Regeneration of the transected rat sciatic nerve after suturing or adhesion with cyanoacrylate glue

Laboratory investigation

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Object. Traditional treatment of transected peripheral nerves has been by suturing the nerve ends to each other. Because this approach is not widely available and is technically demanding, the authors evaluated an easier method for end-to-end anastomosis using cyanoacrylate-based glue.

Methods. The authors used a rat sciatic nerve model. The sciatic nerve was transected in one hind limb in each of 40 rats. In 20 rats, end-to-end anastomosis was performed with suturing, while in the other 20 it was performed using only cyanoacrylate glue. The outcome variables were incapacitance test results; the functional sciatic index; somatosensory evoked potentials; axon counts and sizes at the proximal, anastomotic, and distal levels; local adhesions; and automutilation injuries. Outcomes were measured in a manner blinded to the anastomotic technique.

Results. Only the somatosensory evoked potentials and degree of local adhesions were significantly better in the Suture Group than in the Glue Group. With respect to the remaining outcomes (automutilation injuries, counts of large and medium axons combined, and counts of small axons), either the results were significantly better in the Glue Group or the between-groups difference was not statistically significant. There were no consistent significant correlations between the various outcome measures.

Conclusions. Using cyanoacrylate-based glue for microanastomosis of cut nerves appears to be as effective as microsuturing the nerve ends. Despite more local adhesions in the glued nerves, most functional outcomes were not influenced by the anastomotic technique. Validation of these findings awaits studies of larger groups of animals.

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KEY WORDS • nerve regeneration • cyanoacrylate glue • sciatic index • nerve injury • anastomosis • incapacitance test

Abbreviations used in this paper: FSI = functional sciatic index; IT = incapacitance test; SSEP = somatosensory evoked potentials.

TREATMENT of traumatic transection of peripheral nerves is primary anastomosis, either in the acute phase or during the chronic phase.1,7,17 The usual anastomotic technique is suturing of the nerve endings in an end-to-end fashion, which requires microsurgical skills that are not widely available. Gluing the neural ends to each other has been described, but there are only scarce publications that describe this technique.2,3,10,11,13,20,25 We undertook this prospective blinded study in a rat sciatic nerve model to compare the conventional suturing technique with a gluing technique using a cyanoacrylate-based glue.

Methods

Forty Wistar rats, 3–4 months old (weight 300–400 g) were used in this study. The study included the following elements: 1) surgery; 2) incapacitance test evaluation; and 3) functional sciatic index (FSI) evaluation, SSEP evaluation, and histological analysis of the nerve (including proximal area, anastomosis, and distal area).

Surgical Technique

General anesthesia was induced with intraperitoneal injection of xylazine (15 mg) and ketamine (50 mg). The
right sciatic nerve was exposed and then sharply incised with microscissors. Immediately thereafter, an anastomotic procedure was performed under a microsurgical microscope. The anastomoses were performed either by suturing or application of cyanoacrylate glue, with 20 rats randomly assigned to one group and 20 to the other. Suturing was performed using 3 to 5 single 10-0 Prolene sutures approximating the epineurium of each of the 2 nerve endings. Trimming of the nerve fibers was carried out as needed to preserve all the fascicles within the epineurial sac with good continuity. The gluing procedure was performed using Glubran 2 (GEM S.r.l.), which is a synthetic cyanoacrylic surgical glue modified by the addition of a monomer. It has been approved and used in multiple surgical disciplines, such as cardiac and vascular surgery, although not for neural anastomosis. We placed a small piece of silver foil under the nerve endings to isolate the surrounding tissues from the glue. The nerve endings were then approximated and adjusted to achieve optimal positioning. One or 2 microdrops of glue were placed over the anastomotic area with a 0.1-ml syringe and a 25-gauge needle. The glue dried within seconds, whereupon the construct could be safely manipulated. If additional glue was needed on the unexposed side, the anastomosis was rotated and another microdrop was placed. Dried glue that was not precisely adherent to the nerve ending was carefully trimmed to minimize surrounding tissue exposure to the glue. The silver foil was removed, and the skin was sutured in a single layer with a 3-0 silk suture.

