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ORIGINAL INVESTIGATION **Facial Nerve**

The Tinel Sign and Myelinated Axons in the Cross-Face Nerve Graft: Predictors of Smile Reanimation Outcome for Free Gracilis Muscle Transfer?

Jacqueline J. Greene, MD,*,† Zoe Fullerton, MD, Nate Jowett, MD, and Tessa Hadlock, MD

Abstract

Introduction: During a two-stage free gracilis muscle transfer (FGMT) to restore smile to patients with facial paralysis, some surgeons assess nerve regeneration through the cross-face nerve graft (CFNG) with the Tinel sign and a nerve biopsy.

Objective: To test whether ultimate smile reanimation outcomes are correlated with (1) the Tinel sign or (2) myelinated axons of the biopsied CFNG at the time of FGMT.

Methods: Retrospective case series was performed at a tertiary care facial nerve center. Dynamic smile outcomes were quantified with Emotrics analysis of pre- and postoperative photographs.

Results: Of the 113 FGMT surgeries by CFNG performed since 2002, 92 patients had pre- and postoperative photo-documentation. Most patients (89%, $N = 82$) had a positive Tinel sign at the time of FGMT; however, 14 patients with positive Tinel signs were deemed failures. Interestingly, 4 patients with a negative Tinel sign went on to have successful dynamic outcomes and 16 patients lacking myelinated axons in their CFNG biopsy ultimately achieved successful smile outcomes.

Conclusion: Although the majority of patients had a positive Tinel sign and myelinated axons in the CFNG at the time of FGMT, the presence or absence of either factor did not predict ultimate smile outcome in this series.

Introduction

Free gracilis muscle transfer (FGMT) was introduced in 1976 by Harii et al.[1] and is a well-accepted smile reanimation procedure for longstanding or irreversible facial paralysis.[1,2] Innervating the gracilis muscle with the contralateral facial nerve through a cross-face nerve graft (CFNG) provides the most natural and spontaneous smile, but usually requires a two-stage approach (Fig. 1), longer time until muscle innervation,[2] and has a slightly lower success rate (84% vs. 92% when driven by the masseteric nerve[2–5]). This difference is likely related to the longer distance required for the regenerating nerve.

Although there are currently no tests that predict ultimate success of FGMT by CFNG, the presence of the Tinel sign (a referred sensation to the contralateral face elicited by tapping on the distal end of the CFNG) has

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KEY POINTS

Question: Is it possible to predict whether a smile reanimation surgery will be successful by nerve biopsy or by a clinical test where light tapping on the face creates a referred tingling sensation (the Tinel sign)?

Findings: Most patients undergoing smile reanimation surgery will have both a positive Tinel sign and myelinated axons in a nerve biopsy, but this does not uniformly guarantee success; in addition, a negative Tinel sign or lack of myelinated axons in the nerve biopsy does not predict failure.

Meaning: There are currently no tests that predict success of smile reanimation surgery and further research to assess successful nerve regeneration is needed.

been historically used to deduce neural penetration through the CFNG and thus potential success (Fig. 1). The Tinel sign is named after Dr. Jules Tinel, a French neurologist who attributed the referred ''tingling'' phenomenon to regenerating axons in 1915 after serving as a military physician during the First World War, although a German neurologist Dr. Paul Hoffman published his description of the ''percussion test'' the same year.[7]

Hoffman reasoned that sensory, not motor, axons were responsible for the sign and that a positive sign meant motor functional return was possible but not guaranteed.[7,8] Although the site of the Tinel sign migrates as the axons regenerate through a CFNG and has been used to estimate the average axonal regeneration rate (1.8 mm/day),[9] many patients are not tested until the time of FGMT. It is currently unclear whether the presence of the Tinel sign at the time of FGMT denotes sufficient nerve regeneration through the CFNG to reinnervate the gracilis muscle, and thus predict smile reanimation outcomes.

