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A New Model of Skull Base Reconstruction following Expanded Endonasal or Transoral Approaches – Long-Term Results in Primates

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Key Words
Bone reconstruction model · Primates · Silicone plug · Cerebrospinal fluid leakage · Skull base surgery

Abstract
Objective: The direct endonasal or transoral transclival approaches to the skull base permit effective minimally invasive surgery along the clivus region. Developing consistently effective techniques to prevent cerebrospinal fluid (CSF) leaks and their consequences (infections and healing processes with long and complicated recoveries) remains a major challenge. In this study, we tested over a long period a method of bone reconstruction newly developed by us, which makes use of a specially designed elastic silicone plug that can be employed for bone replacement after minimally invasive skull base surgery without risk of postoperative CSF leaks. After acute testing of plug efficiency in a pig model, which showed a 100% closure of the bone defect without CSF leak, we now tested the long-term accuracy of the plugs. ***Methods:*** In 3 primates, we used an endoscope-controlled transoral transclival approach and after opening the dura we simulated a CSF leakage. We inserted the plug into the bone defect and closed the mucosa of the oral cavity with stitches. The follow-up included blood, weight, and wound control 1, 4 and 8 weeks postoperatively. Social behavior, such as reintegration and postoperative eating abnormalities, was also studied. The aims of this study were: (1) testing the biocompatibility of the material; (2) development of infection against the foreign body; (3) effects of the plug on the surrounding bone, and (4) development of CSF leakages during the postoperative phase. ***Results:*** Clinically no infection was seen. Wound healing, immediate and long-term postoperative social behavior of the animals, feeding and body weight were normal. No CSF leakages developed. The histological examination of the clivus bone showed no abnormalities. The implant was covered by fibrous layer; there was no bone atrophy but osteoid formation. ***Conclusion:*** This novel medical device allows easy, fast and uncomplicated, leak-proof closure of bone defects after minimally invasive craniotomies as seen in transsphenoidal or transoral skull base approaches.

Introduction

Harvey Cushing first popularized the transsphenoidal route to the sella region, and Jules Hardy refined it by adding the operating microscope. With the evolution of endoscopic approaches, the natural expansion of their use to intradural lesions followed. Postoperative cerebrospinal fluid (CSF) leakage is one of the most common complications [1–5]. It is usually amenable to spinal subarachnoid drainage or re-exploration and repacking of the sella by use of various methods and materials [2, 4–8].

Effective and consistent reconstruction of the dura mater has been a major challenge that has significantly hindered the extension of transsphenoidal approaches to the perisellar region [4]. Over the past decade, significant

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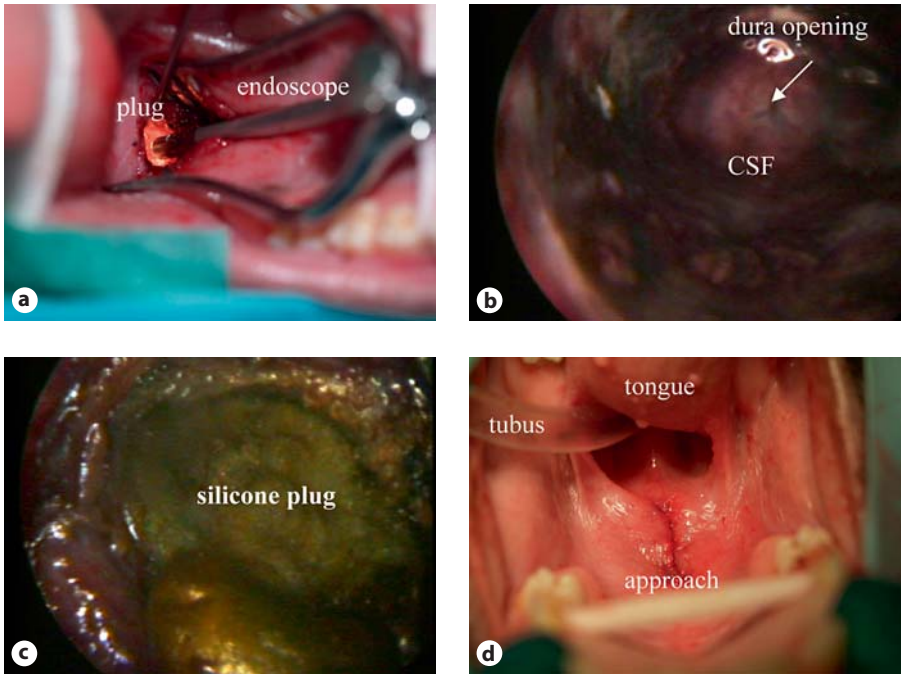

Fig. 1. a Endoscope-controlled transoral approach. **b** Simulation of a CSF leakage. Insertion of the plug into the bone defect (**c**) before closing the mucosa of the oral cavity with stitches (**d**).

anatomical and instrumentation advances have been made, facilitating the exposure and resection of intradural lesions via a fully endoscopically expanded endonasal approach. For this approach to become a viable option, the paramount concerns surrounding consistent reconstruction of the dura mater must be overcome [4].