**Incapacitance Test**

The incapacitance test was performed 4–6 weeks following the surgical procedure in 27 rats, and 14 weeks after the procedure in 4 rats. The remaining rats suffered various automutilation injuries that prevented their participation in this test. We used the 3100 Incapacitance Tester (2Biological Instruments). The test evaluates the pressure of each hind limb while the rat is placed in a chamber with the hind limbs pressing on 2 pressure-sensitive pads. Each rat was tested 3 times for 4 seconds each, and the averaged values were used for statistical analysis. Due to the range of weight in the animals tested, we did not use the absolute pressure value, but rather calculated the ratio of the operated limb to the opposite nonoperated limb (termed the IT value). An IT value of 1 indicates an identical pressure elicited by both hind limbs, and an IT value of less than 1 indicates that a lower pressure was elicited by the operated leg compared with the nonoperated one.

**Functional Sciatic Index**

This widely described test helps to evaluate the functionality of the operated limb compared with the opposite side. The rat is placed on a 40-cm-long, 10-cm-wide track, with sealed sides and top, ending in a dark box. After the rat’s hind limbs are dipped in black nontoxic ink, the animal is released to walk along the track. The walking surface is covered with a long piece of paper, and the ink on the ambulating rat’s hind limbs leaves tracks on the paper (paw prints). These imprints have basic characteristics, such as the maximum distance between anterior and posterior footprint margins (print length [PL]), the distance between the outer margins of the first and fifth digits (total spread [TS]) and the distance between the outer margins of second and fourth digits (intermediary toe spread [ITS]) (Fig. 1).

The formula used for measuring FSI is: FSI = 13.3*(ITS − NTS)/NTS + 109.5*(ETS − NTS)/NTS − 8.8, where the letters N and E before the variables denote normal and experimental limbs, respectively.

A value of 0 indicates a good functional recovery of the operated leg compared with the opposite nonoperated side. The closer the number is to 100, the more complete is the denervation of the paw.

**Electrophysiological Evaluation**

Somatosensory evoked potentials were recorded in both the operated and intact hind limbs of the experimental and control rats using a Nicolet/Viking Quest electro-myography apparatus (10–30 KHz band pass filter). The recordings were performed in a blinded manner at 8.5–11 weeks after surgery. Conductivity of the sciatic nerve and spinal cord were studied by stimulation of the sciatic nerve at the level of the tarsal joint with simultaneous recording from the skull over the somatosensory cortex. The rats were anesthetized using ketamine and xylazine during the electrophysiological study. Two subcutaneous needle electrodes were inserted under the skin of the scalp, with the active electrode over the somatosensory cortex along the midline and the reference electrode between the 2 eyes. The ground electrode was placed subcutaneously on the dorsal neck. The sciatic nerve was stimulated by a set of 2 polarized needle electrodes placed subcutaneously on the lateral aspect of the tarsal joint. Five hundred stimulation pulses of 0.2 msec in duration were generated at a rate of 1.5 Hz. The stimulus intensity was set on 22.3 mA, and a slight twitching of the limb was noted in all rats.

The appearance of an evoked potential in 2 consecutive tests as a response to a stimulus on 2 consecutive tests was considered positive. Latency and amplitude (positive [P] wave peaks) were measured (Fig. 2).

**Histological Evaluation**

Twenty-eight rats were killed by injecting lethal doses of xylazine and ketamine 10–11 weeks after the surgical procedure, and 4 rats were killed 3.5 weeks later. Eight rats died before completion of the study period and were not available for histological analysis. The operated sciatic nerve was exposed, and the adhesions of the nerve to surrounding tissue were graded as no/mild, moderate, or severe. After the nerve was dissected, the anastomotic area was harvested (from 1 cm proximal to 1 cm distal to the anastomosis) and embedded in 10% formalin (Fig. 3). Sections were obtained for histological study at 3 sites: 5 mm proximal to the anastomosis, at the anastomotic region, and 5 mm distal to the anastomosis. Axons were counted by means of immunohistochemical staining with myelin silver. Each slide was carefully inspected under × 60 microscopic magnification, and digital images were
taken of areas suitable for axon counting (Fig. 4). In each image, a round field was defined composing one-third of the image area, and the axons within that field were counted manually. The axon count was divided according to the axon size: less than 2.5 μm, 2.5–5.5 μm, and 5.5–7.5 μm. The mean axon count for each axon size group in each counting area was used for statistical analysis.

