Raymond F. Nistor, M.D., Friedrich M. Chiari, M.D.,
Heinz Maier, M.D., and Klaus Hehl, M.D.

The Fixed Combination of Collagen With Components of Fibrin Adhesive—A New Hemostyptic Agent in Skull Base Procedures

ABSTRACT—CSF leak still is one of the major sources of morbidity after extensive skull base procedures. Of the various standard closure techniques of traumatic or iatrogenic dural defects, none provides a really watertight, persistent closure. Even the supplementary use of fluid fibrin glue did not substantially improve the rate of postoperative CSF leaks. The application of a collagen sheet covered with a fixed layer of solid components of a fibrin tissue glue (TachoComb®) overcomes the major drawbacks of dural sealing in skull base surgery. The dural defects of 58 patients undergoing extensive skull base procedures were sealed with this new hemostyptic agent. The series includes 44 patients undergoing primary surgery, 6 patients with traumatic or iatrogenic tears of venous sinuses, and 8 patients with postoperative leaks after previous skull base procedures in which other sealing methods were previously used. In the group of primary surgery, none of the patients had postoperative CSF leakage or venous rebleeding. One patient developed a delayed pneumatocephalus. All cases of patent CSF fistulas were resolved without any adjuvant therapy. Preliminary experience shows that the good sealing and hemostyptic performance of this new agent will considerably reduce the risk of postoperative CSF leak and infection after skull base procedures.

Dural reconstruction and interest in dural substitutes date from 1897 when Beach, cited by Fisher, suggested the use of a gold foil to prevent meningocerebral adhesions.[1] Since then, various substances have been used, such as periosteum, fascia lata, metals, rubber, celluloid plates, peritoneum, fat, muscle, omentum, cellophane, mica, dermal grafts, Cargile membrane, hernia sack, catgut, polyvinyl sponge, Gelfoam, fibrin, Silastic, Teflon, freezed-dried dura mater cardiac pericardium, and methyl methacrylate, but only a few of these materials are still successfully in use. Though today the formation of meningocerebral adhesions is no longer of relevance, leaks following dural closure are still an unresolved problem.[2]

Although standard dural closure procedures in combination with fluid fibrin glue in extensive skull base procedures have improved the cerebrospinal fluid (CSF) leak-related morbidity and mortality,[3] the rates of postoperative CSF leaks still range from 2% to 30%.[4,5] It is not that dural closure techniques have not improved, but that skull base procedures have become more aggressive and radical, and surgeons have to deal with increasingly larger dural defects.

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The use of fluid fibrin sealants (FFS) for augmentation of the watertightness of dural reconstructions led initially, especially in Europe, to enthusiasm and sometimes also to an overestimation of this sealing method.[3,6,7] The incidence of persistent postoperative CSF leaks still depends much more on the skill of the neurosurgeon as on the qualities of the reconstructive and sealing materials used.

Since June 1993, we have used a new product—a fixed solid combination of collagen with the lyophilized components of a fibrin adhesive—as an alternative to fluid fibrin glue for dural sealing. We were interested in using this new product because of the way in which it overcomes the major disadvantage of the currently used fluid fibrin glue.[7] The fluid glue needs a dry application surface to polymerize, and its components have a very short optimal polymerization interval, whereas the fixed combination needs blood-, CSF-, or water-contact for polymerization. As both the collagen and the fibrin glue are traditionally used in neurosurgical procedures, no specific experimental and preclinical work-up or legal approval was necessary to use this new product in clinical routine.

For neurosurgical procedures we have used the product in three main indications: dural reconstruction, dural sealing, and hemostasis. The purpose of this paper is to describe this new gluing technique and our preliminary experience with this new product and to discuss its clinical application and its potential benefits in reducing the CSF-related morbidity and mortality in skull base procedures.

Table 1. The Fixed Combination

The sheet	
Surface	9.5 × 4.8 × 0.5 cm or 4.8 × 4.8 × 0.5 cm
Collagen	1.3–2.0 mg/cm^2
The solid (gluing) layer	
Human fibrinogen	4.3–6.7 mg/cm^2
Bovine thrombin	1.5–2.5 I.U./cm^2
Bovine aprotinin	0.055–0.087 Ph.Eur.U./cm^2
Riboflavin	added as a marker dye

MATERIAL AND METHODS

A new fixed combination of collagen with the solid components of a fibrin-based tissue adhesive provided by Nycomed Arzneimittel GmbH, Munich, was used in-

