

Effectiveness of Fibrin Adhesive in Facial Nerve Anastomosis in Dogs Compared With Standard Microsuturing Technique

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Purpose: Epineural suturing is the most common technique used for peripheral nerve anastomosis. In addition to the foreign body reaction to the suture material, the surgical duration and difficulty of suturing in confined anatomic locations are major problems. We evaluated the effectiveness of fibrin glue as an acceptable alternative for nerve anastomosis in dogs.

Methods: Eight adult female dogs weighing 18 to 24 kg were used in the present study. The facial nerve was transected bilaterally. On the right side, the facial nerve was subjected to epineural suturing; and on the left side, the nerve was anastomosed using fibrin adhesive. After 16 weeks, the nerve conduction velocity and proportion of the nerve fibers that crossed the anastomosis site were evaluated and compared for the epineural suture (right side) and fibrin glue (left side). The data were analyzed using the paired *t* test and univariate analysis of variance.

Results: The mean postoperative nerve conduction velocity was 29.87 ± 7.65 m/s and 26.75 ± 3.97 m/s on the right and left side, respectively. No statistically significant difference was found in the postoperative nerve conduction velocity between the 2 techniques ($P = .444$). The proportion of nerve fibers that crossed the anastomotic site was $71.25\% \pm 7.59\%$ and $72.25\% \pm 8.31\%$ on the right and left side, respectively. The histologic evaluation showed no statistically significant difference in the proportion of the nerve fibers that crossed the anastomotic site between the 2 techniques ($P = .598$).

Conclusions: The results suggest that the efficacies of epineural suturing and fibrin gluing in peripheral nerve anastomosis are similar.

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J Oral Maxillofac Surg 70:2427-2432, 2012

Injury to the peripheral nerves in the head and neck, including the inferior alveolar, lingual, and facial nerves, is not uncommon and can occur from maxillofacial trauma and iatrogenic causes during the practice of dentistry and medicine. The iatrogenic causes include maxillary and mandibular orthognathic surgery, esthetic surgery, dentoalveolar surgery, and injection of local anesthesia. These nerve disturbances often undergo spontaneous recovery; however, some can be permanent and re-

quire surgical intervention.¹⁻⁴ Several techniques have been described in published reports for peripheral nerve repair, including suturing, gluing,^{5,6} grafting,⁷ and laser welding.⁸ At present, epineural suturing is the most commonly used method for peripheral nerve anastomosis. However, this technique is not the ideal method and has many disadvantages. These disadvantages include foreign body reactions to the suture material,⁹⁻¹¹ excessive handling and manipulation of the nerve ends, conse-

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0278-2391/12/7010-0\$36.00/0

doi:10.1016/j.joms.2011.11.007

quent trauma from needle penetration through nerve tissue, and difficulty suturing in confined anatomic locations.

The possibility of performing nerve anastomosis without the use of sutures and with accurate approximation of the nerve ends would be ideal because this would limit fibrosis and inflammation, which could interfere with axon sprouting.

Recently, attention has been paid to replacing the suture neuroanastomosis techniques with adhesives, including fibrin and cyanoacrylate glues, to overcome the accompanying difficulties.^{1,12}

Cyanoacrylate, when used as a tissue adhesive, has been shown to induce a stronger tissue reaction than nonresorbable sutures, resulting in a more pronounced foreign body inflammatory reaction. Others have also found it to cause tissue necrosis *in vivo*.^{13,14}

Fibrin adhesive, unlike cyanoacrylate and nylon suturing, causes no foreign body reaction or scarring, because it is a physiologic component found in tissue repair.¹⁵⁻¹⁸ It is easily applied, involves less tissue handling and consequent trauma to the nerve ends, and facilitates the reanastomosis of the nerve stumps.

The purpose of the present study was to assess the effectiveness of using fibrin adhesive in facial nerve anastomosis compared with the microsuturing technique. We hypothesized that fibrin glue and epineural sutures will have similar effectiveness in peripheral nerve repair. The specific aims of the present study were to compare the nerve conduction velocity (NCV) and proportion of the nerve fibers that crossed the anastomotic site of epineural suture and fibrin glue.

Materials and Methods

STUDY DESIGN

Eight adult female dogs weighing 18 to 24 kg were used in the present prospective animal study. The study was approved by the Torabinejad research center animal care and use committee. All surgical procedures were performed by the same surgeon. General anesthesia was achieved with intramuscular injection of 50 mg/kg ketamine and 5 mg/kg acepromazine maleate.

