Objective: To assess the utility of distraction osteogenesis (DO) when applied to closure of a hard palate cleft in dogs.

Methods: A midline hard palate cleft was created in 10 mature dogs. Two were controls and had no distraction; the other 8 dogs underwent osteotomies with installation of customized DO devices to the hard palate. After a 10-day latency, distraction commenced at 1 mm/d. After a 14-day consolidation period, the device was removed and the mucosa closed. Each dog was injected with fluorochrome labels and serially killed at 2-week intervals. Bone healing was analyzed further with traditional histologic analysis and fluorochrome labeling.

Results: No serious complications occurred. Bone resorption and cleft widening occurred in both control dogs. Complete bone closure of the hard palate cleft was achieved with DO in 5 of 8 experimental dogs. Three experimental dogs had bone resorption and incomplete palatal closure.

Conclusions: The application of DO techniques in closure of a hard palate cleft in a canine model is safe and well tolerated. Furthermore, in some cases, it proved effective in achieving bony closure of the cleft. Further investigation is warranted into innovative use of DO in treating children born with cleft palate.

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Cleft palate is a common birth defect, with an average incidence of 1 per 700 to 1000 live births. Patients with cleft palate experience feeding difficulties, middle-ear disease, impaired speech, oronasal fistula, anomalous dentition, and cosmetic deformities. Currently, surgical repair is considered the optimal treatment. The surgeon’s goals are to reconstitute normal anatomy, close the oronasal fistula, promote healthy eustachian tube function, and improve swallowing, speech, and dental occlusion. Also, an effort is made to preserve normal subsequent midfacial growth, thereby decreasing the need for secondary reconstructive procedures. Modern surgical techniques involve the mobilization of palatal mucosal flaps that are sutured together over the cleft. The bony cleft defect is not repaired, nor does mucosal closure alone induce new bone formation in the cleft.

Critical analysis has revealed the deficiencies and limitations of current surgical management of cleft palate. Contemporary techniques often leave areas of hard palate bone exposed. This exposed bone heals with scar contraction, contributing to subsequent impairment of midfacial growth.1,2 A child with an underdeveloped midface may have poor cosmetic appearance and dental malocclusion. Furthermore, tension placed on the palatal mucosal flaps at the time of surgical repair in combination with the lack of any bony repair increases the risk of wound dehiscence and oronasal fistula. Tension on soft palate tissues contributes to scar formation, soft palate shortening, and subsequent velopharyngeal insufficiency. These complications often necessitate further invasive procedures as the child ages.

Recent advances in the surgical approach have been designed to address these limitations and complications. The focus has been on presurgical manipulation of tissue to create more favorable dynamics at the time of the definitive repair. For example, dentoalveolar orthopedic appli-
ances pull the alveolar segments together in the cleft. However, these appliances do not correct the deficiency of bone and soft tissue; rather, they move existing tissue into a better location. Furthermore, this approach does not treat defects of the secondary hard palate.

One method to potentially enhance current treatment is to induce new bone formation and soft tissue migration over the cleft before definitive surgery. Distraction osteogenesis (DO) is a technique in which bone is lengthened gradually under tension after an osteotomy. The application of DO to craniofacial disorders is being actively investigated. Midfacial advancement, hard palate suture expansion, elongation, and alveolar cleft closure have all been attempted with DO.3-7

To date, there have been no reports of the use of DO to close a hard palate cleft in humans. Hard palate bone is quite thin, and it is not well known how this bone would respond to the forces of DO. Yet, it is possible that the application of DO techniques to the repair of cleft palate offers improvement over current surgical methods. To investigate this question, we designed an experiment in which a customized DO device was used for cleft palate closure. Our hypothesis is that hard palate cleft can be closed successfully with DO techniques in a canine model.

Ten adult, skeletally mature hounds (mean weight, 28 kg) were used in this study. All the animals were cared for according to the guidelines of the institutional animal care and use committee under the direction of the Department of Veterinary Medicine at Mayo Clinic. Two dogs served as controls and 8 underwent the experimental procedure. The control group had the surgically created cleft but no repair. The experimental group had the surgical procedure and twice daily for 5 days after the first operation. The dogs were returned to their usual cages and fed soft foods. Analgesia consisted of 0.02 mg/kg of buprenorphine hydrochloride subcutaneously and 1 mg/kg of intramuscular (IM) ketoprofen twice daily for 48 hours and then as needed. For antibiotic prophylaxis, each dog received 20 mg/kg of IM cephalaxin hydrochloride at the time of each surgical procedure and twice daily for 5 days after the first operation. The dogs were returned to their usual cages and fed soft canned dog food. The dogs were weighed weekly to ensure adequate nutritional intake.

