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Nerve transfer of the anterior interosseous nerve to the thenar branch of the median nerve - an anatomical and histological analysis

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Summary *Objective:* Nerve transfer has become a vital method in the reconstruction of hand function. Reconstructing the motor function to the thenar musculature has proven to be difficult and is rarely satisfactory following direct anatomic repair. The aim of this investigation was to describe the anatomic results obtained by transferring the anterior interosseous nerve to the thenar branch of the median nerve and analyze the histomorphometric results.
Material and Methods: Nerve transfers were performed in 15 fresh anatomic specimens. Nerve samples were excised from 13 fresh specimens and histologically investigated. The nerve diameter, fascicle number, and cross-sectional area of the individual fascicles were measured.
Results: The results of this investigation revealed that the anterior interosseous nerve and the thenar branch of the median nerve could be identified at their expected locations and a tension-free coaptation could be achieved. The anterior interosseous branch had a mean

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number of 606 ± 254 axons vs. 2160 ± 1326 in the thenar branch ($p < 0.001$). The anterior interosseous branch had a mean density of axons per fascicle mm^2 of 2398 ± 829 vs. 3012 ± 740 in the thenar branch ($p = 0.390$). The ratio of axons between the thenar branch of the median nerve and the anterior interosseous nerve yielded a mean of 1:4.16.

Conclusion: Nerve transfer of the anterior interosseous nerve to the thenar branch of the median nerve should be considered as a viable option but remains a subject of investigation owing to its critical axon ratio. Furthermore, larger clinical studies will be required to validate or neglect this nerve transfer.

Introduction

Nerve transfer has become a vital method in the reconstruction of hand function, especially in the reconstruction of the intrinsic muscles of the hand after injury of the ulnar nerve or the median nerve.[1-3] A majority of peripheral nerve injuries occur at the level of the wrist and the hand, often compromising the function of the median and ulnar nerve.[4] Reconstructing the motor function to the thenar musculature has proven to be difficult and is rarely satisfactory following direct anatomic repair or nerve grafting. The probable main reason for the unsatisfactory results is the sensory nature of the median nerve at this level, which causes the regenerating motor axons to grow into the wrong endoneurial tubes.[5-8] Extensor indicis proprius opponensplasty is in most incidences the treatment of choice to restore the function of the thenar musculature, which allows for the reconstruction of thumb opposition by tendon transfers.[9] As discussed in the literature, tendon transfers may frequently lead to limited thumb function because of limited functional reconstruction and persistent thumb contractures.[10]

Facing this substantial limitation, surgeons have turned their attention to distal nerve transfers to restore the function of the thenar musculature.[10,11] The rationale behind this shift in attention is the idea that a distal nerve transfer can approximate the donor axons to the target endplate and avoid misdirected growth in the endoneurium of motor axons by using a relatively pure motor donor nerve to connect with a relatively pure motor recipient nerve. Hence, the anterior interosseous nerve was transferred to the thenar branch of the median nerve with an end-to-end coaptation to reconstruct the thenar muscle function.[2,12,13] The principal indication for this transfer is that the median nerve suffered a complete injury distal to the origin of the anterior interosseous nerve.[2,14] Following end-to-end coaptation, supercharged end-to-side coaptations were introduced to augment partial recovery of incomplete injuries of the ulnar nerve. Supercharged end-to-side coaptations involve the transfer of the anterior interosseous nerve to the side of the deep motor branch of the ulnar nerve. In the clinical setting, intrinsic muscle reinnervation was observed.

The aim of this investigation was to describe the anatomic results obtained by transferring the anterior interosseous nerve to the thenar branch of the median nerve and analyze the histomorphometric results of the two coaptated nerves.

Material and Methods

Study Sample

Nerve transfers were performed in 15 fresh anatomic specimens. Specimens were screened and not included into this analysis if previous lower arm surgery or diseases disrupted the integrity of the lower arm. Each body donor had given informed consent while alive for the use of his or her body for medical, scientific, and educational purposes. All aspects of the study conform to the laws of the country where the study was conducted (Germany and Austria).

