



Reconstruction of cleft palate with bone morphogenetic protein in sheep: a feasibility pilot study

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ARTICLE INFO	ABSTRACT
<p>Article Type: Original Article</p> <p>Received: 6 Sep 2014 Revised: 13 Oct 2014 Accepted: 15 Nov 2014</p> <p>*Corresponding author: Mohammad Bayat Department of Oral and Maxillofacial Surgery, Craniomaxillofacial Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran.</p> <p>Tel: +98 21 84902473 Fax: +98 21 84902473 Email: bayatm@sina.tums.ac.ir</p>	<p>Introduction: Surgical repair of cleft palate with a bony bridge may offer some distinct advantages including a lower rate of fistula formation. The goal of this study was to evaluate the feasibility of surgically inducing cleft palate and reconstruction of the cleft with the use of bone morphogenetic protein-2 (BMP-2) in sheep.</p> <p>Materials and Methods: In the control group (two sheep), the cleft palate was repaired with standard von Langenbeck technique. In the study group (two sheep), the cleft was repaired with the same technique with the exception that a BMP-2 gel was placed between the two oral and nasal layers. Two months after cleft repair surgery, animals were sacrificed and the cleft sites were evaluated histologically with the use of light microscopy.</p> <p>Results: The results showed that surgically inducing cleft palate and repairing the cleft is feasible in sheep. Microscopic evaluation showed no bone formation in control group and minor bone formation in the study group.</p> <p>Conclusion: To determine whether BMP-2 is a useful adjunct to standard cleft palate repair techniques, an animal study with larger population is required.</p> <p>Keywords: Cleft palate, Reconstruction, Bone morphogenetic protein, Sheep.</p>

Introduction

There are multiple techniques to repair cleft palate including von Langenbeck, Bardach, Wardill-Kilner, and Furlow [1]. All these techniques attempt to use local flaps to provide a soft tissue seal in the hard palate and a functional reorientation of muscles in the soft palate. None of these techniques attempt to provide a bony bridge in the hard palate and the ultimate goal would be a soft tissue seal [2].

Recent advancements in bone regeneration materials could potentially be helpful in improving the outcome of cleft palate surgery [3]. Bone morphogenetic protein-2 (BMP-2) is widely studied and one of the most successful osteoinductive materials currently in use both in clinical and experimental settings [4,5]. However its potential to enhance the outcome of cleft palate repair has not been examined. The goal of this study was to evaluate the

feasibility of surgically inducing cleft palate in sheep as well as surgical repair of the cleft with the use of BMP-2 as an adjunct to standard von Langenbeck technique.

Materials and Methods

A total of five sheep were used as test subjects in this study. In the control group, two male sheep (aged 1 month) underwent a surgery to make an artificial cleft-like defect in their hard palate. This first stage surgery was performed in an aseptic condition under general anesthesia with the use of intramuscular ketamine (1mg/kg). A prophylactic dose of penicillin G Procaine (800,000 IU) was administered intramuscularly 30 minutes before surgery. A 5mm-wide and 2cm-long anteroposterior cleft-like defect was created in the midline of the hard palate with the use of a surgical bur. The surgical defect was made so that a route of communication was created between the oral

and nasal cavities. Hemostasis was achieved with the use of tranexamic acid-impregnated gauze pack for 15 minutes. After recovery from general anesthesia, the sheep remained under close observation for signs of bleeding and infection of the surgical site. One month later, the surgically created cleft-like defect was repaired with the standard von Langenbeck technique. This second stage surgery was also performed in aseptic conditions under general anesthesia.

In the experimental group, two male sheep (aged 1 month) underwent the exact first and second stage surgical procedures with the only exception of using BMP-2 as an adjunct to cleft repair. The used BMP-2 containing product was Rafugen BMP-2 DBM Gel (Cellumed, Seoul, Korea). This product consists of recombinant human BMP-2, demineralized bone matrix, and porcine collagen. The consistency of the product prevented it from dissipating from surgical site once formed into defect. After repairing the nasal side, 0.5 cc of the product was placed in the defect and the oral mucosa was tightly closed over the gel.