Two axon quantification measures were used—an absolute count and a percentage value. The percentage values were calculated as follows: for each nerve, the number of axons at the anastomosis and distal site were each divided by the corresponding axon count at the proximal site. The rationale for this way of counting was to standardize all nerves (by defining the proximal axon count as “1”), thus presumably increasing the accuracy of the comparisons between nerves and study groups.

The study was approved by the Tel-Aviv Sourasky Medical Center institutional review board. It had a blinded and randomized design. Each rat was marked with a serial number that was used for tracing. The group assignments (Suture vs Glue) were disclosed only after the axon counting had been completed.

**Fig. 1.** Functional sciatic index. Representative paw prints from the control side (A) and the operated side (B). ITS = intermediate toe spread (digits 2–4); PL = print length (maximum anteroposterior measurement); TS = total spread (digits 1–5).

**Fig. 2.** Somatosensory evoked potentials. The upper 2 waveforms denote 2 different SSEP studies on the control side. The lower 2 waveforms denote the SSEP studies in the operated side. The SSEP variable was defined as the time lag between first positive peaks of the operated (A) and control studies (B) divided by the time to the first peak in the control study.

**Fig. 3.** Photographs showing the anastomotic area in a glued nerve (A) and in a sutured nerve (B).
Statistical Analysis

Comparison between the Glue and Suture groups was performed using the Mann-Whitney U-test. Correlation between variables was assessed by means of the Pearson correlation coefficient and Spearman rank correlation coefficient (rho). Significance was defined as a p value < 0.05.

Results

Of the 40 original study rats, 32 survived to complete the entire study protocol, 16 in each group. (Eight died at various stages prior to the formal completion of the study.) The incapacitance test was performed in 31 rats (1 was too agitated to perform the test adequately). Somatosensory evoked potentials were available for only 27 rats due to death of 1 during the test and to technical difficulties related to severe mutilation of the operated leg in 4 animals in the Suture Group. The FSI was calculated in only 16 rats, either because of automutilation of the operated limb that precluded the rat from adequately performing the task, or due to severe contractures in the operated limb causing it to produce an unacceptable paw print.

Comparison Between the Glue and Suture Groups

The differences between the 2 study groups were significant (p < 0.05, Mann-Whitney U-test) for the following outcome variables: adhesions, SSEPs, axon counts in the proximal site (all axon sizes), and absolute axon counts of the large and medium sizes (combined) and small axons at the anastomotic and distal sites. All the differences favored the Glue Group except for the SSEPs and adhesions, which favored the Suture Group (Table 1).

There was no significant intergroup difference with respect to IT value, FSI, or percentage values of axon counts (relative to the proximal site) for any axon size.

Intivariable Correlations

Both the Pearson and Spearman tests were used to correlate between outcomes. Correlations were analyzed for each group (Glue and Suture) and for the whole study group (Glue and Suture groups combined). We looked for the following correlations: 1) correlations between absolute axon counts at the anastomosis or distal sites and the respective percentage value (relative to the proximal count); 2) correlation between axon counts (absolute and percentage values) at the various sites for the same axon size; 3) correlations between the axon counts (absolute and percentage values) and the non-axonial outcome variables (for example, adhesions, SSEPs, IT values, and FSIs); and 4) correlations between various non-axonial outcome variables (adhesions, SSEPs, IT values, and FSIs).

Correlations Between Absolute Counts and Percentage Values

There was a significant (p < 0.05) correlation between the absolute counts and percentage values for large axons at the anastomosis and at the distal sites (the latter in the Suture Group and the 2 groups combined), but only in the anastomosis site for the Glue Group. A significant correlation was also found between absolute counts and percentage values for large and medium axons (combined) at the distal site in the Suture Group.

