

## PAPER DETAILS

TITLE: Beyin omurilik sivisi rinoresi onanini: Tavsan modelinde insan temporal fasyasi, dura mater ve otolog kas fasyasi ile greftlemenin histopatolojik bulgularinin karsilastirilmesi

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## EXPERIMENTAL STUDY

# The repair of cerebrospinal fluid rhinorrhea: comparison of histopathologic findings with cadaveric human temporal fascia, dura mater, and autologous fascia in a rabbit model

Beyin omurilik sıvısı rinoresi onarımı: Tavşan modelinde insan temporal fasyası, dura mater ve otolog kas fasyası ile greftlemenin histopatolojik bulgularının karşılaştırılması

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**Objectives:** To evaluate the repair of cerebrospinal fluid rhinorrhea through the transnasal approach, we investigated histopathologic findings of grafting with human temporalis fascia and dura mater in a rabbit model.

**Design and Methods:** Thirty-two rabbits were assigned to three groups according to the graft material to be used: human dura mater, human temporalis fascia, and autologous muscle fascia (control group). The repair of the surgically induced bony opening was performed via the transnasal approach. To evaluate healing process histopathologically, decapitation was performed at the end of 1, 2, 3, and 4 weeks in the control group; 1, 2, 3, 4, 32 and 40 weeks in the dura mater group; 4, 32 and 40 weeks in the temporalis fascia group.

**Results:** Macroscopically, adhesions to the cerebral cortex were not observed with any of the grafts. Histopathologically, complete healing occurred in four weeks in the control group. Healing took longer in both cadaveric graft groups, in which formation of giant cells was the most prominent feature at the end of four weeks, suggesting a late rejection. Nevertheless, these cells disappeared and complete resolution was observed at the end of 32 and 40 weeks. Despite prolonged healing, no adverse clinical effects were observed.

**Conclusions:** This experimental model showed that human temporalis fascia can be used instead of dura mater in the repair of cerebrospinal fluid rhinorrhea.

**Key Words:** Cerebrospinal rhinorrhea/surgery; disease models, animal; dura mater/surgery/transplantation; fistula/surgery; graft survival; rabbits.

**Amaç:** Transnazal yaklaşımla beyin omurilik sıvısı rinoresi onarımını değerlendirmek amacıyla, tavşanda insan temporal fasyası ile dura mater greftleriyle onarımın histopatolojik bulguları değerlendirildi.

**Çalışma Planı:** Otuz iki tavşan kullanılan grefte göre üç gruba ayrıldı: İnsan dura mater, insan temporal fasyası ve otolog kas fasyası (kontrol grubu). Cerrahi olarak yaratılan açıklığın onarımı için transnazal yaklaşım uygulandı. Kontrol grubu denekleri 1, 2, 3, 4. haftalarda; insan dura mater kullanılan denekler 1, 2, 3, 4, 32 ve 40. haftalarda; insan temporal fasyası kullanılan denekler 4, 32 ve 40. haftalarda öldürülerek iyileşme ile ilgili histopatolojik bulgular değerlendirildi.

**Bulgular:** Hiçbir grupta makroskobik olarak serebral kortekse yapışıklık gözlenmedi. Kontrol grubunda yara iyileşmesi histolojik düzeyde dört haftada tamamlandı. Kadavra insan greftleri ile tedavi edilen her iki grupta ise iyileşme süreci kontrol grubuna göre daha uzun sürede tamamlandı. Bu iki grupta dördüncü haftada en belirgin bulgu geç bir atılım reaksiyonuna işaret edebilecek olan dev hücrelerin varlığı idi; ancak bu hücreler 32 ve 40. haftalarda tam bir iyileşmeyle kayboldu. İyileşme sürecinin uzamasına rağmen klinik bir yan etki gözlenmedi.

**Sonuç:** Bu deneysel model BOS rinoresi onarımında insan temporal fasyasının dura mater yerine kullanılabileceğini gösterdi.

