Autologous Fat Graft in Postmastectomy Pain Syndrome

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Background: Mastectomy with axillary dissection is still one of the most common procedures in oncologic surgery. Unfortunately, a condition of neuropathic pain, termed postmastectomy pain syndrome, can appear after mastectomy. Although evidence regarding the epidemiology of postmastectomy pain syndrome is well researched, an effective therapy is still unknown. The aim of this study was to assess the clinical effectiveness of lipoaspirate graft in the treatment of postmastectomy pain syndrome.

Methods: From February of 2006 to August of 2008, a total of 113 patients affected by postmastectomy pain syndrome and severe scar retractions were enrolled for this clinical study. Seventy-two patients were treated with autologous fat grafted in painful scars, and 41 patients did not undergo any further surgical procedure. Pain assessment was performed using a visual analogue scale before and after treatment, with a mean follow-up of 13 months. In addition, antalgic drug intake was recorded in the 34 patients who received a surgical treatment. Results were analyzed using the Wilcoxon rank sum test.

Results: A significant decrease in pain according to the visual analogue scale was detected in patients treated with autologous fat graft (3.23-point reduction, $p = 0.0005$). Twenty-eight of 34 patients stopped their analgesic therapy with a significant follow-up (13 months).

Conclusions: Autologous fat grafting is a safe, relatively noninvasive, and rapid surgical procedure. The authors' results suggest its effectiveness for treatment of postmastectomy pain syndrome. (*Plast. Reconstr. Surg.* 128: 349, 2011.)

CLINICAL QUESTION/LEVEL OF EVIDENCE: Therapeutic, II.

During the nineteenth century, radical mastectomy was considered the best choice for breast cancer management. Fortunately, survival from breast cancer improved, but morbidity associated with surgical techniques increased. Although breast conserving therapy gained popularity because it provided a less invasive treatment, today 40 percent of breast surgical procedures are characterized by mastectomy with axillary dissection.[1]

Persistent pain after mastectomy was first reported in the 1970s by Wood.[2] The International Association for the Study of Pain defined postmastectomy pain syndrome as chronic pain in the anterior side of the thorax, in the axilla, and/or in the upper half of the arm beginning after mastectomy or quadrantectomy and persisting for more than 3 months after surgery.[3]

The pain in postmastectomy pain syndrome is typically neuropathic in nature, characterized as a dull, burning, and aching sensation exacerbated by movement of the shoulder girdle.[4] Caffo et al. estimated a prevalence of 39.7 percent of 529 patients in one study.[5] Medications commonly used to treat nociceptive pain, such as opioids, may be less effective for neuropathic pain.

Recently, our team demonstrated that fat injection can improve pain control in patients with Arnold neuralgia, a condition of neuropathic pain similar to postmastectomy pain syndrome.[6] Since 1980, several articles have highlighted different findings on fat transplantation obtained by liposuction. In 1995, Coleman first described a

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new technique to improve adipose cell survival.[7] Today, liposuction and fat injection are commonly used in different clinical fields. For example, after breast reconstructive surgery, a difference in breast size or shape could appear, and autologous fat grafting can represent an important tool for correction.

Fat has been investigated and microstructural studies have been developed. Adipose tissue contains extracellular matrix (collagens, laminin, fibronectin) and cellular components such as adipocytes and many others. Moreover, recent interest has arisen regarding stem cells in adipose tissue.[8] Rigotti et al. showed in their study the presence of mesenchymal stem cells in the isolated stromal vascular fraction of lipoaspirate.[9] Klinger et al. grafted purified autologous fat tissue in several burn scars, obtaining a considerable improvement of mimic features, skin texture, and skin thickness, and clinical reduction of pain of treated areas.[10] These are theoretical bases for treatment of postmastectomy pain syndrome with the fat graft technique.

