Editorial Commentary

Striving for higher levels of evidence in sensory restoration in DIEP flap breast reconstruction

Anne Huang^, Ethan L. Mackenzie, Min-Jeong Cho^

Department of Plastic and Reconstructive Surgery, College of Medicine, The Ohio State University Wexner Medical Center, Columbus, OH, USA
Correspondence to: Min-Jeong Cho, MD. Department of Plastic and Reconstructive Surgery, College of Medicine, The Ohio State University Wexner Medical Center, 915 Olentangy River Road #2140, Columbus, OH 43212, USA. Email: min-jeong.cho@osumc.edu.
Comment on: Bubberman JM, Brandts L, van Kuijk SMJ, *et al.* The efficacy of sensory nerve coaptation in DIEP flap breast reconstruction - Preliminary results of a double-blind randomized controlled trial. Breast 2024;74:103691.

Keywords: Flap neurotization; flap reinnervation; breast sensation; autologous breast reconstruction

Submitted Dec 03, 2024. Accepted for publication Feb 19, 2025. Published online Mar 26, 2025.
doi: 10.21037/gs-2024-524
View this article at: https://dx.doi.org/10.21037/gs-2024-524

Restoring sensation to the skin after mastectomy is increasingly recognized as an important outcome for patient satisfaction and quality of life (1-4). Studies have demonstrated that decreased protective sensation can lead to inadvertent injury, lower patient satisfaction, and increased patient risk to nocuous events (5). In addition, patients with decreased sensation after non-neurotized breast reconstruction have reported lower quality of life scores, particularly in the "unnatural feeling" domain (6,7). Therefore, the lack of sensation after breast reconstruction has received increasing media coverage over the last decade (8), heightening patient awareness and clinician interest.

First introduced in 1992 (9), sensory recovery in autologous-based reconstruction has undergone multiple technical refinements and advancements, and three recent systematic reviews have demonstrated that flap neurotization improves sensory recovery after abdominally based autologous breast reconstruction (10-12). Various studies have demonstrated that sensory outcomes, which were quantitatively measured with Semmes-Weinstein monofilament (SWM) or pressure-specified sensory device (PSSD) testing, improved with flap neurotization regardless of flap type or neurotization technique (12). Similarly, patients with neurotized breast flaps experienced earlier, superior, and clinically meaningful sensory recovery that was more uniformly distributed throughout the flap (10).

Although these recent systematic reviews demonstrate there is improvement in sensation with flap neurotization, it is challenging to interpret the current literature on breast flap neurotization due to the heterogeneity of available literature (7,13-16). First, there is a lack of standardized neurotization techniques for breast reconstruction due to surgeon preference. While some surgeons prefer allografts due to minimized donor site morbidity by preserving motor nerves of the rectus abdominis muscle (16), others advocate for autografts due to concerns of limited axonal regeneration in the usage of allografts to reconstruct long nerve gaps (17,18). Similarly, there is a wide variability in patient characteristics such as breast and flap size, bilateral versus unilateral reconstruction, type of mastectomy, timing of reconstruction, and the use of adjuvant chemotherapy and radiation therapy (19). The degree to which these patient-related differences affect sensory outcomes is still not fully understood. Finally, it is difficult to compare the current studies on breast flap neurotization because various studies use different protocols and length of follow up time for objective measurements of sensory recovery. There are no standardized patient reported outcome measures (PROMs) specific for sensation in breast reconstruction or protocols to assess patient perception of breast sensation (20). In addition, there is some evidence of spontaneous flap

^ ORCID: Anne Huang, 0000-0002-4972-9391; Min-Jeong Cho, 0000-0003-3517-1523.

reinnervation (21,22), making it difficult to ascertain how much of the sensory recovery seen in flap neurotization can be attributed to sensory nerve reconstruction. These challenges and limitations in rigorously studying breast flap neurotization, coupled with concerns of longer operating time and higher costs (7), have hindered the widespread adoption of autologous breast reinnervation.

Therefore, Bubberman *et al.* sought to address the shortcomings in the current literature by designing one of the first randomized controlled trials (RCTs) investigating sensory recovery of innervated deep inferior epigastric perforator (DIEP) flaps with direct nerve coaptation (23). The study demonstrated that sensory outcomes were superior in the innervated group, and the differences in sensation between the two groups increased over time, with the non-innervated group plateauing at 24 months and the innervated group continuing to improve. This study is consistent with prior findings that neurotization improves flap sensation, particularly centrally, and that it improves sensation to a greater degree than the proposed mechanism of spontaneous innervation from the periphery in non-innervated flaps (2,10-12). Only one other published RCT has examined sensation after breast flap neurotization, which showed statistically significant improvement in patient reported sensory outcomes in 27 women randomized to undergo innervated versus non-innervated free transverse rectus abdominis myocutaneous (TRAM) flaps with direct nerve coaptation (3). However, this RCT is older, has a smaller patient cohort, and is limited by the lack of objective sensory measurements. In addition, the Bubberman *et al.*'s study demonstrates improved sensation of native mastectomy skin after flap neurotization, as 8 out of 9 areas on the breast had lower tactile thresholds (23). This finding was also noted in Tajziehchi *et al.*'s systematic review (12), and the authors hypothesize that nerve fibers from the buried de-epithelialized flap may grow into the overlying mastectomy skin. Bubberman *et al.* also hypothesize that the differences in types of sensory recovery may be explained by different regeneration patterns of various nerve fibers. Further research is needed to investigate these proposed mechanisms.

While the findings of this interim analysis are intriguing and encouraging for proponents of flap sensory innervation, there are a few limitations. First, breast sensation could have been impacted in patients who underwent radiation therapy, as the size of flap skin paddle and the amount of resected native breast skin are typically larger than those who did not receive radiation therapy. Second, the effect of a unilateral versus bilateral reconstruction is difficult to predict and more likely to influence quality of life measures if this discrepancy persists into final analysis. Lastly, the use of the *as treated* principle, which resulted in crossover of six breasts, could potentially introduce bias.

In summary, Bubberman *et al.*'s RCT is expected to finish collecting patients in 2024 and will also include patient reported quality of life measures represented by the BREAST-Q, which will further strengthen the findings of the current study by presenting subjective sensory outcomes in addition to objective measurements. Despite the heterogeneity of surgical techniques, patient demographics, sensory measurements, and length of follow up, there is evidence to support superior sensory improvement after autologous breast flap neurotization. However, it remains to be determined whether the changes in sensation as measured in objective testing translate to clinically significant improvements in protective, tactile, and erogenous sensation, and thus improvement in patient reported outcomes. While there is a lack of validated PROMs specifically for sensation in breast reconstruction at this time, Bubberman *et al.*'s RCT will provide BREAST-Q results which has a validated sensation module (24) and may be extrapolated to reflect patient satisfaction with breast flap innervation. We look forward to the results of the completed RCT and future studies on this developing field.

Acknowledgments

None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Gland Surgery*. The article has undergone external peer review.

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-2024-524/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-2024-524/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Huang A, Mackenzie EL, Cho MJ. Striving for higher levels of evidence in sensory restoration in DIEP flap breast reconstruction. Gland Surg 2025;14(3):268-271. doi: 10.21037/gs-2024-524