During a latency period of 10 days, the device was not manipulated and the mucosa was allowed to heal. On postoperative day 11, distraction commenced at the rate of 0.5 mm/d for each bone island (resulting in 1 mm of cleft closure). The distraction was performed once daily until the device could no longer be turned. After this occurred, the animal was sedated.

Figure 1. The customized distraction osteogenesis device, engineered and manufactured by KLS Martin, Jacksonville, Fla.

Methods

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In collaboration with the authors, KLS Martin (Jacksonville, Fla) engineered 5 customized cleft palate DO devices for the study. The device consists of 1 central body piece and 4 plates. Each plate is 28 mm long, and the device is 28 mm wide. The plates accommodate 1.3-mm diameter screws. The 2 outer plates are fixed and do not move in relation to the central body piece. These were fixed to the stable hard palate bone laterally near the alveolus and teeth. The 2 inner plates are movable in relation to the central body piece. These 2 inner plates were secured to the hard palate bone islands that serve as transport disks. It is these 2 inner plates that are distracted medially, away from the alveolus, to eventually meet in the midline. The hexagonal jackscrew protrudes from the device. A custom-made cap fits over the jackscrew to protect the tongue and to prevent loosening of the jackscrew.

The surgical procedure was performed under general endotracheal anesthesia with the animal secured in the supine position. Anesthesia was induced with 0.5 mg/kg of intravenous (IV) diazepam, 0.5 mg/kg of IV ketamine hydrochloride, and 0.6 mg/kg of atropine sulfate. During the procedure we administered morphine sulfate at 0.24 mg/kg per hour, ketamine hydrochloride at 0.6 mg/kg per hour, IV lidocaine hydrochloride at 3.0 mg/kg per hour, and inhalational isoflurane.

After an oral retractor was placed, the palate mucosa was washed with povidone-iodine (Betadine; Purdue, Stamford, Conn) and infiltrated with 10 mL of 1% lidocaine hydrochloride with 1:100,000 epinephrine. Starting at the anterior aspect of the fourth premolar tooth, a 5-mm strip of midline mucosa was removed with a scalpel. The posterior limit of this strip was the junction of the hard palate and soft palate. Next, mucosal flaps were bluntly elevated off the hard palate bone bilaterally. The greater palatine arteries were identified and preserved during the dissection. With the mucosal flaps retracted, the DO distractor was secured temporarily to the hard palate bone with 4 corner screws. The osteotomies were planned and marked on the hard palate bone with a 1-mm drill. The distractor was removed, and the osteotomies were started with a 1-mm side-cutting drill. After the central portions of the osteotomies were started, the DO device was definitively secured to the hard palate bone with screws, and the osteotomies were completed with the side-cutting drill.

By removing oral mucosa, bone, and nasal mucosa from the anterior aspect of the fourth premolar tooth back to the posterior edge of the hard palate, the midline cleft palate was created. The cleft was 5 mm wide and 45 mm long. Two free-floating bone islands (8 mm wide and 43 mm long) were created parallel to the cleft. These bone islands remained attached to the nasal mucoperiosteum but otherwise were freely mobile. The inner plates were secured to these bone islands that would serve as the transport disks during DO. The steps of the surgical procedure are illustrated in Figure 2. The jackscrew was tested to ensure unimpeded movement of the bone islands. The oral mucosa was closed over the device in the midline without using releasing incisions. It was closed with some tension, but complete mucosa-to-mucosa approximation was achieved except for the central portion where the jackscrew protruded.

For the control group, the surgical procedure consisted of creating the midline cleft, and performing bilateral osteotomies to form the transport disks. In control dog 1, the DO device was not placed and the mucosa was not closed. In control dog 2, the DO device was placed but was not turned for distraction.

Postoperatively, the animals were monitored overnight in the recovery room. Analgesia consisted of 0.02 mg/kg of buprenorphine hydrochloride subcutaneously and 1 mg/kg of intramuscular (IM) ketoprofen twice daily for 48 hours and then as needed. For antibiotic prophylaxis, each dog received 20 mg/kg of IM cephalaxin hydrochloride at the time of each surgical procedure and twice daily for 5 days after the first operation. The dogs were returned to their usual cages and fed soft canned dog food. The dogs were weighed weekly to ensure adequate nutritional intake.