Anatomical dissection

Anatomical measurements were performed in all 15 fresh cadaveric upper limbs. Dissection was conducted using 2.5x magnification surgical loupes. After removal of the skin, the anterior interosseous nerve was identified along the anterior margin of the interosseous membrane of the forearm and prepared in its entire length distally and proximally. Dissection of the anterior interosseous nerve was performed at the proximal edge of the pronator quadratus muscle. The thenar branch of the median nerve was identified at its insertion into the thenar musculature. It was dissected in a retrograde manner until it branched off from the median nerve and from thereon interfascicular neurolization was performed from the median nerve up to the level of the proximal pronator quadratus muscle border, where it could reach the anterior interosseous nerve (Figure 1).

Histomorphometric analysis

Nerve samples were excised from 13 fresh specimens. The anterior interosseous nerve was dissected at the proximal edge of the pronator quadratus muscle, while samples from the thenar branch of the median nerve were obtained by cutting it at the proximal edge of the pronator quadratus muscle and at the level of the carpus. The tissue samples were fixed in 2.5% glutaraldehyde with 0.1 M sodium cacodylate buffer for 60 minutes at 4°C and a pH of 7.4 (Science Services, Munich, Germany). Afterwards, samples were postfixated in 2% aqueous osmium tetroxide and dehydrated in an ascending alcohol series (30%-100%) and

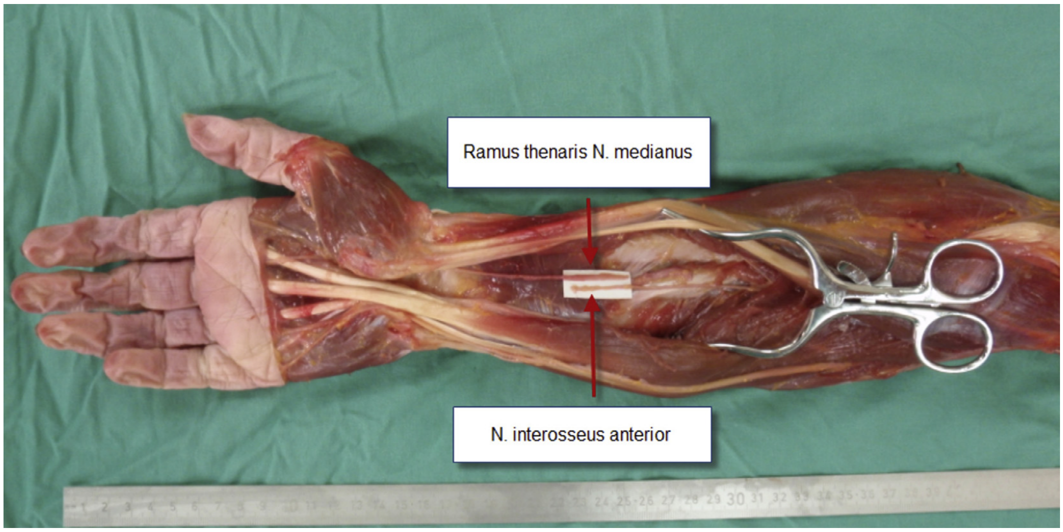

Figure 1 Photograph showing a dissected lower arm and hand. The thenar branch of the median nerve and the interosseous anterior nerve are marked. Note the tension – free coaptation on the white background.