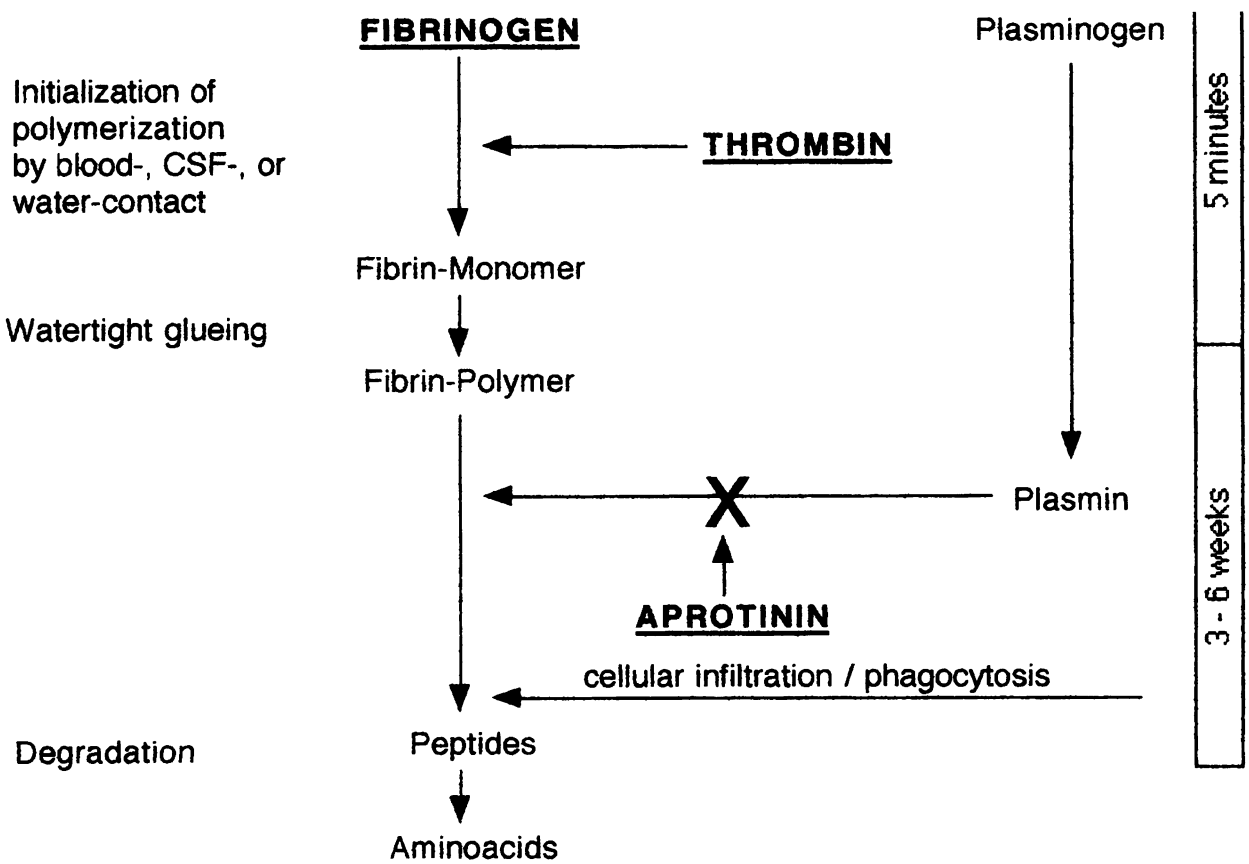

Figure 1. The gluing mechanism of the solid fibrin-based tissue adhesive

stead of the routinely used combination of gelatine with FFS. The solid composite (TachoComb®) consists of a watertight sheet of collagen (95 × 48 × 5 mm or 48 × 48 × 5 mm), containing 1.3 to 2.0 mg collagen/cm^2 covered with human fibrinogen and bovine thrombin. Aprotinin is added to prevent early degradation of the fibrin clot by plasmin. The mixture additionally contains riboflavin as a marker dye for the layer of fibrin adhesive (Table 1). The gluing mechanism is shown in Figure 1.

The sheet is cut with scissors to the required shape and size and is directly applied with the yellowish gluing surface onto the dura, exceeding beyond the margins of the defect by about 1 cm. A wet patty is applied for 2 minutes and gently compressed. After removal of the patty, a watertight seal is obtained (Fig. 2). Depending on whether the approach is intra- or extradural or both, different techniques are used. In extradural procedures, in which the gluing surface faces neural structures, a sheet of gelatine (Gelfoam®), collagen (Tabotamp®), or a second sheet of TachoComb® is applied with the collagen surface toward the brain or myelon to avoid adhesions (Fig. 3).