**Anahtar Sözcükler:** Beyin-omurilik sıvısı rinoresi/cerrahi; hastalık modeli, hayvan; dura mater/cerrahi/transplantasyon; fistül/cerrahi; greft yaşaması; tavşan.

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A persistent communication between the subarachnoid space and the nasal cavity results in cerebrospinal fluid rhinorrhea, which can cause hazardous complications. Traumatic, tumoral, inflammatory, surgical, idiopathic, and congenital factors may play a role in its etiology. Intracranial or extracranial surgical repair is mandatory in most of the cases. The endonasal approach has become widespread among otorhinolaryngologists thanks to the development of endoscopic instruments and increasing experience in endoscopic nasal surgery. Successful results with low rates of morbidity also contributed to the popularity of this approach.<sup>[1-3]</sup>

The dura mater is an excellent protective barrier for the central nervous system and its reconstruction with a graft is the most important and basic step in surgery. Various graft materials such as metal foils, synthetic polymers, and animal membranes were used for this reconstruction, but these were associated with complications.<sup>[4,5]</sup> Autologous tissues were used to avoid graft rejection and excessive inflammatory response; however, donor site-related problems and the need for a second surgery were considered serious drawbacks.<sup>[6]</sup> These attempts have led to the investigation of other graft materials. Hence, repair of dura mater defects with dura mater itself has gained popularity with the introduction of human allografts. Fascia of the temporal muscle, which is well known by otolaryngologists as a dependable graft material in tympanoplasty, is another choice for this reconstruction. It is increasingly used in transnasal endoscopic repair. Temporal fascia can also be used as an allograft, but no experimental data are available to justify its use.

To our knowledge, all experimental studies have been performed with the use of the intracranial approach. In most of them, the graft was approximated to the dura mater with sutures, and in some, foreign body reactions were observed in histologic sections.<sup>[7,8]</sup> On the other hand, in the transnasal route, there is appreciably less space around the defect site for the surgeon and appropriate tightness of the graft may be more difficult to obtain.

The aim of this study was to evaluate the healing process of human cadaveric dura mater and fascia of the temporal muscle in a rabbit model. Unlike other experimental studies, endonasal approach was simulated. Autologous muscle fascia was used in the control group.

## MATERIALS AND METHODS

Cerebrospinal fluid rhinorrhea was induced in 32 New Zealand white rabbits, weighing 2,500 to 3,200 g. Three groups were formed according to the graft material to be used in the repair: solvent dried human dura mater (Tutoplast®, Tutogen Medical GmbH, Germany), solvent dried human fascia of temporal muscle (Tutoplast®, Tutogen Medical GmbH, Germany), and autologous muscle fascia (control group).

To evaluate healing process histopathologically, decapitation using overdose of pentobarbital was performed at the end of 1, 2, 3, and 4 weeks in the control group; 1, 2, 3, 4, 32, and 40 weeks in the dura mater group; and 4, 32, and 40 weeks in the temporalis fascia group. Early evaluations at 1, 2, and 3 weeks were excluded in the temporal fascia group because the pattern of healing was expected to be similar to that seen in the dura mater group.

The rabbits were anesthetized with intramuscular ketamine (35 mg/kg) and xylazine (5 mg/kg). For prophylaxis, 300,000 U penicillin G was administered perioperatively and on the first postoperative day. A midline incision was made through the skin and periosteum. Flaps were raised bilaterally. Autologous fascia of the frontoscutular muscle was collected only in the control group. This muscle was chosen because of the easy access through the initial incision. The bony opening was created with the use of an osteotome in the intercanthal area to expose the skull base-nasal cavity junction anteriorly. A bony window was created between the cranial and nasal cavities by excision of the bone in the ethmoid roof and the neighborhood cephalic nasal septum. The size of the window was approximately 4-5 mm x 8-9 mm. The dura mater was injured in most animals during this excision. A fistula was created by excision of the dura in the same size to fit the bony opening in all the rabbits. Grafts were prepared 6x10 mm in size that fitted the opening. Graft margins were placed between the dura mater and the bone. After grafting, the nasal cavity was packed with a sponge; anterior bony cover of the nasal dorsum was replaced and the overlying musculature, subcutaneous tissue and the skin were closed with 2-0 polyglactin sutures.