PATIENTS AND METHODS

From February of 2006 to August of 2008, a total of 113 patients with severe scar retraction and postmastectomy pain syndrome came to our unit. All patients had undergone mastectomy with axillary dissection and radiotherapy. A subpectoral tissue expander had been implanted during breast reconstruction. The skin expander had been replaced with a silicone prosthesis at least 6 months after reaching full expansion (mean replacement, 9.5 months). Reconstruction of the nipple-areola complex was performed separately, 12 months after the initial breast operation. All patients enlisted for this study had a normal follow-up without complications, such as dehiscence, infection, or scar anomalies.

We performed fat tissue grafting in 72 patients with severe scar retractions and diagnosis of postmastectomy pain syndrome. Forty-one of 113 patients with postmastectomy pain syndrome had not been treated surgically and were considered as a control group for statistical analysis.

Treated patients had been injected at the dermohypodermal junction in painful scar areas with adipose tissue harvested from abdominal subcutaneous fat and processed following Coleman's technique. After clinical assessment and routine preoperative examination, patients were submitted to liposuction of the subumbilical area under sedation and analgesia. The abdominal harvesting area was chosen because it is an easily accessible adipose tissue reservoir. Adipose tissue was obtained and centrifuged at 3000 rpm 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, Roden, The Netherlands) at the dermal-hypodermal junction in the painful scar areas. The mean amount of graft injected was 55 cc.

Data instruments consisted of preoperative and postoperative pain questionnaires. During the first visit, a trained research assistant explained the purpose and methods of this study to each eligible patient who was willing to participate. Patients scored their spontaneous pain using a visual analogue scale ranging from 0 to 10.0. Analgesic requirement and drug intake were recorded. One year after fat grafting, we performed a further postoperative pain evaluation using the same scale and collected data regarding analgesic intake. Control group patients filled out the same questionnaire using the visual analogue scale during the first visit and 1 year later. Analgesic intake was recorded accurately also in the control group.

The mean follow-up period for all patients was 13 months (range, 12 to 15 months). Nine patients in the treated group and six patients in the control group were lost to follow-up. Results were analyzed using the Wilcoxon rank sum test.

RESULTS

In 63 treated patients, a pain decrease according to the visual analogue scale was detected (mean ± SD point reduction, 3.23 ± 2.96). Twenty-eight of 34 patients stopped their analgesic drug therapy. In the group of 28 patients who stopped analgesic therapy, the mean pain decrease was 4.33 ± 2.24, whereas the mean pain decrease in the group that continued analgesic therapy was 1.18 ± 2.89. The control group reported a mean ± SD decrease of pain of 1.04 ± 2.71. Statistical analysis was performed using the Wilcoxon rank sum test. Results showed that pain decreased significantly in patients with postmastectomy pain syndrome treated with autologous fat tissue grafting ($p = 0.0005$) (Table 1).

DISCUSSION

Partial or complete breast amputation has important implications in a woman's quality of life. Surgical scars are located in a critical area where women focus their attention. The scarring process is well known, and consequent fibrosis could result in a strong adherence to the deeper muscular layer, involving a painful syndrome.

Table 1. Measurements of Decrease in Pain in Four Groups of Patients*

Group	No.	Decrease in Pain		
		Mean (VAS)	Median (VAS)	Range
Treated	63	3.23	2.7	2.0–9.6
Control	35	1.04	0.4	3.7–6.3
Stop pharmacologic therapy	28 (63)	4.33	5.0	1.5–9.6
Continue pharmacologic therapy	6 (63)	1.18	0.9	2.6–2.3

VAS, visual analogue scale.
*Analysis of differences between treated and control patients was performed by means of the Wilcoxon rank sum test (mean pain decrease difference, 2.19; $W = 1545$; $p = 0.0005$).

