ORIGINAL ARTICLE

Effect of surgical denervation on orthodontic tooth movement in rats

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Introduction: Tooth movement through bone depends on local inflammatory reactions of the dentoalveolar tissues. Mechanical signals cause sensory afferent nerves to liberate inflammatory peptides around the teeth, creating local inflammation. Relationships between neurogenic inflammation and tooth movement are poorly understood. The objective of this study was to measure the differences in orthodontic tooth movement between rats treated with and without surgical transection of the maxillary nerve. **Methods:** Forty-two Sprague-Dawley rats were divided into 3 groups: (1) those with surgical transection of the maxillary nerve, (2) those with sham surgeries, and (3) those without surgery. After a 2-week healing period, a closed-coil spring appliance was activated to produce a 50 g mesial tipping force on the maxillary first molar. Diastema sizes distal to the first molar were measured in triplicate by using vinyl polysiloxane impression material and stone model pour-ups at 14 and 28 days of tooth movement. Images were captured and measured with a charge coupled device (CCD) microscope camera (Leeds Precision, Minneapolis, Minn) and Optimas measurement software (Media Cybernetics, Newburyport, Mass), respectively. Two-way repeated-measures ANOVA was used for statistical analysis. **Results:** Both weight and diastema size increased for all animals throughout the study. Although there were no significant differences between groups at any time point (log diastema, $P = .43$), the maxillary nerve transection surgery group had a significantly smaller increase in log diastema from 14 to 28 days than either the sham surgery or the nonsurgery group ($P = .045$). **Conclusions:** This study suggests that surgical denervation causes little net effect on orthodontic tooth movement at these force levels. (Am J Orthod Dentofacial Orthop 2007;131:620-6)

Orthognathic surgery combined with orthodontic treatment is an accepted method for correcting dentofacial deformities. Nerve damage and paresthesia are common sequelae of LeFort[1] or mandibular ramus surgical procedures.[2] Patients often have nervous sensory loss for weeks, months, or less commonly, years after corrective jaw surgery. Pulpal sensation and sensations to cold, fine touch, and pin prick generally return within 6 months, although rarely to preoperative levels.[1]

Histologic aspects of tooth movement have been well described,[3-8] but it is still not entirely understood how mechanical forces result in tooth movement through bone. Teeth move by a prerequisite inflammatory reaction of the paradental tissues.[8-19] Mechanical deformation acts as a stimulus, giving rise to changes in blood flow, oxygen tension, and membrane potential, including heightened cellular activity and liberation of inflammatory mediators. These mediators include arachidonic acid metabolites: prostaglandin E_1, E_2, and leukotriene B_4; cytokines: interleukin-1β, interleukin-6, TGF-α, and TNF-β; and neuropeptides: substance P (SP) and calcitonin gene related peptide (CGRP).[20-29] This inflammatory bone remodeling process continues until the forces redistribute to a state of dynamic and then static equilibrium.

Evidence has emerged about the importance of neuropeptides such as SP and CGRP in the process of inflammation[30] and orthodontic tooth movement.[9,14-19,28,29,31,34,35] CGRP and SP are synthesized in the perikaryon of peptidergic nerve cells and are transported anterogradely to free-end nociceptors in the pulp and periodontal ligament.[32,33,36,37] Because of inflammatory and perhaps mechanical signals, these afferent peptidergic nerves display an efferent function by releasing SP and CGRP from nociceptor endings into the dentoalveolar milieu. Once released, SP and CGRP are thought to exhibit potent effects on local tissues. Studies have shown that SP and CGRP cause cultured human pulpal fibroblasts to increase cytokine

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secretion of IL-1β, IL-6, and TNF-α.[28] SP in the local environment is known to cause mast cell degranulation and liberation of PGE_2 from cultured periodontal ligament fibroblasts.[9] Both SP and CGRP are potent vasodilators and induce increases in vascular permeability and plasma extravasation. They are also known to stimulate the proliferation of endothelial cell adhesion molecules.[19] The component of inflammation derived from neuropeptide release is termed "neurogenic inflammation."

