ⑤ degree of scar pain; ⑥ scar color.

3.2. Quality evaluation of the included literature

Of the five included studies [7-11], three RCTs [7, 8, 10] and two experimental-like studies [9, 11] were included. The quality evaluation of the included literature is detailed in Tables 2-3.

Table 2: Quality evaluation of included RCT studies.

First author	Whether to randomize grouping	Whether to assign hidden	Is the baseline comparable	Study subjects were blinded for implementation	Interventionists perform blinded methods	Outcome assessor implementation blind	Are other interventions the same	Complete follow-up and lost visit handling	All randomized study subjects were included in the outcome analysis	The same assessment method	Ending indicator measures are credible	Appropriate data analysis methods	Sound study design	Quality grade
Hu Junqi[8]	Yes	Not sure	Yes	Not sure	Not sure	Not sure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	B
Zhu Xiyun[10]	Yes	Not sure	Yes	Not sure	Not sure	Not sure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	B
Cervelli, V[7]	Yes	Yes	Yes	Not sure	Not sure	Not sure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	B

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Table 3: Quality evaluation of the experimental studies included in the category.

First author	Whether the cause-and-effect relationship in the study is clearly articulated	Whether the baseline is comparable	Are measures other than interventions the same	Whether to set up a control group	Whether to measure diversity of outcome indicators	Whether to describe the end of the lost visit	Whether the outcome indicators were measured in the same way in each study group	Is the outcome indicator measure credible	Appropriateness of data analysis	Quality grade
Liu Jing[9]	Yes	Yes	Yes	Yes	Yes	Yes	Not sure	Yes	Yes	B
Dai Xiaogang[11]	Yes	Yes	Yes	Yes	Yes	Yes	Not sure	Yes	Yes	B

3.3. Meta-analysis results

3.3.1. Effect of fat grafting on total VSS scores

A total of 1 article[9]analyzed changes in VSS scores before and after fractional therapy or hormone therapy combined with autologous fat grafting intervention, which was evaluated in a 2-part experiment using the VSS scale. It was analyzed with inter-study heterogeneity (I^2=97.5%,P＜0.05) and using a random effects model, the results showed that fractional laser treatment or hormonal therapy and autologous fat grafting were similar in improving scarring, with no statistically significant difference [WMD=-0.805,95% CI (-2.804, 1.194),P>0.05]. Subgroup analysis was performed according to the time of intervention and divided into 2 subgroups, i.e., 1 month and 4 months after treatment. 2-part trial evaluated VSS scores after 1 month of intervention and showed that fractional laser treatment or hormonal treatment was similar to autologous fat grafting in improving scarring, with no statistically significant difference [WMD=-0.987, 95% CI (-3.280, 1.307),P>0.05]. 2 part of the trial evaluated the VSS scores after 4 months of intervention and showed that fractional laser treatment or hormonal treatment was similar to autologous fat grafting in improving scarring, with no statistically significant difference [WMD=-0.805, 95%CI(-2.804, 1.194), P>0.05].

3.3.2. Effect of fat grafting on scar thickness

A total of three articles[8, 10, 11] assessed scar thickness, which were evaluated using a modified version of the VSS scale and ultrasound detector, respectively. Analysis of the three articles using the modified version of the VSS scale showed no heterogeneity between studies (I^2=0.0%, P=0.437), and using a fixed-effect model, the results showed that autologous fat grafting combined with laser treatment was significant in improving scar thickness compared with laser treatment alone [WMD=-0.448, 95% CI (-0.503, -0.393), P<0.05]. The three papers analyzed using ultrasound detectors with heterogeneity between studies (I^2=89.1%, P=0.452), using a random effects model, showed that autologous fat grafting combined with laser treatment had a significant effect in improving scar thickness compared to laser treatment alone [WMD=-1.906, 95% CI (-2.320, -1.491),P<0.05].

