Flap Neurotization in Breast Reconstruction with Nerve Allografts: 1-year Clinical Outcomes

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Background: Autologous breast reconstruction is widely regarded as the gold standard approach following mastectomy. However, the lack of sensation continues to present a reconstructive challenge. In this study, clinical outcomes following abdominal flap neurotization with processed human nerve allograft were investigated.

Methods: In this prospective analysis, patients who underwent microsurgical breast reconstruction with (Group 1) or without (Group 2) abdominal flap neurotization at a single institution were investigated. Processed human nerve allograft (Avance, AxoGen, Alachua, Fla.) was used in all cases of flap neurotization. Only patients with a follow-up of ≥12 months were included. Cutaneous pressure threshold was tested using Semmes-Weinstein monofilaments (SWMF) at 9 pre-defined locations.

Results: A total of 59 patients (96 breasts) were enrolled into the registry. Of these, 22 patients (Group 1: N = 15, 22 breasts; Group 2: N = 7, 14 breasts) had a complete data set with ≥12 months follow-up. Measuring cutaneous pressure thresholds, we observed a greater likelihood for return of protective sensation (SWMF ≤ 4.31) in neurotized breasts in 8 of the 9 examined zones. Additionally, flap neurotization was associated with a greater likelihood for return of protective sensation in the majority of the reconstructed breast—that is, ≥5 zones (55% versus 7%; P < 0.01).

Conclusion: Flap neurotization using processed nerve allograft resulted in a greater degree of return of protective sensation to the reconstructed breast than reconstructions without neurotization at ≥12 months. (Plast Reconstr Surg Glob Open 2021;9:e3328; doi: 10.1097/GOX.0000000000003328; Published online 12 January 2021.)

INTRODUCTION

Over the past 4 decades, we have witnessed tremendous advances in the surgical care of women with breast cancer. Although initial reports of post-mastectomy implant-based reconstruction commented on the inability to produce “cosmetic triumphs,” contemporary approaches routinely permit reconstruction of natural appearing breasts. This is equally because of the advances in the ablative surgical technique, such as the introduction of nipple-sparing mastectomy, and also because of innovations in reconstructive surgery.

Of the numerous reconstructive modalities, autologous reconstruction has established itself as the gold standard in post-mastectomy breast reconstruction because of its superior long-term patient-reported outcomes (PRO). Thus, breasts of adequate size, shape, symmetry, and softness can be created reliably. However, a functional component of the breast (ie, sensation) has largely been ignored. Moreover, the insensate breast is prone to thermal and mechanical injuries. The importance of breast sensation has been highlighted in mainstream media, thus unmasking an unexpected and unappreciated outcome (ie, breast numbness) by the patient and surgeon, respectively. Importantly, sensory loss is an unmet problem by “standard of care” surgical approaches. This is rather surprising, considering the reported beneficial impact of sensory recovery on PRO.

It is notable that more than a decade passed between the first report of microsurgical breast reconstruction using abdominal tissue and the innervation of the transverse rectus abdominis musculocutaneous (TRAM) flap reported by Slezak et al in 1992. Since then, various approaches to flap neurotization have been published. Data heterogeneity of procedures and outcomes has precluded a rigorous meta-analysis of the efficacy of flap neurotization in the context of breast reconstruction.

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However, a review of this literature suggests that neurotized flaps show an earlier recovery of sensation and generally result in improved quality and quantity of sensation.4

The increased interest in sensory restoration of the reconstructed breast is reflected by an increase in the number of publications focusing on this topic. However, the reported surgical techniques are quite variable, including differences pertaining to the choice of recipient nerve, extent of intercostal nerve dissection during abdominal flap harvest and the use of nerve conduits.17–20 To address the existing heterogeneity, a simple approach was recently proposed that utilizes nerve allografts and has all the characteristics of a desirable surgical technique, namely technical simplicity, minimal donor-site morbidity, selective coaptation to sensory nerve fibers, prevention of axonal loss, and tensionless repair.4,21

The objective of the present study was to evaluate sensation of the reconstructed breast at ≥12 months postoperatively using a standardized surgical approach, with our hypothesis being that flap neurotization would be associated with a superior sensory recovery.

