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ORIGINAL ARTICLE
Breast

Pain-relieving Effects of Autologous Fat Grafting in Breast Cancer Surgery: A Scoping Review

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Background: Chronic pain is relatively common after breast cancer surgery, including breast reconstruction. Autologous fat grafting (AFG) has gained attention as a novel method for breast reconstruction, and recent clinical studies have also shown effects of AFG on alleviation of chronic pain after breast cancer surgery. Our objective was to conduct a scoping review of studies that have examined these effects with clearly defined clinical outcomes.

Methods: A literature search was conducted using three databases: PubMed, MEDLINE, and Google Scholar, following PRISMA guidelines and the Arkesy and O'Malley framework. The search focused on clinical studies of the effects of AFG on chronic pain after breast cancer surgery. All studies reporting functional outcomes, return to work, and secondary surgery in a repeat operation were identified.

Results: Of the 148 studies identified in the search, 11 studies with a total of 684 patients were included in the review. The average volume of fat grafted was approximately 128 mL over an average of 1.6 sessions. The most common time point for assessment was 1 year post-AFG. In all studies with an evidence level of 3 or lower, AFG showed positive results in alleviating pain after breast cancer surgery. However, one of the three randomized controlled trials did not show clinically significant effects.

Conclusions: Most of the studies examined in this review suggested pain-relieving effects of AFG. However, there was one randomized controlled trial in which these effects were not confirmed, indicating a need for further accumulation of cases and performance of new, well-designed randomized controlled trials.
(Plast Reconstr Surg Glob Open 2024; 12:e5909; doi: 10.1097/GOX.0000000000005909; Published online 14 June 2024.)

INTRODUCTION

Chronic pain persisting for months to years affects 25%–60% of women after breast cancer surgery, including mastectomy and breast-conserving surgery.[1–5] This pain is affected by intraoperative and postoperative factors, and represents a significant clinical challenge. Postmastectomy pain syndrome (PMPS) can extend beyond the anterior chest to the axilla, upper arm, and lateral thoracic region. Eventually, the physical impairments can progress to psychological impacts, leading to a significant decline in quality of life. However, to date, no effective treatment has been established. Management is limited to palliative care, such as pharmacotherapy, leaving an inadequately resolved medical issue for many patients.

Autologous fat grafting (AFG) has recently emerged as an option for alleviation of PMPS and soft tissue damage after radiation therapy. AFG is a simple and minimally invasive technique that is commonly used for reconstruction of soft tissues like the breast.[6,7] Irrespective of whether AFG is accompanied by reconstruction, there has been an increase in clinical studies assessing its efficacy in treating PMPS. Indeed, based on our own clinical experience, we have confirmed the efficacy of AFG for pain relief through subjective feedback from patients. However, the full extent of the therapeutic effectiveness of AFG has yet to be established. Thus, the aim of this study was to conduct

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Received for publication February 22, 2024; accepted April 30, 2024.

DOI: 10.1097/GOX.0000000000005909

Disclosure statements are at the end of this article, following the correspondence information.

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

a scoping review of AFG for treatment of PMPS and to interpret the effectiveness of this method for pain relief.

METHODS

This study was conducted in accordance with PRISMA guidelines and the Arkesy and O'Malley framework[8] for scoping reviews.[8,9] As described by Levac,[10] this framework consists of the following five stages.

Stage 1: Identifying the Research Question

To encompass a wide range of publications, we identified extensive research questions aimed at clarifying current practices and their benefits. The specification of these questions resulted from repeated discussions among the authors and an exploration of clinically significant queries, leading to the following question: Does AFG offer a palliative effect on postoperative pain associated with breast resection, including breast reconstruction?

Stage 2: Identifying Relevant Studies

A comprehensive search of databases was developed with the assistance of a medical librarian (M.S.). The search included keywords and subject headings where available. Records were downloaded and assembled, and duplicates were eliminated using the citation management software "Rayyan." The review of studies was independently conducted by two authors (Y.S. and I.Y.), and any discrepancies were resolved through discussion and consensus with a senior author (K.Y.) as needed. Two authors independently searched the PubMed, MEDLINE, and Google Scholar electronic databases. The search was run on April 15, 2023. The search terms included "fat transfer," "fat graft," "lipo-injection," "breast surgery," "post-mastectomy pain syndrome," "PMPS," "oncological excision," "wide local excision," "breast conserving surgery," "mastectomy," and "breast implant." These terms were combined with adjuncts of "AND" or "OR." The search was limited to articles published since 2000 to provide an overview of past and current AFG techniques for postoperative pain in breast surgery. The reference lists of included articles were also examined to identify further studies meeting the inclusion criteria.