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with propofol and briefly examined to assess the distractor. The mean number of days of distraction was 7.125. Daily distraction was performed with the assistance of the veterinary technicians, and no sedation was needed for most sessions. Occasionally, 6 mg/kg of IV propofol was needed to facilitate the distraction. During daily distraction, the device was cleaned with a dentifrice. After the distraction was completed, the device was left in place for a 4-week consolidation period. During this time, the device was inspected and cleaned weekly. Also, the jack-screw was tested to ensure that it remained tightly closed.

After 4 weeks of consolidation, the device was removed surgically under general anesthesia. This procedure entailed reopening the mucosa sharply and elevating bilateral mucosal flaps to expose the device. The screws were removed manually, and the device was extracted. On removal of the device, there was a small gap in the oral mucosa only at the area where the jack-screw had protruded and there was no previous primary closure. This gap was easily closed by undermining the oral mucosal flaps, which released tension and allowed for primary closure. Therefore, at the time of device removal, all fistulae in

Figure 2. Sequential steps of the distraction osteogenesis procedure illustrated alphabetically in chronological order. Copyrighted illustrations are reproduced with the permission of Mayo Foundation for Medical Education and Research, Rochester, Minn.
The oral mucosa were closed primarily. The dogs were observed and serially killed at 2-week intervals with 15 mL of IV pentobarbital sodium solution. Fluorochrome labels were given before the dogs were killed. Eleven days before an animal was killed, we injected 10 mg/kg of fluorescein-methylene-iminodiacetic acid (Calcein; Sigma Chemicals, St Louis, Mo). Four days before killing, we injected 30 mg/kg of IV tetracycline (Sigma Chemicals).

Immediately postmortem, the hard palate was harvested, measured, and photographed. A core was cut and preserved for histologic analysis. After fixation for a minimum of 2 days in 70% ethanol, the tissue specimen was dehydrated in a series of increasing concentrations of ethanol and embedded without de-mineralization in a mixture of methyl methacrylate and 2-hydroxyethyl methacrylate (12:5:1 for optimal retention of fluorochrome label). Embedded palatal tissues were sectioned in the coronal plane at a thickness of 5 µm. Sections were mounted unstained and viewed with a fluorescence microscope (Nikon Eclipse E400; Nikon, Tokyo, Japan) to detect the fluorochrome labeling. Serial sections were stained with Goldner's Masson trichrome stain (Sigma Chemicals) for morphologic identification of osteoblasts and skeletal tissue.

### RESULTS

The surgical procedure and subsequent device manipulations were well tolerated by all the dogs. All dogs began oral intake of a soft diet within 3 days postoperatively. None required supplemental nutrition or hydration. There were no airway complications. No excessive bleeding, hematoma, or infection occurred in relation to the operation. In 2 dogs, a minor ulcer developed on the midline of the tongue from contact with the protruding jack-screw. These wounds healed spontaneously. No complications developed from the fluorochrome injections.

In the control animals, the mucosa was not approximated and did not heal. In contrast, in the experimental dogs, the mucosa was suture approximated at the end of the initial procedure. Examination showed adequate mucosal healing in all experimental dogs.

The methods and results of bone healing for each dog are summarized in the Table. In the control animals, no bony migration or bony healing in the midline was observed on gross inspection. In control dog 2, the left transport disk had fractured in the middle but was still secured to the plate. Granulation tissue had grown between the osteotomy lines. In contrast, 7 of the 8 experimental dogs had new bone formation at the site of distraction. Complete bone migration and cleft closure were achieved in 5 of these 8 dogs. The transport disks were distracted toward the midline, and there were areas of new bone formation bilaterally. In these cases, the transport disks had fused grossly in the midline to provide secure bone closure of the cleft. One experimental dog did not have bony distraction or cleft closure. In 2 other dogs, cleft closure was incomplete. In the dogs with poor cleft closure, the transport disk had fractured or resorbed. Frequently, granulation tissue had grown in the line of the osteotomies as well as in the midline cleft. The palates of a control dog and an experimental dog are compared in Figure 3.