Methods

Sensation-NOW is a study arm of the industry-sponsored multicenter Registry study of Avance Nerve Graft utilization, Evaluations and outcomes in peripheral nerve Repair (RANGER). This prospective analysis investigated clinical outcomes following microsurgical breast reconstruction at a single institution. Institutional Review Board approval was obtained before patient enrollment. Patients who underwent microsurgical breast reconstruction with free abdominal flaps by the senior author (AM) were included in the study. Study subjects consisted of 2 cohorts: patients who underwent flap neurotization (Group 1) and those without neurotization (Group 2). Of note, all patients were offered flap neurotization. Hence, patients were assigned to the respective study groups based on their own preferences. All patients in Group 1 underwent flap neurotization using a 1–2 mm × 50 mm processed human nerve allograft (Avance, AxoGen, Alachua, Fla.), with the recipient and donor nerve being the anterior cutaneous branch of the third intercostal nerve (ICN III) and ICN 11 or 12, respectively (Fig. 1).4,21 Of note, the nerve allograft was routinely trimmed to permit tension-free epineural nerve coaptation, while minimizing redundancy to decrease the time to sensory recovery (Fig. 2). Nerve coaptation was performed with 9-0 nylon without the use of nerve wraps. Furthermore, in all cases of flap neurotization, the epidermis and dermis of the flap were removed, as opposed to de-epithelialization only. Exclusion criteria included autologous reconstruction using donor-sites other than the abdomen, reconstruction with stacked flaps, and implant-based reconstruction.

Parameters of interest included patient age (in years), body mass index (BMI; in kg/m²), indication for mastectomy (therapeutic versus prophylactic), type of mastectomy ( nipple-sparing mastectomy versus skin-sparing mastectomy), laterality of reconstruction (uni- versus bilateral), timing of reconstruction (immediate versus delayed), and time interval between mastectomy and reconstruction in cases of delayed reconstruction (in days).

Sensory examination was performed in a standardized fashion at 9 pre-defined locations at 0–3, 6, 12, and 18 months (Fig. 3). Only patients with a follow-up of ≥12 months were included in this analysis. Cutaneous pressure threshold (ie static 1-point discrimination) was tested using Semmes-Weinstein monofilaments (SWMF), with each monofilament value representing the logarithm of the force (in milligrams) needed to bend the filament. The examiner was blinded to the study subjects’ group assignment. Testing of the pre-defined locations was done by the same blinded examiner in a random sequence, with patients resting comfortably in a reclined position and having their eyes closed.
**Statistical Analysis**

Continuous variables were analyzed using a two-sample t-test with unequal variance. Categorical variables were evaluated using the Fisher exact test. Data were analyzed using R. \(P<0.05\) was considered significant.

**RESULTS**

A total of 59 patients (96 breasts) were enrolled into the registry. Group 1 consisted of 39 patients (59 breasts), with a mean age and BMI of 48.4 years (range, 24–69 years) and 28.2 kg/m² (range, 21.3–41.2 kg/m²), respectively. The majority of patients underwent bilateral \([N = 20 (51.3\%)]\) immediate \([N = 47 breasts (79.7\%)]\) reconstruction following nipple-sparing mastectomy \([N = 37 (62.7\%)]\) for malignant disease \([N = 34 (87.2\%)]\) (Table 1). Group 2 consisted of 20 patients (37 breasts), with a mean age and BMI of 47.6 years (range, 33–67 years) and 29.5 kg/m² (range, 21.3–45.3 kg/m²), respectively. Similar to Group 1, the majority of patients underwent bilateral \([N = 17 (85\%)]\) immediate \([N = 25 breasts (67.6\%)]\) reconstruction following nipple-sparing mastectomy \([N = 20 breasts (54.1\%)]\) for malignancy \([N = 17 (85\%)]\). No differences were noted for age \((P = 0.76)\), BMI \((P = 0.43)\), race \((P = 0.81)\), indication for mastectomy \((P = 1.0)\), type of mastectomy \((P = 0.45)\), or timing of reconstruction \((P = 0.34)\) between study groups. A