During consideration of this serious problem in endonasal skull base surgery we searched for an easy, fast, practical and biocompatible application for the human body. We developed a specially designed silicone plug from a biocompatible material, which adapts elastically to fill out the bone defect. The plug is covered with a specially prepared thin antibiotic layer to protect the surrounding environment against infections and to enhance bone growth.

After acute testing of plug efficiency in a pig model, which showed a 100% closure of the bone defect without CSF leak [9], we now tested the long-term accuracy of the plug in 3 primates with a follow-up of 2 months.

Materials and Methods

Silicone Plug and Antibiotic Impregnation

Ellipsoid-shaped plugs were made from soft, tear-proof and elastic medical silicone rubber (Shore hardness 23, 10 mm in diameter). The silicone material we used to form the described plug is identical to the silicone material used for shunt catheters by implantation in hydrocephalus. Furthermore, a delayed leak cannot develop due to the fact that this silicone material is not known to shrink after implantation or to change its appearance in any other way.

The ball could easily be inserted into the craniotomy defect. The implanted material was covered with a thin antibiotic layer. We used an impregnation technique to incorporate antibiotics [10] (rifampin for Gram-positive and sparfloxacin for Gram-negative bacteria) in the silicone plug and tested the antibiotic release in vitro for 45 days. We compared the bacterial colonization between silicone plugs which were impregnated and those which were not impregnated with antibiotics.

Experiments

To test the long-term plug efficiency of the new technique, monkeys (n = 3, male, *Papio hamadryas*) with a mean weight of 15 kg were used. Under general anesthesia with 50 mg ketamine plus 10 mg xylazine and 0.1 mg atropine we performed an endoscope-controlled transoral transclival approach (fig. 1a) and simulated a CSF leakage after opening the dura (fig. 1b). The size of the craniotomies was 8 mm in diameter and the dura opening 7 mm. Silicone plugs with a diameter of approximately 120% compared to the existing craniotomy were selected, so that the slightly squeezed plugs could be easily placed into the existing opening.

We inserted the plug into the bone defect (fig. 1c) and closed the mucosa of the oral cavity with stitches (fig. 1d).

The postoperative follow-up included blood, weight, and wound control after 1, 7, 30 and 60 days. Because of the difficulty in obtaining CSF in animals it was decided to perform a liquor puncture only in cases with clinical signs of wound infection, or meningitis, even if the blood tests showed an increase in infection

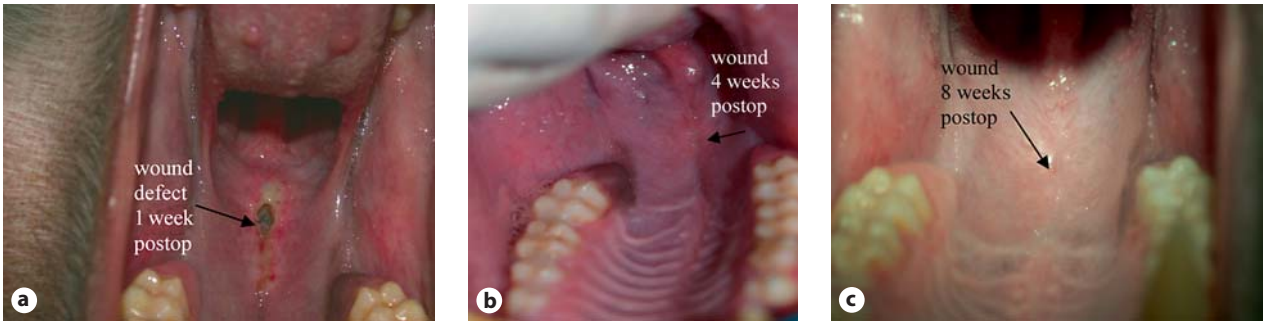

Fig. 2. In the first primate, wound control within the first postoperative week (**a**) showed wound opening due to scratching. 4 (**b**) and 8 weeks (**c**) postoperatively, complete healing of the wound could be observed.