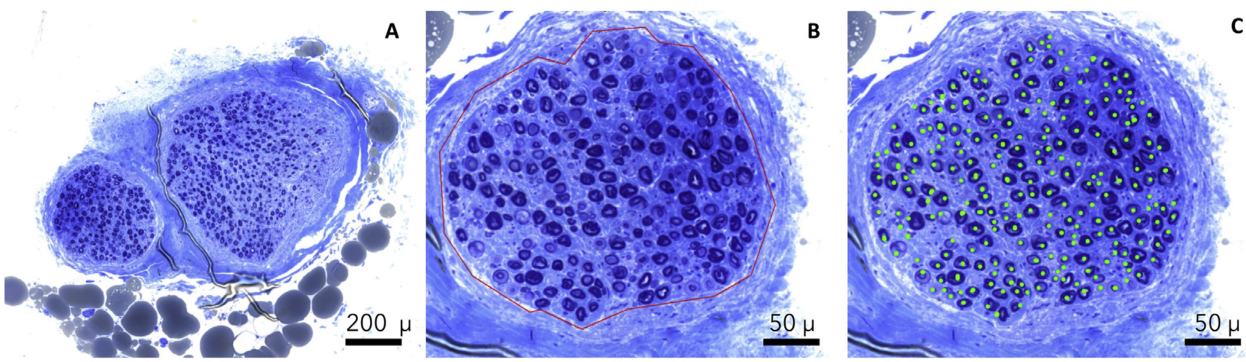

Figure 2 Histomorphometric results of the interosseous anterior nerve were obtained at the height of the coaptation. At 200x magnification, general nerve structures and fascicles were observed (A). At 600x magnification, cross-sectional areas of individual fascicles were determined by a polygon approach (B,C).

propylene oxide (Science Services, Munich, Germany). Subsequently, samples were embedded in epoxy resin (Merck, Darmstadt, Germany), while their orientation was preserved and cured at 60 °C for 24 h. Using an ultramicrotome (Reichert Technologies, Munich, Germany), semi-thin transverse sections (1 μm) were cut and stained for 1 minute with 1% toluidine blue (Sigma-Aldrich, Taufkirchen, Germany) and then scanned at a 20x magnification with a Mirax Scanner (Carl Zeiss, Jena, Germany). The nerve diameter, fascicle number, and cross-sectional area of the individual fascicles were measured at 200x magnification. Specialized software was used to measure the cross-sectional area (Pannoramic Viewer 1.15, 3DHISTECH, Budapest, Hungary). Total areas of fascicles were calculated as the sum of the cross-sectional surfaces of all fascicles. Myelinated axons were counted semi-automatically at 600x magnification (ImageJ 1.42, NIH, Bethesda, MD, USA). The low cut-off value for inclusion of axons was set at 4 μm. The density of the axons was calculated as the ratio of the axon number and fascicle area. Donor-to-target ratios of the mean values were calculated for all parameters. Donor-to-target axon ratios were calculated for each specimen (Figures 2 and 3).

Statistical Analyses

Differences between measurements obtained from the anterior interosseous nerve and the thenar branch were calculated using unpaired Student's t-tests. All analyses were performed using SPSS Statistics 23 (IBM, Armonk, NY, USA), and results were considered significant at a probability level of ≤ 0.05.

Results

Anatomic dissection

The anterior interosseous nerve and the thenar branch of the median nerve were identified at their expected anatomical locations in all 15 investigated hands. The mean overall length, measured from the lateral epicondyle to the styloid process of the forearm, was 252 ± 24 mm. The thenar branch split off the median nerve 299 ± 27 mm distally from the lateral epicondyle and was separated at a mean length of 97 ± 15 mm from the median nerve to reach

