Facial Nerve Neurorrhaphy and the Effects of Glucocorticoids in a Rat Model

Rahul Seth, MD¹, Peter C. Revenaugh, MD¹, James A. Kaltenbach, PhD¹,², Karthik Rajasekaran, MD¹, Noah E. Meltzer, MD¹, Debabrata Ghosh, MD³, and Daniel S. Alam, MD¹

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. After nerve injury, an exaggerated neuroinflammatory process may hinder neuron regeneration and recovery. Immunomodulation using glucocorticoids may therefore improve facial nerve injury outcomes. This study aims to examine the effect of both local and systemic dexamethasone administration on facial nerve functional recovery after axotomy in a rat model.

Study Design. Randomized, placebo-controlled, blinded animal study.

Setting. Animal laboratory.

Subjects and Methods. Seventy-four Wistar rats underwent facial nerve axotomy with immediate neurorrhaphy. Rats were randomly assigned a postoperative group: control (no therapy); systemic dexamethasone 0.5, 1, 5, or 10 mg/kg for 3 administrations; or topically applied dexamethasone at 2 or 4 mg/mL. Blinded, standardized facial assessments and nerve conduction studies (NCS) were performed. Gross facial motion assessments were corroborated with vibrissae frequency video analysis.

Results. At 8 weeks, rats receiving systemic dexamethasone at 5 mg/kg attained greater eye blink closure (P = .004) and vibrissae motion (P = .012) compared with controls. Systemic dexamethasone at 0.5, 1, and 10 mg/kg and intraoperative topical application of dexamethasone at 2 or 4 mg/mL did not produce a significant improvement in facial motion compared with controls. Nerve conduction studies show a trend of increased return of compound muscle action potential amplitude levels compared with baseline among rats that received systemic dexamethasone 5 mg/kg but do not achieve statistical significance.

Conclusion. In a rat facial nerve axotomy model, high-dose systemic dexamethasone therapy may improve functional recovery when administered in the immediate period following neurorrhaphy.

Keywords

facial nerve neurorrhaphy, facial nerve recovery, facial nerve anastomosis, nerve coaptation, nerve regeneration, steroid, dexamethasone

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Facial nerve injury often leads to a significant loss of function of the ipsilateral face and can occur by trauma or tumor infiltration, or it can be done intentionally to obtain margin control in ablative surgical procedures. Deliberate sectioning followed by coaptation (neurorrhaphy) of the facial nerve is performed for certain oncologic indications, during free tissue transfer for reconstruction, and even as most recently described in allograft facial transplantation.¹ Despite meticulous surgical techniques to repair a severed nerve, coaptation can have unpredictable and frequently suboptimal outcomes. Therefore, because of the significant morbidity associated with facial nerve injury and the current inability to significantly improve outcomes after injury, investigations to augment facial nerve recovery are paramount.

After the facial nerve is severed, a complex biological repair process of regeneration occurs within the neuron cell body and axon. Several phases of recovery have been described: (1) an initial acute stress inflammatory response, (2) an upregulation of reparative and inflammatory protein expression, (3) Wallerian degeneration of the distal nerve

¹Head and Neck Institute, Cleveland Clinic, Cleveland, Ohio, USA
²Department of Neurosciences, Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA
³Neurological Institute, Cleveland Clinic, Cleveland, Ohio, USA

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Corresponding Author:
Daniel S. Alam, MD, Assistant Professor, Section Head, Facial Aesthetic and Reconstructive Surgery, Head and Neck Institute, Cleveland Clinic, 9500 Euclid Ave, Desk A71, Cleveland, OH 44195, USA
Email: alamd@ccf.org
segment, (4) axonal regrowth with sprouting of axons from the proximal nerve segment, and (5) adjunction of the neoaxons with the distal end of the nerve lesion sites. During these processes, numerous molecular and cellular events occur in neuron axons and cell bodies. These processes collectively aim to clear debris and by-products of cellular death caused by injury in an effort to regenerate nerve fibers.

One of the primary driving factors of this process appears to be neuroinflammation. However, an excessive neuroinflammatory response to nonviable nerve fibers may in fact lead to a loss of adjacent viable nerve fibers, neurons, and their supporting architecture. Ultimately, this complex process produces an overall variable and usually limited return of nerve function.