Since July 1993, we have used TachoComb® in 131 patients undergoing various neurosurgical procedures. The indications for using this product are presented in Table 2. This paper will focus only on the results and technical aspects in patients who have undergone skull base surgery.

In the majority of cases we constructed anterior and middle fossa defects using TachoComb® for sealing of dural defects and a pericranial, musculopericranial, or galeopericranial vascularized flap as the second layer. The flap was attached with titanium hemoclips or positioning sutures only. In smaller defects, the isolated application of TachoComb® exceeding the margins of the defect by about 1 cm achieved a watertight sealing. In one case of a large adenoid cystic carcinoma of the anterior skull base and of the clivus with a large exposed nasal cavity, we used a premolded titanium grid, TachoComb®, and a large vascularized galeopericranial flap. In this case even after radiation therapy of the tu-

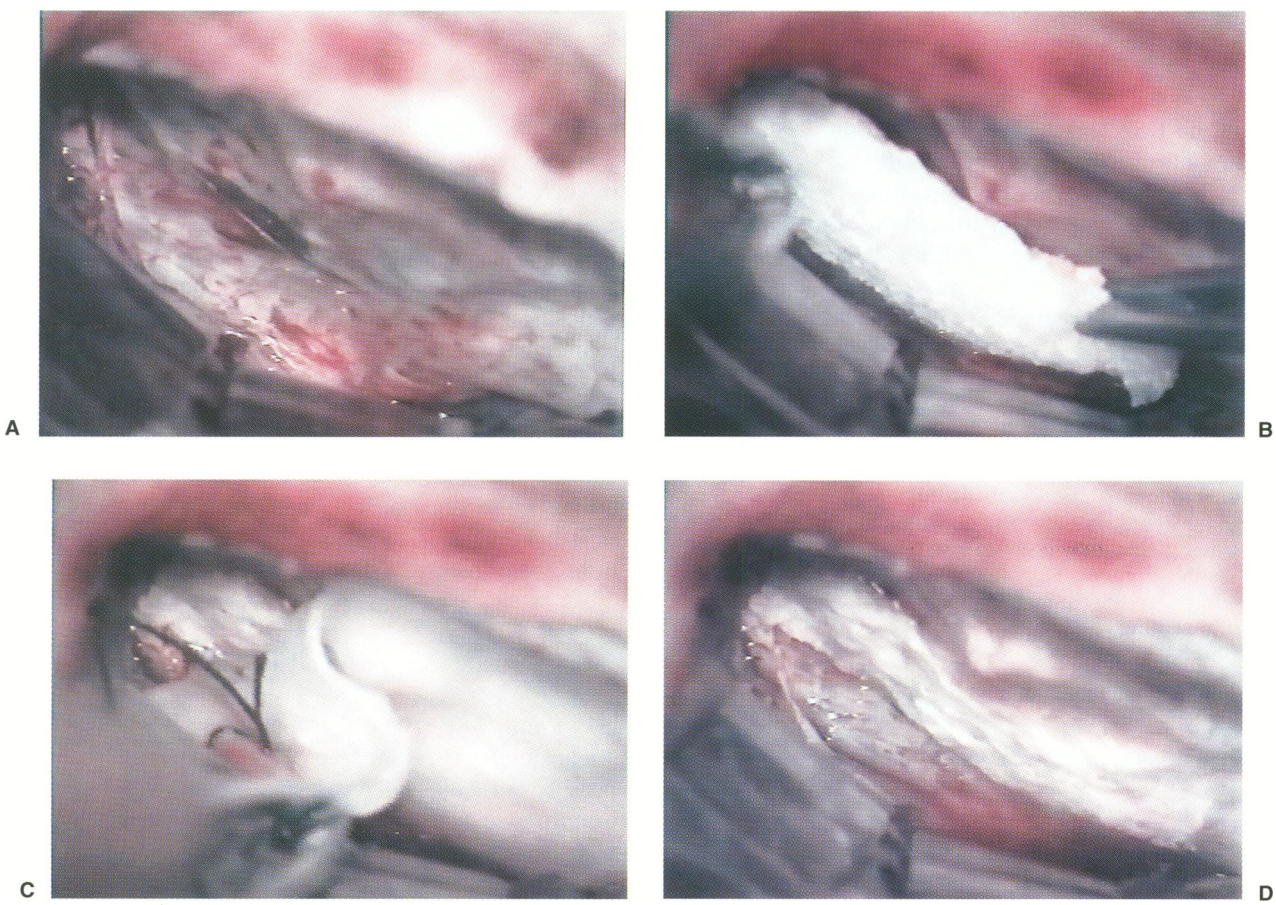

Figure 2. The application technique, a. dural defect; b. the direct application; c. moistening of the sheet with a wet patty for 2 to 3 minutes; d. a watertight seal is obtained.