Maxillary teeth are innervated by the maxillary division (V2) of the trigeminal nerve. Sensory nerves such as V2 are known to release substance SP, CGRP, and other neuropeptides in response to orthodontic forces and concomitant biochemical events. SP and CGRP act to increase vascular permeability to cells of the monocyte lineage, increase proliferation of endothelial cells and fibroblasts, and stimulate tissue remodeling.[14-19] Likewise, denervation of teeth has been shown to attenuate the inflammatory response both by causing a delay in the recruitment of immunocompetent cells to the periodontal ligament and by inhibiting osteoclastic access to the bone surface.[19] Furthermore, axotomy of the inferior alveolar nerve in rats postpones the normal increases in blood flow shown in orthodontic tooth movement.[17] Because iatrogenic nerve damage (evidenced by paresthesia) is such a common finding in patients having orthognathic surgery and orthodontic treatment, it is reasonable to ask whether teeth can be moved a similar amount after the most severe type of nerve damage has occurred. We chose an animal model. The objective was to measure differences in orthodontic tooth movement between 3 groups of Sprague-Dawley rats: (1) those with surgical transection of the maxillary nerve, (2) those with sham surgeries, and (3) those without surgery. The purpose was to determine whether denervation inhibits subsequent tooth movement.

MATERIAL AND METHODS

The sample consisted of 42 male Sprague-Dawley rats (weight, 200-225 g) that were acclimated for 1 week in plastic shoebox housings with a 12-hour light/day cycle and fed powdered rodent chow and distilled water ad libitum during this study.

The rats in the surgery group had V2 transection survival surgery. Those in the sham group received identical incisions; the maxillary nerve was exposed and manipulated but not severed. The rats in the untreated group were not manipulated surgically. All rats received orthodontic appliances 14 days after surgery.

General anesthesia for the surgeries and appliance placements was induced by administering 50 mg per kilogram of ketamine hydrochloride and 10 mg per kilogram of xylazine hydrochloride injected as a bolus dose intraperitoneally. If anesthesia was not effective within 20 minutes, the rats were given a second injection of 150 μL of nembutal. This gave adequate anesthesia for approximately 30 to 45 minutes.

The rats in the surgery group had V2 transection survival surgery. Under general anesthesia, an intraoral incision was made with a battery-powered Solan high-temperature cauterizer (Accutemp Ref # 84-42000, Medtronic Corp, Jacksonville, Fla) proximal to the molars and high in the buccal vestibule on the right side. Once the cautery incision was made, tissue was reflected and carefully dissected aside. After the maxillary division of the trigeminal nerve was visualized (Fig 1) and clamped, it was cauterized both mesially and distally to its entrance into the maxilla. Care was taken to avoid damaging critical nearby structures. The rats in the sham group received identical incisions; the maxillary nerve was exposed and manipulated but not severed. Due to limited access, healing was by secondary intention without sutures. The animals were returned to their housings and fed powdered rodent chow and distilled water ad libitum for 14 days to allow healing and dry-field appliance placement. Tissue edema is an overt sign of inflammation and was observed for approximately 7 to 10 days after surgery. The 14-day recovery period was intended to limit inflammation derived from alternative pathways.