At the time of FGMT, the presence of myelinated axons can sometimes be detected in a biopsy of the distal tip of the CFNG and they are thought to be a positive predictor for dynamic smile outcome. Myelin sheaths are actually individual Schwann cells enwrapping each axon and may be readily visualized using light microscopy on appropriately stained thin sections in *uninjured* sensory and motor axons of the peripheral nervous system. Regenerating axons in contrast, such as those traversing a CFNG, may lack myelin sheaths and typically require electron microscopy for visualization and quantification.[14]

Nerve histomorphometry (axon count, density, myelin thickness, etc.) has often been reported as a measure of successful nerve regeneration in animal nerve studies,[10–13] although published data of regenerating human nerve histomorphometry are limited. One key study used electron microscopy to investigate CFNG biopsies in 30 patients who underwent free pectoralis muscle transfer for facial reanimation.[22] Interestingly, they found a small proportion of small diameter myelinated axons and an abundance of unmyelinated axons and partially myelinated axons in the CFNG, however, long-term

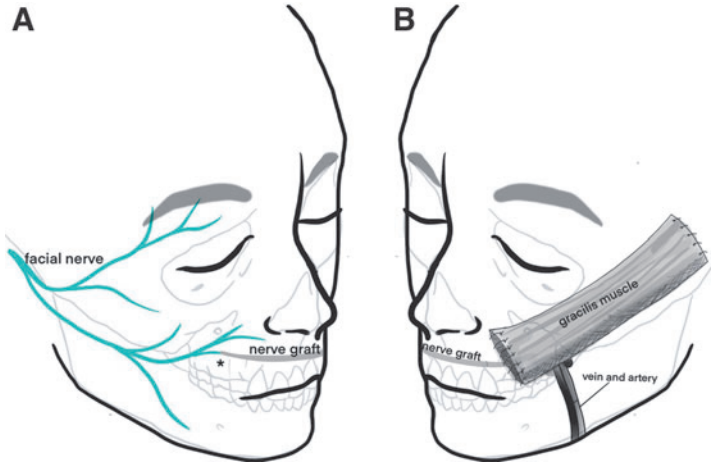

Fig. 1. Two-stage facial reanimation surgery can restore a spontaneous smile to patients with facial paralysis. The importance of the Tinel sign and myelinated axons in the distal CFNG as predictors of ultimate smile reanimation is unclear. **(A)** In the first stage, a CFNG is coapted to a healthy facial nerve branch to smile musculature without a distal hook-up. Neural regeneration through the CFNG takes 6–9 months. The presence of the Tinel sign has been historically used to determine the extent of neural penetration through the CFNG (elicited by tapping on the distal end of the CFNG, resulting in a referred sensation to the coaption site [marked by an asterisk]). **(B)** In the second stage, a free gracilis muscle is transferred to the paralyzed hemiface with vessel anastomosis and nerve coaption to the CFNG. A biopsy of the distal CFNG is done at this time to assess for the presence of myelinated axons. Reinnervation and movement of the gracilis muscle typically begins 10–12 months after this point, resulting in a bilateral spontaneous smile. CFNG, cross-face nerve graft.

clinical outcomes were not reported. Whether the presence of myelinated axons in the CFNG can be used to predict ultimate dynamic smile outcomes is unknown.

Methods

Institutional review board approval was obtained from the Massachusetts Eye and Ear Infirmary (MEEI) Human Studies Committee. A retrospective review of all FGMT surgeries innervated by the contralateral cranial nerve (CN) VII through a CFNG at our center from 2002 to 2019 was completed. FGMT surgeries with different innervating nerves (CN V or multiple cranial nerves) were excluded, as were patients with bilateral facial palsy or patients with functioning or evolving results from other nerve transfers (i.e., CN V–VII or XII–VII transfers).

Data collection

Demographic data including age, gender, and etiology of facial paralysis were recorded. Onset, duration, and category of facial palsy (flaccid or synkinetic) were recorded. Previous static or dynamic reanimation surgeries as well as any baseline facial movement were recorded. Pre- and post-FGMT photographs were analyzed with Emotrics (v2.05; MEEI, Boston, MA). Emotrics is an open-source platform available for download at (https://www.sircharlesbell.com/).