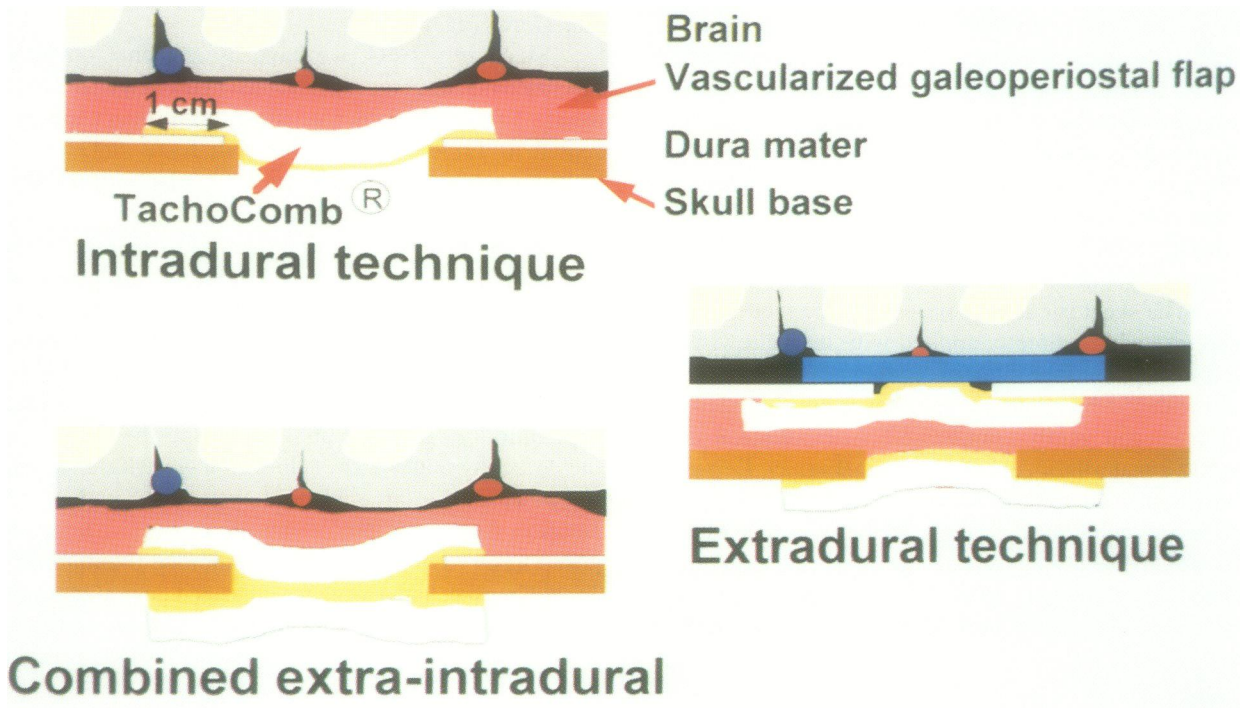

Figure 3. The application technique of TachoComb® depending on whether the approach is intra- or extradural or both.

mor, no CSF leak or delayed infection occurred in the 13 months up to the patient's death.

In tumors involving the orbital walls (Fig. 4) we have consequently reconstructed the bony defects using a split-thickness calvaria grafting technique. The fronto-orbital region was extensively covered with a musculopericranial vascularized graft which was attached with titanium hemoclips; the large excised dural area was covered with overlapping pieces of TachoComb®. In such cases, the upper surface of the bone graft lies against the vascularized flap.

The patients had clinical, laboratory, and neurologic as well as neuroradiologic examinations on day 1 and 7 after surgery and 3 months later. In malignant and semimalignant tumors, further diagnostic procedures were performed every 6 months; in benign tumors at yearly intervals. Apart from traumatic CSF leaks, postoperative MRI was performed in all cases. T_2-weighted coronal and axial images were performed to detect abnormal collections or leaks of CSF. Paramagnetic contrast medium was used to detect infectious complications and/or recurrent or remnant tumor.