Stage 3: Selecting Studies for Inclusion

The inclusion criteria were (1) patients aged 18 and older, and (2) patients with breast cancer who underwent total or partial mastectomy. The presence of some form of outcome data was also a requirement. Studies focusing solely on breast augmentation procedures were excluded. Publications in languages other than English, case reports, letters, conference proceedings, abstracts, and textbook chapters were also excluded. The inclusion criteria were based on clearly identifiable populations, concepts, and contexts. Table 1 shows how populations, concepts, and contexts were applied.

Stage 4: Charting the Data

For all studies, data extracted included the authors' names, year of publication, country where the research was conducted, evidence level, type of study, baseline treatment, pain conditions before AFG, radiotherapy, chemotherapy, axillary dissection, intervention details, number of sessions, volume of AFG, intervention and control groups, timing of assessments, methods of evaluation, assessed outcomes, and conclusions. These data were condensed into tabular format. Two authors independently conducted this step for all articles, and the final tables were compiled following discussions among the authors.

Stage 5: Summarizing and Reporting the Results

Following the methodology of a scoping review, we collate and present the data according to our research questions through thematic analysis. A narrative summary of the results is provided to inform and direct subsequent research endeavors (Fig. 1).

Takeaways

Question: The full extent of the therapeutic effectiveness of autologous fat grafting for pain relief in postmastectomy pain syndrome has yet to be established.

Findings: Our scoping review demonstrated that most of the studies examined in this review suggested pain-relieving effects of autologous fat grafting. However, there was one randomized controlled trial in which these effects were not confirmed.

Meaning: Our research allowed us to understand a need for further accumulation of cases and performance of new, well-designed randomized controlled trials.

Table 1. Eligibility Criteria

Population	Breast cancer patients aged 18 and older who underwent total or partial mastectomy, including breast reconstruction.
Concept	Subjective or objective outcome data for any postoperative breast cancer pain. Studies focusing solely on breast augmentation procedures were excluded.
Context	Studies conducted in a broad geographical context or therapeutic setting since 2000 were considered with no limitations.
Study design	Cross-sectional, qualitative, mixed-method, cohort, case-control, or case study and RCTs. Reviews, opinions, news, comments, and studies for which only an abstract was available were excluded.
Language	Articles were required to be in English. Articles in a language other than English, case reports, letters, conference proceedings, abstracts, and textbook chapters were also excluded.

RESULTS

The initial search yielded 155 articles, and 148 articles were identified after removal of duplicates. Further screening of titles and abstracts, followed by a full-text review, resulted in identification of 17 articles meeting the inclusion criteria. Among these, studies without quantitative evaluation were excluded, but one additional article was found through hand searching. Consequently, a total of 11 articles were selected for the scoping review. All of

