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COMPARATIVE EVALUATION OF NEUROTUBULES AND AUTOLOGOUS NERVE GRAFTS FOR PERIPHERAL NERVE REPAIR: A RETROSPECTIVE CASE SERIES

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Summary

Peripheral nerve injuries are very difficult to treat and current strategies include nerve conduits and autologous grafts. Although, the superiority of one technique over the other is still under debate. This paper aims to review retrospectively our case series of patients who underwent nerve repair with neurotubules and compare them with those who received autologous nerve graft at mid-long term follow-up.

We retrospectively analyzed 6 patients with 12 nerve injuries who underwent to nerve reconstruction with autologous nerve graft and 9 patients with 11 nerve injuries who received a nerve conduit. The outcomes were evaluated with the monofilament test, s2PD and DASH score.

The groups did not differ for the s2PD test in 2021 ($p = 0.87$) and 2023 ($p = 0.7$). We studied the healthy contralateral hand for comparison and the results were comparable for both groups in 2021 ($p = 0.93$) and 2023 ($p = 0.86$). When comparing the affected hand to the healthy contralateral we found no difference in 2021 ($p = 0.14$) but the healthy hand achieved better results in 2023 ($p = 0.002$). The affected hand of grafted patients yielded worse results that the contralateral healthy ($p = 0.02$), but the affected hand treated with a neuroguide and the healthy contralateral scored comparable results ($p = 0.06$). The DASH score was comparable in both groups in 2021 ($p = 0.66$) and 2023 ($p = 0.53$), and it did not improve over time (2023 *vs* 2021: $p = 0.3$).

Our study highlights the comparable outcomes of neuroguides and nerve grafts in various aspects of hand reconstruction. This indicates that neuroguides offer acceptable results in peripheral nerve reconstruction but they still need to be improved in order to be considered as a true alternative to autologous grafts.

Key words: peripheral nerve injury, nerve repair, neuroguides, neurotubules, nerve graft

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INTRODUCTION

Peripheral nerve injuries of the hand can significantly impact the quality of life of affected individuals. These injuries can be caused by a wide range of traumatic events, including lacerations, crush injuries, and fractures, and can lead to the loss of sensation, movement, and function in the hand. While surgical techniques for nerve repair have advanced significantly in recent years, full recovery is often not possible, and patients may experience long-term disability and chronic pain [1].

Direct nerve repair is a technique that involves the suturing of the two ends of a severed nerve together without any additional grafts or implants. This technique is considered the gold standard for nerve repair as it has the potential to restore near-normal function and sensation to the injured area. Direct nerve repair also offers the advantage of a shorter recovery time and a lower risk of complications compared to other techniques. However, this technique is only suitable for cases where there is no loss of nerve tissue or significant tension on the repaired nerve, and requires a high level of surgical skill and precision [2].

On the other hand, whenever there is a loss of substance and direct repair is not possible, autologous nerve graft is considered the gold standard technique. Nonetheless, this technique bears some drawbacks such as donor site pain, paresthesia or anesthesia. The use of a muscle in vein technique, where a small segment of muscle is inserted into a vein graft, can also be effective in nerve repair. In this technique, the vein serves as a conduit to guide the regenerating nerve fibers. Another option is the use of a vein graft alone, which has been shown to produce similar outcomes to the muscle in vein technique. While these techniques have been successful, they are not without limitations and can lead to some functional deficits in the affected limb [3,4].

One emerging approach to nerve repair involves the use of neurotubules, which are engineered structures designed to guide the regeneration of damaged nerves. Neurotubules have emerged as a promising alternative to the gold standard technique of nerve repair using autologous nerve grafts. These tubular structures are composed of synthetic materials and mimic the natural extracellular matrix of nerves, providing a supportive environment for axonal regeneration.

Many neurotubules have been approved by national Authorities for clinical use, and at our Institution we introduced three of them, namely Reaxon, NeuraGen, and Neurolac.