Table 2. Neurosurgical Indications

Dural reconstruction (substitute)
extensive skull base procedures
transsphenoidal surgery
spinal surgery
surgery of the dysraphic disorders
Dural sealing
traumatic CSF leaks
dural closure in recurrent CSF fistulas
sealing of difficult dural sutures
Hemostasis
sealing of tears/lacerations of dural venous sinuses
sealing of severe diffuse brain parenchyma bleeding
temporary sealing of intraoperative aneurysm rupture
hemostasis in areas where bipolar coagulation is prohibited
Prevention of rebleeding
sealing of extensive tumor resection areas
wrapping of fusiform aneurysms
reinforcement of vascular sutures

RESULTS

From July 1993 to November 1996, we used TachoComb® in 44 cases of primary skull base approaches (Table 3), in 6 cases presenting with traumatic or iatrogenic tears of the venous sinuses, and in 8 cases with postoperative CSF fistulas after skull base procedures in which conventional sealing methods were previously used (Table 4). In this latter group, two patients underwent two and three previous surgical closure attempts, respectively.

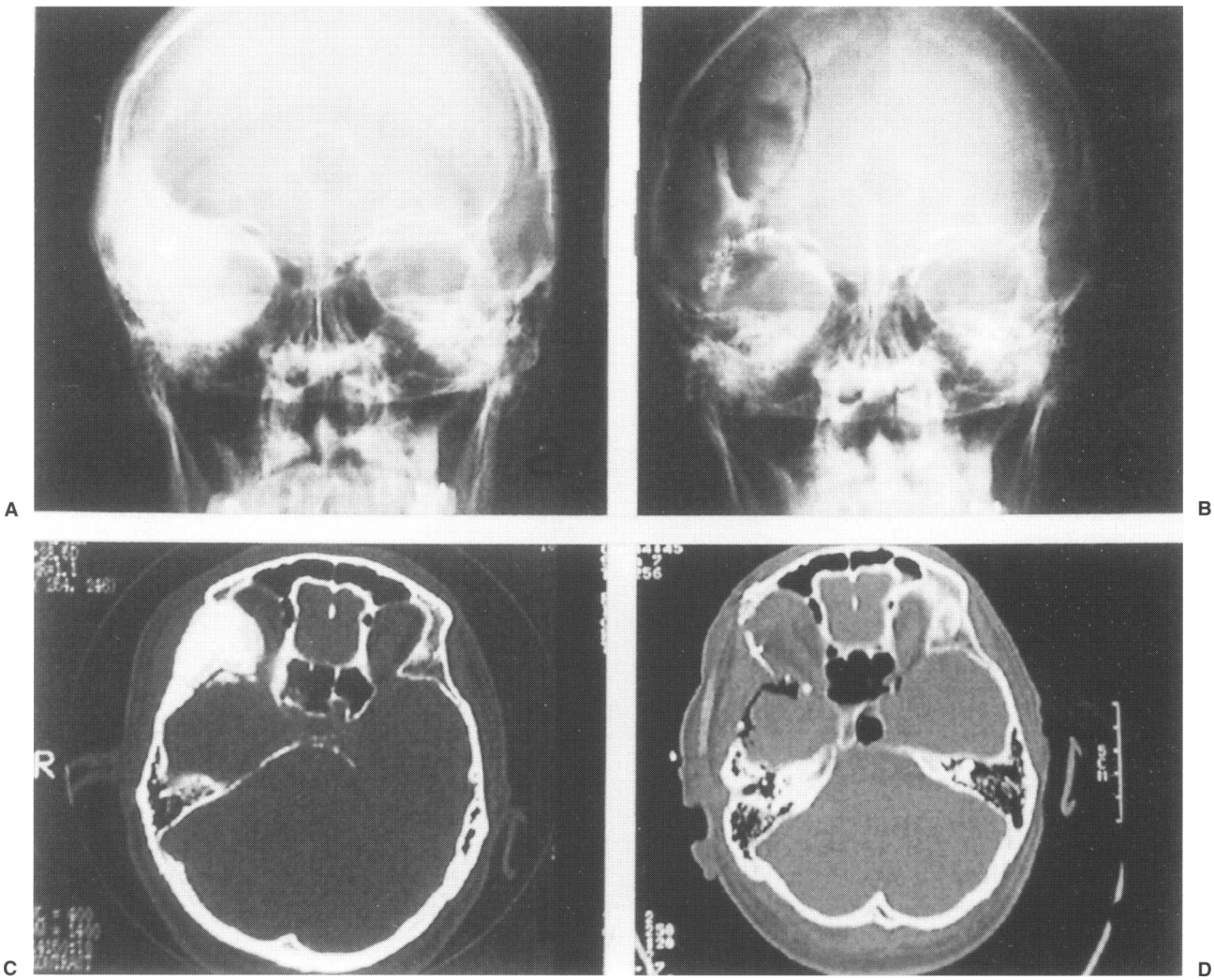

Figure 4. Sphenoid wing meningioma before (a,c left) and after surgery (b,d right). Using a split-thickness calvaria grafting technique, the extensive bony resection of the lateral orbital wall was reconstructed. The large dural excision was reconstructed with TachoComb® (the air-impregnated watertight collagen sheet is seen in the left temporal area of the postoperative CT (d). The fronto-orbital region was extensively covered with a musculopericranial vascularized graft which was attached with titanium hemoclips; the large excised dural area was covered with overlapping pieces of TachoComb®.

