The Use of End-to-Side Nerve Grafts to Reinnervate the Paralyzed Orbicularis Oculi Muscle

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Facial paralysis is a serious neurologic disorder, particularly when it affects the eye. Loss of the protective blink reflex may lead to corneal ulceration and, possibly, visual loss. The purpose of this study was to compare different nerve-grafting techniques to reanimate the paralyzed eyelid. Sixteen adult dogs (25 kg each) were allocated into four groups. Denervation of the left hemi-face was performed in all cases. One dog served as a control animal (group I). Group II dogs ($n = 5$) underwent end-to-side coaptation of the nerve graft to the intact palpebral branch and end-to-end coaptation to the denervated palpebral branch. Group III dogs ($n = 5$) underwent end-to-end coaptation of the nerve graft to the intact palpebral branch and end-to-end coaptation to the denervated palpebral branch. Group IV dogs ($n = 5$) underwent end-to-side coaptation of the nerve graft to the intact and denervated palpebral branches. The animals were monitored for 9 months after the surgical procedures, to allow adequate time for reinnervation. The dogs were postoperatively monitored with clinical observation, electrophysiologic testing, video motion analysis, and histologic assessments. Clinical observation and electrophysiologic testing demonstrated the production of an eye blink in the denervated hemi-face in all experimental groups. There was a trend toward increased speed of reinnervation for group III animals (end-to-end coaptations). It was concluded that end-to-side coaptation can produce a contralateral synchronous eye blink in a clinically relevant, large-animal model. (*Plast. Reconstr. Surg.* 111: 2255, 2003.)

Facial nerve injury produces profound changes in both the appearance and function of the face. It is difficult to estimate the total number of new facial palsies per year; however, the annual incidence of Bell palsy, which is the most common cause of facial nerve paralysis, has been estimated to be 20 to 25 cases per 100,000 population.[1] The causes of facial nerve paralysis vary widely, but common causes include trauma and neoplasia.[2]

The symptoms of facial nerve palsy can be divided into those that affect the upper face and those affecting the lower face. Patients with lower-face deficiencies typically experience facial asymmetry at rest and an inability to smile. In addition, these patients have difficulties with speech articulation, lip incompetence, drooling, and food bolus control while chewing.[3]

Patients with upper-face deficiencies exhibit symptoms that are mainly related to the eye. Loss of facial nerve function in the periocular area leads to three significant problems, namely ectropion, epiphora, and lagophthalmos. Of these three, lagophthalmos, with chronic corneal exposure, is the most serious, because this may lead to conjunctivitis, keratitis, and possible blindness.[3]

Many different methods have been used to prevent the complications of lagophthalmos, including the use of eye drops or ointments, eyelid taping, the use of moisture chambers, and even blinking forced by the patient's own

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finger.[4,5] The frequency with which these measures must be performed tends to foster low compliance. Other operative methods, including lateral or medial tarsorrhaphy, the use of silicone bands,[6] gold weights,[7–10] springs,[11,12] or magnets,[13] and muscle transposition,[14] have demonstrated varying degrees of success. However, none of these methods produces reflex physiologic blinking.

End-to-side neurorrhaphy was introduced by Kennedy in 1901,[15–17] and subsequent efforts were reported by Ballance et al.[18] and Harris and Low.[19] There is renewed interest in using this technique for nerve repair.[20–47] End-to-side nerve grafting has several potential advantages for the treatment of patients with facial nerve palsy. One advantage of this technique is that the function of the side ipsilateral to the facial nerve lesion would be controlled by its intact counterpart on the contralateral side. This approach should produce responses that are synchronous with those of the opposite (uninjured) side. Another advantage is the potential for graded responses (e.g., reflex blink versus forced blink), again controlled by the intact side. The subtleties of facial movement might thus be maintained. Finally, traditional techniques of cross-face nerve grafting have relied on end-to-end coaptation of the nerve graft to the intact contralateral facial nerve, usually with sacrifice of a buccal or zygomatic branch to minimize deformities on the intact side.[48] However, end-to-side coaptation should result in little or no functional deficit on the intact side.[47] The purpose of this study was to determine whether end-to side nerve grafting could reinnervate a paralyzed orbicularis oculi muscle in a clinically relevant, large-animal model.