Reaxon is a chitosan-based neuroguide, and it is obtained by deacetylation of chitin. It is a resorbable and transparent device, distributed as tubules 30 mm long and internal diameter ranging from 2.1 mm to 6.0 mm [5].

NeuraGen is a collagen tube filled with type I bovine collagen, it has a semi-permeable outer membrane and a lumen that supports the axonal regeneration for nerve regrowth [6].

Neurolac, on the other hand, is a biodegradable and bioresorbable tubular scaffold made of copolyester poly(DL-lactide-e-caprolactone) [7].

The use of neurotubules has shown promising results in preclinical studies, and several clinical trials are underway to evaluate their efficacy in humans. However, the literature remains substantially controversial about the long term results and questions remain regarding the optimal design and composition of neurotubules, as well as their comparative effectiveness with traditional nerve autografts.

This paper aims to review retrospectively our case series of patients who underwent nerve repair with neurotubules and compare them with those who received autologous nerve graft at mid-long term follow-up.

MATERIALS AND METHODS

Patient population

We retrospectively analysed all the patients admitted to the Plastic Surgery Unit of the University Hospital of Padua who had peripheral nerve injuries with gaps that could not be repaired with simple end-to-end sutures and required complex reconstruction with autologous nerve grafts or neuroguides from 2012 to 2022.

Inclusion criteria were: only sensory nerve of the fingers involved not amenable of direct repair. Exclusion criteria were: mixed nerve (e.g. median nerve proximal to the carpal tunnel and ulnar nerve proximal to the Guyon's canal), amputations and devascularisation.

We found a total of 27 patients with nerve loss of substance of the hand.

From the total, 5 subjects had suffered mixed nerve injuries and were excluded.

Of the remaining 22 patients, all met the inclusion criteria but 7 of them were lost to follow-up and were therefore excluded.

We ended up with 15 patients and 23 fingers involved. All the patients gave written informed consent to participate to the study.

Of 15 patients finally included in the study:

- 2 patients had a nerve injury with a gap in the sensory branch of the radial nerve;
- 1 patient had an injury to the medial digital nerve of the right great toe;
- 12 remaining patients had nerve injuries with gaps in the digital nerves of the fingers. The patients were divided into 2 groups:

Figure 1. Cases showing the three different neuroguides: A) Neuragen; B) Neurolac; C Reaxon.

- 6 patients underwent peripheral nerve reconstruction with autologous nerve grafts:
  - 3 patients suffered finger injury, and one of them had 3 nerve lesions. All of them were considered individually for a total of 5 cases;
  - 2 patients suffered radial nerve injury that involved all the three sensory branches for the first, second fingers and the third finger and were considered separately, for a total of 6 cases;
  - 1 patient suffered injury to the radial nerve but the lesion involved only one branch for the thumb and was considered as an individual case. We therefore considered 12 cases in total.
- 9 patients underwent peripheral nerve reconstruction with neuroguides for a total of 11 nerves. In 4 cases we used Neuragen, in 4 cases Reaxon and in 3 Neurolac (Fig. 1).

Patient history and surgery data

Each patient was invited to come to office in 2021 and 2023 for a new clinical evaluation. We recorded full medical and personal history, time of follow up and the following data regarding the nerve lesions:

- distance of the lesion from the fingertip involved expressed in centimeters (cm);
- involved nerve;
- nerve gap expressed in centimeters (cm);
- time elapsed from the injury to the reconstruction surgery expressed in months (months);
- type of reconstruction (graft/neurotube);
- necessity of revision surgery.

Clinical test

Each patient underwent the following assessments:

- Static Two-point discrimination test of the affected finger and the healthy contralateral one;
- Sensitivity test with monofilament (WEST test) of the affected finger and the healthy contralateral;
- disabilities of the Arm, Shoulder and Hand (DASH) score.

Two-point discrimination test

The two-point discrimination test was performed on the areas innervated by the nerve that underwent prior reconstruction, using a paper clip and with the patient having closed their eyes. The distances between the two ends of the paper clip were always measured using the same ruler, starting from 2 millimeters between the two ends with a progressive increase of one millimeter. For all patients the threshold, the minimum distance between the two ends, was recorded at the moment when the patient perceived the tactile sensation of two distinct points.