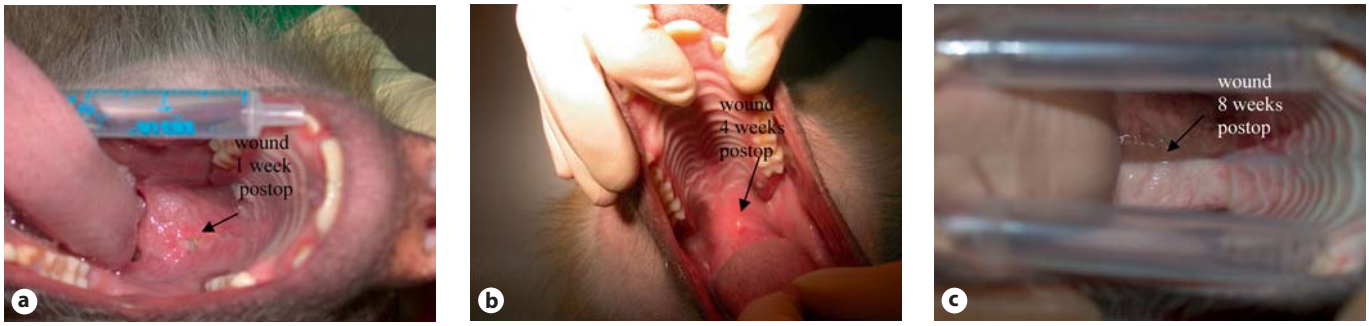

Fig. 3. No healing interference was observed in the 3rd primate at 1 (**a**), 4 (**b**), and 8 (**c**) weeks postoperatively.

parameters. Social behavior, such as reintegration and feeding habits, was also studied.

The aims of this study were to examine the biocompatibility of the material, the development of infection against the foreign body, the effects of the plug on the surrounding bone, and the development of CSF leakages during the postoperative phase.

Pathological and Histological Analysis

Eight weeks after plug implantation the animals were sacrificed. Internal organs were removed and examined macroscopically. The heads were fixed in formalin for 4 days and samples were taken from the implant sites. These were dehydrated in 70% alcohol and xylol and embedded in methacrylate; 4- to 5-μm sections taken from the bone surrounding the implants were histologically examined.

Results

Clinical Results

During the 2-month follow-up period of the 3 primates, weight changes were monitored. In all 3 animals, we saw not only a stable weight but also a normal weight gain of 1–2 kg, which is indicative of successful transoral feeding. Furthermore, temperature, feeding and social habits as well as the wounds were controlled. Temperature was consistently normal, suggesting that clinical signs of an infection were absent. Feeding habits were normal, with no alteration in the amount and type of food. Social behavior within the group, for example playing, fighting and mating patterns in the cage, was also seen to be normal as of the first postoperative day. Integration within the group was immediate.

In 2 primates, wound control within the first postoperative week showed minor openings, due to the fact that primates are aggravated by stitches – a foreign body – and scratch them to eliminate the feeling. This resulted in a few stitches being removed and in wound opening (fig. 2a). Despite this fact, observations after 4 (fig. 2b) and 8 weeks (fig. 2c) showed complete healing of the wound, so that it was no longer possible to identify the exact location of the wound. No healing interference was observed in the 3rd primate at any time (fig. 3a–c).

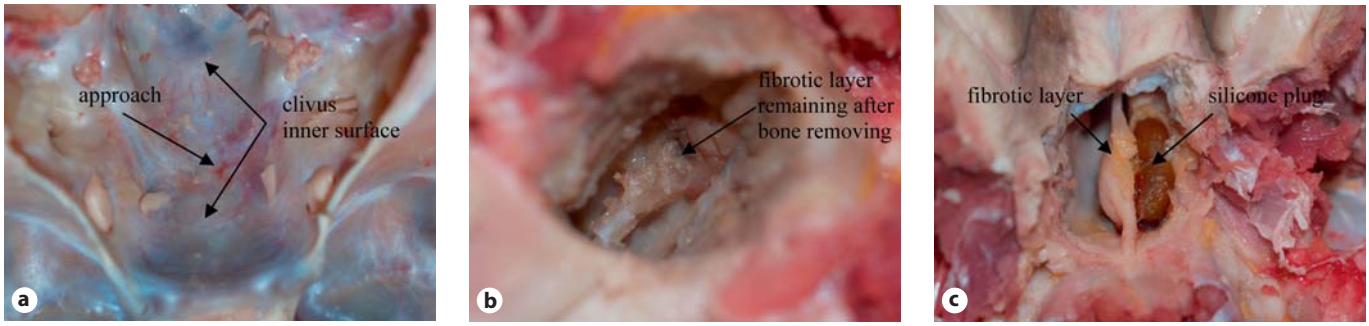

Fig. 4. Good healing of the dura (**a**), strong fibrotic layer (**b**). No infiltration of the implant through the fibrosis (**c**).