All the animals were monitored daily with regard to general condition, oral intake, loss of weight, wound infection, and symptoms related to central

TABLE I  
HISTOPATHOLOGIC SCORES ACCORDING TO THE GRAFT MATERIAL AND TIME

	Autologous muscle fascia				Human dura mater					Temporal muscle fascia	
	Week 1	Week 2	Week 3	Week 4	Week 1	Week 2	Week 3	Week 4	Week 32, 40	Week 4	Week 32, 40
Edema	2	0	0	0	2	0-1	0-1	0	0	0	0
Cellularity	2	1	0-1	0-1	2	2	2	2	0	2	0-1
Angiogenesis	2	1	0	0	2	1	0-1	0-1	0	0-1	0
Fibrosis	1	2	2	3	1	2	2	2	3	2	3

Scores: 0 - None; 1 - Mild; 2 - Moderate; 3 - Severe-significant.

nervous system such as ataxia and convulsion. All experiments were carried out in accordance with the institutional guidelines by the Ethical Committee for Laboratory Animal Use of Hacettepe University Medical Faculty.

After decapitation according to the experiment protocol, an *en bloc* excision of the fistula region was made 3x2x3 cm in size including the bony margins. All the specimens were fixed in formalin solution for 24 hours and decalcified in 40% formic acid solution for three days. They were then embedded in paraffin, sectioned in 5 µm thickness with a microtome and stained with Masson' trichrome and Van Gieson elastic stains in addition to routine hematoxylin and eosin.

## RESULTS

Three animals died during surgery because of bleeding or cardiorespiratory arrest. They were substituted for new ones. The remaining animals survived without any complications.

Macroscopically, none of the samples exhibited adhesions to the underlying cerebral cortex. Components of the healing process including development of granulation tissue, presence of edema, intensity of inflammation-cellularity, vascularization, and fibrosis were examined by microscopic examination and were rated semiquantitatively from 0 to 3 (0: none; 1: mild; 2: moderate; 3: severe-significant (Table I).

*Week 1:* Similar histopathologic findings were observed in both control and dura mater groups. A mixed cellular inflammatory reaction was seen, composed of lymphocytes, macrophages, and a small number of neutrophils. There was edema and a large number of small vessels (Fig. 1a). Basophilic acellular fascia residues were scattered around. Mild

collagen deposition and fibroblasts accompanied the reaction.

*Week 2:* In the control group, granulation tissue extended with a different composition compared to the first week. Edema was absent and a significant recession of inflammation was observed. Vascularization was not as remarkable as in the first week. There was a noticeable increase in collagen deposition.

In the dura mater group, however, histology was different. The repair process was slow. Although there was a decrease in edema, inflammatory reaction persisted with macrophages predominating. There was an ongoing fibrotic activity with collagen deposition.

*Week 3:* In the control group, angiogenesis and inflammation were totally replaced by fibrosis. Trichrome stain showed extensive fibrillar collagenization.

In contrast, healing process was far too low in the dura mater group. Inflammation rich in macrophages persisted, with macrophages forming clusters. Small vascular structures were still seen. Fibroblastic activity continued.

*Week 4:* In the control group, most of the graft area was replaced by cellular connective tissue (Fig. 1b). Trichrome stain revealed dense collagen fibers. Inflammation and vascularization totally disappeared.

In the dura mater group, however, there was a chronic inflammation characterized by clusters of macrophages and giant cells (Fig. 2). Vascularization was not significant. Fibrosis seemed to continue. In the temporal fascia group, findings were similar to those observed in the dura mater group.