Sensitivity test with monofilament (WEST test)

The West Nerve Tester™ (CB-Connecticut Bioinstruments Inc., Danbury, USA) was used. It consists of five monofilaments with varying thickness and pressure values, each distinguished by a specific color to measure skin sensitivity and determine peripheral nerve involvement. The monofilaments were progressively placed three times at the apex of the fingers of all patients, from thickest to thinnest (Fig. 2). The thinnest wire that was

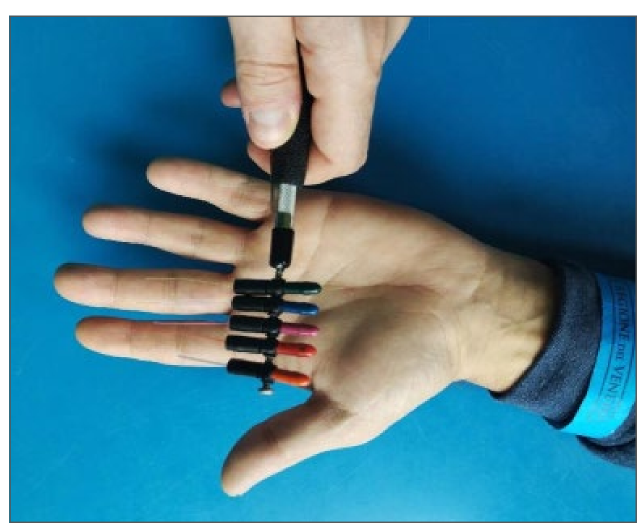

Figure 2. Semmes-Weinstein filaments.

Semmes-Weinstein filaments			
Color	Force (g)	Score	Interpretation
Green	0.05	5	Normal
Blue	0.20	4	Residual texture
Purple	2.00	3	Residual protective sensation
Red	4.00	2	Loss of protective sensation
Orange	7.50	1	Residual deep pressure

Figure 3. Scores assigned for the Semmes-Weinstein filament test.

perceived in two out of three touches was recorded for each examined area and for a given color we assigned a corresponding number as shown in Fig. 3.

Statistical analysis

The means and standard deviations of the linear variables were calculated for the two groups. Data from linear continuous variables were analyzed with the Kolmogorov Smirnov test to distinguish those with normal and non-normal distribution. The normal variables of the 2 groups were compared by performing the two-tailed Student's T test, the non-normal variables were compared by performing the two-tailed U-Mann Whitney test. Data from categorical variables were compared with two-tailed Fisher's exact test and two-tailed Pearson's Chi-squared test for variables with 2 categories and more than 2 categories, respectively. We set a value of 0.05 for statistical significance and we used IBM SPSS Statistics (Version 29.0).

RESULTS

The details of our dataset is resumed in detail in Table 1. Our population had a mean age of 50.26 years, the mean follow up time was 53.78 months and the mean time to reconstruction was 8.55 months.
As far as results, our groups were comparable for age ($p = 0.77$), follow-up time ($p = 0.10$), and time to reconstruction ($p = 0.80$). The groups were not comparable for nerve gap and lesion to fingertip distance: these values were higher in the graft group with $p = 0.0003$ and $p = 0.0001$ respectively.
The groups did not differ for the static 2 Point discrimination test in 2021 ($p = 0.87$) and 2023 ($p = 0.7$). We studied the healthy contralateral hand for comparison and the results were once again comparable for both groups in 2021 ($p = 0.93$) and 2023 ($p = 0.86$). When comparing the affected hand to the healthy contralateral we found no difference in 2021 ($p = 0.14$) but the healthy hand achieved better results in 2023 ($p = 0.002$). In this regard, the affected hand of grafted patients yielded worse results that the contralateral healthy ($p = 0.02$), but the affected hand treated with a neuroguide and the healthy contralateral scored comparable results ($p = 0.06$). The DASH score was comparable in both groups in 2021 ($p = 0.66$) and 2023 ($p = 0.53$), and it did not improve over time (2023 *vs* 2021: $p = 0.3$).
As far as complications, we observed one case of confirmed neuroma and one patient with a suspected neuroma in the neuroguide group.