Correlation of Axon Counts Between Various Sites

There was a significant correlation (p < 0.05) between the proximal and anastomosis site for the absolute...
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count of large and medium (combined) and small axons for both groups combined. The correlation between the anastomosis and distal sites for the percentage values for all axon sizes was also significant.

In the Glue Group, there was a significant correlation between the distal percentage values for large axons and those for large and medium axons (combined), while in the Suture Group there was a significant correlation between the values for the small axons and the large and medium (combined).

**Correlation Between Axonal Counts and Other Outcome Variables**

No significant correlation was found between the IT value and SSEPs and any of the axon counts in the combined group. There was a significant correlation between SSEP findings and the absolute axon counts at the proximal site (the combined large and medium sizes and the small axons) and the percentage value at the distal site (the small axons) in the Glue Group. The FSI was significantly correlated with the absolute axon counts at the proximal (the large and medium axons combined and the small axons) and distal sites (the small axons). The degree of adhesions correlated with the counts at the anastomosis (the large and medium axons combined and the small axons) in the combined (Glue and Suture group). The degree of adhesions correlated with the absolute small axon count at the proximal site and with the percentage value of the large axons at the distal site in the Glue Group. No similar correlations were found in the Suture Group. There was no significant correlation between the IT value, FSI, SSEP results and adhesions in either group or overall (Glue and Suture groups combined).

**Correlation Between Non–Axonal Count Outcome Variables**

There was no significant correlation between the variables of IT value, FSI, and SSEPs in either subgroup or the overall study group.

**Limb Injuries**

The operated limb was injured in 16 of the 32 rats that survived to the completion of the protocol—4 in the Glue Group and 12 in the Suture Group. The injuries included autoamputations, pressure wounds, missing digits, and severe contractures. There was a significant correlation between the study group and the occurrence of injured limbs, with the animals in the Glue Group having significantly fewer injuries than those in the Suture Group (p < 0.005).

**Discussion**

Treatment of a transected nerve is primary anastomosis whenever possible. Approximation of the nerve endings and nontensile adaptation is the preferred treatment, either in the acute or in the chronic phase following the trauma.

The common anastomosing technique is microsurgical suturing, which requires technical skills that are not widely available. Other anastomotic techniques have been tried, including gluing the nerve endings with biological (fibrin) or cyanoacrylate glue and direct laser soldering, but each method has its drawbacks. For example, fibrin glue is weak and will not hold the nerve endings satisfactorily. Additionally, there is a possible risk of virus transmission if the biological glue is of human origin, and fibrin glue may induce local inflammation and granuloma formation that may hinder axon regeneration. Previous reports that compared fibrin glue with sutures noted that the tensile strength of the anastomosis achieved with glue is weaker than that achieved with sutures, and that motor evoked potentials and histological evaluation of axons (including fibrosis and fascicle alignment) showed slightly better results in the sutured nerves. Conflicting results have also been reported in the literature. Cyanocrylate causes a foreign body inflammatory reaction and retractile fibrosis, thus severely reducing the nerve diameter. Histoacryl has been shown to decrease the action potential amplitude compared with fibrin glue, although other reports have stated that cyanoacrylate and sutures have similar nerve regeneration capabilities. Additionally, prior studies have shown toxic effects of cyanoacylate-based glues on the brain in animal models. We did not find any literature regarding the safety of these glues on the peripheral nervous system. The results of the current study show comparable results in the Glue and Suture groups; thus, even in the presence of toxic effects of the glue, there is probably no added damage to the nerves, and the regeneration potential remains similar between both groups. Direct laser soldering does not simplify the procedure since it necessitates a basic suture anastomosis.

