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Autologous fat grafting efficacy in treating PostMastectomy pain syndrome: A prospective multicenter trial of two Senonetwork Italia breast centers

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Abstract

Postmastectomy pain syndrome (PMPS) represents a common complication following breast surgery defined as a chronic neuropathic pain located in the front of the chest, in the axilla and in the upper arm that for more than 3 months after surgery. Several medications prove to be ineffective while autologous fat grafting revealed to be an innovative solution in the treatment of neuropathic pain syndromes based on retrospective studies. For this reason, we performed a prospective multicenter trial to reduce the memory bias and further increase the evidence of the results. From February 2018 to March 2019, 37 female patients aged between 18 and 80 years, underwent mastectomy or quadrantectomy with pathologic scarring and chronic persistent neuropathic pain, compatible with PMPS, are been included in the study and treated with autologous fat grafting. During the enrollment phase, patients were asked to estimate pain using the Visual Analogue Scale (VAS) and POSAS questionnaire in order to evaluate scar outcomes. The VAS scale, starting from 6.9 (1.3), decreased in the first month by 3.10 (1.59), continuing to fall by 0.83 (1.60) to 3 months and by 0.39 (2.09) at 6 months. Statistical analysis showed a significant reduction after 1 month ($P < .0001$) and 3 months ($P < .005$). All POSAS grades documented a statistically significant reduction ($P < .0001$) of the scores by both observers and patients. We observed that no significant association was found between age, BMI, menopausal status of patients, days from oncologic surgery to autologous fat grafting and reduction of VAS values over time while both smoking and axillary dissection were observed as the main factor significantly associated with a reduced clinical efficacy (respectively, $P = .0227$ and $P = .0066$). Our prospective multicenter trial confirms the efficacy of fat grafting in the treatment of PMPS based on the principle of regenerative medicine with a satisfactory response in terms of pain reduction and improvement of the quality of the treated tissues. Clinical questionnaires show that the cicatricial areas improve in terms of color, thickness, skin pliability, and surface irregularities. Regenerative effect is based also on the adoption of needles. The combined effect of fat grafting and needles determines a clinical full response.

KEYWORDS
fat grafting, lipostructure, neuropatic pain, PMPS, regenerative surgery

1 | INTRODUCTION

Breast cancer represents now the most frequent malignant pathology in women, with 2.1 mln new diagnosis in 2018.[1] Although breast surgery and breast reconstruction techniques are rapidly evolving obtaining high patient satisfaction, they are not free from risks and complications.

One of the most significant and debilitating consequences of breast surgery is the postmastectomy pain syndrome (PMPS), defined by the International Association for the Study of Pain (IASP) as a chronic neuropathic pain located in the front of the chest, in the axilla and in the upper arm that arises after mastectomy or quadrantectomy and persists for more than 3 months after surgery.[2] About 20%-50% of patients undergoing breast surgery for oncologic reasons develop this syndrome, describing it as a painful, burning sensation exacerbated by the movements of the ipsilateral upper limb with functional limitations due to scarring[3] and tend to manifest increased anxiety and depressive symptoms compared to patients without persistent pain.[4]

Medications commonly used to treat nociceptive pain, such as opioids, have proven to be ineffective for neuropathic pain. Analgesic therapies with antidepressants[5,6] and topical capsaicin,[7] despite the efficacy in PMPS, have numerous side effects. New antiepileptics such as levetiracetam are well tolerated; however, Vilholm et al[8] could not demonstrate a significant effect in patients with PMPS.

Autologous fat grafting is a safe and minimally invasive technique, proven to be effective in the treatment of neuropathic pain syndromes, such as Arnold's occipital neuralgia.[9]

Our group extensively adopted such a procedure to treat scar tissue-related pathologies, degenerative diseases, and volume deformities.[9-17]

In 2006, we were the first to treat patients undergoing mastectomy and axillary dissection followed by radiotherapy,[10] demonstrating the ability of the lipostructure to alleviate PMPS symptoms. Subsequently, the indications to autologous fat grafting were extended to patients undergoing quadrantectomy followed by radiotherapy.[11] In both groups, it has been observed a significant reduction in pain and analgesic therapy intake.

However, many of these results derive from retrospective studies that are subject to memory bias. For this reason, a prospective and multicenter study has proven useful, in order to reduce the memory bias and further increase the evidence of the results, definitively confirming the effectiveness of the procedure in different centers.

We conducted this study is to evaluate the clinical efficacy of autologous adipose tissue grafting in pain reduction using the VAS scale. In addition, we adopted POSAS questionnaire in order to evaluate scar outcomes, and possible factors which influence the effectiveness of the procedure.