*Weeks 32 and 40:* In both the dura mater and temporal fascia groups, the histologic features were sim-



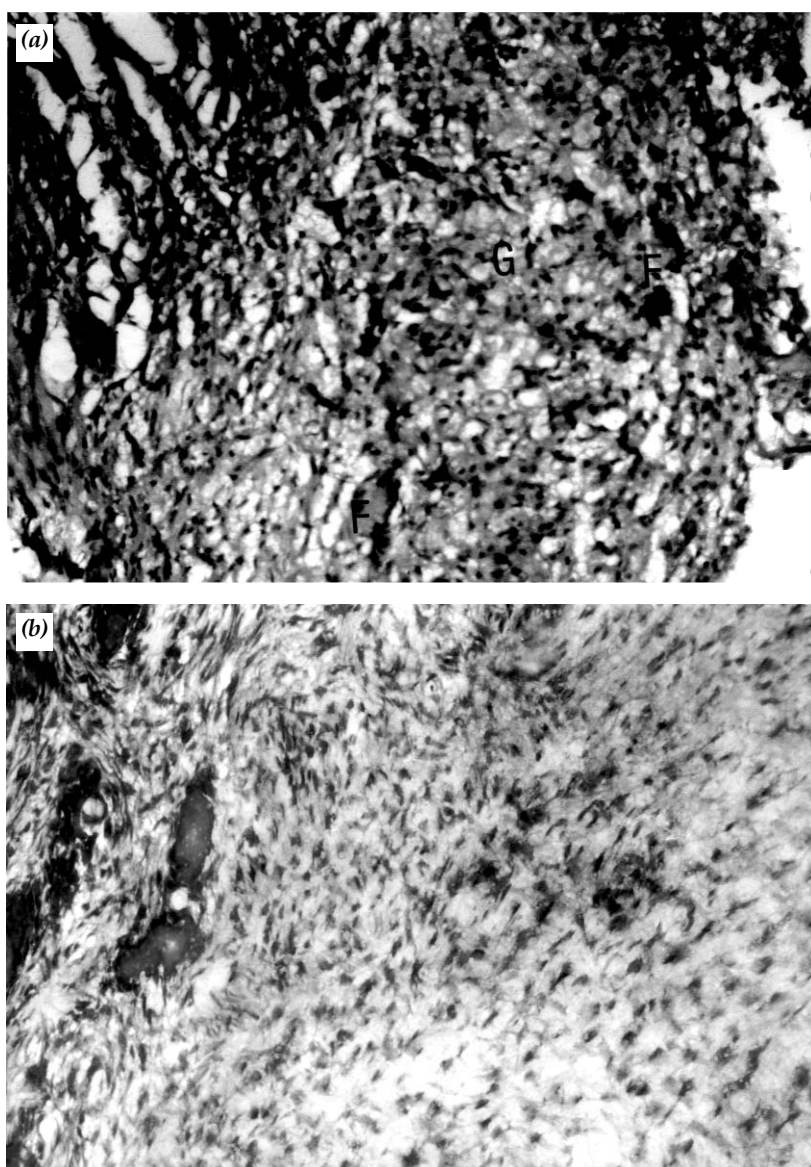
ilar to those seen in the autologous fascia group at week 4. Residual graft tissue was not observed. Chronic inflammation was replaced by dense connective tissue (Fig. 3).

The most rapid repair process was observed in the control group, with remarkable vascularization and inflammatory cell infiltration during the first two weeks. Fibroplasia which began in the first week replaced most of the graft area in four weeks (Fig. 4a). In the dura mater and temporalis fascia groups, angiogenesis and inflammatory cell infiltration also showed a peak followed by a gradual decline, but still persisted at the end of the fourth

week (Fig. 4b). In contrast to the control group, giant cells formed by the fusion of macrophages were observed. This inflammatory reaction and angiogenesis was replaced by a well-organized scar tissue in all biopsies at week 32 and 40.