The clinical advantage of an anastomosing technique is measured by the ease with which it is performed, the availability of the necessary equipment and qualified personnel for performing it, and whether it has a good functional outcome. These qualifications bestow theoretical advantages to gluing over microsurgical anastomosis of transected nerves.

| Table 1: Outcome variables with statistically significant intergroup differences* |
|-----------------|-----------------|-----------------|-----------------|
| Variable         | Glue            | Suture          |
| SSEP in msec     | 26.3 ± 15.08    | 12.67 ± 14.28   |
| degree of adhesions | 1.88 ± 0.89  | 1 ± 0           |
| prox area, large axons | 2.41 ± 1.42 | 1.39 ± 0.68    |
| prox area, large & med axons | 20.67 ± 11.51 | 11.36 ± 5.29   |
| prox area, small axons | 23.04 ± 11.77 | 12.69 ± 5.18   |
| anastomosis, large & med axons | 15.09 ± 6.76 | 9.73 ± 4.23    |
| anastomosis, small axons | 19.47 ± 7.3 | 13.88 ± 5.59   |
| distal area, large & med axons | 13.3 ± 6.51 | 9.03 ± 4.7     |
| distal area, small axons | 22.91 ± 6.73 | 17.75 ± 4.7    |

* Values represent means ± SDs. The degree of adhesions was classified as mild, moderate, or severe, represented numerically as 1, 2, and 3, respectively. The values for axons represent the number of axons in the given size range identified within a specified area, as described in Methods. Abbreviations: med = medium; prox = proximal.
According to our results, gluing the nerve endings to each other achieves a stable anastomosis, with significantly more axons along the glued nerves than along the sutured nerves. Despite the association of this technique with local adhesions, the only functional outcome variable for which we found a significant difference between the 2 surgical techniques was SSEP. Moreover, the rats in the Glue Group had significantly fewer automutilation injuries to their operated limbs.

Adding low-power laser radiation to the anastomotic region and corresponding spinal segment has been shown to increase axon counts in the distal end, supposedly improving functional outcome.\textsuperscript{6,10,18,19} This method has been studied in sutured anastomoses, and studies incorporating low-power laser radiation are warranted to quantify its value in combination with the gluing technique.

We found no consistent correlation between the variables in the following 4 comparisons: 1) the absolute axon count at the anastomosis and distal sites versus the percentage value relative to the proximal site (for the same axonal size); 2) absolute counts and percentage values at various sites for the same axon sizes; 3) the axon count versus other variables (IT value, SSEP, FSI, and adhesions); and 4) between the non–axon count variables (IT value, SSEPs, FSI, and adhesions). We did, however, find some significant correlations between specific variables in certain groups. The clinical implication is that there was no ideal single outcome variable that could measure the nerve regeneration. Histological measures, such as axon counts, have been used frequently, but they seem to be poorly correlated with the clinical outcome. This failure to elicit a definitive yardstick for the regeneration of peripheral nerves questions the reliability of the currently employed variables as adequate outcome measurements.

\textit{Incapacitance Test}

This test has not been studied as an outcome measure for neural regeneration but is rather used to evaluate pain control in pain models.\textsuperscript{21} It seems reasonable to consider that a good functional recovery will enable the rat to regain normal motor behavior and use of the operated limb. We did not find any correlation between the IT value and any other outcome variable, nor did the IT value differ significantly between the 2 study groups. Some of the limitations of the IT are that contractions in the operated limb with resulting asymmetrical posture of the rat yield low values even if the nerve has theoretically regained full electrical conduction function.

\textit{Functional Sciatic Index}

The FSI has been used to evaluate the actual motor function of the nerve by comparing the paw print of the operated side with that of the healthy side. We noted that there were major technical limitations of this test due to contractions in the operated side. Even if the nerve regenerates well, we suggest that the presence of contractions precludes a meaningful FSI. A review of the literature revealed that the FSI has been used for crush models and that it was performed within 32 days of the injury.\textsuperscript{4,8,15,24} Studies of FSI in transected and repaired nerves reportedly yielded significantly lower values.\textsuperscript{4,8} Other limitations of the FSI are as follows: difficulty in interpretation in hesitant rats, a falsely widened imprint of the healthy side due to unnatural excessive weight load on the nonoperated side, and missing digits and heel ulcerations on the operated side.\textsuperscript{23} According to the findings of the current study, there were no significant FSI differences between the Suture and Glue groups. This is in accordance with the findings of Menovsky et al.,\textsuperscript{11} who compared the FSI of transected nerves anastomosed by suture, fibrin glue, and local laser soldering. A similar nonsignificant difference was reported by Martins et al.,\textsuperscript{13} who compared the FSI following suture- and fibrin glue–based anastomoses.