DISCUSSION

The results of our study provide important insights into the comparative outcomes of neuroguides and nerve grafts in hand reconstruction. We observed that both treatment modalities yielded comparable results in various aspects. The groups were comparable for age, follow-up time and time to reconstruction. All the parameters under investigation have shown comparable results, such as the static 2-Point discrimination test, Semmes-Weinstein filament test and Disability of Arm, Shoulder, and Hand (DASH) scores. These findings suggest that both neuroguides and nerve grafts can be effective options for hand reconstruction in long-term follow-up periods.
73.33 and 66.66% of our patients reported an acceptable sensitive recovery (s2PD test < 15 mm) in 2021 and 2023 respectively. Our results are similar to those described in a systematic review of Kim et al., who did not find significant differences in sensory recovery among different techniques. The authors found that a time of intervention of less than 15 days has a good prognosis on the outcomes, but our mean time-to-intervention was considerably higher [3]. Another positive predictor, described by Fakin et al. was the surgeon's experience, and we strongly agree with this statement as all of our patients were operated by an expert hand surgeon. Although we did not correlate the nerve gap with the surgical outcome, it seems that this value did not influence our results. This datum is in contrast with the findings of Chiriac et al. and Loymer et al. who found significantly worse results in patients who had gaps > 11 mm and 15 mm respectively [6,7].
Our first retrospective analysis was conducted in 2021 and with a mean follow-up time of 38.61 months we did not encounter any difference between the affected hands and the corresponding healthy contralateral ($p = 0.14$). A notable difference emerged when comparing the affected hand to the healthy contralateral hand in 2023, with a mean follow-up time of 53.78 months. Specifically, the nerve graft group exhibited worse outcomes in comparison to the healthy contralateral hand, while the

Table I. Details of the results.

Case	Conduit	Time to reconstruction (months)	Gap length (cm)	Age	Follow- up (months)	S - 2Point Discrimination 2021	S - 2Point Discrimination 2023	DASH Score 2021	DASH Score 2023	Monofilament test 2021	Monofilament test 2023
1	Autologous graft	0	1	66	39	12	12	-	-	3	2
2	Autologous graft	36	4.5	60	82	8	8	6.6	13.15	3	4
3	Autologous graft	36	4.5	60	82	8	8	6.6	13.15	3	4
4	Autologous graft	36	4.5	60	82	8	8	6.6	13.15	3	2
5	Autologous graft	3	6.5	39	128	0	0	34.2	32.2	0	0
6	Autologous graft	3	5	39	128	5	7	34.2	32.2	1	3
7	Autologous graft	3	4	39	128	5	10	34.2	32.2	2	4
8	Autologous graft	0.7	2.2	60	25	4	5	9.2	54	4	3
9	Autologous graft	0.5	3	23	28	15	20	34.2	5.26	3	4
10	Autologous graft	0	6	49	24	0	0	48.5	22.8	0	0
11	Autologous graft	0	6	49	24	0	0	48.5	22.8	1	0
12	Autologous graft	0	6	49	24	0	0	48.5	22.8	0	0
13	Neuragen	0	3	59	68	4	10	10.7	3.2	3	3
14	Neuragen	0	2	59	68	3	5	10.7	3.2	4	4
15	Neuragen	7	2	59	80	6	5	34.2	28.4	2	3
16	Neuragen	24	2	66	60	4	-	51.3	-	3	-
17	Reaxon	0	1	52	24	4	-	-	-	4	-
18	Reaxon	3.5	3	53	24	9	7	5.9	2.63	5	4
19	Reaxon	21	3	55	43	-	0	-	59.2	-	0
20	Reaxon	2	3	57	5	-	5	-	75.7	-	4
21	Neurolac	7	2	19	24	10	15	1.3	2.63	3	4
22	Neurolac	7	2	19	24	6	3	1.3	2.63	3	5
23	Neurolac	7	2	65	23	0	0	72.4	84.2	3	5