2 | MATERIALS AND METHODS

2.1 | Population

This is a multicenter prospective interventional study conducted in two centers which are part of Senonetwork Italia: Humanitas research Hospital and the AOU Policlinico di Modena. The study was approved by both ethics committees of the related hospitals (Prot. nr 353/18, 699/2018/SPER/AOUMO). From February 2018 to March 2019, 37 female patients aged between 18 and 80 years, underwent mastectomy or quadrantectomy with pathologic scarring and chronic persistent neuropathic pain, compatible with PMPS, are been included in the study (inclusion criteria in Table 1). During the enrollment phase, patients were asked to estimate pain using the Visual Analogue Scale (VAS) with values from 0 to 10, in order to select only those with values ≥4.

The following data were also collected and evaluated: Age, BMI, menopausal status, smoking habits, surgery (mastectomy, lumpectomy, and axilla dissection), therapies (radiotherapy, chemiotherapy, and ormonal therapy), days from oncologic surgery to autologous fat grafting (AFG) (Table 2.).

Each eligible patient was informed about the goals and methods of this study and expressed her consent.

2.2 | Preoperative evaluation

After a careful clinical examination and the collection of photographic documentation, the pain values indicated by the VAS scale were recorded. POSAS scale was used for the evaluation of the scars. Each part contains six elements, each of which is evaluated with a score from 1 to 10, where 10 indicates "the worst scar imaginable" and 1 indicates "a situation corresponding to normal skin."

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Symptomatology of PMPS (VAS ≥ 4) according the definition of International Association for the Study of Pain (IASP)	• confirmed or presumed pregnancy
• History of previous mastectomy or quadrantectomy surgery	• Breastfeeding
• Persistent Pain (>3 mo)	• inadequately controlled dysmetabolic states
• Pain that does not respond to NSAID or steroids	• concomitant steroid therapies
	• drug or alcohol abuse

The overall score of each part is calculated by summing the scores of the individual elements, for a total between 6 and 60. Furthermore, an "overall opinion" of the quality of the scar is evaluated separately for both the patient and the observer.

All the data were collected even at 1, 3, and 6 months after the procedure.

2.3 | Procedure and follow-up

In order to reduce any bias linked to differences concerning the treatment technique between the two centers, one single operator was used for Humanitas and one for the Policlinico di Modena.

Coleman's technique was previously agreed and performed by both the operators.

Each enrolled patient underwent one autologous fat grafting procedure. After clinical assessment and routine preoperative examination, patients were submitted to liposuction of the hips area under sedation and analgesia. The hips harvesting area was chosen because it is an easily accessible adipose tissue reservoir. Adipose tissue was obtained and centrifuged at 837 *g* for 5 minutes following Coleman's procedure. The adipocyte cell fraction was isolated and injected using an 18-gauge angiographic needle with a snap-on wing (Cordis, a Johnson & Johnson Company, N.V) at the dermal-hypoder-mal junction in the painful scar areas but also in surrounding tissues and along mastectomy flaps. The mean amount of graft injected was 60 cc.

All the data were collected even at 1, 3, and 6 months after the procedure. Each visit included functional and painful evaluations of the treated area and compilation of the VAS scale. In addition, the POSAS scale was completed during the 6-month visit. All patients had regular follow-up without complications.

2.4 | Statistical analysis

Considering a first type error of 5%, 37 patients would have been necessary to show that the treatment decreases pain by 2.5 points with a similar variability with a power of 90%.

All data were analyzed with a double-tailed Student's *t* test for paired data. The influence of each of the factors explored on the VAS variable was tested through ANOVA, an analysis of variance with repeated multifactorial measures. A value of $P \leq .05$ was considered to be significant.

3 | RESULTS

The VAS scale, starting from a preoperative average of 6.9 (1.3), decreased in the first month by 3.10 (1.59), continuing to fall by 0.83 (1.60) to 3 months and by 0.39 (2.09) at 6 months. The statistical analysis showed that the pain is significantly reduced after 1 month ($P < .0001$) and 3 months ($P < .005$), confirming the already known efficacy (Figure 1).

The POSAS scale documented a statistically significant reduction ($P < .0001$) of the scores reported by both observers and patients. All the parameters aimed at quantifying the qualitative improvement of scar tissue have been reduced considerably, in particular skin pliability (52.1%) (Table 3).

4 out of 37 patients did not benefit from treatment and were identified as "non-responder" (patients characteristics described in Table 4)

Analyzing factors affecting fat grafting clinical efficacy we observed that no significant association was found between age, BMI, menopausal status of patients, time from oncologic surgery to autologous fat grafting and reduction of VAS values over time.