Glucocorticoids have been used to reduce perineural inflammation for many disease processes, particularly in the central nervous system. Attenuation of the acute neuroinflammatory response with glucocorticoids may prevent excessive motor neuron death and promote improved recovery after injury. In a similar disease model of facial nerve injury, steroids have been advocated to improve facial nerve recovery in Bell’s palsy.

Transferring this concept, the present study aims to examine both local and systemic glucocorticoid administration on facial nerve regeneration and functional return after complete axotomy (severing) with immediate microsurgical repair in a well-established rat facial nerve model. To date, no studies have accurately described the functional effects of short-term glucocorticoid administration after facial nerve axotomy and coaptation—a condition that a head and neck surgeon may encounter.

**Methods**

**Animals**

Male Wistar rats (~225 g) obtained from Harlan (Indianapolis, Indiana) were used in all experiments. Animals were exposed to a 12-hour light/dark cycle and were fed standard rodent diet and water ad libitum. All animal procedures were approved by the Institutional Animal Care and Use Committee.

A total of 74 animals were studied (Figure 1). Sixty animals were initially randomly assigned to 1 of 5 treatment groups: control (no local or systemic steroid therapy), systemic dexamethasone (1 mg/kg or 5 mg/kg), and local dexamethasone (2 mg/mL or 4 mg/mL [stock solution]). Based on preliminary results, 2 additional groups of systemic dexamethasone (0.5 mg/kg and 10 mg/kg) were studied with 7 animals per group. Randomization was performed by first assigning and tagging each animal with a 3-digit number.

![Figure 1: Experiment treatment groups. All animals underwent a left-side facial nerve axotomy. Over the axotomy site, a gelfoam pad was secured to deliver local dexamethasone (Dex) treatment. Placebo saturation of the gelfoam was accomplished using saline. All animals underwent placebo saline intraperitoneal (IP) injection or systemic dexamethasone therapy.](image-url)
and then random nonsequential allocation of numbers into different treatment groups. After initial drug treatment, this allocation key was concealed and experimenters were blinded throughout the duration of the study.

**Surgical Procedure and Drug Delivery**

Left facial nerve axotomy was performed under anesthesia with ketamine (30 mg/kg) and xylazine (6 mg/kg) injected intraperitoneally (IP). Sterile technique was used, including retroauricular hair removal and Betadine skin prep. The facial nerve was identified as it exits the stylomastoid foramen. The nerve was divided sharply using microscissors approximately 5 mm from the point of emergence at the stylomastoid foramen. Immediate tension-free microsurgical coaptation of the nerve was performed using a 10-0 nylon suture (Ethilon; Ethicon, Somerville, New Jersey) placed as 2 perineural microsutures (Figure 2). All coaptations were performed with this standardized and similar technique. The right facial nerve served as an innervated control for each rat. Puralube Vet Ointment (Henry Schein Butler, Dublin, Ohio) was applied daily to the left eye to prevent corneal ulceration due to loss of blink reflex.

Local drug delivery was performed by application of a dexamethasone-saturated 5 × 5-mm piece of compressed gelfoam placed over the coaptation site. This was secured in place by tucking it between the trapezius muscle and coaptation site. Systemic drug delivery was performed via an IP injection of the drug at the same concentration for 3 administrations each consecutively 12 hours apart, with the first administration immediately after facial nerve surgery.

As a standardization measure for the surgical procedure and to provide a placebo treatment, a saline-soaked gelfoam pad was also placed over the coaptation site in control animals and those receiving systemic therapy. Similarly, placebo saline injections were administered to animals in the control group and those receiving local steroid therapy.

**Functional Testing**

All animals had normal and equal bilateral vibrissae movement prior to conducting these experiments. Rats were observed for return of left facial nerve function over an 8-week period. The observations recorded included eye blinking, vibrissae orientation, and motion of vibrissae. Assessments were made every fourth day. Each animal’s right side of the face was used as a control for normal facial movement. A standardized rat facial grading system was used (Table 1), with larger numbers indicating a greater recovery of motion. To maintain accuracy and corroborate ratings, functional assessments were independently performed in blinded fashion and compared between 2 experimenters (R.S. and P.C.R.).