3.3.3. Effect of fat grafting on scar tenderness

A total of 4 papers[7, 8, 10, 11] assessed scar tenderness, 3 of them[8, 10, 11] with a modified version of the VSS scale and one [7]using the MSS scale. Analysis of these 3 papers showed no heterogeneity between studies (I^2=0.0%, P=0.379), and using a fixed-effect model The results showed that autologous fat grafting combined with laser treatment had a significant effect in improving scar tenderness compared to laser treatment alone [WMD=-0.751, 95% CI (-0.852, -0.650),P<0.05]. 1 article assessed scar tenderness and this literature was evaluated in a total of 2 part experiments using the MSS scale. It was analyzed with inter-study heterogeneity (I^2=81.9%, P=0.019) and using a random effects model, the results showed that autologous fat grafting or laser treatment combined with fat grafting was similar to laser treatment in improving scar softness, with no statistically significant difference [WMD=0.270, 95% CI (-0.367, 0.907),P>0.05].

3.3.4. Effect of fat grafting on scar pruritus and pain

A total of 3 papers [8, 10, 11] assessed scar pruritus, all on a modified version of the VSS scale, and analysis of these 3 papers showed no heterogeneity between studies (I^2=0.0%, P=0.858), using a fixed effects model, which showed that compared with laser treatment alone, autologous fat grafting combined with laser treatment was improvement of scar pruritus was significant [WMD=-0.406, 95% CI (-0.438, -0.374),P<0.05]. A total of 3 papers[8, 10, 11] assessed scar pain, all on a modified version of the VSS scale, were analyzed, and there was no heterogeneity between studies (I^2=0.0%, P=0.463), using a fixed-effects model, which showed that autologous fat grafting combined with laser treatment had a significant effect on improving scar pain compared with laser treatment alone [WMD=-0.489, 95% CI (-0.528, -0.450),

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P<0.05].

3.3.5. Effect of fat grafting on scar color

A total of four papers[7, 8, 10, 11] assessed scar color, three of them[8, 10, 11]with a modified version of the VSS scale and one[7] using the MSS scale, and these three papers were analyzed with no heterogeneity between studies (I^2=0.0%,P=0.647), using a fixed effects model. The results showed that autologous fat grafting combined with laser treatment was significant in improving scar color compared to laser treatment alone [WMD=-0.425, 95% CI (-0.479, -0.371), P<0.05]. 1 article evaluated scar color, and this literature was evaluated in a total of 2 part experiments using the MSS scale. It was analyzed with heterogeneity between studies (I^2=74.2%, P=0.049) and using a random effects model, the results showed that autologous fat grafting or laser treatment combined with fat grafting was similar to laser treatment in improving scar softness, with no statistically significant difference [WMD=0.049, 95% CI (-0.539, 0.637),P>0.05].

4. Discussion

4.1. Methodological quality of the included literature

The five included papers [7-11]were comparable at baseline and the overall quality of the literature was moderate. None of the five included literatures stated whether the study subjects or the implementers and assessors were blinded. When blinding is not used in an experiment, it may lead to more bias. It is recommended that future studies use blinding more often and implement rigorous randomized controlled studies as a way to improve the quality of research.

4.2. Effect of fat grafting on scarring

4.2.1. No significant effect of fat grafting on total VSS scores

This study showed that laser combined with fat grafting did not significantly improve scar VSS scores compared to laser treatment alone. It is not consistent with the results of related studies [12, 13]. Scar is a product of abnormal wound healing due to inflammatory factors, excessive fibroblast proliferation, and collagen deposition[14]. Tian Jiao et al[13] pointed out that adipose and adipose-derived stem cells can inhibit excessive collagen deposition and have antifibrotic and reduce inflammatory mediators and reactions, while adipose and adipose-derived stem cells can stimulate vascular regeneration, thus accelerating blood circulation to the scar site, which can improve scarring. Yingjin Zhou et al[13] also pointed out that nano-fat, which is rich in numerous pro-angiogenic factors, can not only improve blood circulation in scar tissue but also effectively improve the appearance of the scar. The analysis of the reasons for this result may be: the inclusion of Meta-analysis experiments is only 2 part experiments by the same authors, the sample size is too small and there is a certain publication bias; secondly, the sample size included in the included experiments is small.