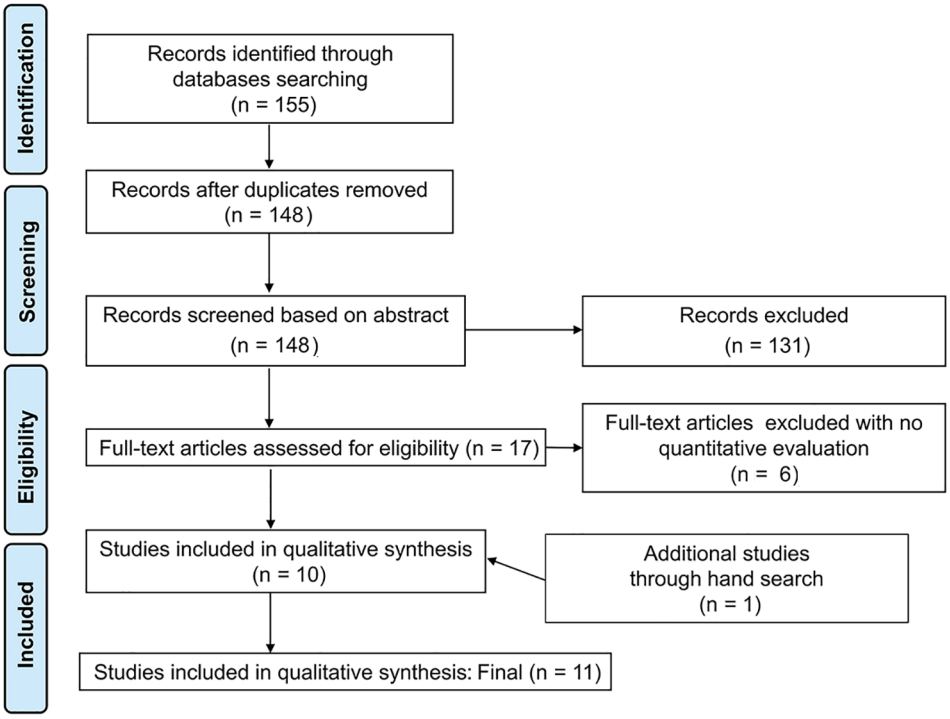

Fig. 1. PRISMA flow diagram.

these studies were conducted in Europe, including in Italy (seven studies, 63.6%), Denmark (two studies, 18.2%), Germany (one study, 9.1%), and Sweden (one study, 9.1%). This indicates that the effects of AFG for breast pain are being examined most actively in Europe, and particularly in Italy. The studies included three randomized controlled trials (RCTs; 27.3%), one prospective multicenter trial (9.1%), six prospective studies (54.5%), and one retrospective study (9.1%). The evidence levels were level 2 in three studies (27.3%), level 3 in four studies (36.4%), and level 4 in four studies (36.4%). There were 684 patients in the 11 studies[11–21] (Table 2). (**See table, Supplemental Digital Content 1**, characteristics of selected articles with results from observational studies other than RCTs. **http://links.lww.com/PRSGO/D300**.)

The patient backgrounds in the 11 articles varied considerably. Regarding breast cancer surgery, four studies (36.4%) involved mastectomy, two (18.2%) included both mastectomy and breast-conserving surgery, and only one study (9.1%) exclusively evaluated breast-conserving surgery. Regarding axillary dissection, three studies (27.3%) did not mention this procedure, but all others involved axillary dissection, and three included only cases in which axillary dissection was performed. Three observational studies (27.3%) included only cases in which breast cancer surgery was accompanied by radiotherapy.

In studies with clearly described numerical data, the average volume of AFG was 128 mL (SD, 118 mL), the average number of sessions was 1.6 (SD, 0.8), and the average follow-up period was about 15.8 months (SD, 14.6 months, range 3–18 months). The most common timing for evaluation post-AFG was at 1 year (six of 11 studies), with an average of 15.7 months (ranging from 0.5 to 75 months) across the 11 studies.

The visual analogue scale (VAS) is a common visual scale indicating the current level of pain by showing patients a 10-cm black line, while the numerical rating scale (NRS) also ranges from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain, to indicate the current level of pain, providing a stepwise scale. The assessment tools used to report outcomes most commonly included the VAS and NRS scales (eight of 11 studies, 72.7%). Because the evidence level is likely to differ between RCTs and observational studies, we divided the results into two tables and conducted independent evaluations (Table 2). (**Supplemental Digital Content 1**, **http://links.lww.com/PRSGO/D300**.) The outcomes in two of the three RCTs showed pain reduction effects of AFG, but one RCT did not observe such effects, contradicting our hypothesis. Of the other eight observational studies, four lacked control groups, which makes evaluation of the effects of AFG inconclusive, and the lower evidence level requires caution in interpretation of these findings. However, the broad conclusion drawn from all eight studies was that postoperative pain levels in the intervention groups decreased based on reduced pain scores reported by patients. In the four observational studies that compared pain levels using the VAS and NRS with a control group, the scores for pain evaluation were lower, confirming the effectiveness of the improvement.