\textit{Somatosensory Evoked Potentials}

Electrophysiological studies of repaired nerves include nerve conduction time studies, motor evoked potentials, and SSEPs. Martins and colleagues\textsuperscript{11,12} compared the nerve action potential and motor action potential between 3 anastomotic groups: suture, fibrin glue, and combined. They found no significant between-groups difference in the nerve action potential and a better motor action potential result in the fibrin group. We chose to perform an SSEP test because it is technically easier and because it requires measurement of the differential latency between the operated and healthy legs. Previous studies have used SSEP testing to demonstrate the advantage of adding local laser radiation to the anastomotic region and the corresponding spinal cord segment.\textsuperscript{19} An earlier study by Włodarczyk\textsuperscript{26} showed that Histoacryl (TissueSeal, LLC) abolished electrical activity across the gap when directly injected into it. In the current study, we elicited SSEP responses in all the glued nerves, and our results showed that the SSEPs were significantly longer (about twice as long) in the Glue Group compared with the Suture Group.

We did not find any constant correlation between the SSEP values and other variables. Varejão et al.\textsuperscript{22} noted that electrophysiological studies do not necessarily correlate with the motor and sensory functions in a regenerating nerve. It is not clear whether the reason lies in limitations of electrophysiological studies or the other outcome variables that were tested.

\textit{Histomorphological Outcome}

Axon counts are used to evaluate nerve regeneration, but sprouting axons do not necessarily yield effective motor functions, thus limiting the usefulness of this parameter as being indicative of a functional outcome.\textsuperscript{22} We found a significant positive effect of using glue compared with sutures on the quantitative measures of large and medium axons (combined) and small axons in all 3 levels (proximal, anastomosis, and distal). The effect on the proximal count is not fully understood. It may be that a better “conduit” through the anastomosis results in less wallerian degeneration.

We evaluated the quantity of adhesions between the nerve and the surrounding tissue. The Glue Group had significantly more adhesions than the Suture Group. This may be secondary to an inflammatory and granulation response to the glue.\textsuperscript{23} Adhesions may further injure the nerve as adjacent muscles contract and pull on the adher-
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Ent nerve. Choi et al.² performed a histological comparison of cyanoacrylate glue and suture anastomoses and their results showed no significant differences between the 2 methods in the quantity of adhesions.

Study Limitations

This paper has several limitations. The small study population (20 rats in each subgroup) limits the power of the results. The high rate (50%) of limb injuries secondary to autoamputations, missing toes, pressure wounds, and contractions, precluded adequate measurement of outcome in some of the rats, thus limiting the statistical power of the study. Previous studies have described limb injuries secondary to nerve injury and stated that the etiology of self-mutilation limb injury is most probably related to sensory loss in the affected limb. In the current study, we were unable to differentiate whether the difference in limb injuries between the study groups was due to any difference in neural recovery between the groups. We speculated that the limb injuries occurred before neural recovery had time to take place.

Conclusions

We compared the 2 anastomotic techniques of microsurgical and cyanoacrylate glue and found significant advantages for the gluing technique as measured by the histological outcome, despite significantly more local adhesions and prolonged SSEP lag time. Other functional outcomes were similar for both techniques. Despite the limitations of this study, we suggest that cyanoacrylate-based glue may be useful for nerve anastomosis. Given the important clinical application of this finding, we stress the need for a larger study comparing the suture and glue techniques.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Roth, Rochkind. Acquisition of data: Roth, Shitokman, Shamir. Analysis and interpretation of data: Roth, Shitokman, Rochkind. Drafting the article: Roth, Shamir, Rochkind. Critically revising the article: Roth. Reviewed final version of the manuscript and approved it for submission: all authors. Administrative/technical/material support: Roth, Shitokman, Shamir, Nissan, Shchetinkov, Leonor. Study supervision: Roth, Rochkind.

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