SURGICAL TECHNIQUE

Fur was shaved from both periauricular areas of each dog. After preparing and draping, a 2-cm incision was made directly over the zygomatic arch. After tissue dissection, the frontal branch of the facial nerve was identified, isolated, and transected. Before nerve transection, the NCV was determined using PowerLab (ADInstruments, Sydney, Australia). On the right side, the nerve was anastomosed with 3 epineural micro-

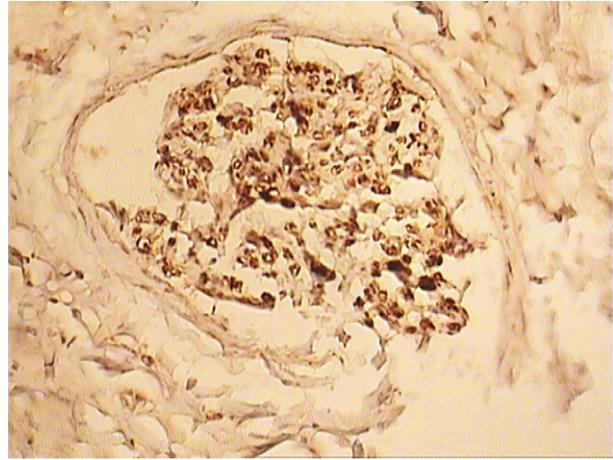


FIGURE 1. Photomicrograph showing cross-section of distal segment of facial nerve in suture group (hematoxylin and eosin stain, original magnification $\times 400$).

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sutures using 8-0 nylon suture. On the left side, fibrin glue (Tisseel, Baxter AG, Vienna, Austria) was used for nerve anastomosis. When applying the fibrin glue, the edges of the nerve stumps were manually approximated using forceps, and drops of glue were then applied over the apposed nerve edges using a double-syringe system (DUPLOJECT System, Baxter International, Deerfield, IL). The nerve ends were then held for 60 seconds to allow complete setting at body temperature. Before closing the skin incision, a mark was made close to the anastomosis site using 4-0 silk suture to facilitate its identification in the second surgery. All skin incisions were closed using 3-0 nylon suture. The skin sutures were removed after 2 weeks.

ELECTROPHYSIOLOGIC AND HISTOLOGIC EVALUATIONS

After 16 weeks, the previous operative site was re-entered. After identification of the anastomosis site, the NCV was determined on both sides using the following formula: $NCV = \text{distance between stimulation sites} / \text{difference between latencies}$, where the distance between the stimulation sites was taken as the distance between the stimulating electrode and the recording electrode in meters, and the difference in latencies was taken as the time from stimulus to peak response in seconds. A 6-mm nerve specimen (3 mm proximal and 3 mm distal to the anastomosis site) was harvested from each nerve. Next, the nerve stumps were reanastomosed using 8-0 nylon suture. The specimens were fixed in 10% formalin solution and stained with hematoxylin and eosin. Two 6- μm -thick cross-section preparations were made from each specimen (1 from the proximal and 1 from the distal segments of the anastomosis site). Histologic

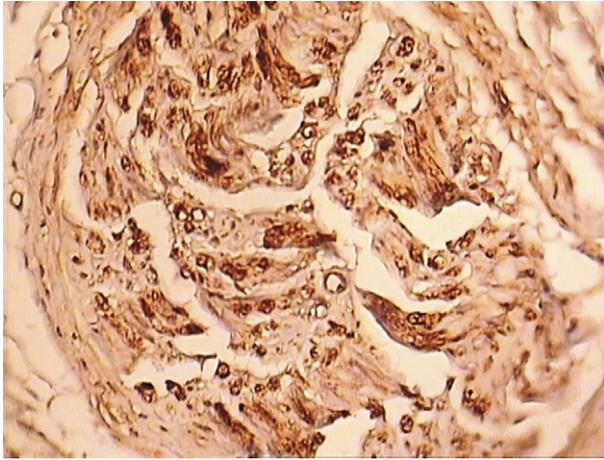


FIGURE 2. Photomicrograph showing cross-section of distal segment of facial nerve in fibrin glue group (hematoxylin and eosin stain, original magnification $\times 400$).

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evaluation was done using light microscopy at a magnification of $\times 400$. The number of the nerve fibers in the proximal and distal segments of each specimen was counted by a histologist who was unaware of the surgical techniques (Figs 1 and 2). Next, the proportion of the nerve fibers that crossed from the proximal to the distal part of the anastomosed nerve (PNF) was calculated: $\text{PNF} = \text{number of nerve fibers in distal segment} / \text{number of nerve fibers in proximal segment} \times 100$.