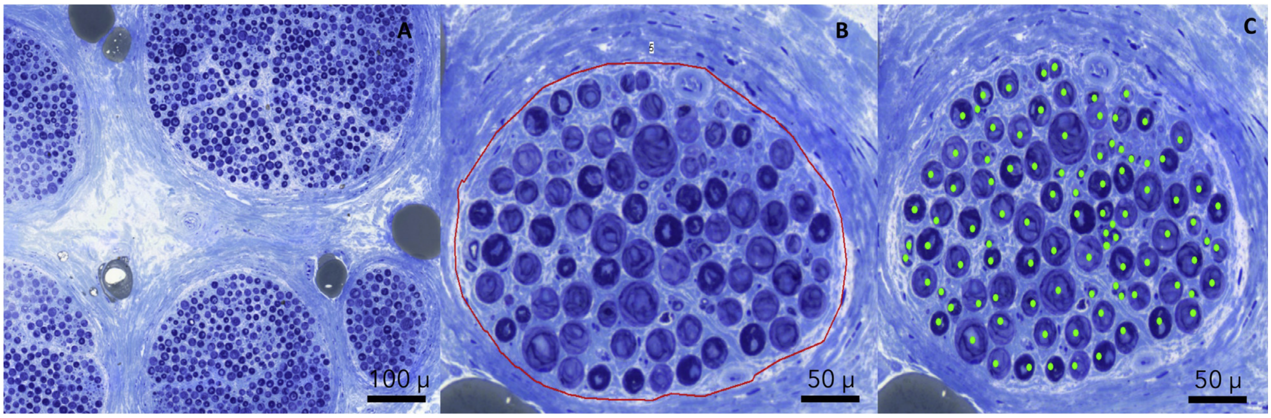

Figure 3 Histomorphometric results of the thenar branch of the median nerve were obtained at the height of the coaptation. At 200x magnification, general nerve structures and fascicles were observed (A). At 600x magnification, cross-sectional areas of individual fascicles were determined by a polygon approach (B,C).

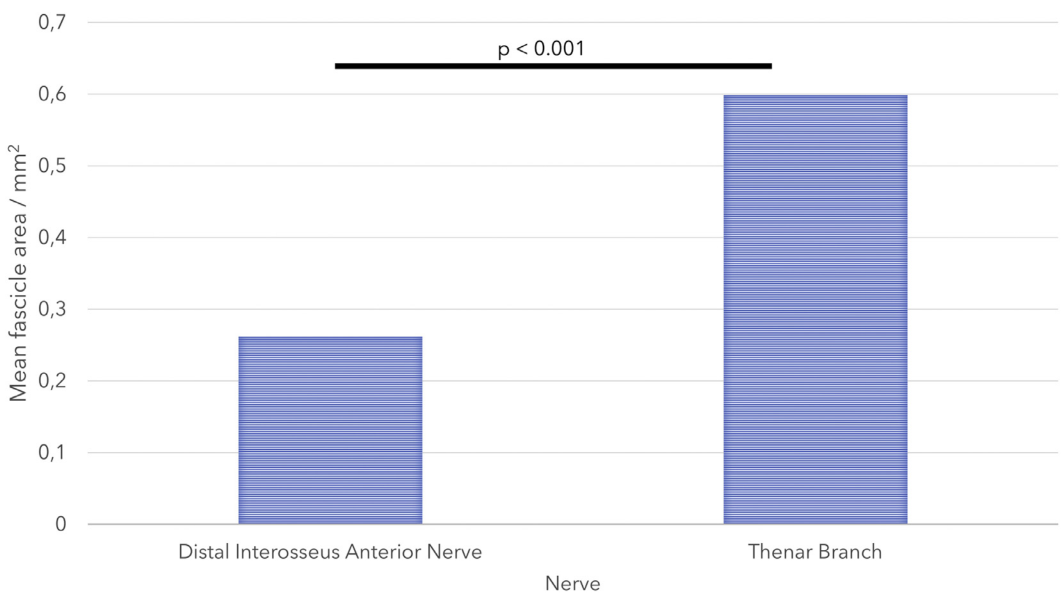

Figure 4 Bar chart showing the mean fascicle area at the coaptation site of the distal interosseous anterior nerve and the thenar branch of the median nerve.

the coaptation site with the anterior interosseous nerve. The site for coaptation of the thenar branch and the anterior interosseous nerve, the proximal border of the pronator quadratus muscle, was identified 201 $\pm$ 15 mm distally from the lateral epicondyle. At the coaptation site, the interosseous anterior nerve and the thenar branch had a measured diameter of 0.79 $\pm$ 0.24 mm and 1.28 $\pm$ 0.34 mm, respectively.