Prior to animal sacrifice at 8 weeks, vibrissae motion was video recorded. Playback of video was performed in slow motion, and a vibrissae motion frequency was calculated for each side. Under slow-motion videography, varying frequencies were typically appreciated on each side. Therefore, 3 clips from the video recordings were assessed on each side, and an average was calculated to represent the vibrissae motion frequency for each vibrissae pad per animal. Vibrissae motion frequency was obtained for the surgical (left) and nonsurgical (right) sides of each animal. A frequency proportion of surgical to normal (left to right side) was calculated to represent a percentage of vibrissae motion frequency regeneration of the surgical side, serving as an objective standardized comparison method between study groups.

**Nerve Conduction Testing**

Biweekly nerve conduction studies (NCS) were performed using a Medtronic-Dantec (Minneapolis, Minnesota) electromyography (EMG) machine. Prior to axotomy and with the

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**Table 1. Facial Movement Scoring Scale**

<table>
<thead>
<tr>
<th>Eye Blinking</th>
<th>Vibrissae Movement and Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>1—Absence of eye blinking and closure</td>
<td>1—Absence of movement and posterior position of the vibrissae</td>
</tr>
<tr>
<td>2—Presence of orbicular muscle contraction, without blinking reflex</td>
<td>2—Slight shivering and posterior position</td>
</tr>
<tr>
<td>3—50% of eye closure through blinking reflex</td>
<td>3—Greater shivering and posterior position</td>
</tr>
<tr>
<td>4—75% of closure</td>
<td>4—Normal movement with posterior position</td>
</tr>
<tr>
<td>5—Presence of complete eye closure and blinking reflex</td>
<td>5—Symmetrical movement of the vibrissae, with anterior position</td>
</tr>
</tbody>
</table>
animal anesthetized, a baseline NCS was obtained to compare subsequent measurements performed at weeks 4, 6, and 8 of the study. For each NCS, sedation was administered as described above. Standard monopolar needle electrodes were inserted into the vibrissal muscle pad (recording), forehead (reference), and back (ground) of each animal. A bipolar stimulatory needle electrode was inserted in the retroauricular region such that the tip of the needles approximated the exit point of the facial nerve from the stylomastoid foramen. A stimulating pulse of 0.1 ms duration was administered to generate a compound muscle action potential (CMAP). The supramaximal stimulus (current delivered at 20% above the level necessary to achieve maximal CMAP amplitude) was determined. This allowed standardization of measures between all animals and time points for CMAP measurements. Wave pattern recordings were made at the supramaximal level (Figure 3), and wave amplitude at the supramaximal level was calculated by EMG software (Key Point, San Carlos, California) along with the assistance of an EMG-certified neurologist (D.G.).

**Statistical Analysis**

Power analysis determined that at least 7 animals per steroid level within each treatment group were needed to provide power of 0.8. The Kruskal-Wallis test was performed for each facial function testing method for all animals. This test was used to determine the presence of a global difference between study groups for each functional testing method. Post hoc pairwise comparisons of continuous measures were then performed using a standard Wilcoxon rank-sum test due to nonparametric distributions.

The majority of the literature on this subject uses the post hoc Wilcoxon rank-sum test to determine significance. However, this may lead to a type I error. To further reduce any potential for type I error in this study, in addition to the Wilcoxon rank-sum test, the Steel method was used to compare each treatment group with controls. The Steel method is used in nonparametric data sets to compare experimental means with a control group while strictly reducing the chance of any type I error. Both statistical methods are demonstrated (Table 2); however, conclusions from this study are determined based on a more rigorous significance level as determined by the Steel method to eliminate any potential of type I error in this study’s conclusions. Significance was ascertained with $P$ values of $<.05$.

**Results**

Figure 4 displays the progression of facial movement over the studied time using a standardized scale for rat facial function. Facial nerve regeneration appears to begin at approximately 15 days postaxotomy and reaches a plateau of functional recovery by 30 days in all groups. No difference in degree of improvement was observed prior to 15 days. Between days 15 and 30, we observed differing degrees of functional improvement among treatment groups. At 8 weeks (Figure 5 and Table 2), animals that underwent systemic dexamethasone therapy at 1 mg/kg and 5 mg/kg had a greater degree of improvement of vibrissae motion and eye blink when compared with controls (Wilcoxon test). Using rigorous statistical methods to reduce the chance of any type I error, statistical significance was achieved for eye blink and vibrissae motion for animals treated with systemic dexamethasone at 5 mg/kg ($P = .004$ and $P = .012$, respectively). Animals that underwent local dexamethasone therapy did not have different outcomes from controls.