Blood cell count results were controlled on the 1st and 7th day as well as 4 and 8 weeks postoperatively. Leukocyte count remained stable during the whole observation period.

Regarding a possible CSF leak at the skull base neither the clinical behavior nor the healing of the wound showed any serious abnormalities. Therefore, it was assumed that no CSF leakage was present.

Autopsy Results

A slight spleen hypertrophy was seen which was identified by the animal pathologist as a reaction to a foreign body but not pathologically proven. In comparison to other nonoperated primates examined at the Primate Institute, Göttingen, Germany, these changes were not seen as a disease but as a minor reaction to a foreign body.

Macroscopic Results of the Clivus Bone Including the Plug Material

None of the 3 animals showed changes of the brain substance or infection after opening the dura. The brain showed neither necrosis, fibrosis, arachnitis, nor infection.

After removing the brain the clivus showed no abnormalities (fig. 4a). Good healing of the dura was seen. The frontal surface of the clivus where the implant was positioned showed strong fibrosis (fig. 4b), which had grown over the surface of the implant. The implant itself exhibited no infiltration by fibrous tissue (fig. 4c). The fibrosis formed boundary layers over the implant, thus creating a barrier both against CSF leakage and invasion of bacteria.

Histological Results of the Clivus Bone Including the Plug Material

At the borderline between implant and craniotomy defect a thick fibrous layer had formed (fig. 5). No bone atrophy was detected. The bone in the surrounding area had reacted by building osteoid. At the time of animal death the remodelling mechanism of the clivus bone was not finished, which is not surprising [11]. Infection and signs of inflammation were not seen except for few lymphocytes. The foreign body reaction was moderate. Only in the second animal was one foreign body giant cell detected.

Discussion

Transsphenoidal approaches have been used for a century for the resection of pituitary and other sellar tumors. In the last decade, with progressive evolution in technology, the transsphenoidal approach had been expanded to remove lesions from the whole middle axis, such as the planum sphenoidale or clivus. The primary advantages are that it allows direct extracerebral access to the pathology, it avoids brain manipulation on important neurovascular structures and it permits a more favorable surgical trajectory for the removal of these difficult lesions. The reconstruction phase today still remains the most challenging step in this procedure. A limitation of this approach is the higher risk of postoperative CSF leak and the following complications, as compared with the transcranial route. Considering the difficulty in suturing through the nose, accurate reconstruction with a multilayer strategy has been recommended by various experienced groups [4, 12, 13]. Because of the obvious large dural defect and consequent intraoperative copious CSF leakage, reconstruction with the available methods is not sufficient [12]. A watertight closure of the defect is fundamental in preventing the complications related to postoperative CSF leakage [12, 13].