Histomorphometry

Fascicle Area

The cross-sectional fascicle area of the anterior interosseous nerve had a mean of 0.26 $\pm$ 0.1 mm^2, while the thenar branch of the median nerve had a fascicle area of 0.72 $\pm$ 0.4 mm^2 at the level of the proximal pronator quadratus muscle. The fascicle area of the anterior interosseous nerve and the thenar branch of the median nerve showed significant difference with $p < 0.001$ (Figure 4).

Fascicle number

The mean number of fascicles in the anterior interosseous nerve was 2.29 $\pm$ 1.5, whereas the thenar branch of the median nerve had a mean number of 3.85 $\pm$ 2.4 fascicles at the level of the proximal pronator quadratus muscle. The number of fascicles of the anterior interosseous nerve and the thenar branch of the median nerve did not show significant difference, with $p = 0.135$.

Number of Axons

The anterior interosseous branch had a mean number of 606 $\pm$ 254 axons, whereas the thenar branch had a mean number

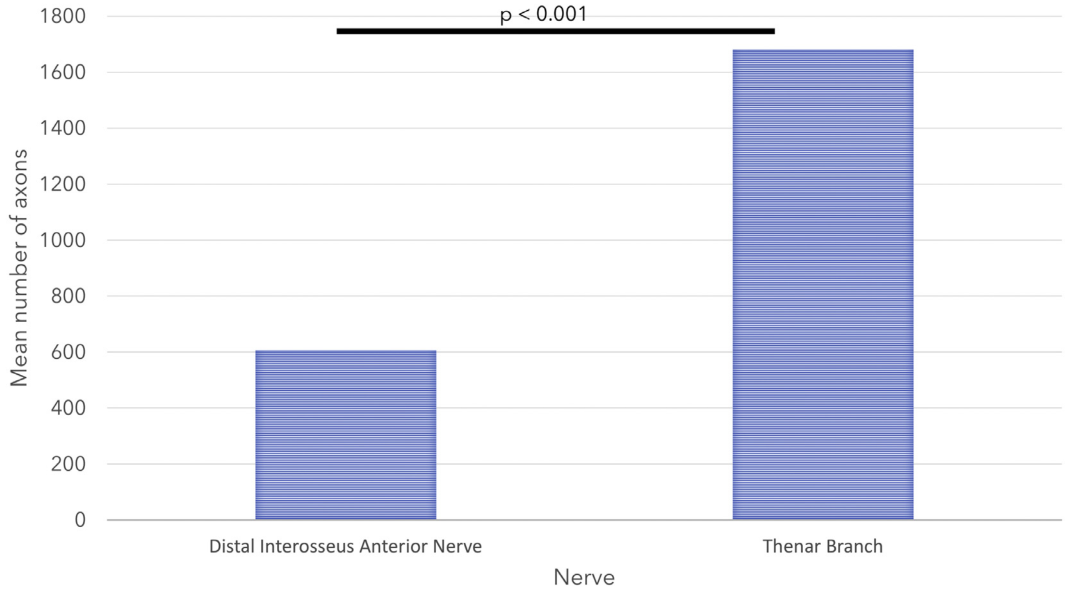

Figure 5 Bar chart showing the mean fascicle area at the coaptation site of the distal interosseous anterior nerve and the thenar branch of the median nerve.