TABLE 2 Study population characteristics

Parameters	Humanitas Research Hospital (Rozzano, Milan) (n = 28)	AOU Policlinico di Modena (n = 9)	Total (n = 37)
Demographic			
Age	47	50	48 (±6.2)
BMI	22.35	22.04	22.27 (±3.2)
Menopause	26 (93%)	8 (89%)	34 (92%)
Smoking	8 (28%)	2 (22%)	10 (27%)
Therapy			
Radiotherapy	17 (60%)	5 (55%)	22 (60%)
Chemiotherapy	16 (57%)	6 (66%)	21 (57%)
IA	9 (32%)	2 (22%)	11 (30%)
LHRH + TAM	12 (43%)	3 (33%)	15 (41%)
Type of Procedure			
Mastectomy	17 (60%)	7 (77%)	24 (65%)
Quadrantectomy	11 (39%)	2 (22%)	13 (35%)
Axillary dissection	18 (64%)	4 (44%)	22 (60%)
Time from oncologic surgery to AFG	1743 (220-7505)	364 (174-595)	1195 (174 - 7505)

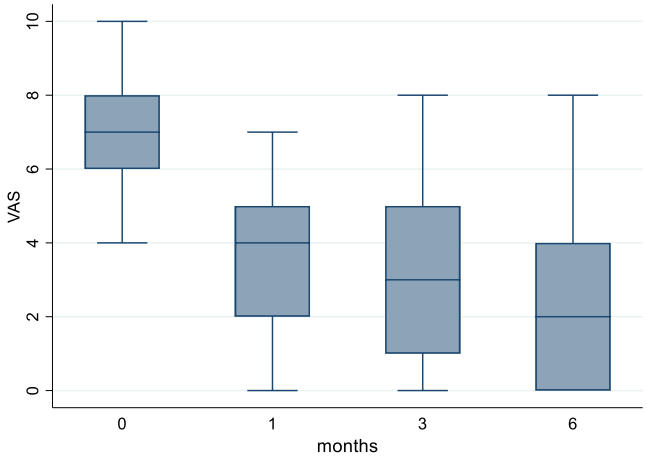

FIGURE 1 Reduction of pain

TABLE 3 POSAS scale parameters for observer and patient with percentage reduction at 6 mo compared to presurgery

Observer		Patient	
Parameters	**Reduction %**	**Parameters**	**Reduction %**
Vascularity	36.8%	Pain	54.9%
Pigmentation	37.7%	Itching	15.3%
Thickness	40.0%	Colour	38.2%
Relief	44.8%	Stiffness	39.3%
Pliability	51.2%	Thickness	35.9%
Surface Area	39.9%	Irregularity	42.4%

Differently exposure to smoking and axillary dissection were observed as the main factor significantly associated with a reduced clinical efficacy (respectively, $P = .0227$ and $P = .0066$). (Figures 2 and 3).

Analyzing the effect of endocrine therapy we observed that patients on aromatase inhibitor therapy had a significantly lower reduction in VAS values compared to the group without hormone therapy ($P = .0348$) while pain was reduced differently in the Tamoxifen group when compared with the group without therapy and that with aromatase inhibitors, respectively, but the differences were statistically insignificant ($P > .005$) (Figure 4).

4 | DISCUSSION

Regenerative effects of adipose tissue grafting in the treated tissues are well described in literature. This effect is probably due to the presence of mesenchymal stem cells (ADSC) in the stromovascular component of adipose tissue,[12,13] with consequent new deposition of collagen, neoangiogenesis, and dermal hyperplasia. Based on this evidence our group adopted autologous fat graft in various clinical conditions characterized by atrophy or fibrosis of the skin, such as burns,[14] perioral sclerodermia,[15] irradiated tissues,[16] and chronic post-traumatic ulcers.[17]

According to the most reliable hypotheses, the pathogenic mechanism of PMPS is to be found in intraoperative nerve damage and their subsequent entrapment in cicatricial fibrosis, which represents a continuous triggering of nervous excitement. Further, the development of the pain syndrome could depend on an inflammatory reaction, often aggravated by radiotherapy, with increased production of proinflammatory cytokines such as IL-1, IL-6, TNFa, TGFb, and chemokines such as IL-8 and eotassin. This inflammatory reaction can induce peripheral and central sensitization with damage to the nociceptive system, which leads to the increase of pain.[18]

The efficacy of fat grafting in the treatment of PMPS is actually based on the principle of regenerative medicine. Specifically, the stromovascular component of fat tissue has an important source of mesenchymal stem cells (ADSC).[19,20] ADSCs play a key role in the survival of grafted fat cells, through the secretion of various cytokines and growth factors, resulting in neoangiogenic,[21,22] immunomodulatory,[23,24] and anti-inflammatory activity.