All FGMT operations were performed as previously described.[6] Intraoperative details, including gracilis weight at the time of inset, static slings with fascia lata, CFNG length, and neural innervation source, were recorded. The length of the CFNG was recorded (short CFNG extended to the contralateral oral commissure and long CFNG extending to the subzygomatic triangle). Postoperative complications were recorded. FGMT failures based on lack of movement after 18 months or need for a revision or repeat FGMT were noted.

Tinel sign

Patients were assessed on the day of FGMT. Patients with a positive Tinel sign would describe an ''electrical,'' ''buzzing,'' or ''crawling'' sensation at the donor facial nerve site when tapping on the upper lip in a location corresponding to the tip of the CFNG.

CFNG histopathology

During FGMT surgery, the tip of the CFNG was identified by previously placed surgical clips or a 4–0 nylon loop. The distal CFNG tip was sent for axon counts. Nerve was postfixed in osmium, mounted in resin, cross-sectioned using an ultramicrotome, and counterstained using toluidine blue. Semiquantitative manual counting of myelinated axons was reported on bright field microscopy images.

Postoperative outcomes assessment

Patients were evaluated in person at 6–12 and 18 months postsurgery. In this study, we defined failure as complete lack of dynamic movement after 18 months or gracilis muscle salvage by reinnervation using the masseteric nerve or repeat FGMT surgery.

Results

Patient demographics

Between 2002 and January 2019, 326 patients underwent FGMT. Of this group, 113 patients underwent FGMT innervated by the contralateral CN VII through a CFNG in a two-stage procedure. The demographics of this cohort are given in Table 1. There were slightly more female (56%) than male patients (44%). Patients were generally young adults (mean age 26.6 years), although age ranged from 3 to 69 years of age at the time of FGMT surgery. The majority of patients had flaccid facial palsy (83%), and the top 3 causes of facial palsy were central nervous system neoplasm, congenital facial palsy, and acoustic neuroma.

Postoperative outcomes assessment

Of the 113 cases of FGMT innervated by contralateral VII through a CFNG (FGMT by CFNG), 92 had complete pre- and postoperative clinical assessment with photodocumentation (Table 2). Fifty-nine patients had photodocumentation at least 18 months after FGMT.

Table 1. Demographics

	Patients
Total *N*	113
Gender, *n* (%)	
Male	50 (44)
Female	63 (56)
Age at gracilis mean (SD) [range] years	26.6 (16.3) [3–69]
Duration of facial palsy mean (SD) [range] years	9.3 (10.9) [1–54]
No. of patients with flaccid palsy (%)	94 (83)
No. of patients with synkinetic facial palsy (%)	19 (17)
Gracilis recipient side right	56
Gracilis recipient side left	57
Etiology of facial paralysis	
CNS neoplasm	26
Congenital	17
Acoustic neuroma	16
Trauma (temporal bone fracture or other facial nerve injury)	13
Head and neck malignancy	8
Otological disease	6
Benign parotid mass	6
Facial nerve schwannoma	4
Stroke	4
Iatrogenic	3
Viral (chronic Bell's palsy, pregnancy-associated Bell's palsy, Ramsay–Hunt)	3
Lyme disease-associated facial palsy	2
Infectious (polio, meningitis)	2
FROWN	2
Geniculate ganglion hemangioma	1

CNS, central nervous system; FROWN, facial palsy, radiographic and other workup negative; SD, standard deviation.

Table 2. Gracilis free muscle transfer details

No. of flaps with pre- and postoperative data	92
No. of flaps with >18 months postoperative data	59
CFNG length	
Long (subzygomatic triangle)	6
Short (contralateral oral commissure)	86
CFNG histopathology	
Myelinated axons	58
No myelinated axons	16
Not recorded	18
Tinel's sign at the time of FGMT	
Positive	82
Negative	4
Not recorded	6
Mean time onset of Tinel's sign (SD) [range] months	7.3 (16) [1–149]
Gracilis	
Time between CFNG and gracilis surgery (SD) [range] months	9.7 (15.0) [5–151]
Mean weight (g) of gracilis initial inset (SD) [range]	22.9 (12.6) [6.2–51.2]
Mean follow-up time after Gracilis (SD) [range] months	30.7 (26.7) [5–132]

FGMT, free gracilis muscle transfer; CFNG, cross-face nerve graft.