![Fig. 3. Sensory examinations were performed by blinded examiners at pre-defined locations in a random sequence, using SWMF.](image)

| **Table 1. Patient Demographics** | Group 1 \((N = 39)\) | Group 2 \((N = 20)\) | \(P\) |
|----------|------------------|------------------|------|
| **Age (y)** | Mean 48.4 | Mean 47.6 | 0.76 |
| **BMI (kg/m²)** | Mean 28.2 | Mean 29.5 | 0.43 |
| **Race** | White 22 | White 11 | 0.81 |
| **Indication for mastectomy** | Malignancy 34 | Malignancy 17 | 1.0 |
| **Laterality** | Unilateral 19 | Unilateral 3 | 0.01 |
| | Bilateral 20 | Bilateral 17 | |
| **Type of mastectomy (by breast)** | NSM 37 | NSM 20 | 0.48 |
| | Acreola-sparing 1 | Acreola-sparing 2 | |
| | SSM 18 | SSM 11 | |
| | Simple 3 | Simple 4 | |
| **Timing of reconstruction (by breast)** | Immediate 47 | Immediate 25 | 0.39 |
| | Delayed-immediate 10 | Delayed-immediate 9 | |
| | Delayed 2 | Delayed 3 | |
significant difference was noted merely in regard to laterality, with patients in Group 2 having undergone more bilateral reconstructions ($P = 0.01$) (Table 1).

Of all patients enrolled in the registry, 22 patients (Group 1: $N = 15$, 22 breasts; Group 2: $N = 7$, 14 breasts) had a complete data set with ≥12 months follow-up, and thus were included in the final analysis. Of note, no significant differences were noted for any of the patient demographic variables between study groups, with the exceptions being in regard to laterality ($P = 0.02$) and timing of reconstruction ($P = 0.01$) (Table 2).

**Outcomes Comparison**

Measuring cutaneous pressure thresholds, we observed a greater likelihood for return of protective sensation (SWMF ≤ 4.31) in neurotized breasts in 8 of the 9 examined zones (Fig. 4). Further analysis demonstrated that flap neurotization was associated with a greater likelihood for return of protective sensation in the majority (ie, ≥5 zones) of the breast (55% versus 7%; $P < 0.01$) (Fig. 5). This is contrasted by 64% (versus 27%) of non-neurotized flaps having no return of protective sensation at all (ie, ≤1 zone) at ≥12 months ($P = 0.04$) (Fig. 5).

**DISCUSSION**

The importance of breast skin sensation on PRO has been reported. Yet, it is surprising that sensory recovery remains an undervalued aspect of breast reconstruction. The fact that flap neurotization is not routinely considered as a potential treatment modality is surprising given the availability of appropriate sensory nerves, both recipient and donor, within the mastectomy operative field. Over 2 decades ago, Blondeel et al reported earlier sensory restoration as well as an increase in the quality and quantity of sensation following flap neurotization. More recent reports have corroborated those findings and the concept of restoring sensation to the reconstructed breast is gaining traction, with novel approaches being introduced. Yet, a recent review of the literature details profound heterogeneity of data, thus precluding a comparative analysis. Overall, flap neurotization appears to be associated with improved sensory recovery at an earlier time point following surgery. In the present study, using a standardized surgical approach, we observed a greater likelihood for return of protective sensation in the majority of the breast (55% versus 7%; $P < 0.01$). Importantly, to the best of the authors’ knowledge, this is the first report of nerve allografts being used for flap neurotization in autologous breast reconstruction.

Several technical factors need to be taken into consideration when performing flap neurotization in the context of breast reconstruction. These include the type of nerve coaptation (ie, direct versus assisted), choice of donor nerve, gap bridging (ie, use of an autograft versus nerve allograft), choice of recipient nerve (ie, anterior cutaneous branch versus lateral branch of the intercostal nerve), and whether to de-epithelialize versus de-skin the flap before inset.

Historically, the vast majority of studies have reported direct nerve coaptation, necessitating dissection of the intercostal nerve over a long distance. Two main concerns exist with this approach, with the first being donor-site morbidity, particularly if the large type 2 nerve, as described by Rozen et al, is sacrificed. The second concern is related to the inability to selectively target sensory nerve fibers, as motor fibers are included by default in an attempt to obtain a long nerve segment with the flap.