Materials and Methods

Animal Model

Experiments were performed with 16 adult mongrel dogs, weighing approximately 25 kg. The study was performed in accordance with the guidelines of the Animal Care and Use Committee of the University of Louisville and with the *Guide for the Care and Use of Laboratory Animals* (National Research Council).

The dogs were kept in separate cages in rooms with temperature (24°C), light (12 hours/day), and air-flow regulation. They were provided with a balanced canine diet and water ad libitum. The animals were anesthetized for all surgical procedures with an intravenous injection of sodium pentobarbital (35 mg/kg) and were intubated with an endotracheal tube. During the surgical procedures, anesthesia was maintained with an isoflurane/oxygen/nitrous oxide mixture, delivered at a rate of 1 liter/minute per 5 kg. The face and head of each dog were shaved and then prepared and draped in a sterile manner. Sterile technique was used for all survival procedures. After completion of the experiments, the animals were killed with an overdose of Beuthanasia (Schering Animal Health, Kenilworth, N.J.).

To examine the effects of chronic facial paralysis on the orbicularis oculi muscle, we previously developed a canine unilateral facial paralysis model. In this model, a preauricular incision was made and branches of the facial nerve were identified distally and then traced back proximally. The facial nerve was divided just distal to the stylomastoid foramen, and a 2-cm segment of the facial nerve was resected. The distal end of the facial nerve was then turned in a cephalad direction under the skin flap and held in place. With this model, denervation of the hemi-face was complete for more than 9 months (N. N. Soma, G. S. Rash, M. J. Sundine, M. D. Gossman, and J. H. Barker, unpublished data).

Experimental Design and Surgical Procedures

The study involved three experimental groups of dogs and a control dog (Table I). All dogs underwent denervation on the left side of the face, as described above. The first dog served as a control and underwent only the denervation procedure, leaving an intact right hemi-face and a paralyzed left hemi-face (Fig. 1).

Each animal in group II ($n = 5$) underwent the denervation procedure. Then, through the preauricular incision, the facial nerve palpebral branch (which is the canine equivalent of the human zygomatic branch that innervates the orbicularis oculi muscle) was dissected free from the surrounding tissues and divided where it joined the main trunk of the facial

TABLE I
Experimental Groups

Group	No. of Animals	Right Coaptation	Midline Coaptation
I	1	None	None
II	5	End-to-side	End-to-end
III	5	End-to-end	End-to-end
IV	5	End-to-side	End-to-side

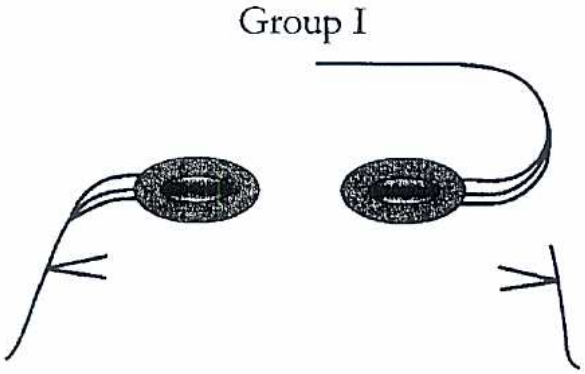

FIG. 1. Group I configuration.

nerve. A subcutaneous tunnel was then created between the lateral border of the orbicularis oculi muscle and the glabella. A small counter-incision was placed in the glabella. The proximal branch of the palpebral nerve was passed through the subcutaneous tunnel to the glabella. The right-side palpebral branch (intact facial nerve) was then identified. A superficial peroneal nerve graft was harvested from the right hind limb. Another subcutaneous tunnel was created between the palpebral branch on the intact side and the glabellar counter-incision. The nerve graft was carefully passed through this tunnel. A window was created in the epineurium of the intact palpebral branch, and an end-to-side coaptation was performed between the end of the sural nerve graft and the side of the palpebral branch. The epineurium of the nerve and that of the graft were approximated by using 10-0 nylon sutures. Appropriate care was taken to avoid injuring the nerve fascicles of the intact palpebral branch. In the midline wound, an end-to-end coaptation was performed between the nerve graft and the denervated palpebral branch. The wounds were then closed in layers (Fig. 2).