Table 3. Approaches for Primary Skull Base Pathology

Anterior craniofacial osteotomy	4
Bifrontal subfrontal	12
Bifrontal with midfacial split	1
Combined frontotemporal-orbitozygomatic	5
Orbito-fronto-ethmoidal osteotomy	2
Suboccipital retrosigmoid	5
Subtemporal-preauricular infratemporal	3
Transsphenoidal	6
	4
	44

As our series is still small and very inhomogeneous, we feel that a statistical analysis would not be valid: we are reporting only on our clinical observations—further examination is needed in controlled trials.

In primary operative procedures, none of the operated patients had postoperative CSF leakage or meningitis during a median follow-up period of 18 months. Postoperative MRI did not reveal any CSF or infectious abnormalities. Even after radiation therapy, which was performed in 10 patients, no CSF leakage occurred. One patient who underwent surgery for a severe traumatic midfacial injury with extensive frontal lacerations was readmitted 6 months later with a subdural abscess. This complication was considered to be a trauma- and not a product-related event. In one case of dural sealing in the

Table 4. Skull Base Pathology

Indications	*n = 58*	*Complications*
Dural sealing in skull base procedures	44	
Sphenoid wing/orbital meningioma	3	
Olfactory groove meningioma	4	
Petroclival meningioma	2	
Tuberculum sellae meningioma	3	
Esthesioneuroblastoma	2	
Adenoid cystic carcinoma	2	
Pituitary adenoma	4	
Chordoma	3	
Chondrosarcoma	2	
Osteogenic sarcoma	1	
Traumatic midfacial and frontobasal defects	13	one case of subdural abscess 6 months after trauma
Acoustic neuroma	3	
Trigeminal neuroma	1	
ACA-Aneurysm (frontal sinus opened)	1	pneumatocephalus after 3 weeks
Hemostasis	6	
Dural sealing in tears of the venous sinuses		
Cavernous sinus	2	
Transverse sinus	2	
Sigmoid sinus	2	
Dural closure	8	
Patent CSF fistulas (recurrent surgery)		
After posterior fossa surgery	4	
After anterior skull base surgery	3	
After petrous bone surgery	1	

presence of an extensively opened frontal sinus during clipping of an anterior communicating artery aneurysm, the patient presented 3 weeks later with a pneumocephalus. She developed a delayed frontal collection of loculated air under pressure, causing drowsiness and severe frontal lobe compression symptoms. This case required recurrent surgery and resealing of the dura and frontal sinus. Air entered through the partly organized TachoComb® fleece just adjacent to the frontal sinus, which disrupted during respiratory exercises of the patient.

Notable was one patient with a spheno-orbital meningioma who underwent reoperation for a calvaria plastic. The TachoComb® used for the primary dural reconstruction was removed and lyophilized dura was implanted and fluid fibrin sealant was used. This patient developed a massive postoperative subgaleal CSF leak which prolonged the hospitalization by 7 days.

Dural sealing of posttraumatic or persistent postoperative CSF leaks was successful in all cases, without adjuvant therapy (lumbar drainage, reoperation). Notable is one case of iatrogenic injury of the petrous bone and of the adjacent dura during an antrotomy with persistent CSF fistula and two failed enaural closure attempts. This fistula was resolved by a temporo-subtemporal approach using a combined extra- and intradural closure with TachoComb® and a musculoperiostal and a galeal vascularized flap, respectively.

The impressive performance of this new product also includes the ability to seal tightly larger tears in the venous sinuses without any adjuvant procedures and without any postoperative hemorrhagic or ischemic complications. The tightness of the seal was checked intraoperatively under PEEP-ventilation or jugular compression. Even under these conditions the closure remained tight in all cases.