There were 14 patients with confirmed lack of movement of the transferred gracilis muscle, yielding a failure rate of 15% (14 out of 92 patients) from the cohort with adequate postoperative documentation. If the patients lost to follow-up or with missing photo or video documentation were included as failures (21 patients), the failure rate would rise to 31% (35 out of 113 patients).

Although the etiology of failure was difficult to determine, several patients had notable postoperative complications that may have influenced the final dynamic result. One patient had a postoperative facial seroma that required drainage, one patient had a venous thrombosis that required revision, and one patient who underwent salvage surgery was found to have dehiscence of the CFNG from the obturator nerve. Eleven patients lacked clear etiology for FGMT failure.

Tinel sign

Of the 92 patients who underwent FGMT by CFNG, most patients (89%, $N=82$) noted a positive Tinel sign on average 7.3 months after CFNG placement, although some patients reported feeling a positive Tinel sign as early as 1 month (Table 2). One patient had a CFNG placed at an international hospital >10 years previously but had not undergone FGMT—her Tinel sign remained present over that time and her CFNG was used to innervate the FGMT with ultimate successful dynamic reanimation. Six patients did not have a Tinel sign recorded.

Four patients had a confirmed negative Tinel sign on the day of FGMT placement (7–10 months after CFNG) and all of these patients were pediatric (6–14 years old). All four patients with a negative Tinel sign ultimately had successful dynamic movement from FGMT. Within the cohort of failed FGMT by CFNG, 11 patients had a positive Tinel sign.

CFNG histopathology

Of the 92 patients who underwent FGMT by CFNG, 58 patients had CFNG biopsies containing myelinated axons (Table 2). Sixteen patients did not have myelinated axons in their CFNG biopsies, and 18 patients were missing pathology reports. Quantification of axon counts and myelination was inconsistent and varyingly described as ''rare,'' ''low,'' ''moderate,'' ''scattered,'' or ''numerous'' myelinated fibers; pathology reports of the CFNG without myelinated axons ranged from ''no neural tissue'' to ''fibroadipose tissue'' to ''nerve twigs in a fibrous background'' to ''traumatic neuroma.''

Examination of the histopathology slides confirmed how the varying orientation of the nerve specimen could significantly affect myelin thickness, axon diameter, and axon density and thus limited further quantification. Of the 16 patients with no myelinated axons visible in the CFNG, all patients went on to have successful dynamic movement after FGMT. There was no significant age difference between those with myelinated axons in their CFNG (20.1 (14.6)[5–46] years) and those with no myelinated axons (26.4 (16.3)[5–68] years).

Of the cohort of confirmed failed FGMT by CFNG (14 patients), 42% (6 patients) had myelinated axons in their CFNG and 57% (8 patients) did not have pathology reports (biopsy of CFNG was not sent or misplaced). Some of these patients had their surgeries before the incorporation of electronic medical records.

Discussion

There is no standardized method to assess neural regeneration through a banked CFNG or to predict ultimate outcomes of smile reanimation surgery. At the time of FGMT, a positive Tinel sign and myelinated axons in the tip of the CFNG have historically suggested higher likelihood of successful smile outcome. Our findings were generally in agreement with this principle, however, we did not find that these factors could be used to predict ultimate smile outcome (most patients [89%, $N=82$] had a positive Tinel sign at the time of FGMT but 14 of these patients ultimately were deemed failures). Similarly, although a positive Tinel sign did not ensure successful smile reanimation, lack of a Tinel sign did not predict failure.

All four patients with a negative Tinel sign at the time of FGMT went on to have successful dynamic outcomes; however, it should be noted these were all pediatric patients. It is possible that their age (6–14 years) limited their articulation of a positive Tinel sign although they were thoroughly examined by the senior author using

age-appropriate language; none of these patients had cognitive impairment. Three of these patients with a negative Tinel sign had myelinated axons on their CFNG biopsy, and one patient's report was missing.