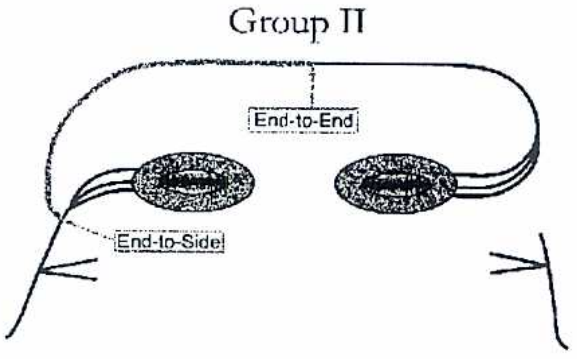

FIG. 2. Group II graft configuration.

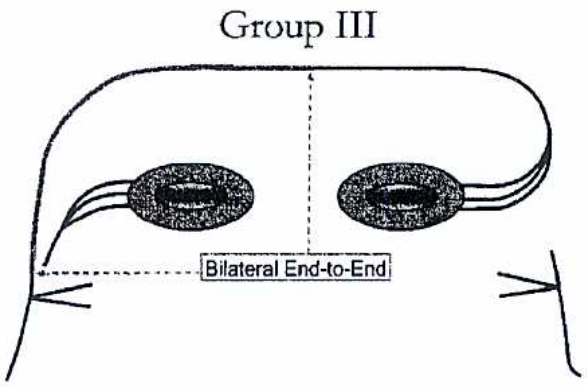

FIG. 3. Group III graft configuration.

Group III animals underwent the same procedures as did group II animals; however, the configuration of the nerve coaptations was different. In this group, an end-to-end coaptation was performed between the intact right palpebral branch and the nerve graft. An end-to-end coaptation was also performed between the nerve graft and the denervated left palpebral branch in the midline (Fig. 3).

Group IV animals also underwent the same procedures as for group II, but with a different configuration of the nerve coaptations. An end-to-side nerve coaptation was performed between the side of the intact (right) palpebral branch and the end of the nerve graft. A window in the epineurium was again created on the intact palpebral branch. The end of the denervated palpebral branch was ligated with a 4-0 silk suture and, in a similar manner as before, an end-to-side coaptation was performed between the end of the nerve graft and the side of the denervated palpebral branch (Fig. 4).

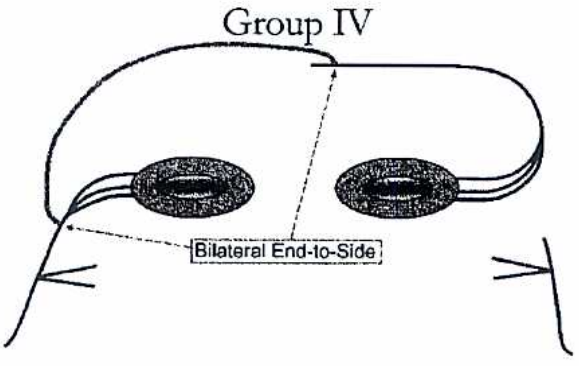

FIG. 4. Group IV graft configuration.

Video Motion Measurements

Video motion measurements were used to assess the eye blink of all animals. The measurements were performed preoperatively, immediately postoperatively, and at 3- to 4-month intervals, according to follow-up protocols. Group I was monitored for the full 9 months after surgical treatment. Group III, with end-to-end coaptations of the nerve graft to both the intact and denervated palpebral branches, was monitored for 7 months, because the eye blink had returned in all animals by that time. Groups II and IV were monitored for 9 months.