All groups received appliances under general anesthesia. Occlusal, buccal, lingual, and mesial surfaces of the right first molar were etched with phosphoric acid for 30 seconds, and then rinsed and air dried for 5 seconds. A thin coating of 3M Transbond XT light-cure adhesive primer (3M Unitek, Monrovia, Calif) was added to the etched surfaces and light cured. Tetric-Flow flowable composite (shade B3, Ivoclar Vivadent, Amherst, NY) was chosen to improve bond strength due to the highly irregular surfaces of the rats' first molars. This material was placed over the primer layer and light cured. A modified molar cleat was bonded to the occlusal surface with Transbond XT. A 3-mm length of 50 g Sentalloy closed-coil spring (GAC International, Bohemia, NY) was attached to a modified molar cleat (#430-004, Orthodontic Organizers, San Marcos, Calif) on the occlusal surface of the maxillary first molar and extended to the maxillary incisors. Tetric-Flow flowable composite was placed over the molar cleat and latch assembly to stabilize

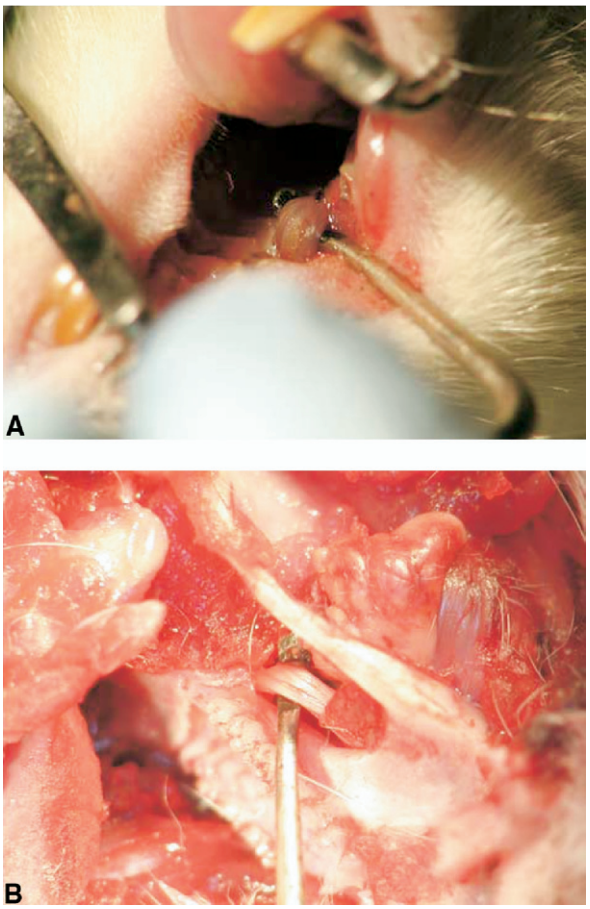

Fig 1. A, Maxillary nerve isolation during sham surgery; **B,** gross dissection.

the spring to the cleat. The appliances should thus have delivered a constant tipping force of 50 g to the mandibular first molar. Sentalloy manufacturer information states that the coil delivers a constant force of 50 g when activated in the range of 3 to 12 mm.

The closed-coil spring was activated from the molar cleat to the incisors and bonded just cervical to the crown near the level of the gingiva (Fig 2).

Diastemas were measured indirectly by using impressions, image acquisitions, and computer-aided measurements. The rats were anesthetized 14 days after appliance activation. Impressions of the diastema were taken with Vinyl Polysiloxane Imprint-II (VPS) wash material low viscosity (3M, St Paul, Minn) and ESPE Garant (3M) mixing tips with an intraoral injectable syringe attachment tip. This material was allowed to set for 4 minutes before removing it from the mouth. Impressions were stored from 1 to 14 days before pouring with stone. According to the manufacturer, no appreciable expansion or contraction occurs for these storage times and conditions. The stone

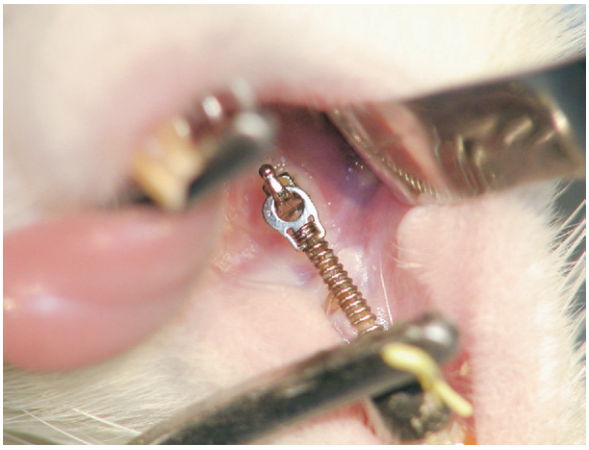

Fig 2. Activated closed-coil spring appliance.