Our results were confirmed at the cellular level through histologic analysis of the specimens, which showed the temporal and osteogenic response to distraction. The appearance of osteoblasts and resorption lacunae signaled the initiation of the remodeling process. With time, an increased area of bone surface was covered with osteoid. This was demonstrated by numerous bone-forming osteoblasts interfacing with the surface of nonmineralized bone matrix (Figure 4). Fluorochrome labels deposited in mineralizing tissues allow the pattern of bone growth to be analyzed. As shown in Figure 5, the bone surface was extensively double-labeled with bone fluorochromes, indicating high turnover of bone during the healing process. By 10 to 12 weeks, formed osteoid was almost completely mineralized, as demonstrated by the bone occupying the surgically created cleft.
Recent efforts to improve surgical therapy of cleft palate have focused on presurgical manipulation of tissue. The dentoalveolar appliance is an example of this. This device puts tension on the alveolar ridges and slowly brings them into closer approximation. At the time of definitive repair, the alveolar cleft is not as wide and gingivoperiosteoplasty can be performed. This essentially closes the alveolar cleft and frequently obviates the need for later grafting with iliac crest cancellous bone. This represents an important advance in cleft palate surgery. However, such appliances do not address the bony and soft tissue defects of the secondary hard palate. Some of the innovations attempted here include preoperative or intraoperative expansion of the soft tissue. The goal is to recruit soft tissue to achieve a tension-free closure. This potentially would decrease the incidence of persistent oro-nasal fistula, velopharyngeal insufficiency, and perhaps midfacial growth impairment. This intervention is too recent for long-term evaluation of its efficacy.

Distraction osteogenesis was first introduced in orthopedic surgery nearly 100 years ago by Codvila. Distraction osteogenesis is a technique in which bone is lengthened gradually under tension after osteotomy. The process relies on the mechanical induction of new bone formation between bony surfaces that are gradually separated.
Port osteogenesis is a specific type of DO in which a transport disk is created and moved to fill in a defect. First, osteotomies are made and the distraction device is applied. A short latency period is allowed to elapse before the distraction phase begins. The bone segments are separated by about 0.5 to 1 mm/d, and osteogenesis is induced between the 2 bone segments. After the bone has been distracted the selected distance, a consolidation period ensues during which the device is left securely in place to hold the bone segments in their new position. The regenerate of immature bone that was laid down is allowed to mature and remodel. Ilizarov’s technique of osteodistraction also demonstrated distraction histogenesis.12 The tension placed on the bone as the segments are gradually separated also stimulates soft tissue expansion and accommodation of the lengthened bone. Not only is new bone created but any related muscles, blood vessels, nerves, and mucosa also elongate.

In 1973, Snyder et al13 reported the first experimental work with DO in the craniofacial region. They elongated the mandible in a canine model. Karp et al14 repeated these experiments in the same animal model and further analyzed histologically the newly formed bone. They described a central zone of fibrous tissue that developed parallel to the force of distraction and described lateral zones of new ossification.15 The clinical report of craniofacial DO was that by McCarthy et al13 in 1992. They described gradual mandibular elongation in patients with congenital hypoplasia. This early work was the springboard for future application of DO, and soon the technique was applied throughout the craniofacial skeleton, including the maxilla, orbits, cranium, and mandible. Recently, DO has been applied in reconstructive procedures of secondary cleft palate. Clefts of the alveolus, retruded midface, and velopharyngeal insufficiency have all been addressed with DO instead of more traditional surgical techniques.3,4,6,16 Distraction osteogenesis is used not only to elongate bones but also to change their form and structure and to reconstruct ablated defects of the facial skeleton.

In 1997, Carls et al17 published a study on the use of DO for lengthening the hard palate in a canine model. In their study, 6 adult dogs had palatal osteotomies and application of an orthodontic distraction device. These authors achieved 7 to 10 mm of posterior distraction of the alveolus, retruded midface, and velopharyngeal insufficiency have all been addressed with DO instead of more traditional surgical techniques.3,4,6,16 Distraction osteogenesis is used not only to elongate bones but also to change their form and structure and to reconstruct ablated defects of the facial skeleton.

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Ascherman et al18 also studied hard palate lengthening with DO in a canine model. They used a 10-day latency period, and distracted at a rate of 0.675 mm/d for 15 consecutive days, with 8 weeks of consolidation. All 5 dogs they studied had new bone formation at the site of distraction. Ascherman et al18 concluded that it is possible to lengthen the canine hard palate with DO.