## DISCUSSION

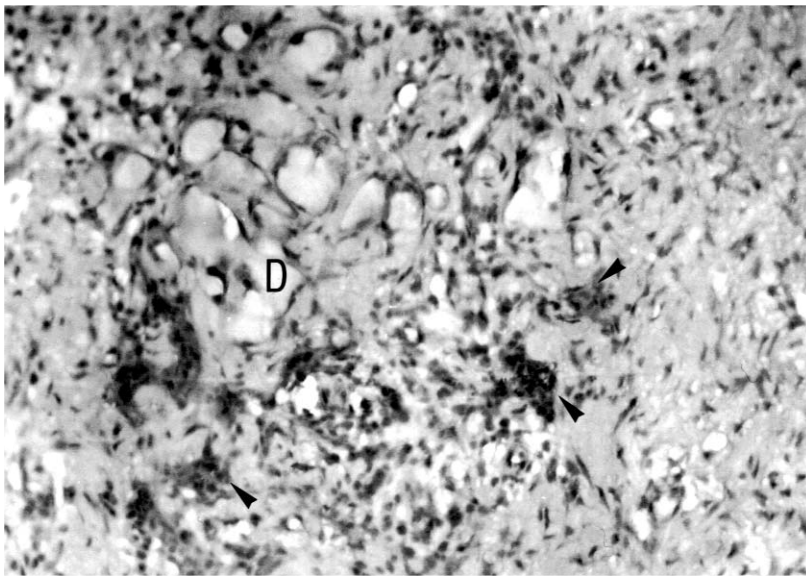
Surgical repair of dural defects is performed either by intracranial or extracranial approaches. In intracranial approach, duraplasty is performed under direct vision through a craniotomy as a neurosurgical procedure and even suturing of the graft is possible depending on the site of the lesion.



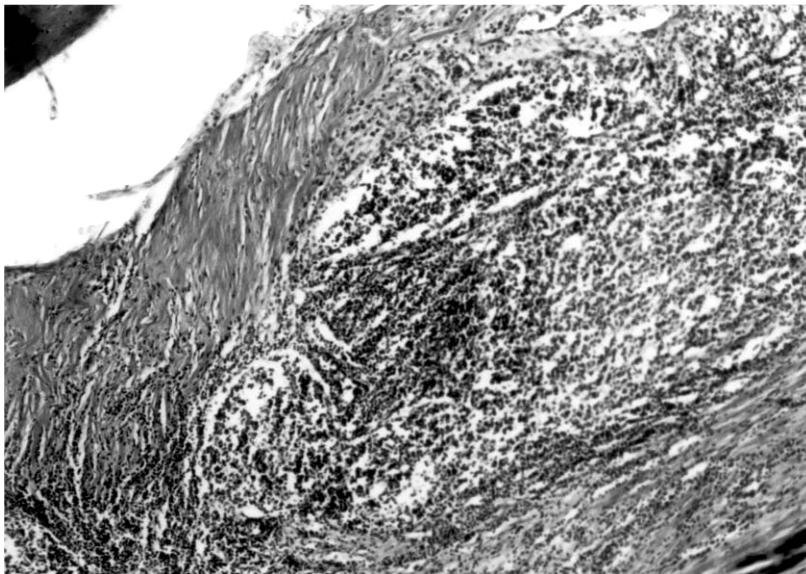
**Fig. 1 - (a)** Early granulation tissue (G) is seen around the autologous fascia (F) residues at the end of the first week. Increased cell density and formation of new small vessels are observed in the edematous granulation tissue. **(b)** At the end of the fourth week, granulation tissue is seen. It is collagenous and less cellular. Vascular structures decreased. There are no fascia residues in the area (H-E x 400).