DISCUSSION

CSF leaks are the result of an abnormal communication between the subarachnoid space and the aerial cavities of the skull base. The dural defects of the anterior, middle, and posterior fossa cause CSF rhinorrhea and/or otorrhea. Sometimes there is no clinically detectable leakage and the defect becomes clinically apparent because of meningitis, abscess formation, or tension pneumocephalus. Traumatic and operative dural tears, especially those in the vicinity of the paranasal sinuses and the aerial cavities of the petrous bone, are still associated with a relatively high rate of CSF leaks and its related morbidity.[2,4,8]

Although in posttraumatic CSF fistulas the standard surgical treatment is often successful, CSF leaks after skull base procedures generally require an aggressive surgical closure.[2] This is why the use of a fibrin glue is advisable to supplement a successful standard closure technique.[3,9]

Adequate reconstruction after extensive tumor resections or in traumatic dural tears is of major impor-

tance. Apart from the bony reconstruction of the orbital wall, there is no need for more complex bone grafting, especially in anterior skull base procedures. With firm dural sealing and reconstruction, brain herniation is generally not a problem. We have used only generous vascularized pericranial flaps, sometimes also in continuity with temporal muscle, as this type of flap provides the best protection against bacterial colonization. As this type of dural reconstruction is not watertight, the closure should be supplemented using a fixed combination of collagen sheet and solid tissue glue.

The reason for using fibrin adhesive is to obtain a temporary watertight closure, creating an additional barrier to CSF until dural healing and local fibrosis occur.[8] The currently used fluid fibrin sealants are biocompatible and nontoxic, but still insufficient in adhesive strength, mechanical properties, and handling qualities. A recent study on a fibrin-based composite tissue adhesive reports a considerable improvement of these qualities for fluid sealants in an experimental model.[8] These qualities were tested in small- to medium-sized dural defects in rats and are not applicable to large dural tears or severe venous sinus bleeding as encountered in extensive skull base procedures.

The gluing qualities of TachoComb® were very convincing according to the preclinical trials published by Schelling et al in 1987 and 1988.[10,11] In the first published trial, arteriotomies of the iliac artery of pigs were treated by application of TachoComb® without sutures. After raising arterial pressure up to 275 mm Hg, the sealed arteries remained tight. In a second trial one year later, large, heavily bleeding areas of the injured liver and spleen of dogs were successfully treated by application of the hemostyptic agent. No recurrent bleeding occurred despite raising the intrasplenic pressure to three times the normal level.

The new fixed combination has been used in Europe since the late eighties and was especially successful in surgery of parenchymatous organs (liver, spleen, pancreas, lungs, kidneys, and thyroid gland). Surgeons using this method have greatly increased the percentage of saved injured spleens, as injured spleens were routinely removed to prevent exsanguination of the patient.[12]

The fluid fibrin glue requires a dry application surface. Otherwise a carrier for the activated glue is necessary. The combination of gelatine with fluid fibrin glue reduces the risk of the glue being washed away by blood or CSF, but still has some obvious drawbacks: the preparation is relatively cumbersome, the method requires experienced and skilled personnel, and the preparation time is 10 to 15 minutes. Excessive amounts of fibrin prolong resorption, and delay the healing process.[13,14] The fluid fibrin glue alone is not able to stop diffuse brain parenchyma bleeding, to glue watertight tears of venous sinuses, or to close larger dural tears, because it is washed away by flowing blood or CSF. That is why this product can be optimally used only on relatively dry surfaces, and in combination with a Gelfoam® sheet only in small tears of the dura mater.

The use of a collagen sheet covered with solid fibrin glue allows direct application to a surface without the risk that the glue will be washed away. The probability of a mistake during the application is largely reduced, and the product can be stored at 2° to 8° C, so that it is immediately ready for use in emergencies. Due to the uniform coating of the collagen sheet, a homogeneous gluing is achieved.

Until now we have experienced only one case of delayed tensile pneumocephalus, and all cases of persistent CSF leaks were resolved by surgery alone. Even if not yet statistically significant because of the small and inhomogeneous series, a more effective gluing appears to be obtained compared with fluid fibrin sealants.

TachoComb® has many admirable characteristics as a dural substitute and sealant in skull base procedures. Compared with the classic method of using gelatine in combination with fluid fibrin glue, it has a comparable price, is easy to handle (one may cut the sheet to the right size with scissors), is absorbed over time, and, in cases of intact pia, arachnoid adhesions do not form. No preliminary preparation is necessary, and the sheet is therefore ideal for emergencies.