used to pour the impressions was Fujirock II (GC Europe, Leuven, Germany), an improved die stone that exhibits only 0.08% linear setting expansion according to the manufacturer's data. To decrease the surface free energy, a dilute Mizzy (Keystone Industries, Cherry Hill, NJ) silicone emulsion was used to coat the surface of the impression material. After rinsing with water, 100 g of stone was added to 20 mL of distilled, deionized water. The material was vacuum mixed under 25 psi for 30 seconds, and impressions were poured by using a vibrating surface. The impressions were inverted and allowed to sit 24 hours before separation from the impression material.

A macro zoom 18-108 lens (Navitar, Rochester, NY) attached to a CCD camera (MTI 3, Leeds Precision, Minneapolis, Minn) was used to capture the diastema images (Fig 3). A laminated millimeter ruler was digitized at a constant focal length for calibration purposes. Diastemas were measured indirectly from acquired images of the stone models with the CCD camera and Optimas 6.0 software (Media Cybernetics, Newburyport, Mass). A measurement tool on the software program calculated linear distances on the stone models from the calibrated ruler algorithm. Images were captured by orienting the camera angle from the lingual aspect perpendicular to the widest aspect of the diastema.

The groups were compared according to weight gain by using a mixed linear model. The model treated each rat's weight as following a linear trend in days, with random effects for the slope and intercept of each rat's linear trend. Fixed effects were treatment group, time (days), and their interaction; the latter was tested to compare groups according to weight gain. The analysis was executed in the MIXED procedure with the REML method and the Type 3 analysis (SAS, Cary, NC).

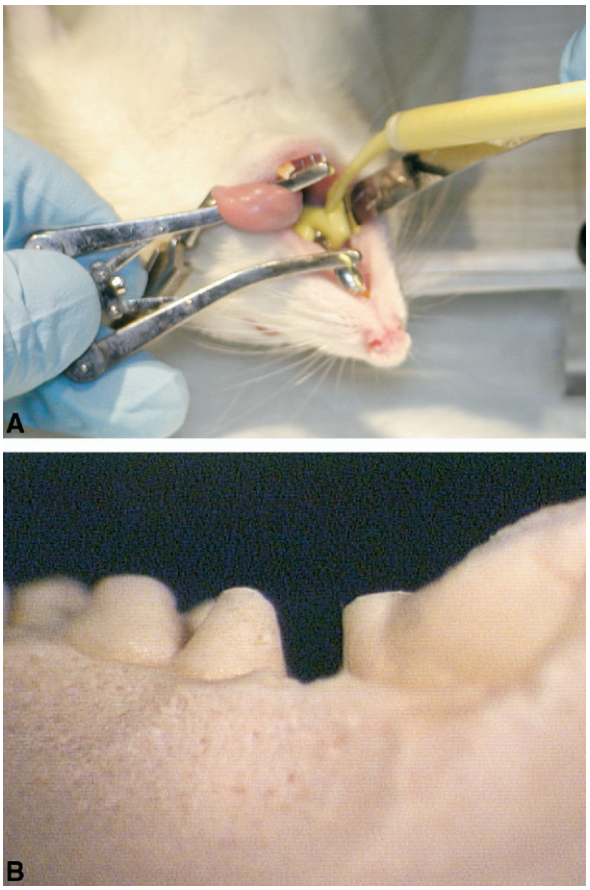

Fig 3. A, VPS impression; **B,** image capture of stone pour-up.