All of this results in a decrease in inflammation in the treated tissues and a decrease in the scar tissue tension, with consequent release of the trapped nerves, with improvement of the pain symptomatology.

Moving from our evidences after more than 10 years treatment of pain syndromes with fat grafting we are strongly convinced that regenerative effect is not only based on a cell therapy, injecting biologically active cells in fibrotic tissues, but the adoption of needles is a fundamental aspect of all surgical procedures. Needles allow the operator to penetrate fibrotic tissue, which leads to pain sensation through the aforementioned reasons, creating a plane made by autologous fat grafting able to substitute scar with a regenerated tissue.

Needling effect is well known and leads to regeneration itself increasing the production of citokyne and local mediators.[13]

The combined effect of fat grafting and use of needles is the responsible of the effect of fat grafting in pain syndromes and both aspects are needed for a full response.

This statement is based on our clinical observation and further data are needed to confirm this evidence.

Nevertheless, 4 of 37 patients did not benefit from treatment and were identified as "non-responder," leading us to hypothesize a possible role of individual characteristics on the vitality and efficacy of grafted cells. We decided to evaluate the association of these factors with the average VAS values in the entire population.

Smoking results the main factor associated significantly ($P < .005$) to reduced efficacy of fat grafting.

Several studies demonstrated the negative effect of smoking on fat graft. In an experimental study on rats, Ercan et al demonstrated that fat graft takes with the same mechanisms as a wound heals. To our knowledge, ours is the first study to report the effect of smoking on the engraftment and effectiveness of adipose tissue.

Hirotaka Suga et al proved that severe ischemia and hypoxia induces degenerative changes in adipose tissue and subsequent

TABLE 4 Nonresponder characteristic

	Nonresponder patients			
	1	2	3	4
Age	41	57	51	39
BMI	19.1	23.84	26.22	21.78
Smoking	NO	NO	NO	NO
Menopause	After ovarienctomy	Phisiologic	Phisiologic	After medical treatment
Surgery	Mastectomy	Mastectomy	Mastectomy	Mastectomy
Axillary Dissection	YES	YES	YES	YES
RadioTherapy	YES	YES	YES	NO
ChemioTherapy	YES	YES	YES	NO
Hormone Therapy	NO	NO	IA	LHRH + TAM

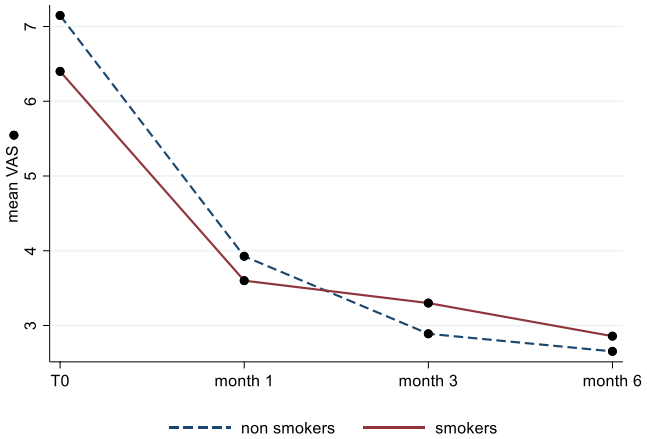

FIGURE 2 Impact of smoking

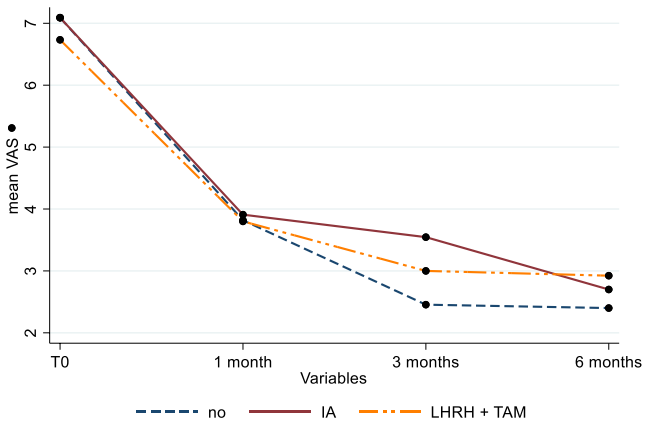

FIGURE 4 Impact of hormone therapy. IA: aromatase inhibitor; LHRH: LHRH agonist; TAM: Tamoxifen