The presence of myelinated axons at the distal tip of the CFNG would be expected to reflect successful nerve regeneration and correlate with ultimate FGMT dynamic function[15–18]; however, in this study, the presence of myelinated axons in the CFNG biopsy did not predict smile outcomes. The majority of patients (63%, $N=58$) had myelinated axons within the CFNG biopsy at the time of FGMT, but lack of myelinated axons was not correlated with ultimate outcome as 16 patients had no myelinated axons in the CFNG and all of these patients experienced successful dynamic movement after FGMT.

Within the group of confirmed failures (14 patients), 43% ($N=6$) had myelinated axons present; the remaining 8 patients (57%) were missing pathology reports. There are several clinical studies of CFNG biopsies in humans that show no correlation between the number or diameter of myelinated fibers and ultimate functional results.[19–21] It is possible that these patients lacking myelinated axons in their CFNG had a greater proportion of unmyelinated axons that were not visible on light microscopy; unfortunately, in our study, it was not possible to confirm this due to the cost and time-intensive nature of electron microscopy, which was not routinely performed at our institution.

This study has several limitations including patient cohort size, loss of follow-up, lack of pathology reports of the CFNG, and photodocumentation. There was no standardized language to describe axon counts and myelination beyond what was described and nerve specimen orientation was arbitrary and too inconsistent for quantification on cross section. Research efforts to develop a rapid intraoperative assessment of neural regeneration are ongoing.[23]

Conclusion

Although the majority of patients will have a positive Tinel sign and myelinated axons in the distal CFNG at the time of FGMT, neither factor can be used as a positive predictor for ultimate smile outcome. Similarly, lack of a Tinel sign in pediatric patients or lack of myelinated axons in the CFNG also does not predict failure. Further research into predictive factors for smile reanimation success after FGMT is needed.

Authors' Contributions

All coauthors have reviewed and approved the article and submission form. J.J.G. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design were done by J.J.G. and T.H. Acquisition, analysis, or interpretation of data was carried out by J.J.G., Z.F., N.J., and T.H. Drafting of the article was taken care by J.J.G., Z.F., and T.H. Critical revision of the article for important intellectual content was done by J.J.G., Z.F., N.J., and T.H. Statistical analysis was carried out by J.J.G. and T.H. Administrative, technical, or material support was taken care by T.H. Study supervision was done by T.H.

Ethical Publication

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author Disclosure Statement

The authors have no financial relationships and no conflicts of interest relevant to this article to disclose.

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INVITED COMMENTARY **Facial Nerve**

Commentary on: "The Tinel Sign and Myelinated Axons in the Cross-Face Nerve Graft: Predictors of Smile Reanimation Outcome for Free Gracilis Muscle Transfer?" by Greene et al

Babak Azizzadeh, MD* and Adrian E. House, MD

We would like to congratulate Dr. Greene and her colleagues on a very informative article about an important issue that most contemporary facial reanimation surgeons consider routinely in their clinical practice. This is a well-written article examining the usefulness of the Tinel sign and the presence of myelinated axons in cross-face sural nerve grafts (CFNGs) in predicting smile outcomes after second-stage free gracilis muscle transfer (FGMT).[1] FGMT powered by CFNG is a favored method and one of my own personal preferred reanimation techniques for patients with complete facial paralysis desiring a natural and spontaneous smile outcome.[2–4]

There are currently no reliable methods for predicting the success of FGMT based on CFNG criteria. Factors considered to predict success are a positive Tinel sign, short sural nerve grafts (extending to the contralateral oral commissure), and high axonal load of the donor facial nerve.[5,6] Although the Tinel sign is the most common signal to determine the success of CFNG, it is inherently subjective, and no studies have examined it critically as it relates to successful smile outcomes after secondary FGMT. Most surgeons, including myself, do biopsy of the CFNG intraoperatively before proceeding with FGMT; however, the use of histopathology to assess CFNG myelination density has only been previously compared with masseteric nerve and not examined for determining the outcome of FGMT.[3]

The findings of this study are very interesting. The most clinically relevant information is that several patients (all pediatric) with negative Tinel sign had

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