Two months after second stage surgery, all four sheep were sacrificed and portions of the hard palate containing the cleft-like defect were removed and placed in 10% formalin solution for histologic evaluation using light microscopy. One male sheep that did not undergo any surgery was also sacrificed at the age of 4 months and a section of its hard palate was prepared for histologic evaluation similar to the study and control groups.

Results

All four sheep survived the first and second stage surgical procedures under ketamine anesthesia. The postoperative period was unremarkable and bleeding from surgical site was not significant.

Histologic evaluation of the hard palate in the unoperated sheep revealed normal mature bone, with abundant osseous matrix and osteoblast-like cells (Figure 1). In the control group, necrotic and fibrous tissue was abundant, without any bone matrix and cells (Figure 2). In the study group, minor amount of bone matrix was observed without any osteoblast-like cells (Figure 3). Necrotic tissue and amorphous cartilage-like matrix was also noticeable.

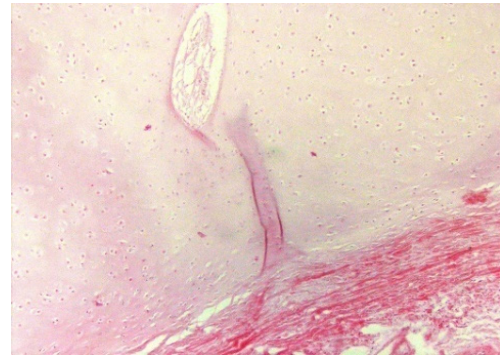


Figure 1. Normal bone and overlying epithelium from the intact hard palate of a sheep.

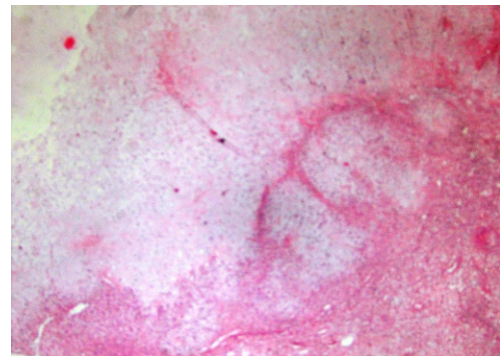


Figure 2. In the control group, the gap was filled primarily by a fibrous tissue and necrotic bone was evident in gap margins.



Figure 3. In the study group, the gap was mainly filled with an amorphous material, without significant new bone formation.

Discussion

There are at least three plausible advantages in closing cleft palate with bony bridge instead of soft tissue. First, a bony bridge may provide a support for soft tissue seal and thus reduce the risk of fistula formation following conventional cleft palate repair. Second, a transverse bony bridge across the palate acts as a strong horizontal buttress that provides strength and support for the facial skeleton. Third, a bony bridge across the palate could possibly make future orthognathic surgery

more reliable and less prone to relapse, particularly in a transverse direction.

This pilot study was designed to assess the feasibility of using BMP2 for cleft palate surgery to achieve a bony bridge and evaluate the possible side effects. The results showed that surgical creation of a cleft-like defect in sheep is possible and this procedure and the resultant defect does not threaten the survival of the animal. Furthermore, the results showed that surgical repair of the cleft-like defect is possible and reasonably successful. The main disadvantage of this study was that the sheep were not newborn and less growth potential remained as compared to an infant with cleft palate. An animal model in which the surgical defect is created in utero might be more promising. To further develop this model, more experiments with larger and younger populations are recommended.

At present, there is no satisfying animal model accurately simulating cleft palate in a standardized defect, and furthermore, providing the possibilities for extensive surgical procedures [6-8]. A number of authors (e.g. Wenghoefer and colleagues) have attempted to develop such a model [9]. Papadopoulos and colleagues [10] developed a sheep model for alveolar cleft repair and showed the feasibility of intrauterine autogenous bone transplantation for cleft repair.

Conclusions

To determine whether BMP-2 is a useful adjunct to standard cleft palate repair techniques, an animal study with larger population is required.

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Conflict of interest: The authors declared no conflict of interest.

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