Another relevant study is that by Liu et al,19 who conducted suture expansion osteogenesis for the management of the bony and soft tissue defect in a cleft palate model in 45 young dogs. Instead of using a typical DO device, Liu et al used a ring-shaped suture expander made of nickel titanium alloy. This material has shape memory and was fixed to the palate with transmucosal pins. In one arm of the study, the researchers used suture expansion to achieve closure of a surgically created midline palatal cleft. In another arm of the study, they applied the suture expander transversely to distract the maxilla anteriorly and the hard palate posteriorly. They achieved 5 to 6 mm of anterior maxillary advancement and 5 mm of posterior displacement of the palatal bone. They concluded that bony closure of a surgically created hard palate cleft is possible with a ring-shaped suture expander made of nickel titanium alloy. This experiment avoided osteotomies and demonstrated the osteoinductive capacities of craniofacial sutures.

To our knowledge, the use of DO for the closure of secondary cleft palate defects has not been described in the English-language literature. The application of DO in this area has several potential benefits. The idea is to apply the DO device as a presurgical intervention. Inducing new bone and concomitant soft tissue growth would create a more favorable setting for definitive repair. The goal would be to align and approximate the hard palate shelves. Definitive surgical repair could then be performed. The repair could be performed at the time of device removal and would be a relatively simple procedure of suture approximating the mucosa in the midline. Little mucosal undermining would be required; the suture line would have minimal tension; and hard palate bone would not have any exposed areas at the end of the procedure. Furthermore, the bony shelves would meet and fuse. The repair would truly be able to reconstitute normal anatomy by providing a competent bony and mucosal hard palate. By not leaving exposed bone, midfacial growth would potentially be more normal. This could eliminate the need for major secondary reconstructive procedures. Also, the repair would be more secure and less likely to have dehiscence and persistent oronasal fistula. Finally, the repair of the soft palate would also benefit because the closure would be tension free and more secure. This may decrease the incidence of subsequent velopharyngeal insufficiency.

The results of our study demonstrate that the use of DO for closure of a cleft palate is potentially feasible. Some degree of new bone formation was observed in 7 of 8 experimental dogs. Furthermore, complete cleft closure with fusion in the midline was achieved in 5 dogs without any complication. This clearly was better than the results observed in the control dogs. The factors most important to successful DO are the biomechanical rate and rhythm of distraction, the blood supply to the tissue and bone, the soft tissue compliance, the stability of the rigid fixation, and the bone type on which the distraction is per-
formed. Periosteum is highly vascular and is a critical component in supplying blood to the bone undergoing distraction.12 In our series of successful cases, the distractor was able to maintain rigid fixation of the transport disks, to keep them in the desired plane of distraction, and to separate them at a controlled rate.

However, 1 of the 8 experimental dogs did not demonstrate any bone distraction, and cleft closure was incomplete in 2 others. Devascularization of the transport disks was the likely cause of inadequate healing in these dogs. Elevation of the oral mucosa, inadvertent interruption of the nasal mucosa, and screw placement all compromise the blood supply to the transport disks. Perhaps a critical devascularization point was reached, causing the devitalized bone to resorb rather than maintain its osteoinductive capacities.

Careful analysis of our failed cases serves as an introduction to new areas of research and innovation. Through collaboration with mechanical engineers, surgeons can continue to improve DO devices. The continuing goal will be to create less invasive, more agile distractors capable of operating in multiple vectors. Different methods of device fixation and force application are also worth investigating. Attempting DO without osteotomies is another modification being considered.19 Specifically in regard to cleft palate, future innovations could focus on distracting the cleft alveolus along with the hard palate. Furthermore, in the current technique, DO requires multiple insults to the periosteum and this may impair facial growth. Through creative insight, perhaps the technique can be modified so that the integrity of the periosteum is preserved. Then, it will be important to conduct studies on young animals and follow craniofacial growth to accurately predict the potential benefits of DO. Finally, the design of this study did not test the feasibility of distraction histogenesis in cleft palate repair. Yet, the expansion of soft tissue is an important attribute of distraction osteogenesis. This project successfully achieved distraction of the hard palate bone. Future projects will attempt to distract bone and soft tissue as a subsequent step in the research process before applying the technique to patients.

In conclusion, our study has demonstrated that the application of DO techniques in the closure of a surgically created hard palate cleft in a canine model was safe and well tolerated. In most cases, it was effective in achieving bony closure of the cleft. The results of this study are promising and warrant further investigation of the innovative use of DO in the treatment of children born with cleft palate.

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