DISCUSSION

In recent years, an increasing number of studies have suggested the effectiveness of AFG for pain relief in areas

Table 2. Characteristics of Selected Articles with Results from RCTs

Study	RCT 1	RCT 2	RCT 3
Authors	Juhl et al[11]	Gentilucci et al[12]	Sollie et al[13]
Publication year	2016	2020	2022
Country	Denmark	Italy	Denmark
Evidence level	2	2	2
Type of study	RCT	RCT	RCT
Baseline treatment	Total mastectomy	Total mastectomy + silicone breast implants	Total mastectomy
Pain condition before AFG	PMPS	Postoperative pain after breast reconstruction with SBI	PMPS
Radiation	Intervention group: 4 (57%) Control group: 6 (75%)	Partial cases	Intervention group: 18 (100%) Control group: 13 (77%)
Chemotherapy	Intervention group: 4 (57%) Control group: 6 (75%)	Partial cases	Intervention group (%): 14 (78%) Control group: 10 (59%)
Axillary dissection	Intervention group: 5 (71%) Control group: 6 (75%)	Partial cases	Intervention group: 12 (67%) Control group: 11 (65%)
Intervention	Fat grafting	Fat grafting	Fat grafting
Sessions	1	3	1
Fat grafting volume (mL)	71	Unknown (310–560 mL)	50
Treated patients	7	30	17
Control patients	8	30	18
Assessment timing	At baseline and 3 and 6 months after surgery	Baseline, at TE removal and 1 year after surgery	3 and 6 mo after surgery
Pain assessment tools	VAS + NPSI	LENT-SOMA scale pain scores, including subjective postoperative pain assessment	Primary outcomes: maximum and average pain level on NRS. Secondary outcomes: quality and degree of neuropathic pain measured using NPSI
Outcome indicators and key findings	Significant improvement in pain on the VAS ($P < 0.001$) and an average reduction of 54.9% on NPSI ($P < 0.002$)	Improvement in LENT-SOMA pain scores, including for subjective postoperative pain	No significant changes in average or maximum pain or neuropathic pain
Conclusion	AFG is safe and effective for alleviating persistent pain after mastectomy	Fat injections may be effective in reducing tissue radiation damage and improving QOL, including improving reconstructive surgery outcomes and pain	No clear evidence supporting the superiority of fat grafting over placebo in treatment of PMPS

LENT-NOMA, Late Effects Normal Tissue Task Force (LENT)-Subjective, Objective, Management, Analytic (SOMA) scales; NPSI, Neuropathic Pain Symptom Inventory; QOL, quality of life.

other than the breast. For example, Klinger et al showed pain-relief effects of fat injections in 20 patients with retractile and painful scars compromising normal daily activity and mobility of the involved joint.[22] There have also been reports of the efficacy of AFG in alleviating chronic pain associated with neuropathic pain,[23] autoimmune conditions,[24,25] thermal injuries,[26] radiation injury,[27,28] and vulvar lichen sclerosus.[29,30]

Pain in the breast area, which is referred to as PMPS, is a significant concern due to its high prevalence, the prolonged nature of the pain, and the lack of effective treatment beyond palliative care. The pathophysiology of PMPS is not fully understood, but several hypotheses have been proposed. One possibility is that tissue inflammation caused by surgery and subsequent formation of fibrotic tissue contribute to PMPS. Scar tissue formed in layers where breast tissue, fascia, or adipose tissue near nerves has been dissected during surgery may entrap these nerves. Postoperative seromas, hematomas, and minor infections may also contribute to abnormal nerve excitation.[31,32] Additionally, radiotherapy induces an inflammatory response associated with increased production of inflammatory cytokines such as interleukin-1,6, tumor necrosis factor-α , transforming growth factor-β, and chemokines like interleukin-8 and eotaxin, which makes it a major risk factor for development of PMPS.[33–35] Such inflammatory responses can induce peripheral and central sensitization of nerves, leading to breakdown of nociceptive systems and amplifying pain. Additionally, it is well known that radiotherapy enhances local fibrosis.[36] Given that persistent pain following surgical procedures is strongly suspected to be caused by such inflammation and associated scar formation, this hypothesis leads to the possibility that antiinflammatory molecules and growth factors released by mesenchymal stem cells in lipoaspirate may ameliorate neuropathic hypersensitivity.[37–39] Regarding antiinflammatory effects, adipose-derived stem cells within fat tissue can downregulate immune responses by inhibiting activation of T cells, proliferation of natural killer cells, and production of inflammatory cytokines.[16,40]

Regarding the effect of scar release, the group led by Caviggioli focused on structural remodeling of scar tissue

and promotion of angiogenesis through fat grafting, drawing on the findings of Rigotti et al[41] for treatment of tissue damage caused by radiation therapy. The results histologically demonstrated that AFG contributes to resolution of scars and the release of entrapped nerves.[42] Furthermore, there are reports suggesting that lipoaspirate, which is rich in mesenchymal stem cells, can attenuate pain responses[22,42,43] and prevent formation of neuromas.[44,45] Thus, although pharmacotherapy has been the mainstay of treatment, emerging evidence suggests that AFG is a promising adjunctive approach for management of PMPS.