Before each motion measurement session, the dog was mildly sedated with xylazine and gently restrained with its head in contact with a standard veterinary table. Reflective markers (2.5 mm in diameter) were placed on the upper eyelids and forehead. The markers were attached with toupee tape by the same investigator, to minimize marker placement variation. Two markers were placed on each upper eyelid, one at the highest point (usually in the center and 1 mm above the lid margin) and the other at the lateral corner of the eyelid. A T-shaped reference bar with three 2.5-mm-diameter reflective markers was affixed to the forehead of the dog, between the nasion and the eyelids, to serve as a local coordinate system. Finally, one marker was placed on the veterinary table, as a fixed reference point. Eye blinks were stimulated by puffs of air to the eyes.

Eyelid movement was recorded with a camcorder (model PB330d; Panasonic, Secaucus, N.J.) that sampled at 30 frames/second. The camera was mounted on a tripod at approximately the same height as the dog's head, and the lens was adjusted so that the dog's head filled the viewing field. Video images were digitized with an Ariel Performance analysis system (Ariel Dynamics, Trabuco Canyon, Calif.), which split each frame into its two component fields and determined the image plane coordinates of each marker with respect to a camera-based coordinate system.

A local coordinate system was established by using coordinate data from the markers on the T-bar. The x axis of the local coordinate system originated at the leftmost marker and was directed toward the rightmost marker. The y axis was formed as a vector perpendicular to the x axis and in the same plane as the three points on the T-bar. All camera-based coordinates of the eyelid markers were rotated and translated into the local coordinate system before eyelid movements were calculated. Displacement of the central eyelid marker in the y axis direction was calculated, to represent vertical eyelid motion. For each dog, the peak left eyelid displacement/peak right eyelid displacement ratio was calculated for preoperative sessions and established as a baseline value.

$$\text{Displacement ratio}_{\text{preop}} = \frac{\text{peak displacement}_{\text{preop,left}}}{\text{peak displacement}_{\text{preop,right}}}$$

In the final session for dogs in groups II and IV, the final peak left eyelid displacement/final peak right eyelid displacement ratio was determined as

$$\text{Displacement ratio}_{\text{final,II\&IV}} = \frac{\text{peak displacement}_{\text{postop,left}}}{\text{peak displacement}_{\text{postop,right}}}.$$

For group III, the postoperative displacement ratio was determined as the final peak left eyelid displacement/preoperative peak right eyelid displacement ratio.

$$\text{Displacement ratio}_{\text{final,III}} = \frac{\text{peak displacement}_{\text{postop,left}}}{\text{peak displacement}_{\text{preop,right}}}$$

The final displacement ratio was then expressed as a percentage of the preoperative displacement ratio.

$$\text{Final displacement ratio} = \frac{\text{displacement ratio}_{\text{final}}}{\text{displacement ratio}_{\text{preop}}}$$

One dog in group IV was too sedated to undergo video motion analysis.

Electrophysiologic Testing

At the conclusion of the experiment, the dogs were anesthetized as described previously. The original surgical incisions were reopened, and careful dissections of the nerve trunks and branches were performed. The sites of previous nerve coaptations were also exposed. The nerve graft was stimulated (0.9-msec pulse du-

ration, 2 to 10 V) at 3-cm intervals along the course of the nerve, with an A310-b Accupulser stimulator (World Precision Instruments, New Haven, Conn.) with a platinum electrode. The nerve was stimulated starting at the right side (intact facial nerve) and progressing to the left side (denervated). A positive response was defined as the production of a left-side eye blink.

Histologic Analyses

After electrophysiologic testing, both orbicularis oculi muscles were dissected free en bloc, with the attached palpebral branches and the intervening nerve graft. Great care was taken not to disrupt the nerve coaptations. The nerve and both orbicularis oculi muscles were histologically and morphometrically analyzed.

The nerve specimen was cut every 3 cm and marked proximally and distally with different markers. The nerve samples were harvested consecutively from right to left. This generally resulted in six or seven nerve segments per animal and two muscle segments per animal. A section was obtained from each nerve coaptation site.