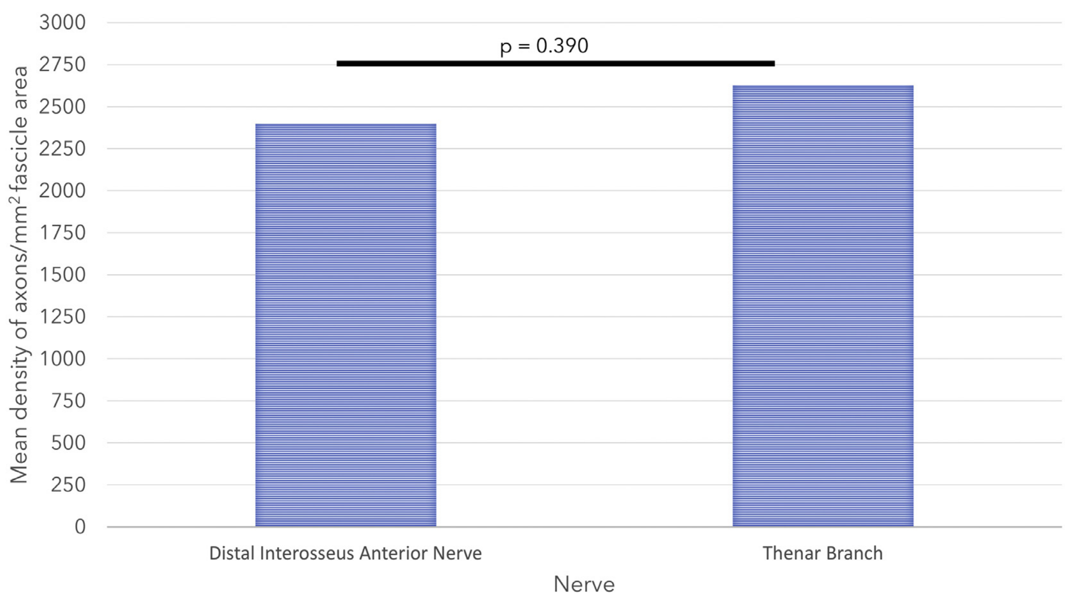

Figure 6 Bar chart showing the mean density of axons per mm^2 fascicle at the coaptation site of the distal interosseous anterior nerve and the thenar branch of the median nerve.

of 2160 ± 1326 axons at the level of the proximal pronator quadratus muscle. The number of fascicles did not show significant difference between the anterior interosseous nerve and the thenar branch of the median nerve, with $p < 0.001$ (Figure 5).

Density of axons per fascicle area

The anterior interosseous branch had a mean density of axons per fascicle mm^2 of 2398 ± 829, whereas the thenar branch had a mean number of 3012 ± 740 axons per fascicle mm^2 at the level of the proximal pronator quadratus. The number of fascicles did not show significant difference between the anterior interosseous nerve and the thenar branch of the median nerve, with $p = 0.390$ (Figure 6).

Ratios of axons

The ratio of axons between the thenar branch of the median nerve and the anterior interosseous nerve yielded a mean of 1:4.16. Of all investigated coaptations, 6 (42%) coaptations had a rounded ratio greater or equal to 1:3. One coaptation (7%) had a ratio smaller than 1:9, whereas the remaining seven coaptations ranged between a ratio of 1:3 and 1:9. A total of 8 (57%) coaptations had a ratio greater than 1:5 (Table 1).

Table 1 The ratio of axons between the thenar branch of the median nerve and the anterior interosseous nerve at the site of coaptation in each performed hand.

Coaptation	Ratio
1	1:6
2	1:5
3	1:9
4	1:3
5	1:6
6	1:4
7	1:3
8	1:6
9	1:2
10	1:4
11	1:3
12	1:1
13	1:1

Discussion

The results of this investigation revealed that the anterior interosseous nerve and the thenar branch of the median nerve could be identified at their expected locations and a tension-free coaptation could be achieved by interfascicular neurolization of the thenar branch. The axon ratio between the anterior interosseous nerve and the thenar branch of the median nerve averaged at 1:4.16, which created a subject for discussion for the suitability of this nerve transfer.

Limitations of this study are the relatively small sample size and the strict inclusion and exclusion criteria in the counting of the axons compared to those reported in previous studies. Moreover, the coaptations in fresh specimens naturally did not allow monitoring and examination of the function of the thenar musculature, which is of great interest for the practicing clinician.

Anatomy

The anterior interosseous nerve passes along the anterior surface of the anterior interosseous membrane between the ulna and radius, which makes the nerve vulnerable to injuries in the forearm.[11] We harvested the anterior interosseous nerve at the proximal border of the pronator quadratus muscle to maximize the axon numbers, which distinguished our study setup from those in previous investigations in which the anterior interosseous nerve was harvested in the middle of the pronator quadratus muscle.[3,14] Our technique will result in partial loss of pronation force, which can be compensated by the pronator muscle, as shown in previous investigations.[14] The branches of the anterior interosseous nerve to the long flexors of the hand were not affected by the nerve transfer. We achieved tension-free coaptation between the anterior interosseous nerve and the thenar branch of the median nerve in every observed instance.