The groups were compared according to diastema by using repeated-measures analysis of variance (ANOVA). Because variations in diastema were found to increase with increasing diastema size, the common logarithm (base 10) of diastema was analyzed instead of the raw measurements. Each diastema was measured 3 times; the dependent variable in the ANOVA was the average of the log diastemas. The subject or random effect was rat; the fixed effects were group, time since appliance placement (2 vs 4 weeks), and their interaction. Post-hoc tests with the Bonferroni correction were applied to the 3 pairwise comparisons between pairs of treatment groups. Twenty-nine percent of the rats had unexpected orthodontic extractions at 4 weeks of tooth movement. Our analysis excludes measurements from accidentally extracted teeth. An alternative analysis included these teeth by using the most distal edge of the alveolus as the boundary of the diastema. The main and alternative analyses gave qualitatively identical results, so we omit the alternative analysis.

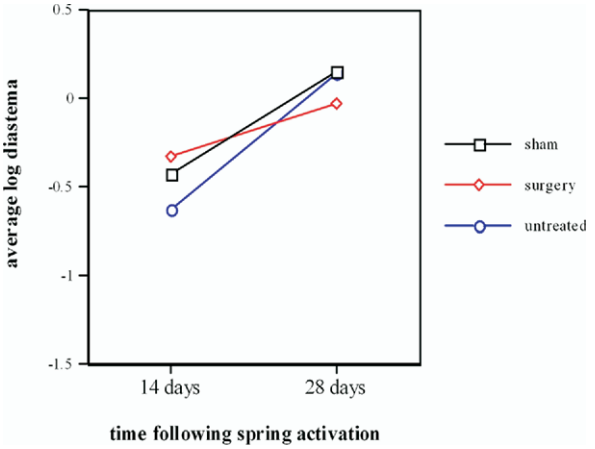

Fig 4. Average log diastema after 2 and 4 weeks of appliance activation.

RESULTS

Of the 42 animals at the start, 29 (69%) survived with their appliances intact for the 28-day measurement. Animal losses were due to the following reasons: appliance dislodgement (24%), surgery and anesthesia complications (5%), and temporomandibular joint rigor (2%). Eleven rats had orthodontically extracted first molars after 4 weeks of appliance activation. This unexpected finding was not associated with any group.

Weight data were collected at each anesthesia event. The 3 groups gained an average of 1.2 g per day (standard error 0.13, $P = .0001$) during this study. The groups had different rates of weight gain: surgery, 1.57 g per day (SE 0.28); sham 1.36 g per day (SE 0.23), and untreated 0.56 g per day (SE 0.28; $P = 0.027$). In post-hoc tests, the surgery and sham groups had higher rates of weight gain per day than the untreated group ($P = .012$ and .030, respectively) but did not differ from each other ($P = .51$).

Averaged over the treatment groups, the diastema increased between the 2- and 4-week measurements ($P < .0001$) by a factor of 3.6. The changes in diastema (2-4 weeks) were not the same in the 3 treatment groups ($P = .045$). Specifically, the sham and untreated groups increased by a similar amount from 2 to 4 weeks on average, whereas the surgery group was higher at 2 weeks and increased by a smaller amount between 2 and 4 weeks. Figure 4 and the Table show these results.

DISCUSSION

These results suggest that there is little net effect on orthodontic tooth movement at these force levels

Table. Diastema changes over time in 3 groups

Group	*Time*	*Average log (diastema)*	*SE log (diastema)*	*Average actual diastema*
Sham	14 days	−0.43	0.05	0.372
Sham	28 days	0.15	0.06	1.413
Surgery	14 days	−0.33	0.05	0.468
Surgery	28 days	−0.03	0.15	0.933
Untreated	14 days	−0.63	0.04	0.234
Untreated	28 days	0.14	0.07	1.38

Standard error was calculated by using ANOVA mean squares for log (diastema).

when nervous input to the teeth is surgically lost. Statistically, there were no differences between groups in diastema size at any time point. The surgery group, however, had a smaller increase in average log diastema from week 2 to week 4 than either the untreated or the sham group ($P = .045$). This might indicate a difference in the characteristic of the curve for the surgery group. New studies with titratable forces and additional time points might be necessary to understand this difference.