In this study, we focused on the critical issue of whether AFG procedures published since 2000 have had an effect on pain relief after breast cancer surgery. We screened articles that conducted quantitative and qualitative research on this specific theme and reviewed RCTs and other observational studies separately.

The studies had various timings of evaluation of 6 months, 1 year, and 2 years, but most of them utilized common assessment tools based on Likert scales, such as the VAS and NRS.

A meta-analysis of observational studies that used quantitative evaluations showed a significant improvement in pain in all studies, as assessed by VAS and NRS scores. If only these results are considered, combining AFG as an adjunctive treatment seems to be more effective, given the refractory nature of neuropathic pain. In higher-level evidence RCTs, secondary outcome measures, including the Neuropathic Pain Symptom Inventory, showed significant pain improvement, as reported by Juhl et al.[11] However, in contrast, Sollie et al found no difference between the control and intervention groups in the treatment of PMPS using AFG. Furthermore, Juhl et al[11] found improvements in all areas of health-related quality of life, whereas Sollie et al[13] found no significant improvement in quality of life using the 36-Item Short Form Health Survey. Consequently, it may still be premature to draw definitive conclusions about the breast pain reduction effects of AFG.

The limitations of this review include the low quality of evidence in many studies. The studies reviewed had small patient cohorts, publication bias, inconsistent follow-up periods, and a lack of uniformity in outcome measures, making it challenging to derive reliable conclusions. There were inconsistencies in identification of the level and completeness of injuries, leading to exclusion of some studies. Consequently, this resulted in a smaller number of cases being considered. Follow-up periods and timings also varied among studies, with RCTs using assessments at baseline and after 3 and 6 months, whereas observational studies had average follow-up durations of 10 months to 2.5 years. For these reasons, the scoping review article style was adopted as a preliminary stage of the typical systematic review process to comprehensively map and organize existing knowledge and identify areas that have not been sufficiently researched (gaps).[9] Registration with PROSPERO was also not mandatory if it was a scoping review.[46]

It was an intriguing subject to determine the extent to which AFG is effective in pain control for lumpectomy, which, despite typically involving radiation therapy, involves a smaller extent of breast removal compared with mastectomy. Unfortunately, there was only one observational study[20] that included lumpectomy, and it did not compare the outcomes between lumpectomy and mastectomy. Another point of interest was the discrepancies in the conclusions of the RCTs.[11–13] For one of the studies,[12] the timing of evaluation and the methods of assessment differed. For the other two studies, it was speculated that a significant factor was the disparity in the use of adjunctive radiation therapy; in one intervention group,[11] only about half of the cases (57%) received radiation therapy, whereas in the other,[13] it was administered to 100% of the cases. To examine these points in more detail, larger sample-size, high-quality RCTs, and more refined subgroup analyses are also needed for patients who have undergone adjunct treatments, including radiotherapy and chemotherapy, and axillary clearance, to eliminate potential sources of bias. It is also desirable for systematic review and meta-analysis studies to conduct a more comprehensive analysis of the limitations of included research, such as evidence level, small sample sizes, potential publication bias, and so forth.

CONCLUSIONS

The results from this scoping review of the breast pain relief effects of AFG may be useful in counseling of patients and surgical decision-making. Most studies in this review suggested pain-relieving effects of AFG. However, one RCT did not show an effect, which indicates the need for accumulation of more cases and performance of new, well-designed RCTs.

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DISCLOSURE

The authors have no financial interest to declare in relation to the content of this article. No funding or funder involvement was associated with the work in the article.

ACKNOWLEDGMENTS

We are greatly indebted to Ms. Mari Sone, a librarian at Shizuoka Graduate University of Public Health, for her assistance with literature searching, and to Ms. Hiroko Mori and Ms. Noriko Kojimahara for technical guidance for writing a review article.

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