The tissue was immediately placed in 10% neutral buffered formaldehyde, for a maximum of 16 hours, and then embedded in paraffin. Sections (3 to 5 μm thick) of the nerve and muscle were obtained and stained with hematoxylin and eosin and Masson trichrome stain.

The nerves were graded in a blinded manner by a board-certified pathologist, using light microscopy. The nerves were assessed on a scale of 1 through 5, using the following criteria: grade 1, total absence of viable axons; grade 2, scattered small but viable axons occupying less than 10 percent of the diameter of the nerve; grade 3, clusters of small axons occupying up to 50 percent of the diameter; grade 4, clusters of slightly larger, clearly myelinated axons occupying up to 80 to 90 percent of the diameter; grade 5, normal appearance, with well-myelinated axons of almost normal diameter, and some clustering of axons may still be visible. Neuroma formation was often observed and was recorded but was not used to grade the extent of regeneration.

Data Analysis

The video motion analysis data (final displacement ratios) were analyzed with a permutation test, using one-way analysis of variance.[49]

RESULTS

All of the animals survived the surgical treatment and were available for evaluation. No dog experienced any untoward effects as a result of the facial denervation, and there were no problems with corneal ulceration as a result of the facial paralysis. There also did not seem to be any significant donor-site complications resulting from the nerve graft harvest.

There was a trend toward increased speed of reinnervation in group III (end-to-end coaptations at both sites). With clinical stimulation (a puff of air on the eyeball), all of the group III dogs had achieved a blink by 7 months, whereas the full 9-month period was necessary for maximal reinnervation for groups II and IV. The results of the electrophysiologic testing demonstrated that all animals in the experimental groups were able to achieve eye blinks on the denervated side with stimulation of the intact palpebral nerve branch.

The results of the video motion analysis are presented in Table II. Although the mean final displacement ratio was smallest for group III animals (end-to-end coaptation at the palpebral branch and end-to-end coaptation in the midline), the difference did not achieve statistical significance ($p = 0.1137$). This is likely attributable to the small sample size and the wide range of values observed within each group of animals.

Animals in groups II and IV demonstrated synchronous blinks, although there was variation in the completeness of eyelid closure (as measured by video motion analysis). Representative motion analysis curves are presented in Figures 5 and 6. Figure 5, *above*, and Figure 6, *above*, demonstrate the presence of an intact synchronous blink. Figure 5, *center*, and Figure 6, *center*, demonstrate loss of the blink (3 to 4 months postoperatively); Figure 5, *below*, and

TABLE II
Final Displacement Ratio (Left Eye Displacement/Right Eye Displacement × 100) Data

	Final Displacement Ratio			
Animal No.	Group I	Group II	Group III	Group IV
1	0.0	22.20*	5.17	70.60
2		81.70	20.05	31.42
3		8.70	19.40	
4		23.31	43.68	19.86
5		41.00	14.37	42.88*
Mean	0.0	35.38	20.53	41.19

* Animals represented by the displacement curves in Figures 5 and 6.