Vibrissae motion frequency assessments corroborate well with our scaled gross vibrissae movement assessments, as seen in Figure 6. Similar to the results of the functional assessment scale, postaxotomy systemic dexamethasone therapy at 1 mg/kg and 5 mg/kg led to improvements of proportion of vibrissae motion frequency regeneration when compared with control animals at the end of the study period (Table 2). Reducing type I error, statistical significance is evident for the systemic 5-mg/kg-treated animals compared with control animals ($P = .012$).

**Table 2**

<table>
<thead>
<tr>
<th>Animal Group</th>
<th>Pre-op Amplitude</th>
<th>4 weeks post-op Amplitude</th>
<th>6 weeks post-op Amplitude</th>
<th>8 weeks post-op Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>5.3</td>
<td>0.7</td>
<td>2.1</td>
<td>3.8</td>
</tr>
<tr>
<td>4 weeks post-op</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>6 weeks post-op</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8 weeks post-op</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

**Figure 3.** Electrophysiological studies. Examples of nerve conduction studies in a single animal over the duration of the study. The compound muscle action potential (CMAP) is generated and recorded following a supramaximal stimulation. The wave amplitude is calculated and is seen to increase over study duration. Comparisons of amplitude were made at each time point relative to preoperative CMAP amplitude.
Given these findings of improved facial nerve return of function with systemic dexamethasone, further studies were performed using 0.5- and 10-mg/kg systemic concentrations on 7 additional animals per group. At 0.5- and 10-mg/kg systemic dose concentrations, functional scores of eye blink ($P = .929$ and $P = .203$, respectively) and vibrissae motion ($P = .298$ and $P = .541$, respectively) were not statistically different from controls at 8 weeks. Furthermore, slow-motion video analysis did not reveal any difference between controls and the groups receiving 0.5- and 10-mg/kg systemic concentrations ($P = .176$ and $P = .591$, respectively).

Using functional outcomes from all systemic dexamethasone concentrations, a dose-response curve (Figure 7) demonstrates that at 8 weeks, a maximal benefit of systemic

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**Table 2. Facial Assessment Scores by Study Group**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (SD)</th>
<th>Wilcoxon P Value</th>
<th>Steel P Value</th>
<th>Mean (SD)</th>
<th>Wilcoxon P Value</th>
<th>Steel P Value</th>
<th>Mean (SD)</th>
<th>Wilcoxon P Value</th>
<th>Steel P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 12)</td>
<td>2.08 (0.79)</td>
<td>2.54 (0.69)</td>
<td>0.37 (0.27)</td>
<td>0.44 (0.12)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local 2 mg/mL (n = 12)</td>
<td>2.17 (0.78)</td>
<td>2.33 (0.62)</td>
<td>0.28 (0.15)</td>
<td>.953</td>
<td>0.47 (0.12)</td>
<td>.176</td>
<td>0.593</td>
<td>0.34 (0.06)</td>
<td>.076</td>
</tr>
<tr>
<td>Local 4 mg/mL (n = 12)</td>
<td>2.07 (0.53)</td>
<td>2.21 (0.39)</td>
<td>0.47 (0.12)</td>
<td>.176</td>
<td>0.593</td>
<td>0.34 (0.06)</td>
<td>.076</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic 0.5 mg/kg (n = 7)</td>
<td>3.41 (1.20)</td>
<td>.011</td>
<td>.903</td>
<td>1.000</td>
<td>0.47 (0.28)</td>
<td>0.100</td>
<td>0.68</td>
<td>0.49 (0.25)</td>
<td>1.000</td>
</tr>
<tr>
<td>Systemic 1 mg/kg (n = 12)</td>
<td>3.88 (1.03)</td>
<td>.001</td>
<td>.929</td>
<td>1.000</td>
<td>0.71 (0.28)</td>
<td>.014</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic 5 mg/kg (n = 12)</td>
<td>2.79 (1.04)</td>
<td>.203</td>
<td>.651</td>
<td>3.00 (1.19)</td>
<td>.981</td>
<td>0.39 (0.29)</td>
<td>.866</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Systemic 10 mg/kg (n = 7)</td>
<td>3.88 (1.03)</td>
<td>.001</td>
<td>.929</td>
<td>1.000</td>
<td>0.71 (0.28)</td>
<td>.014</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Scores reported are at study end at 8 weeks. Means and standard deviations (SD) are given. Bolded values represent a $P$ value less than 0.05, and are statistically significant at that threshold.