Between the wrist and the distal forearm, the thenar branch of the median nerve is found volar and radial, accompanying the sensory nerve and travelling to the index finger and the thumb. Interconnection between fascicles decreases the ratio of purely sensory and purely motor fascicles of the median nerve.[8,15] Identification of motor fascicles at this level can often not be conducted reliably by electrical stimulation.[16] Hence, to obtain purely motor fascicle, the thenar branch of the median nerve and the sensory part of the median nerve were divided retrograde from each other for a length of 97 $\pm$ 4.0 mm. Intraneural fascicular dissection allows motor fiber identification at the aforementioned length and furthermore a tension-free coaptation between the thenar branch of the median nerve and the anterior interosseous nerve at the proximal border of the pronator quadratus muscle. Alternatively, an interposition nerve graft, e.g., sural nerve of corresponding length can be used.[13-15] During intraneural dissection, we identified minor plexuses between sensory and motor fascicles of the median nerve. These can be considered as expendable, but care should be taken not to injure the sensory part of the median nerve.[17]

Caution should be taken, as mismatching of mixed fascicles or a nerve graft may substantially diminish the outcome of nerve transfer.[2,18]

Keeping the donor nerve in close proximity to the denervated end-plate is a basic principle in the transfer of motor nerves.[19] By performing the presented procedure, the distance required for axonal regeneration to the thenar muscles was greatly shortened. This may minimize the regeneration time and provide faster reinnervation. Transfer of the anterior interosseous nerve to the thenar branch of the median nerve showed a better and earlier recovery of intrinsic muscle function than direct anatomical coaptation in the rhesus monkey model.[11] Our measurements indicate that the best suitable coaptation site of the anterior interosseous nerve and the thenar branch of the median nerve was located 202 $\pm$ 4 mm distal from the lateral epicondyle of the humerus (Figure 3). This allows estimation of the distance and reinnervation time according to the rate of nerve regeneration.[20] An attractive feature of choosing the anterior interosseous nerve as a donor is the synergistic motor function of the thenar muscles, which facilitates the postoperative re-education.[21] Moreover, this technique allows the coaptation site to be remote from the injury site. Reduced scar formation and this well-vascularized environment supports and aids nerve regeneration.[22]

Histomorphometry

Histomorphometric analysis is the most commonly used method to investigate nerve regeneration.[23] Axon number and density are particularly important because they relate to the functional outcome of nerve recovery.[24] Clinical experience showed that an optimal axon ratio of donor to recipient needs to be higher than 1:3, while the diameter of the donor to recipient nerve should be similar to allow for microsurgical coaptation techniques. We investigated the donor-to-recipient ratio of the anterior interosseous nerve to the thenar branch of the median nerve. Our study indicated that the mean axon number was 606 $\pm$ 254 in the anterior interosseous nerve and 2160 $\pm$ 1326 in the thenar branch of the median nerve. In the literature, axon numbers of 866 $\pm$ 144 and 1120 $\pm$ 97 were reported in the anterior interosseous nerve and in the thenar branch of the median nerve, respectively.[22] Difference in our measurements and measurements in the literature can be partially explained by the inclusion and exclusion criteria in axon identification. Statistically significant differences between the anterior interosseous nerve and thenar branch of the median nerve could only be found for the fascicle area and number of axons ($p < 0.001$ for both). The mean axon ratio of the anterior interosseous nerve and the thenar branch of the median nerve was 1:4.16 (Table 1).