4.2.2. Fat grafting can improve scar thickness

This study showed that fat grafting can effectively improve scar thickness. This may be related to the fact that adipose-derived stem cells in adipose tissue can effectively reduce the number of fibroblasts, regulate the ratio of different types of collagen, and improve the collagen nodular structure, thus inhibiting scar proliferation and reducing scar thickness[15]. Compared with surgical treatment, pharmacological treatment, tension reduction treatment, and compression treatment, autologous fat grafting is a minimally invasive treatment with the advantages of faster postoperative healing, shorter treatment period, and more significant scar improvement[16]. However, it also has certain limitations, and complications such as infection, hematoma, skin necrosis, skin erythema, local skin induration, and pigmentation may occur after surgery[17]. Therefore, the technical requirements for surgeons are more stringent, and nursing staff are also required to observe patients more after surgery, to improve their self-related nursing knowledge, and to communicate more between doctors and nurses as a way to prevent postoperative-related complications.

4.2.3. Fat grafting improves the softness of the scar

The results of this study showed that fat grafting improves the softness of the scar. This is consistent with the results obtained by Wang Yue et al[18] who performed fat grafting on patients with burn scars. Fang Lu et al[19] concluded that the regenerative ability of adipose-derived stem cells can stimulate adipogenesis, which ensures the amount of fat needed to improve the scar, and adipose-derived stem cells

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can stimulate angiogenesis to improve the ischemia and hypoxia of the trauma, in addition to various growth factors in adipose-derived stem cells can increase scar flexibility and improve the texture. In addition, a study[20] found that silicone adjuvant therapy for keloid scars can effectively improve the softness of the scar and enhance patient comfort. To further improve the treatment effect, clinical nurses can explore the effect of combined application of silicone dressing on improving the softness of the patient's scar based on fat grafting treatment.

4.2.4. Fat grafting can reduce the degree of scar itching and pain

The results of this study showed that fat grafting can effectively reduce the degree of scar itching and pain of patients and improve their comfort. Itchy and painful scars are the most common clinical symptoms that not only affect the quality of life of patients but also damage their psychological health[21, 22]. When caring for such patients, clinical nurses should actively assess the level of itching and pain and intervene as early as possible. Clinical nurses can use some qualitative assessment scales to understand the patient's scar status, such as the Patient Scar Assessment Scale[23], which allows for more systematic assessment of invisible scar characteristics, such as scar itching and pain. Encouraging the establishment of patient-directed care to provide patients with a comprehensive understanding of scar progression leads to improved patient compliance. In addition, the glycosidic ligands in eggplant vegetables can cause itching in patients, and konjac glucomannan in konjac can reduce itching by inhibiting neuroinflammation[24]. The relevant dietary instructions should be noted during nursing education.

4.2.5. Fat grafting can improve scar color

The results of this study showed that fat grafting can improve scar color. The reason for the different color of the scar from the normal skin color is the pigmentation and dense distribution of blood vessels at the scar site. Abnormal color at the scar is more likely to lead to psychological problems such as anxiety and low self-esteem, which affect the patient's healthy psychological state[25]. Therefore, in addition to taking basic preventive and curative measures, nursing staff should educate patients about avoiding scar pigmentation and improve their knowledge related to scar care. For example, avoid direct sunlight on the scar site as much as possible and apply sunscreen or take some physical sun protection such as wearing a sun umbrella when going out. If you are more concerned about the abnormal color of the scar area and do not want to attract excessive attention from others, you can apply concealer to cover up the scar area to reduce the patient's inner anxiety and ensure normal work and life.

5. Conclusions

In conclusion, fat grafting or fat grafting combined with laser treatment is better than laser treatment alone for scar prevention and treatment, with fat grafting combined with laser treatment being more effective than laser treatment in improving scar thickness, softness, itching, pain and scar color. The literature included in this study was of moderate quality and the results were relatively stable, but the following limitations remain: the number of included literature was small, the data were insufficient, and the outcome indicators could not be analyzed for bias; none of the included literature was blinded; and the fat grafting modality was not standardized in the included studies. More original studies of high quality and longer duration of intervention are needed for subsequent validation. Given that fat grafting combined with laser treatment increases the nursing workload compared with laser treatment alone, future studies may consider improving the relevant nursing process and work content, improving nursing staff's relevant work knowledge, and improving patient satisfaction and quality of life.

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