STATISTICAL ANALYSIS

Two variables were analyzed in the present study: an electrophysiologic continuous variable (NCV) and a histologic discontinuous variable (proportion of the nerve fibers that crossed the anastomotic site). The postoperative NCV on both sides was analyzed using univariate analysis of variance, and the paired *t* test was used to analyze the PNF on the right and left sides.

Table 1. CONDUCTION VELOCITY OF FACIAL NERVE IN EPINEURAL SUTURE VERSUS FIBRIN GLUE TECHNIQUES

Variable	Conduction Velocity (m/s)		P Value*
	Epineural Suture	Fibrin Glue	
Preoperative	51.02 \pm 8.33	48.53 \pm 7.16	.316
Postoperative	29.87 \pm 7.65	26.75 \pm 3.97	.444
P Value [†]	< .001	< .001	—

*Univariate analysis of variance.

[†]Paired *t* test.

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Table 2. NERVE FIBER COUNT AND PROPORTION OF NERVE FIBERS THAT CROSSED ANASTOMOSIS SITE OF FACIAL NERVE IN EPINEURAL SUTURE AND FIBRIN GLUE TECHNIQUES

Variable	Epineural Suture	Fibrin Glue	P Value*
NFC in proximal segment	138.75 \pm 34.34	143.25 \pm 27.15	.327
NFC in distal segment	98.37 \pm 23.56	103.12 \pm 21.01	.265
PNF (%)	71.25 \pm 7.59	72.25 \pm 8.31	.598

Abbreviations: NFC, nerve fiber count; PNF, proximal to distal part of anastomosed nerve.

*Paired *t* test.

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Results

ELECTROPHYSIOLOGIC TESTING

The mean preoperative NCV was 51.02 \pm 8.33 m/s and 48.53 \pm 7.16 m/s on the right (epineural suturing) and left (fibrin glue) sides, respectively. The postoperative NCV was 29.87 \pm 7.65 m/s and 26.75 \pm 3.97 m/s on the right and left sides, respectively (Table 1). Comparison using the paired *t* test revealed a statistically significant decrease in the mean NCV between the preoperative and postoperative measurements for both epineural suturing ($P < .001$) and fibrin gluing ($P < .001$). The difference in the postoperative NCV between the right and left sides was analyzed using univariate analysis of variance. No statistically significant difference was found between the postoperative NCV on the right and left sides ($P = .444$).

HISTOLOGIC EVALUATION

The mean number of nerve fibers of the proximal segment was 138.75 \pm 34.34 and 143.25 \pm 27.15 on the right and left sides, respectively. The mean number of nerve fibers in the distal segment was 98.37 \pm 23.56 and 103.12 \pm 21.01 on the right and left sides, respectively. The PNF was 71.25% \pm 7.59% and 72.25% \pm 8.31% on the right and left sides, respectively (Table 2). Using the paired *t* test, no statistically significant difference was found between the PNF on both sides ($P = .598$).

Discussion

The purpose of the present study was to assess the effectiveness of using fibrin adhesive in facial nerve anastomosis compared with the microsutures technique. We hypothesized that fibrin glue and epineural suturing have similar effectiveness in peripheral nerve

repair. The specific aims of the present study were to compare the NCV and PNF of epineural suturing and fibrin glue. In the present study, fibrin glue (Tisseel) was used as an alternative to epineural suturing for the anastomosis of the facial nerve in dogs. The results showed that fibrin glue can be a good alternative to epineural suturing in nerve anastomosis. After 16 weeks of anastomosis, the NCV and PNF were similar between the 2 sides undergoing epineural suturing and fibrin gluing.

Anastomosis with epineural suturing is the reference standard for the repair of an injured nerve¹⁹; however, this technique further traumatizes the nerve fibers,²⁰ takes a considerably long time,²¹ can cause foreign body reactions,⁹⁻¹¹ and can be difficult to perform when surgical access is limited. It can also result in the formation of suture granulomas, which obstruct myelin regeneration and axon sprouting.²²

The idea of using tissue adhesives for nerve anastomosis seems attractive owing to the theoretical advantages of less tissue handling, and consequent trauma, and the ease of performance in confined anatomic locations.