Previous studies used VPS impressions to directly measure tooth movement with interproximal filler gauges and noncontact digital microscopic gauges, although none used indirect computer imaging for measurements.[38-42] Indirect measurement methods in general have proven to be highly reliable, practical, and less technique sensitive than direct methods. Indirect techniques are noninvasive, easy to accomplish, and compatible with life. In addition, pilot experiments conducted by our laboratory showed that the indirect measurement technique provided reproducible and highly accurate measurements. This noninvasive VPS technique might be ideal for measuring tooth movement in humans.

The problem of orthodontically extracted first molars after 4 weeks of appliance activation was not associated with any group. Force levels were considered optimal for orthodontic tipping and were not deemed excessive. Because this finding has not been observed before, it might be due to any or all of the following variables: operator, individual differences in rat physiology, or manufacturing differences in the coil springs.

The LeFort 1 osteotomy is tantamount to the LeFort 1 "axotomy": the osteotomy site transects the anterior, middle, and posterior superior alveolar nerves. Knowing that sensory nerves play an important role in the propagation of inflammation, the question arises: "Will teeth move at a similar rate after nervous input is compromised?" We performed V2 nervous transection survival surgery on rats and compared the amount of tooth movement with untreated and sham controls. Although we found no differences between groups in the amount of tooth movement at either 2 or 4 weeks, there was a slight inhibition in the change from 2 to 4 weeks for the surgery group.

All animals gained weight during this study. The untreated rats (0.56 g per day) gained statistically less weight than either the surgery (1.57 g per day) or the sham (1.36 g per day) animals. This might be due to increased appetite and biologic demands after surgical insult. It clearly demonstrates each group's positive ability to thrive during this experiment.

The classic signs of inflammation as described by Celsus and appended by Virchow are redness (rubor), pain (dolor), swelling (tumor), fever (calor), and loss of function (functio laesa).[43] The rats demonstrated evidence of some signs for 7 to 10 days after surgery; thus, reciprocal inflammatory pathways were undoubtedly activated. Fourteen days were allowed for postsurgical healing to minimize these effects during our experiment.

To avoid surgical reciprocal pathway activation altogether, future research might focus on using chemical denervation treatments. Capsaicin is known to destroy peptidergic nerves for approximately 21 days in adult rats. If given to neonatal rats, it will permanently inhibit the development of peptidergic nerves. A similar tooth-movement study with this type of sensory attenuation protocol is a logical next step.

There is much evidence that inflammation derived from neuropeptide release has real and tangible biochemical effects on the dentoalveolar apparatus. Our data, however, suggest that neurogenic inflammation plays a relatively minor role on the net effect of orthodontic tooth movement.

CONCLUSIONS

1. Diastema size increased in all cases from 2 to 4 weeks in rats fitted with orthodontic appliances.
2. There were no significant differences in the amount of orthodontic tooth movement among the sham, untreated, and surgery groups at any time.
3. The surgery group had significantly smaller increases in diastema size from 2 to 4 weeks when compared with the untreated and sham groups.
4. Neither the appliance nor the surgery interfered with the animals' ability to thrive.
5. A highly accurate and simple measurement technique using VPS impressions, stone models, and a CCD camera is described; it could easily be incorporated into human tooth-movement studies.

Nervous insults to rat teeth, such as those in human orthognathic surgery patients, appear to be consistent with the timely movement of teeth through bone. Nervous insult does not appear to prolong the rate of orthodontic tooth movement at these time points and force levels.

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