neuroguide group achieved comparable results. This finding suggests that neuroguides may have an advantage in achieving outcomes similar to a healthy hand at longer distance follow-up, but we need further investigation to because this result may have been influenced by the smaller nerve gap and lesion-to-fingertip distance. When assessing significant changes over time, the only parameter that showed a statistical variability was the comparison between the s2PD of the affected finger versus the contralateral one. The values were comparable in 2021 but the contralateral hand scored better values in 2023. This suggests that patients need to be followed up to 5 years to draw definitive conclusions on their reconstruction. As showed by the literature, we recommend assessing the patients for at least one year because at 12 months the regeneration process is still incomplete [8].
We are aware of some limitations of the study. Firstly, the small sample size of our study needs to be acknowledged. A small sample size reduces the statistical power of the study and may limit our ability to detect subtle differences. Additionally, the occurrence of neuromas in two patients should be noted, as extreme values can influence the overall results and introduce bias into the analysis.
Another factor to consider is the difference in nerve gap and lesion-to-fingertip distance between the neuroguide and nerve graft groups. These differences inherently introduce variability and make the two groups not fully comparable. The nerve graft group had higher values for both nerve gap and lesion-to-fingertip distance, which could have contributed to the observed difference in outcomes between the two groups. It is important to recognize that these anatomical differences may impact the regenerative capacity and functional recovery in hand reconstruction.
Furthermore, the lack of improvement in the DASH scores over time is an important finding. It suggests once again that we do not need more than 3 years to set the definitive results of a nerve reconstruction. In addition, the variability among the different associated lesions, coupled with individual patient factors, may have contributed to the stagnant DASH scores. It is possible that additional factors, such as rehabilitation protocols, patient compliance, and other underlying comorbidities, could have influenced the lack of improvement in functional outcomes over time.
Future research on bioengineered materials for optimizing the outcome of neurotubules in nerve reconstruction is of paramount importance, as the current state of the art does not guarantee optimal results. In fact, despite being the gold standard, pure sensitive nerves have less regenerative potential than motor or mixed nerves, but the donor site morbidity of them is considerably higher and they cannot be considered as a first choice [9]. We need a solution for nerve reconstruction, especially for mixed nerved like the median and ulnar nerve, which are often involved in upper limb injuries. On this regard, the study of Dienstknecht et al. has showed promising results using conduits for median nerve repair [10].
In addition to the importance of this research, there are promising developments in the field that warrant attention. Neurotubules enriched with growth factors, such as nerve growth factor (NGF), and carbon nanotubules have shown promising results in preclinical settings. These advancements offer the potential for enhanced nerve growth, improved guidance, accelerated healing, and better signal transmission [11-14]. By delving deeper into understanding the mechanisms underlying nerve regeneration, scientists can develop novel bioengineered materials that have improved biocompatibility, mechanical properties, and guidance cues. Furthermore, addressing challenges related to long-term stability and integration of neurotubules within the body can pave the way for groundbreaking advancements in nerve surgery, offering hope for patients with nerve injuries or disorders. Continued investigation and refinement of these bioengineered materials hold great potential for revolutionizing nerve reconstruction techniques and improving patient outcomes.

CONCLUSIONS

In conclusion, our study highlights the comparable outcomes of neuroguides and nerve grafts in various aspects of hand reconstruction. However, the difference observed in 2023 between the affected and healthy hand in the nerve graft group, indicates that neuroguides may offer advantages in achieving outcomes similar to a healthy hand at long-distance follow-up. The limitations of our study, including the small sample size and differences in nerve gap and lesion-to-fingertip distance, need to be considered when interpreting the results. Further research with larger sample sizes and stricter matching criteria is necessary to provide more definitive evidence on the comparative efficacy of neuroguides and nerve grafts in hand reconstruction. Continued advancements in surgical techniques and understanding of nerve regeneration mechanisms will contribute to optimizing outcomes for patients with hand injuries.