Chronic pain is defined as postmastectomy pain syndrome if it responds to three criteria: pain properties, location, and timing. Pain should have neuropathic characteristics with unpleasant and peculiar sensations described as numbness, pins and needles sensations, burning, or stabbing. Its location should be recorded at the same side of surgery, in the axilla, arm, shoulder, or chest wall area. It should persist either continuously or intermittently beyond the normal healing time of 3 months; for that reason, it is qualified as chronic.[11]

Postmastectomy pain syndrome has a prevalence of 65 percent in young women with ages ranging from 30 to 49 years and a prevalence of 26 percent in women older than 70 years.[12] In another study, postmastectomy pain syndrome prevalence seems to decrease with age: 65, 40, and 26 percent in the 30- to 49-year, 50- to 59-year, and older than 60-year groups, respectively.[13] The exact pathogenic mechanism of postmastectomy pain syndrome is unclear, but various etiologic theories have been postulated, including dissection of the intercostobrachial nerve, intraoperative damage of axillary nerve pathways, pain caused by neuromas, and nerves entrapped in scar fibrosis, which would represent a continuous trigger of nerve excitation.

First-line medications for postmastectomy pain syndrome include tricyclic antidepressants such as nortriptyline and amitriptyline, which target neurotransmitter activity.[14] Anticonvulsant medications such as gabapentin may also relieve neuropathic pain. For topical application, up to three lidocaine patches per day can be placed directly over the painful area for up to 12 hours. Some patients find that applying capsaicin cream or cold packs located on the painful area can be helpful. Neuropathic pain may respond better with more treatments combined. Furthermore, a pharmacologic therapy lasting for a long period is poorly tolerated.[15]

In contrast, autologous fat graft treatment is well tolerated. This procedure can be an innovative solution for this problem. Pathophysiologic, cellular, and molecular mechanisms involved are not defined yet.

After mastectomy, reconstructive surgery should aim to restore the patient's quality of life to preoperative conditions. Frequently, fat tissue transplantation can improve volume where only a muscular flap could supply the lost tissue.[16]

Rigotti et al. first grafted purified lipoaspirate for treatment of radiotherapy effects on the breast, demonstrating regenerative mechanisms. Histologic study of treated tissues showed progressive regeneration, including neovessel formation and improved hydration.[9,17,18] Histologic examination in Klinger's studies showed patterns of new collagen deposition, local hypervascularity, and dermal hyperplasia in the new tissue context. We suppose that release of this tissue with nerve liberation could be the pathophysiologic explanation for our study effect and pain control improvement in patients with Arnold neuralgia.

The key point of our strategy was to hypothesize a regenerative role of lipostructure in the scar area causing nerve entrapment, keeping in mind principles of regenerative medicine which, in the definition of Daar and Greenwood, "aims to repair tissue or organ to restore impaired function."[19] As shown in experimental models of spinal cord injuries, the nervous system fails to regenerate because of intrinsic inhibitory factors expressed by the extracellular matrix of posttraumatic scar.[20] We hypothesize that use of autologous fat graft could result in an improvement in tissue differentiation and scar softness, which could have beneficial effects on nerve entrapment, leading to a successful clinical result.

Another possible explanation is linked to a mechanical effect of adding soft tissue to scars. However, this would not demonstrate improvement in scar flexibility and skin texture.

Surgery-associated tissue injury in irradiated breasts leads to an inflammatory reaction accompanied by increased production of proinflammatory cytokines. This inflammatory reaction can induce peripheral and central sensitization with a failed nociception system, leading to pain augmentation.[21]

Keyser et al. reported that mesenchymal stem cells and adipose-derived stem cells could efficiently reduce T-cell activation. Results suggest that mesenchymal stem cells from adipose tissue

can be useful for modulation of graft-versus-host disease after allogenic stem cell transplantation or to enhance engraftment across major histocompatibility complex barriers.[22] Others have demonstrated that human mesenchymal stem cells have immunosuppressive properties. Mesenchymal stem cells inhibited the proliferation of $CD4^+$ and $CD8^+$ T lymphocytes.[23] Moreover, we hypothesize a possible analgesic effect caused by inflammation inhibition resulting from autologous fat grafting.

Finally, we showed that autologous fat graft treatment can be used for postmastectomy pain syndrome. Considering results shown in this and our other studies, we presume that this effect depends on scar remodeling demonstrated by adipose tissue grafted. Morbidity related to the procedure is minimal and is similar to that experienced with restricted liposuction, with acceptable safety.

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