No patient experienced adverse effects in our series, and no such effects have been reported in any patient treated so far by surgeons, urologists, and thoracic surgeons. This was to be expected, because all of the components of this product have been used for years as single registered drugs, or as components of the fluid fibrin glue. The collagen sponge Tachotop® has been used in over 600,000 applications, and fibrin glue has been used by neurosurgeons for many years.[12]

Collagen is the only component of the fixed preparation which has to be considered with respect to potential immunogenicity. Adelmann-Grill and Otto[15] have studied the cell-mediated and humoral responses of the collagen preparation in guinea pigs. There was no immune response even when Freund's adjuvant was added. Only when the collagen preparation was applied in a finely dispersed form, together with adjuvant, was there an immune response elicited. Thus, it is very unlikely that the collagen preparation would induce immune reactions. As in reactions to platelets, immunogenicity seems to depend very much on the form in which the collagen is presented.

The subjective evaluation shows that the new sealant has a promising future. In the field of neurosurgery, and especially of extensive skull base surgery, both methods (the solid and the fluid sealants) have important uses, and of course there will also be personal preferences.

The presented technique, which includes a vascularized pericranial flap and gluing with TachoComb®, provides a practical method of maximizing the tightness

of the closure between the intradural space and the paranasal sinuses and promises to minimize the chance of postoperative CSF leakage. Further experience and studies will show that the most effective procedure will also reduce local and secondary complications. In persistent postoperative hardly controllable CSF leaks there is yet strong evidence for the superior sealing qualities of the new solid fibrin-based tissue adhesive.

Finally, we want to point out that no hemostyptic agent or dural substitute will or should replace established skull base and neurosurgical techniques. The technical problems and obvious intra- and postoperative complications are not the result of using one or the other gluing technique, but are known and accepted complications of neurosurgical procedures. Our preliminary experience promises a considerable reduction of CSF- and hemorrhagic-related complications after extensive skull base procedures.

REFERENCES

1. Fisher WS III, Six EG: Cervical myelopathy from dural substitute. Neurosurgery 13:715–717, 1983
2. Sen C, Snyderman CH, Sekhar LN: Complications of skull base operations. In Sekhar LN, Janecka IP (eds): Surgery of Cranial Base Tumors. New York: Raven Press, 1993, pp 831–839
3. Shaffrey CI, Spotnitz WD, Shaffrey ME, Jane JA: Neurosurgical application of fibrin glue: augmentation of dural closure in 134 patients. Neurosurgery 26:207–210, 1990
4. Couldwell WT, Weiss MH: Cerebrospinal fluid fistulas. In: Apuzzo ML (ed): Brain Surgery: Complications, Avoidance and Management. New York: Churchill Livingstone, 1993, pp 2329–2342
5. Deschler DG, Gutin PH, Mamelak AN, McDermott MW, Kaplan MJ: Complications of anterior skull base surgery. Skull Base Surgery 6(2):113–118, 1996
6. Waldbaur H: Fibrinklebung in der Neurochirurgie. In Scheele J (ed): *Fibrinklebung*, Berlin: Springer-Verlag, 1984, pp 262– 264
7. Lamers B, Roosen C, Medhorn HM: Operative und traumatische Duradefekte—Abgrenzung der Indikation zur Fibrinklebung. In Scheele J: *Fibrinklebung*, Berlin: Springer-Verlag, 1984, pp 265–267
8. Rock JP, Sierra DH, Castro-Moure F, Jiang F: Skull base cerebrospinal fluid leakage control with a fibrin-based composite tissue adhesive. Skull Base Surgery 6(3):137–140, 1996
9. Stechison MT: Rapid polymerizing fibrin glue from autologous single-donor blood: Preparation and indications. J Neurosurg 76:626–628, 1992
10. Schelling G, Block T, Blanke E, Hammer C, Brendel W, Gokel M: The effectiveness of a fibrinogen-thrombin-collagen-based hemostatic agent in an experimental arterial bleeding model. Ann Surg 205:432–435, 1987
11. Schelling G, Block T, Gokel M, Blanke E, Hammer C, Brendel W: Application of a fibrinogen-thrombin-collagen-based haemostyptic agent in experimental injuries of liver and spleen. J Trauma 28:472–475, 1988
12. Schiele U, Kuntz G, Riegler A: Haemostyptic preparations on the basis of collagen alone and as fixed combination with fibrin glue. Clin Materials 9:169–177, 1992
13. Edinger D, Heine WD, Muhling J, Schroeder F, Will C: Wound closure with fibrin tissue adhesive. Int J Oral Surg 1:193–197, 1981
14. Peitersen E: Tisseel in rhinoplastic surgery. Acta Immuno Scientific Workshop. Vienna, Immuno AG:113–117, 1982
15. Adelmann-Grill BC, Otto K: Immunological safety evaluation of a hemostatic agent and wound dressing made of horse collagen fibrils. Arzneim Forsch/Drug Res 37:802–805, 1987