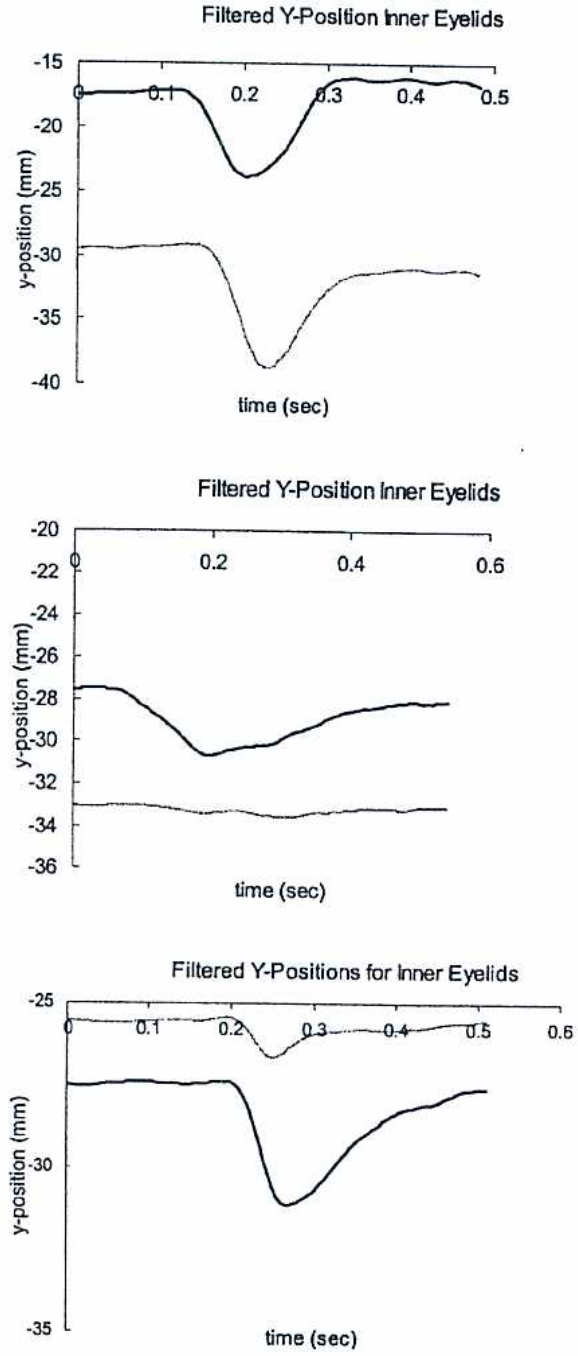

FIG. 5. Eyelid displacement curves for a dog in group II (end-to-side/end-to-end coaptation). (*Above*) Before surgical treatment. (*Center*) Three to 4 months after surgical treatment. (*Below*) Seven to 9 months after surgical treatment. *Black lines*, right inner eye; *gray lines*, left inner eye.

Figure 6, *below*, demonstrate restoration of the blink (7 to 9 months postoperatively), although the amplitude was less than on the intact side.