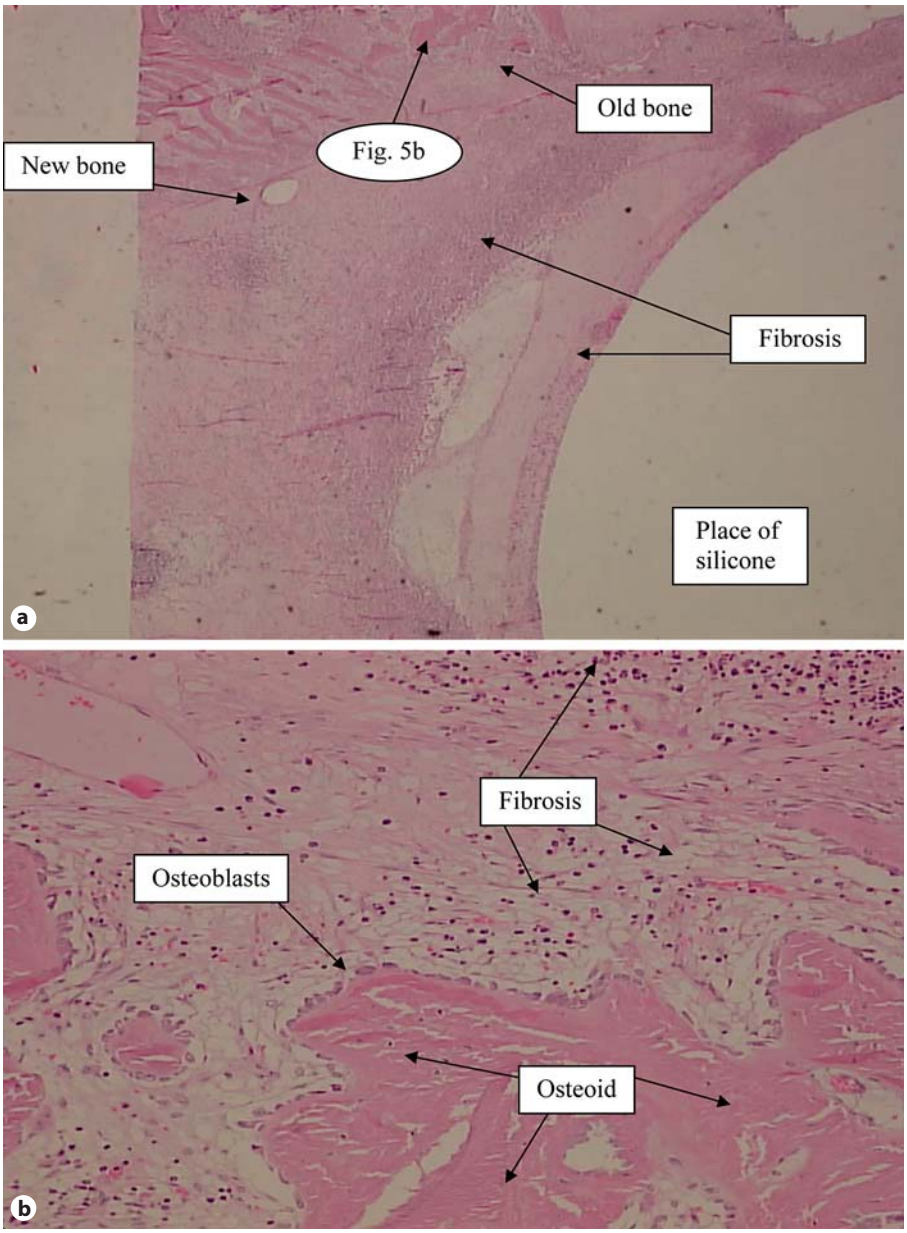

Fig. 5. Histological examination of the clivus bone. Appearance of a thick fibrosis layer and building of new bone. The material shows no infection, only a few lymphocytes are detected. **b** A magnification of **a**.

We have found that materials, in order to qualify for bone reconstruction in those areas, must obey strict rules. (a) Such material should have an origin not traumatic for the patient, i.e. it should not require further surgery for the removal of fat or muscle. (b) It should be easily applicable to the bone defect, and (c) have an elastic consistency allowing it to fill the craniotomy completely. (d) It should be easily adaptable to close craniotomies of irregular shape without protruding over the bone, and thus compressing neurovascular structures such as optic nerve, brainstem, or basilar artery. (e) The material should be biocompatible, and (f) guarantee acute and long-term tightness of the bone defect without the need for additional surgical or conservative therapies. (g) Implants might benefit from a cover with a thin layer to enhance bone growth. (h) The results showed that the impregnated silicone plug prevents the spreading of microorganisms in that it discharges antibiotics over a long period of time into the surrounding area. Moreover, the impregnated silicone plug should be suitable to inhibit contamination of the material during implantation not only by preventing colonization but also by killing bacteria preexisting in the surgical field.

The implants used follow these rules. The testing of the long-term accuracy of the plug in primates provided excellent results for ease of application, absence of infection or long-term CSF leakage and biocompatibility resulting in an easy, fast, uncomplicated, and biocompatible solution for reconstruction of the skull base bone after transsphenoidal or transoral skull base approaches. Because of the smooth consistence, the plug could be formed before and during implantation. Therefore, cutting in size was not necessary. Postoperatively the plug did not change its consistency.

De Divitiis et al. [14] showed that, in order to reach a satisfactory craniotomy in the clivus region, the bone defect must be extended approximately to 2 cm in length and 1.5 cm in width. Conceivable would be a medical set with different ellipsoid elements graduated in diameters. The smallest form would begin with a width of 1.5 × 1.2 cm (120%) and a length of 2 × 1.2 cm (120%) resulting in 2.4 and 1.8 cm and continue in 2-mm steps to 3 × 1.2 cm (120%) = 3.6 cm length and 2.7 × 1.2 cm (120%) = 3.2 cm width.

In order to introduce it into clinical practice industrial partners are required ready to produce sufficient quantities at an acceptable price. After this step, further clinical trials are required before using the plug in a daily routine.

Conclusion

This novel medical device allows for a leak-proof closure of bone defects left after minimally invasive craniotomies of the skull base; no additional surgeries or other therapies are necessary. The handling during application is easy and fast. The device itself is made of cost-effective and biocompatible material.

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