In regard to the choice of donor nerve, particular attention is paid to choose the most centrally located nerve within the flap. Furthermore, we implemented a technique that limits the dissection of the donor nerve to the sensory branch only. This allows the surgeon to preserve motor innervation to the rectus abdominis muscle and facilitate coaptation to the sensory fibers only. Because the nerve segment obtained is short, the use of a material that bridges the nerve gap of ~40 mm, that is typically encountered upon flap transfer, is mandatory (Fig. 6). Available bridging materials include nerve autografts, tube conduits, and processed nerve allograft. Of these, processed nerve allografts seem to be best suited for the task because they avoid autograft-associated donor-site morbidity and are not restricted to short gaps, as is the case with nerve conduits. Only 1 study to date has reported favorable outcomes following the use of 40-mm polyglycolic acid nerve conduits in the context of breast reconstruction. These results, however, have not yet been replicated by others.

In addition to the choice of bridging material, surgeons can choose to divide the lateral and anterior cutaneous branches of the medial intercostal nerve (ICN) as recipient nerves. Historically, the anterior ramus of the lateral cutaneous branch has been chosen more commonly. Advantages of the lateral ICN include its larger size and the fact that it is the main nerve to the nipple-areola...
Disadvantages, however, include its susceptibility to iatrogenic injury and restrictions imposed on freedom of flap inset because of the presence of 2 pivot points. Blondeel et al comment on the difficulty of using the lateral ICN in delayed reconstructions and describe transposition of the posterior ramus (versus its use as a free nerve graft) after identification of the ICN in the 4th intercostal space at the midaxillary line. In contrast, the anterior cutaneous branch of the medial ICN is easily identified and dissected, and is adjacent to the recipient.

Fig. 4. Cutaneous pressure measurement. A greater likelihood for return of protective sensation (SWMF ≤ 4.31) was noted in Group 1 in 8 of the 9 examined zones.

Fig. 5. Sensory recovery at ≥12 months. Flap neurotization was associated with a greater likelihood for return of protective sensation in the majority (ie, ≥5 zones) of breasts (P < 0.01).
vessels (ie, internal mammary vessels), thus avoiding all restrictions related to flap inset. The use of processed nerve allograft, furthermore, precludes the need for harvest of a nerve autograft, thus avoiding donor-site morbidity and simplifying the procedure.

Another important aspect to consider is related to changes in mastectomy technique over the years (ie, increase in skin-sparing and nipple-sparing techniques). The implications of buried abdominal flaps on sensory recovery of the native breast skin as well as PRO remain to be determined. The concept of neural sprouting has been discussed. However, factors that mediate neural sprouting remain unclear. In the present study, all skin from the abdominal flap was removed as opposed to de-epithelialization, with the intent of removing a barrier to reinnervation of the overlying breast skin.

Limitations of the study include lack of randomization and the small sample size. Although favorable results are reported, larger studies with longer term follow-up are unquestionably needed to corroborate our observations. Furthermore, we did not address the issue of cost in this study. The use of nerve allografts adds cost to the procedure, and while emerging evidence demonstrates efficacy of this approach, future studies are warranted to address the issue of cost. Finally, we did not include a PRO instrument and, thus, are not able to comment on the impact of sensory recovery on PRO. However, we will include the BREAST-Q Sensation Module as we continue to enroll more patients in the registry. Increasingly, clinical data are being published demonstrating the efficacy of flap neurotization. Here, we present the first clinical study demonstrating the efficacy of using processed nerve allograft for flap neurotization. After presenting our surgical technique, this study demonstrates favorable long-term (≥12 months) clinical outcomes in a small subset of patients. However, unanswered questions remain, including the impact of flap weight on sensory recovery. Given that only 1 nerve coaptation was performed in the study, one could argue that smaller flaps might have more favorable outcomes. Additionally, the impact of numerous nerve coaptations on clinical outcomes remains unclear, as one may hypothesize that increasing the number of nerve coaptations could further improve sensory recovery. Finally, the impact of factors such as past medical history (eg, diabetes mellitus), chemotherapy, or radiotherapy on sensory outcomes requires further investigation. These questions may be best answered in future studies.

In conclusion, flap neurotization using processed nerve allograft allowed for a tension-free and selective coaptation to sensory nerve fibers, which resulted in the return of protective sensation to the reconstructed breast to a greater degree than in reconstructions without neurotization at ≥12 months.

**Fig. 6.** Limiting dissection to the sensory branch only when raising the abdominal flap results in a rather short nerve segment that mandates the use of a bridging material for flap neurotization upon flap transfer.

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