**Figure 4.** Facial function over study duration. Eye blink and vibrissae movement were graded every fourth day using a standardized scale shown in Table 1. Animals treated with systemic 1 or 5 mg/kg appear to achieve a greater functional return.
Dexamethasone occurred at 5 mg/kg for both return of eye blink and vibrissae motion. The proportional return of vibrissae frequency at 8 weeks of all systemic therapy groups produces a nearly identical curve (figure not shown).

The CMAP wave amplitudes generated at a supramaximal stimulus during NCS studies were compared with baseline preoperative amplitude levels. These comparisons, made for each animal at each time point of 4, 6, and 8 weeks postaxotomy, are presented as a proportion to preoperative amplitude levels. At 8 weeks, unlike the results of functional testing, systemic dexamethasone dosing did not produce a statistically significant electrophysiologic difference across groups (Kruskal-Wallis $P = .1386$). However, there appears to be a trend of increased return of CMAP amplitude among animals receiving 5 mg/kg dexamethasone (Figure 8). Local dexamethasone application did not significantly improve return of CMAP amplitude.

During the study, 2 animals died of anesthesia-related complications during NCS assessments. One animal receiving dexamethasone 10 mg/kg required sacrifice because of a corneal ulceration.

**Figure 5.** Eye blink and vibrissae motion scores at 8 weeks. The eye blink and vibrissae motion scores are compared at the 8-week time point. Error bars represent standard deviation from the mean.

**Figure 6.** Vibrissae motion frequency comparisons. Using slow-motion videography, the vibrissae motion frequency of the surgical left and nonsurgical right sides was calculated, and a left/right proportion of frequency recovery was obtained. Functional assessments appeared to correlate well with objective results of frequency analysis. Error bars represent standard deviation from the mean.

**Figure 7.** Dose-response curve of systemic dexamethasone therapy. Systemic dexamethasone concentrations tested included 0 mg/kg (controls), 0.5 mg/kg, 1 mg/kg, 5 mg/kg, and 10 mg/kg. The dose-response curve peaks at 5 mg/kg. Error bars represent standard deviation from the mean.
Discussion

Facial nerve recovery after Bell’s palsy has demonstrated improved outcomes with early administration of prednisone therapy. Applying similar principles to a facial nerve axotomy injury, steroid administration may also be beneficial after facial nerve neurorrhaphy.

Previous studies on nerve regeneration provide limited clinical applicability. Graham et al. in 1982 were the first to study the use of glucocorticoids on a motor nerve. They showed improved hand function with the placement of triamcinolone on monkey median nerves that were severed and then immediately coapted. Again in the 1980s, studies on axotomized rat sciatic nerves treated with triamcinolone time-release pellets showed similar improvements. More recently, Galloway et al. used a rat sciatic nerve crush injury model to investigate the application of local dexamethasone at the injury site. Although there was no statistically significant difference, there was a trend toward improved functional results in those animals treated with dexamethasone. In addition, Al-Bishri et al. have shown that systemically administered betamethasone accelerates recovery of sciatic nerve crush injury in rats.

Although these studies provide support for a role of steroid therapy in facial nerve injury repair, several study limitations potentially prohibit clinical application to the facial nerve. Facial nerve crush injury (axonotmesis) is rarely encountered clinically, and this type of injury exhibits differing healing mechanisms and recovery profiles from axotomy-induced nerve injury (neurotmesis). Also, variance of nerve regeneration is affected by location of the nerve injury and distance of injury from the central nervous system. Therefore, studies describing results from crush injuries or sciatic nerves may not be applicable to the facial nerve transection injury or deliberate axotomy such as that observed surgically. In addition, previous investigations have not compared local and systemic steroid delivery methods at varying drug dosages.

The glucocorticoid dexamethasone sodium phosphate was chosen for use in this study because of its high potency, relatively long half-life, and known local activity. Concentrations for both delivery routes were chosen based on previous literature. Steroid therapy was administered during the acute inflammatory phase following nerve injury.