Keeping in mind that with a ratio of 1:3, if preferable as shown by Lutz et al. in the animal model, the suitability of this nerve coaptation needs to be questioned.[25] The idea of a suitable ratio of 1:3 is stretched by the findings of Jiang et al., who reported that up to 3-4 collaterals can be developed by one axon, thus showing that one axon can send off several collateral axons into the motor end-plate.[26] Fu et al. showed that axons can send off 3 to 5 axons into a new motor unit. On the basis of these reports, nerve coaptations with an axon ratio between 1:3 and 1:5 may be regarded to have the same ability of reinnervation as that of coaptations with an optimal ratio greater than 1:3.[27] Thus, according to the findings of Fu et al.[27], we assume that in the living model, 8 out of 13 coaptations in our study would have been feasible for a transfer of the anterior interosseous nerve to the thenar branch of the median nerve for the reconstruction of the thenar musculature.

However, the individual discrepancy of donor-to-recipient axon ratio in our study needs to be pointed out. Seventeen cases of transfers of the anterior interosseous nerve to the thenar branch of the median nerve and deep branch of the ulnar nerve were followed up by Wang et al. Their results revealed a normal electromyogram in 10 cases, while 7 cases showed a poor myodynamic performance, which is close to our findings.[22] Moreover, Huang et al. transferred half branches of the anterior interosseous branch to the thenar branch of the median nerve in two rhesus monkey models and revealed that the functional outcome of the thenar musculature was not statistically significant between the half branch transfer and the whole branch transfer.[11] The transfer of the anterior interosseous nerve to the thenar branch of the median nerve may provide a new treatment choice for distal median nerve injury to restore the thenar musculature; however, the divergent axon numbers might pose a limitation.

We expect the clinical outcomes of the discussed nerve transfer to be comparable to those of other transfers with "unfavorable" donor-to-recipient ratios. The anterior interosseous nerve to the deep branch of the ulnar nerve has an average donor-to-recipient ratio of 1:4.8 as reported by Schenck et al.[28] This transfer has shown to be very efficient in the clinical setting, as laid out by Novak et al.[29] Considering that the anterior interosseous nerve provides successful results when transferred to the deep branch of the ulnar nerve, we remain optimistic that it will hold up to our experiences in the clinical setting. Furthermore, opposition of the thumb can be considered rather a delicate positional change with a huge impact on hand dynamic rather than a movement that requires great strength. Fewer axon counts in the anterior interosseous nerve might still be sufficient to transfer the positional changes as grip strength is provided by the flexor muscles. Using a side-to-end transfer with the anterior interosseous nerve to the deep branch of the ulnar nerve has been accepted increasingly.[30] We think that the anterior interosseous nerve to the thenar branch of the median nerve transfer also holds great potential to be used for end-to-side reinnervation.

Using a nerve transfer from the interosseous anterior branch to the thenar branch of the median nerve is less invasive for the biomechanical properties of the hand than an opponensplasty. An early surgical intervention can prevent irreversible damage because of faster innervation. In proximal injuries of the median nerve or in cases in which the regeneration potential is difficult to assess, we also recommend performing the proposed nerve transfer end-to-side. To avoid compromising the intrinsic regeneration of the thenar branch, we recommend an end-to-side coaptation using a nerve interposition graft, according to the babysitter principle of McKinnon.[31]

Conclusion

We investigated nerve coaptations between the anterior interosseous nerve and the thenar branch of the median nerve in 15 fresh frozen upper limb specimens. Statistically significant differences between the anterior interosseous nerve and thenar branch of the median nerve could be found only for the fascicle area and number of axons ($p < 0.001$ for both). There was no statistically significant difference for the fascicle number or density of axons per fascicle area ($p > 0.005$). The axon ratio of the anterior interosseous nerve and the thenar branch was 1:4.2, which is 25% below the threshold of successful donor-to-recipient ratios. The axon ratio between the anterior interosseous nerve and the thenar branch of the median nerve should remain the subject of investigation. Furthermore, larger clinical studies will be required to validate or neglect this nerve transfer.

Author disclosure

None of the authors listed have any commercial associations or financial disclosures that might pose or create a conflict of interest with the methods applied or the results presented in this article.

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