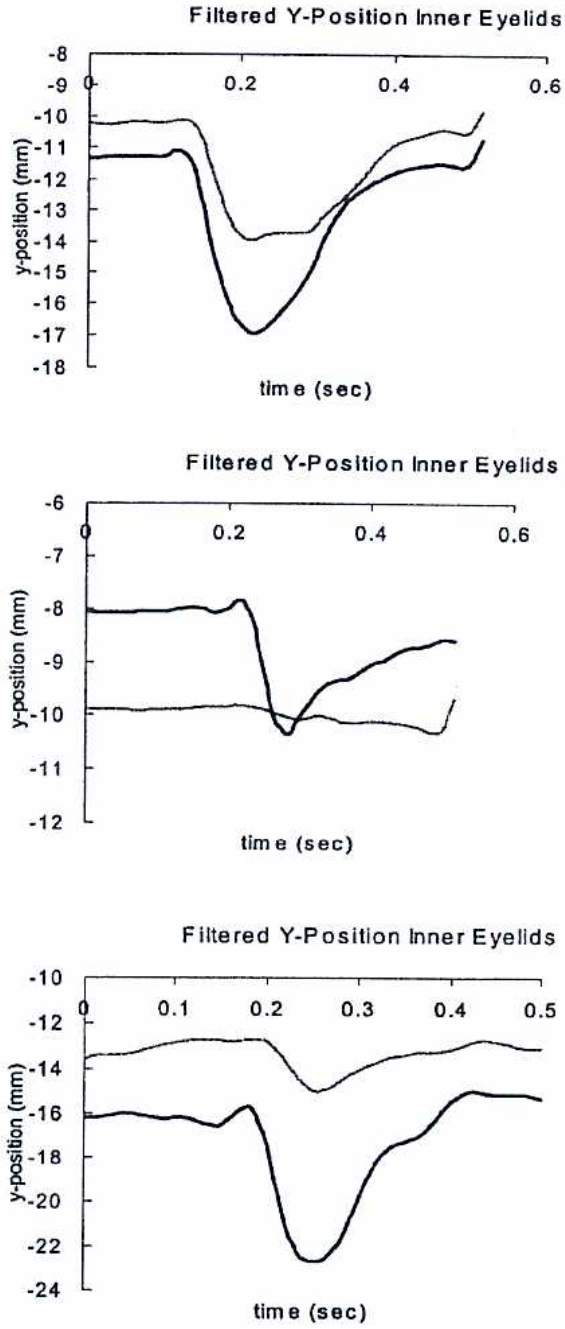

FIG. 6. Eyelid displacement curves for a dog in group IV (end-to-side/end-to-side coaptation). (*Above*) Before surgical treatment. (*Center*) Three to 4 months after surgical treatment. (*Below*) Seven to 9 months after surgical treatment. *Black lines*, right inner eye; *gray lines*, left inner eye.

The results of the nerve histologic assessments are presented in Figure 7. The quality of nerve regeneration was excellent at the proximal coaptation in all animals and deteriorated in the next 3 cm in all experimental groups.

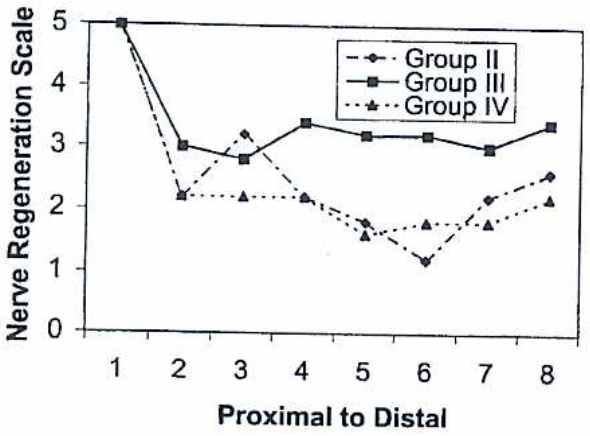

FIG. 7. Nerve regeneration as a function of distance from the proximal coaptation.

The regeneration and myelinization results were constant throughout the groups, with a decrease in the regeneration results after the initial coaptation.

DISCUSSION

The results of this animal study demonstrated that end-to-side neurorrhaphy can produce facial reanimation in a clinically relevant, large-animal model. Both group II and group IV animals (both with end-to-side neurorrhaphy at the proximal coaptation) were able to produce clinically observable eye blinks, with puffs of air as stimuli and with direct nerve stimulation. It was also noteworthy that affected-side eye blinks for both end-to-side coaptation groups (groups II and IV) were synchronous with blinks on the opposite side, with intact facial nerves.

A dog model represented a more clinically relevant model for future human nerve grafting than would a lower-species rat model. Regenerative capacity generally differs between "higher" and "lower" species (with lower species tending to have greater capacity for regeneration). Therefore, the results obtained with a more developed species are more likely to mimic human results. Increased difficulty of producing dense facial paralysis in lower animals also contributed to the choice of a dog model.[50]

The investigational protocol was intended to mitigate confounding effects associated with the use of mixed motor and sensory nerves, as in previous studies. Such studies used combinations of grafting between tibial and peroneal nerves[23–25,30,32,34–36,38,41–44,46,47]; musculocutaneous and median nerves[27]; median and ulnar nerves[31]; sciatic and obturator nerves[33]; sciatic nerves[40]; and median, ulnar, and radial nerves.[45] In these mixed-nerve models, the sprouting sensory axons might compete with sprouting motor axons for channels in the nerve graft, reducing the number of motor axons that reach the target muscle. By using a "pure" motor nerve, our protocol sought to maximize the number of axon sprouts that would reach the contralateral orbicularis oculi muscle.

To date, no experimental animal studies have involved the facial nerve and end-to-side nerve grafting. One published report involved five clinical cases with end-to-side nerve grafts.[21] The experimental model used seems to be good for the examination of facial paralysis and reinnervation. The model uses an agonist muscle (orbicularis oculi) that is innervated separately from its antagonist (levator palpebrae). The endpoint of reinnervation is the production of an eye blink. The two end-to-side graft configurations used were chosen because they would have direct clinical application among human subjects. The ideal situation would involve direct cross-face nerve grafts from an intact facial nerve to the corresponding nerve branches in the paralyzed hemi-face, without loss of function in the donor nerve.