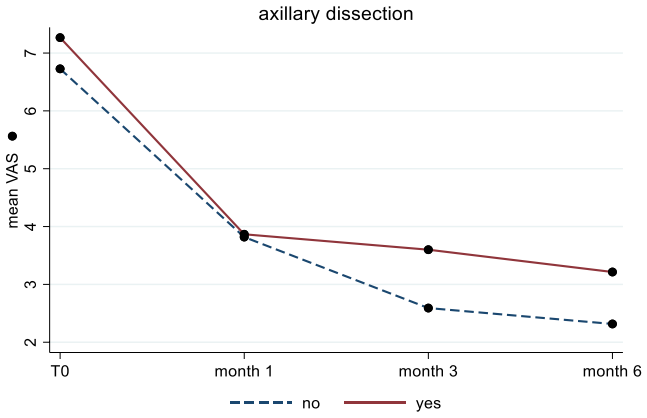

FIGURE 3 Impact of axillary dissection

adaptive tissue remodeling since adipocytes die easily under ischemic conditions.[25]

We think that this is due to the effects that smoking has on the microcirculation, characterizing vasoconstriction, and endothelial damage. This leads to a reduction in local vascularization and consequent reduced engraftment of adipose tissue.

Our evidences confirm that cigarette smoking seems to present a negative effect on fat graft survival so that patients should be properly informed before procedure.[26]

Patients undergoing axillary dissection are more exposed to developing a PMPS.[27]

In our case series, we note that these patients not only have a higher preoperative VAS score than controls, but also a reduced improvement after treatment. This can be explained by the nervous trauma suffered during surgery and the greater incarceration of surviving nerve fibers in the healing process.

Estrogens are an important regulator of adipose tissue, exerting their effects mainly through two receptors: ER-α and ER-β. Hormone therapy, an integral part of the therapeutic protocol of hormone-dependent breast tumors, can therefore influence the level of estrogen and consequently its effects on adipose tissue.

Data in literature relating to the effect of Tamoxifen on adipose tissue are contrasting and based primarily on in vitro studies or animal studies.[28,29]

One in particular, conducted by Pike et al, showed that tamoxifen has cytotoxic effects on human ASCs through apoptosis and inhibition of proliferation in dose- and time-dependent manners,

down regulating the capacity of ASCs for adipogenic and osteogenic differentiation and inhibit the ability of the ASCs to subsequently formed cords in Matrigel. This study demonstrated that tamoxifen inhibited ASC proliferation and multilineage ASC differentiation rates.[28]

These results are inconsistent with our observations. Sure enough, we divided the patients into three groups, based on the hormone therapy taken, comparing them in pairs. Our results show that patients undergoing aromatase inhibitor therapy had significantly lower VAS values reduction than patients not taking such a medication while tamoxifen therapy did not show such an effect.

In our knowledge, our study is the first prospective trial to analyze the effect of several clinical factors on the efficacy of autologous fat grafting, we observed how smoking, axillary dissection, and therapy with aromatase inhibitors determine a reduction in the VAS score reduction.

Such information is strongly biased by the limited number of patients, and bigger data set is needed although a first observation is useful to correctly inform patients.

In our clinical protocol, we consider the use of the POSAS questionnaire as one of the main advantage combining a subjective to an objective evaluation.

POSAS scores confirm the amelioration of breast surgery scars in particular we observed an amelioration in pliability scores which was related to the antifibrotic autologous fat grafting effect. The study we conducted is a multicenter prospective study, which offers a greater level of scientific evidence to definitively confirm the efficacy of fat grafting in treating PMPS.

5 | CONCLUSION

Persistent pain following surgical treatment for breast cancer is a complication recognized as PMPS. This syndrome represents a major clinical challenge, which affects an increasing number of patients. As classic medical therapies seem to be ineffective, especially in the long term, autologous fat grafting has been shown to be a promising treatment option.

This prospective and multicenter study confirms with a high level of scientific evidence its efficacy in the reduction of pain symptoms, since the previous data were derived from retrospective and monocentric studies.

In light of the results obtained from the study, it is possible to confirm that autologous fat grafting is an effective and safe technique in the treatment of PMPS. The clinical evaluation by the operators and subjective by the patients shows that the cicatricial areas take on an aspect more and more similar to the normal skin during the follow-up, in terms of color, thickness, skin pliability, and surface irregularities. The analysis of the possible factors influencing the effectiveness of the adipose graft highlighted the negative impact of smoking as a prevalent factor among all those explored.

Oncologic evaluation about autologous fat grafting safety is becoming fundamental since more and more patients will be submitted to such a procedure and Senonetwork Italia is actually promoting a large multicenter retrospective trial to definitely confirm its oncologic safety.

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