Functional assessments every fourth day scored eye blink and vibrissae motion to assess return of function. Variation in scores likely reflects inherent minor variability of reviewer assessment. High-resolution, slow-motion video-monitoring to determine vibrissae motion frequency was used to corroborate our scored functional assessments for each animal. Interpretation of these data indicated that systemically delivered dexamethasone at 1 and 5 mg/kg appeared to improve functional outcomes at 8 weeks postaxotomy compared with control animals. However, when rigorously adjusting for any type I error produced by statistical methods, use of the Steel method for P value determination demonstrated a lack of statistical significance of the systemic 1-mg/kg dexamethasone study group compared with control group animals. Other systemic concentrations of 0.5 and 10 mg/kg did not demonstrate improved function. The 0.5-mg/kg dose may simply be too low to produce an effect, whereas the 10-mg/kg dose may be producing a detrimental toxic effect for nerve regeneration. Local administration of dexamethasone at 2 and 4 mg/mL to the axotomy site did not yield improved functional outcomes compared with control animals.

Biweekly NCS provided electrophysiological data on each animal. Compared with controls, there were no statistically significant differences found in proportional return of CMAP amplitude. The animals receiving systemic dexamethasone at 5 mg/mL showed a trend toward achieving a statistically significant difference compared with control animals. We observed that the CMAP amplitude proportional return appears to gradually return at a rate slower than functional return. Therefore, a greater amount of time than 8 weeks may be required to perceive any significant changes in electrophysiologic recovery.

In the translation of these results to humans, use of high-dose systemic steroids in the setting of facial nerve neurorrhaphy will need to be carefully balanced with the substantial possible side effects of high-dose steroids. Side effects of high-dose steroids were not assessed in this study.

An important recovery mechanism after a nerve injury is the regeneration of injured axons. Numerous molecular and cellular events have been shown to occur in neuron axons and cell bodies following axotomy of the facial nerve. These collectively aim to clear debris and cell death products caused by injury and then to regenerate nerve fibers. One of the important driving factors of this process appears to be neuroinflammation via numerous neuroinflammatory factors. One neuroinflammatory mechanism may be through local production of reactive oxygen species. Free radicals induce apoptosis in neurons and glial cells by irreversible oxidization of cellular elements. Another mechanism may be via nitric
oxide (NO). After facial nerve injury, the amount of NO produced has been shown to markedly increase. Recently, inhibition of nitric oxide synthase (NOS) has been shown to directly improve axonal regeneration in the rat facial nerve axotomy and immediate neurorrhaphy model.\textsuperscript{21}

Although the effects of neuroinflammation are essential in neuronal healing, an exaggerated inflammatory response may adversely affect the recovery process. Modulation of the immune response to be less aggressive may create an ideal compromise between the useful and deleterious effects of inflammation. Such a mechanism may provide insight into the observed improved outcomes seen in our study with systemic dexamethasone therapy.

Conversely, excessive immunomodulation may inhibit the recovery process. In a recently published study, Lieberman et al.\textsuperscript{22} demonstrate that adult mice treated for 7 days with either systemic dexamethasone 1 or 10 mg/kg both exhibited a decreased functional recovery. The authors speculate that this may be due to the degree of immunosuppression induced by this steroid regimen. On the other hand, our experimental design focuses on drug administration during the immediate postinjury time period. We speculate that our administration schedule targets the acute inflammatory process while minimizing prolonged immunosuppression.

\textbf{Conclusion}

In a rat facial nerve axotomy model, we demonstrate that postcoaptation systemic dexamethasone therapy at 5 mg/kg for 3 total administrations given every 12 hours immediately after injury improved facial nerve functional outcomes. A similar effect was not seen in topically delivered dexamethasone. This study suggests a potential benefit of high-dose systemic dexamethasone on facial nerve functional recovery when administered in the acute period following axotomy and coaptation. Prospective human clinical trials are needed to further study this effect.

\textbf{Author Contributions}

Rahul Seth, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published; Peter C. Revenough, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published; James A. Kaltenbach, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published; Karthik Rajasekaran, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published; Noah E. Meltzer, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published; Debabrata Ghosh, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published; Daniel S. Alam, substantial contributions to conception and design, acquisition of data or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published.

\textbf{References}