Our results seem to indicate a quicker return to function for the group with end-to-end proximal coaptation (group III), compared with the groups with end-to-side proximal coaptation. Although the time to return of function was not specifically addressed as an endpoint in the study, the animals in group III had developed a blink in response to stimulation by 7 months after the reanimation procedure. At the end of the full 9-month postoperative period, we were able to demonstrate function in the end-to-side coaptation groups.

We chose to compare the ratio of the left eyelid displacement (paralyzed side) to the right eyelid displacement. In human studies, we found video motion tracking to be reliable and repeatable for evaluation of eyelid kinematic features.[51] However, application in this animal model was complicated by the need for sedation and head restraint for the video motion measurements. Because the magnitudes of eyelid motion could be variable among test sessions, displacement ratios, rather than absolute magnitudes, were considered. In future

studies, perhaps video calculations of the area of cornea exposed at maximal eye blink, relative to the open resting position of the eyelid in nonsedated animals, would allow more meaningful assessment of the results of the reinnervation procedure.

Comparison of the final displacement ratios is of value especially for groups II and IV, because the facial nerve on the right side remained intact in those groups. There were some difficulties in assessing the final displacement ratios for group III, in which the animals underwent partial denervation of the right orbicularis oculi muscle when the palpebral nerve branch was killed as a donor nerve for the contralateral side. There was no significant difference in the final displacement ratios among the three groups.

We chose to create an epineurial window on the donor facial nerve to optimize the potential for axonal sprouting. The evidence for removal of an epineurial window is conflicting; there is evidence that removal of the window improves nerve regeneration,[31,34,39,40] whereas others did not demonstrate improved results with an epineurial window.[35] Noah et al.[34] actually observed the perineurium to be a significant barrier to end-to-side neurorrhaphy. We did not assess the effect of leaving the epineurium intact in our experiment.

One of the primary goals of our experiment was to prove that there was no significant loss of function in the donor facial nerve. The eyelid displacement curves demonstrated preservation of motion in the right upper eyelid after end-to-side coaptation of the nerves (Figs. 5 and 6). These data are consistent with those of Cederna et al.,[47] who observed that end-to-side neurorrhaphy did not affect the function of the muscles innervated by the donor nerve. We were able only to prove maintenance of motion and not to otherwise quantify the motion.

There are several potential problems with our initial study. Most of these difficulties are related to objective measurement of the endpoints of the study. Quantification of facial reanimation remains problematic. For this reason, we used video motion analysis, which we previously observed to be reliable and repeatable. Our video motion data for different measurement sessions were inconsistent, however, and we were not able to use raw displacement data for analysis of function. We did not use electromyographic data for the orbicularis oculi, as performed in several previous studies.[25,27,29,32,41,42,44,46,47] To our knowledge, there are no such data for the canine orbicularis oculi muscle. We did not use muscle weight as an indicator of muscle health and nerve regeneration, because the canine orbicularis oculi muscle appears as a series of circular cables with varying amounts of connective tissue between the cables, especially at the periphery of the muscle. Inclusion of varying amounts of connective tissue during muscle harvesting could significantly affect the muscle weights. We did not perform axon counting because of the large size of the nerve grafts. We thought that this would introduce a greater degree of difficulty into the experiment and not significantly improve the evaluation of the histologic results. Also, we thought that the most important endpoint of the study was function in the paralyzed orbicularis oculi muscle and that the histologic results provided confirmatory evidence of reinnervation.

In summary, we have observed that end-to-side neurorrhaphy can produce a contralateral synchronous blink in a clinically relevant, large-animal model. Our future efforts will address improvement of the quality of nerve regeneration, preservation of muscle health while reinnervation is occurring, and refinement of the measurements of facial reanimation

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