Of extracranial approaches, transnasal endoscopic surgery has gained popularity in recent years due to a high rate of successful closures and a low morbidity rate. Although surgery through a narrow passage is difficult, it is a routine route for the experienced otorhinolaryngologist. Grafting the dural defect prevents leaking and infection by a tight closure between the nasal and cranial cavities and permits healing. Various materials have been used for this purpose, including metal foils, synthetic materials, and animal membranes, all of which have been abandoned because of complications.<sup>[4,5]</sup> Autologous tissue, such as fascia lata and pericranium was recommended to avoid excessive

inflammatory response and rejection. Autologous temporal fascia has been successfully employed by otolaryngologists in routine otologic surgical procedures, and has been increasingly used in the transnasal endoscopic repair of rhinorrhea.<sup>[9]</sup> Lyophilized or solvent dried human cadaveric tissues have been available in the market for a long time. Shorter operation time and avoidance of donor site problems have contributed to their wide use instead of autologous grafts. Human dura mater has become the most recommended cadaveric graft for intracranial repair of dural defects, with good surgical outcome.<sup>[10]</sup> Cadaveric graft of temporalis fascia is also available in the market,



*Fig. 2 - At the end of fourth week, granulation tissue is seen in the animal grafted with human dura mater. Dura mater graft residues (D) are still observed and surrounded by inflammatory cells with macrophages predominating. Arrow head indicates giant cell formation (H-E x 400).*



*Fig. 3 - At the end of 40 weeks, dense collagen bundles and aggregates of focal lymphocytes in the animal grafted with human temporal muscle fascia (H-E x 200).*

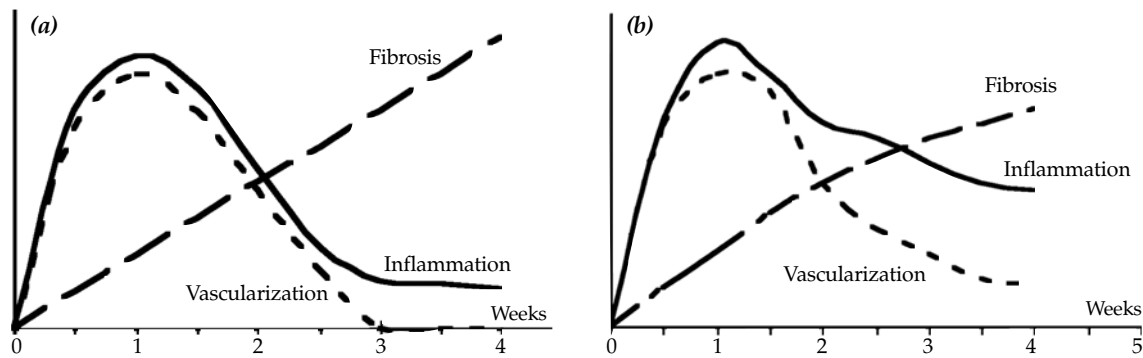


Fig. 4- Inflammation and healing process (a) in the control group, and (b) in the dura mater and temporal fascia groups

but an account on its histopathologic results is lacking. In this study, the use of temporal fascia was evaluated in comparison with human dura mater.

Transnasal repair is different from the intracranial approach in various ways. Grafts with epithelial lining can be used through the mucosal surface. Nasal packing is often necessary as part of a rhinologic procedure. Adhesions to the cerebral cortex may be less than expected since no additional dissection is required to reach the fistula site in the skull base. On the other hand, physical factors such as maintenance of the graft against cerebrospinal fluid pressure is more important. In contrast to the intracranial approach, the surgeon cannot suture the graft to the margin of the dura or freely place a graft of a larger size than that of the defect. These factors affect both healing and success. Histopathologically detected foreign body reactions can be attributed to graft sutures<sup>[7,8]</sup> which are not used in transnasal surgery.

Some experimental studies reported varying degrees of adhesions of the human dura mater graft to the underlying cerebral cortex.<sup>[8,11]</sup> In contrast, Filippi et al.<sup>[12]</sup> did not find any adhesions with human solvent dried and lyophilized dura mater, and autologous perichondrium. In our study, there no adhesions to the underlying cortex were observed with any of the grafts and it was impossible to distinguish the grafted site at weeks 32 and 40. Discrepant findings concerning adhesions may result from different surgical techniques used or from the degree of trauma caused in the surrounding tissues.