Fibrin was first noted to have a hemostatic effect on wounds by Bergel²³ in 1909 and was subsequently used by Grey,²⁴ who applied fibrinogen to a cerebral hemorrhage. In 1940, Young and Medawar²⁵ used fibrin as a glue in microsurgery for peripheral nerve repair. In 1944, Tidrick and Warner²⁶ reported the first use of fibrin glue to secure human skin grafts. However, their products had suboptimal adhesive properties owing to the absence of fractionation technologies capable of providing concentrated fibrinogen. In the 1960s, Cohn fractionation led to the ability to generate highly concentrated fibrinogen preparations.²⁷ In 1972, Matras et al²⁸ introduced commercially available fibrin glue with a high fibrinogen content. Since then, refinements have added to the strength, efficacy, and safety of fibrin glues.

Fibrin glue is now a popular tool in many aspects of modern day surgery.²⁹⁻³³ Fibrin adhesives are derived mainly from plasma components; most commercially available products contain purified, virally inactivated human fibrinogen and thrombin, with different quantities of factor XIII, bovine aprotinin, and calcium chloride. When fibrinogen and thrombin are mixed in the presence of calcium, fibrinogen is converted to fibrin. A fibrin polymer is formed that has a stable structure that facilitates the growth of collagen-producing fibroblasts.³⁴ Factor XIII is a fibrin-stabilizing factor, and aprotinin is an antiplasmin that protects the fibrin polymer clot from premature fibrinolysis.

Different investigators^{16,18,25,35-39} have analyzed new alternatives to peripheral nerve anastomosis for optimizing nerve regeneration. Among these, cyanoacrylate synthetic glue should be mentioned, because

it is easy to use, maintains the anastomosis even while under tension, and avoids all risk of viral transmission.⁴⁰⁻⁴² However, this adhesive has been criticized because of its toxicity, excessively slow resorption, and induction of an inflammatory reaction in perineural tissues.^{43,44} Therefore, it is not recommended for nerve anastomosis.⁴⁵ Laser welding was also used for nerve repair, and its efficacy was similar to that of epineural suturing in some studies,^{38,39} but inferior to it in others.⁴⁶ Laser welding can provide a seal around the epineurium without the potential of introducing a foreign material into the underlying fascicular structure. In contrast, the thermal effects of laser-assisted nerve repair can result in the destruction of myelin and the loss of axons immediately adjacent to the anastomosis site. Thus, although laser welding will not produce foreign body reactions, its tissue destruction could lead to fibrous tissue formation, which could be as detrimental to axonal growth as that induced by retained suture material. The results of our study are consistent with the results of several earlier studies.^{16,18,46-49} Júnior et al⁴⁸ reported that axonal growth after epineural suturing was significantly faster and greater than after anastomosis with fibrin adhesives; however, the NCV was similar for both techniques. In our study, the histologic evaluation showed good axonal regeneration across the anastomotic site with no difference in the outcome of nerve regeneration between epineural suturing and fibrin gluing. This was also confirmed by other investigators.^{18,22} Feldman et al¹⁸ reported that the amounts of anastomotic perineural fibrosis, axonal regeneration, and alignment of axons were superior with the fibrin adhesive technique compared with epineural suturing.

Some investigators have reported that fibrin glue does not have sufficient tensile strength to hold a peripheral nerve repair and might produce stricture at the anastomosis site.¹² However, we did not see any case of anastomotic failure at the end of the follow-up period (16 weeks), and the 2 techniques (suture and fibrin glue) were equally adequate to stabilize the reanastomosed nerves during regeneration. The commercially available fibrin adhesives are of human origin; thus, there might be a potential risk of viral transmission. This can be minimized by the use of donor selection, screening, and viral inactivation. Autologous fibrin adhesives provide an attractive option because of the absence of a viral transmission risk. However, this technique is time-consuming (the process requires about 60 to 90 minutes for preparation) and requires extensive equipment.

Most of the earlier studies of peripheral nerve repair were on small animals (rats, rabbits, and so forth). However, we chose to use dogs in our study because the nerve size and number of nerve fibers in

each nerve are more similar to those of humans. In the present study, the evaluation of nerve repair was done electrophysiologically and histologically. The follow-up period was 16 weeks, which is sufficient for nerve repair. The number of dogs included in the present study was not large enough for significant conclusions to be made.

From our results, we can conclude that epineural suturing and fibrin adhesives are equally alternative techniques in microsurgery repair of the transected nerves. Although financial considerations should be considered, fibrin glue could be advantageous to achieve nerve approximation in confined anatomic locations in which suture application is difficult or impossible for technical reasons.

Acknowledgment

The authors are thankful to Applied Physiology Research Center of Isfahan University of Medical Sciences, where the electrophysiologic testing was done.

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