Conflict of interest statement
The authors declare no conflict of interest.

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Author contributions

A: FM, CT, FB
D: FM, GL
DT: FM, GL
S: FM
W: FM, GL
O: CT, FB supervised and coordinated the study, reviewd and approved the final draft.

Abbreviations

A: conceived and designed the analysis
D: collected the data
DT: contributed data or analysis tool
S: performed the analysis
W: wrote the paper
O: other contribution (specify contribution in more detail)

Ethical consideration

Our Institution does not require formal ethical approval for retrospective analyses.

References

1. Raza C, Riaz HA, Anjum R, et al. Repair strategies for injured peripheral nerve: Review. Life Sci 2020;243:117308. https://doi.org/10.1016/j.lfs.2020.117308
2. Fakin RM, Calcagni M, Klein HJ, et al. Long-term clinical outcome after epineural coaptation of digital nerves. J Hand Surg Eur 2016;41:148-154. https://doi.org/10.1177/1753193415578986
3. Kim JS, Bonsu N, Leland H, et al. A systematic review of prognostic factors for sensory recovery after digital nerve reconstruction. Ann Plast Surg 2018;80(5S Suppl 5):S311-S316. https://doi.org/10.1097/SAP.0000000000001440
4. Marcoccio I, Vigasio I. Muscle-in-vein nerve guide for secondary reconstruction in digital nerve lesions. J Hand Surg Am 2010;35(9):1418-1426. https://doi.org/10.1016/j.jhsa.2010.05.019
5. Bąk M, Gutlowska O, Wagner E, et al. The role of chitin and chitosan in peripheral nerve reconstruction. Polim Med 2017;47:43-47. https://doi.org/10.17219/pim/75653
6. Lohmeyer JA, Kern Y, Schmauss D, et al. Prospective clinical study on digital nerve repair with collagen nerve conduits and review of literature. J Reconstr Microsurg 2014;30:227-234. https://doi.org/10.1055/s-0033-1358788
7. Chiriac S, Facca S, Diaconu M, et al. Experience of using the bioresorbable copolyester poly(DL- lactide-ε- caprolactone) nerve conduit guide NeurolacTM for nerve repair in peripheral nerve defects: report on a series of 28 lesions. J Hand Surg Eur 2012;37:342-349. https://doi.org/10.1177/1753193411422685
8. Chrząszcz P, Derbisz K, Suszyński K, et al. Application of peripheral nerve conduits in clinical practice: a literature review. Neurol Neurochir Pol 2018;52:427-435. https://doi.org/10.1016/j.pjnns.2018.06.003
9. Arslantunali D, Dursun T, Yucel D, et al. Peripheral nerve conduits: Technology update. Med Devices (Auckl) 2014;7:405-424. https://doi.org/10.2147/MDER.S59124
10. Dienstknecht T, Klein S, Vykoukal J, et al. Type I collagen nerve conduits for median nerve repairs in the forearm. J Hand Surg Am 2013;38:1119-1124. https://doi.org/10.1016/j.jhsa.2013.03.028
11. Porzionato A, Barbon S, Stocco E, et al. Development of oxidized polyvinyl alcohol-based nerve conduits coupled with the ciliary neurotrophic factor. Materials (Basel) 2019;12:1996. https://doi.org/10.3390/ma12121996
12. Stocco E, Barbon S, Lora L, et al. Partially oxidized polyvinyl alcohol conduit for peripheral nerve regeneration. Sci Rep 2018;8:604. https://doi.org/10.1038/s41598-017-19058-3
13. Stocco E, Barbon S, Lamanna A, et al. Bioactivated oxidized polyvinyl alcohol towards next- generation nerve conduits development. Polymers (Basel) 2021;13:3372. https://doi.org/10.3390/polym13193372
14. Pinho AC, Fonseca AC, Serra AC, et al. Peripheral nerve regeneration: current status and new strategies using polymeric materials. Adv Healthc Mater 2016;5:2732-2744. https://doi.org/10.1002/adhm.201600236