Inflammation and healing are so closely interrelated that they cannot be separated with distinct bound-

aries. Ideally, the inflammatory reaction is expected to neutralize the injury stimulus and should end with complete restoration. Healing by connective tissue replacement, in other words fibrosis, takes place after substantial tissue destruction. Sometimes the repair process begins as early as 24 hours following injury. If resolution has not occurred, fibroblasts and vascular endothelial cells begin to proliferate to form a granulation tissue. Histologic features of this process are the formation of new blood vessels and the proliferation of fibroblasts. These vessels are leaky, making the newly formed granulation tissue edematous. Chronic inflammation may follow acute inflammation or the response may be chronic from the onset due to persistent infection or to prolonged exposure to injurious stimulus. Delays in the degradation of foreign material cause prolonged exposure.<sup>[13,14]</sup> In our study, all the animals showed chronic inflammation. Graft material could not be adequately resorbed, resulting in delayed healing. Fibrotic scar tissue grew to replace the inflammation by time.

In the first stage of our study, healing was completed in the control group at the end of the fourth week, a result that obviated any further evaluations. However, this was not the case in the dura mater and temporal fascia groups, in which formation of giant cells was observed as an indication of foreign body reaction. Persistence of vascularization and inflammation might be due to the secretion of stimulatory growth factors and cytokines mediated by macrophages. Thus, healing process could result in a complete restoration or a late rejection.

In the second stage, postoperative period was extended to see the clearance of inflammatory reac-



tion. Early evaluations until the fourth week were not designed for the use of temporal fascia because no comparable findings were expected to be obtained.

In our study, autologous muscle fascia was better tolerated and resulted in faster repair compared to cadaveric grafts. However, the results of the second stage with both dura mater and temporal fascia grafts suggested that healing was delayed but was not interrupted. Inflammatory reaction continued to decrease and fibrosis continued to increase (Fig. 6), ending with complete restoration at weeks 32 and 40.

Distinct antigenic properties of a graft can cause rejection in allogeneous and xenogeneous transplantation. Acute rejection occurs in 7 to 10 days. Sensitization of the host by multiple transplantations shortens this period. On the other hand, inert materials have no antigenic properties and their rejection takes longer, which is mainly associated with chronic inflammation characterized by foreign body reaction or involvement of infection rather than antigen-specific response. Cadaveric grafts have reduced antigenicity due to the way they are preserved.<sup>[15,16]</sup> Observation of giant cells in this study suggests the influence of weak antigenic properties of the cadaveric grafts, inducing macrophage fusion and giant cell formation. Healing delayed in cadaveric grafts, but this delay was not associated with any clinical effects such as rhinorrhea or symptoms related to the central nervous system.

Long-term persistence of inflammatory reaction with giant cell formation has also been reported in other studies with the use of dura mater. Macfarlane and Symon<sup>[17]</sup> used lyophilized dura mater in baboons. After 12 months, they still observed foreign body giant cells. Meddings et al.<sup>[11]</sup> reported that those cells existed for six months in the rabbits treated with lyophilized dura mater.

In a recent study with rabbits, Kadioglu et al.<sup>[8]</sup> used solvent dried human dura mater as a dural substitute. They observed giant body cells for 90 days with human dura mater and, interestingly enough, with autologous fascia lata. They concluded that histopathologic findings at the end of 90 days were satisfactory, without any comment on the persistence of those cells and their influence on the progress of healing. However, the presence or absence of giant cells was not mentioned in some

studies in which microscopic evaluations were made.<sup>[12,18]</sup>

This study indicates that cadaveric temporalis fascia can be used in place of dura mater in the repair of rhinorrhea. Although, in recent years, the use of human dura mater graft is restricted in some countries due to the risk for Creutzfeldt-Jakob disease (CJD), it is still used in the USA with some strict criteria in processing and donor selection. There is indeed a potential risk for CJD infection when tissues associated with the central nervous system are transplanted. However, allograft temporal fascia is not related to neurological transmission, and thus, can be used as a dural substitute instead of cadaveric dura mater to minimize the transmission of this disease. In this rabbit model, wound healing delayed with both temporal fascia and dura mater grafts compared to autologous muscle fascia, without any clinical significance. Controlled clinical studies are required to determine whether this delay will also occur and cause a significant clinical effect on humans.

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**Objectives:** We evaluated histopathologic findings following repair of cerebrospinal fluid rhinorrhea with human temporalis fascia and dura mater using the transnasal approach in a rabbit model.

**Design and Methods:** Thirty-two rabbits were assigned to three groups according to the graft material to be used: human dura mater, human temporalis fascia, and autologous muscle fascia (control group). The repair of the surgically induced bony opening was performed via the transnasal approach. To evaluate healing process histopathologically, decapitation was performed at the end of 1, 2, 3, and 4 weeks in the control group; 1, 2, 3, 4, 32 and 40 weeks in the dura mater group; 4, 32 and 40 weeks in the temporalis fascia group.

**Results:** Macroscopically, adhesions to the cerebral cortex were not observed with any of the grafts. Histopathologically, complete healing occurred in four weeks in the control group. Healing took longer in both cadaveric graft groups, in which formation of giant cells was the most prominent feature at the end of four weeks, suggesting a late rejection. Nevertheless, these cells disappeared and complete resolution was observed at the end of 32 and 40 weeks. Despite prolonged healing, no adverse clinical effects were observed.

**Conclusions:** This experimental model showed that human temporalis fascia can be used instead of dura mater in the repair of cerebrospinal fluid rhinorrhea.

**Key Words:** Cerebrospinal rhinorrhea/surgery; disease models, animal; dura mater/surgery/transplantation; fistula/surgery; graft survival; rabbits.

**Amaç:** Tavşan beyin omurilik sıvısı (BOS) rinoresi onarımında transnazal yaklaşım kullanılarak insan temporal fasyası ile dura mater greftlerinin histopatolojik bulguları değerlendirildi.

**Çalışma Planı:** Otuz iki tavşan kullanılan grefte göre üç gruba ayrıldı: İnsan dura materi, insan temporal fasyası ve otolog kas fasyası (kontrol grubu). Cerrahi olarak yaratılan açıklığın onarımı için transnazal yaklaşım uygulandı. Kontrol grubu denekleri 1, 2, 3, 4. haftalarda; insan dura materi kullanılan denekler 1, 2, 3, 4, 32 ve 40. haftalarda; insan temporal fasyası kullanılan denekler 4, 32 ve 40. haftalarda öldürülerek iyileşme ile ilgili histopatolojik bulgular değerlendirildi.

**Bulgular:** Hiçbir grupta makroskopik olarak serebral kortekse yapışıklık gözlenmedi. Kontrol grubunda yara iyileşmesi histolojik düzeyde dört haftada tamamlandı. Kadavra insan greftleri ile tedavi edilen her iki grupta ise iyileşme süreci kontrol grubuna göre daha uzun sürede tamamlandı. Bu iki grupta dördüncü haftada en belirgin bulgu geç bir atılım reaksiyonuna işaret edebilecek olan dev hücrelerin varlığı idi; ancak bu hücreler 32 ve 40. haftalarda tam bir iyileşmeyle kayboldu. İyileşme sürecinin uzamasına rağmen klinik bir yan etki gözlenmedi.

**Sonuç:** Bu deneysel model BOS rinoresi onarımında insan temporal fasyasının dura mater yerine kullanılabileceğini gösterdi.

**Anahtar Sözcükler:** Beyin-omurilik sıvısı rinoresi/cerrahi; hastalık modeli, hayvan; dura mater/cerrahi/transplantasyon; fistül/cerrahi; greft yaşaması; tavşan.