A clinicopathological study of collagen sponge as a dural graft in neurosurgery

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There is frequently a need for dural grafts to cover defects resulting from retraction, shrinkage, or excision following neurosurgical procedures. Several materials have been evaluated both experimentally and clinically, and then discarded. Collagen, in its various forms, continues to be an area of intense interest. In this study the authors examined the suitability of collagen sponge to effect dural repair.

In a 5-year clinical study 102 collagen sponge implants were examined macroscopically and histologically. Graft encapsulation, neomembrane formation, delayed hemorrhage, and foreign body reactions were not found. The porous nature of the collagen sponge encouraged fibroblastic ingrowth and dural repair. Meningocerebral adhesions were present in 11 patients, all of whom had required significant cortical resection or had pia-arachnoid disruption during the initial surgery. Inflammatory cells were seen only in response to infection.

Postoperative cerebrospinal fluid leaks developed in only three of 67 patients who underwent an intradural posterior fossa procedure. In a prospective arm of the study involving 459 patients, the wound infection rate using collagen sponge was 6.1%, which compared favorably (p = 0.67) with the 5.7% rate in a similar group of 637 patients in whom collagen sponge had not been used.

KEY WORDS • collagen • collagen sponge • dura mater • dural graft • duraplasty

Dural healing in a defect occurs initially by neomembrane formation. This is followed by fibroblastic activity, which may extend into adjacent cerebral defects that are caused by injuries to the brain or by surgery and these ultimately heal by gliosis and fibrosis. Initial interest in dural grafts arose from attempts to minimize meningeocerebral adhesions and brain scar formation, which had been implicated in post-traumatic epilepsy. More recently, however, emphasis has shifted toward evaluating the physical properties of grafts and the host tissue’s response to these grafts. Many synthetic materials and processed membranes have been used over the past century, but they have been subsequently abandoned as a result of excessive tissue reaction, graft encapsulation, neural compression, or delayed hemorrhage. More recently, commonly used cadaverous dura mater has been implicated in the transmission of slow viral infections, such as Creutzfeldt-Jakob disease. Although screening methods have been introduced, the ever-increasing fear that other viral agents could be similarly transmitted has resulted in a more cautious approach and, in some countries, abolition of the use of human dural tissue (KR Foster, personal communication, 1993).

With respect to biological materials, in general a minimal amount of fibrous adhesion was noted with porcine biomembrane; however, severe adhesions followed when infection occurred in animal studies. Autologous grafts, harvested from temporalis fascia, pericranium, or fascia lata are also popular. However, sufficient quantities may not always be available and a second operation is required for harvesting fascia lata. Much newer synthetic materials, such as vicryl mesh, polyurethane, and polysiloxane–carbonate film also appear to exhibit potential as clinical, resorbable dural grafts.

For many years collagen has continued to be of interest in the development of dural grafts. In the past, collagen film and laminate underwent special processing so that they could specifically hold sutures to achieve watertight surgical closure. This, however, induced severe inflammatory reactions and meningeocerebral adhesions. Although pliable, Xenoderm, a cell-free matrix, limited the penetration of host fibroblasts into the graft, with graft extrusion occurring in one case. Collagen sponge (Bicol), which was derived from bovine tendons, was initially developed as a protective material for use on the brain surface beneath retractors.

* Xenoderm manufactured by Ethicon Ltd., Peterborough, Ontario, Canada.
† Bicol manufactured by Codman & Shurtleff, Randolph, Massachusetts.
Experimental studies using collagen sponge as a dural graft in animals proved highly successful. In these studies, collagen sponge was found to be inert and easy to use as an onlay graft. The collagen sponge fibers acted as a scaffold on which fibroblasts lay down new collagen. Although useful, these animal studies provided limited information because only a histological response could be examined. In addition, tissue response to graft materials obviously differs between animal models and humans.

In this report, we relay findings from our extensive human clinical study of collagen sponge as a permanent dural graft by examining its safety regarding postoperative wound infections, cerebrospinal fluid (CSF) leakage and, in an extensive prospective histopathological analysis, its ability to effect dural repair.

Clinical Material and Methods

Clinical Studies

Collagen sponge was cut to size, moistened, then applied as an onlay graft in patients undergoing both cranial and spinal surgery. After this procedure, the overlying tissues were meticulously reconstituted. One section of the study focused on wound infection rates, which were prospectively determined over a 30-month period in patients undergoing craniotomy. The group of patients in which collagen sponge was used was compared to a cohort of patients in which the dura was either left open or sutured according to the preference of the attending surgeon. The incidence of infection was not significant even with respect to different levels of contamination (Table 1).

Cerebrospinal Fluid Leaks. Postoperative CSF leaks occurred in only three of 67 patients who received collagen sponge as a dural graft for intradural posterior fossa surgery. The first patient had a large glomus jugular tumor and experienced extensive soft-tissue, dural, and petrous bone loss at surgery. A subsequent repair with Lyodura, together with lumbar CSF drainage, was successful. The second patient, who had a Chiari malformation experienced a transient CSF leak that was successfully managed with lumbar CSF drainage. The third patient, an infant who also had a Chiari malformation, developed a pseudomeningocele and, subsequently, a CSF leak, probably due to associated hydrocephalus. External ventricular drainage was instituted and Lyodura was used to repair the defect. The child, however, died of meningitis.

Postoperative CSF leakage was not seen in 80 patients, 24 with tumors, for whom collagen sponge had been used in spinal surgery. Two of 11 patients with penetrating injuries to the spine initially presented with CSF fistulae. In 10 of 45 patients who had undergone surgery for degenerative spinal disease or spinal stenosis, inadvertent tears in the dura were covered with collagen sponge alone. In 35 patients, collagen sponge was used to minimize the formation of epidural fibrosis.

Pathological Studies

Specimens for histological examination of repaired areas and the underlying brain were obtained prospectively from 100 patients over a 5-year period either at reoperation or at postmortem examination. Specimens were fixed in 10% buffered formalin in saline, then blocked in paraffin wax. Standard histological techniques were used, followed by light microscopic examination.

Results

Clinical Studies

Craniorary Wound Infection. There was no significant difference (chi-square test, p = 0.671) in wound infection rates between the group of 459 patients in which the collagen sponge group was used (6.1%) and the cohort of 637 patients in which the collagen sponge was not used (5.7%). There was no significant difference between the two groups in the incidence of infection even with respect to different levels of contamination (Table 1).

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Twenty-five patients underwent craniotomy for repair of anterior skull base CSF fistulae; collagen sponge was used in nine of these cases. Transient postoperative CSF leakage occurred in two patients. Both leakage closed following intermittent lumbar punctures with CSF removal. Cerebrospinal fluid leaks also occurred during the same period in two of 16 patients in whom pericranium had been used. One of these leaks required later...
transsphenoidal repair, whereas the other settled following continuous lumbar drainage (Fisher’s exact test \( p = 0.602 \), not significant).

Pathological Studies

**Macroscopic Studies.** Of 102 histological specimens, 52 were harvested at reoperation and 50 at autopsy from patients undergoing various surgical procedures for a wide range of pathologies (Table 2). (Two patients had two samples each from a second operation for subtotal excision of a malignant glioma.)

In specimens collected soon after surgery (Days 2 to 10) the collagen sponge was already clearly adherent to the dura. Fibrin, derived from blood in the area of surgery, had formed a good seal against the CSF at the edges (Fig. 1 left). At 40 days collagen sponge formed a nonadherent separation layer between the brain tissue and the overlying muscle (Fig. 1 right). By 3 months the sponge had blended well with the host dura. Meningocerebral adhesions were seen in only 11 patients, all of whom had pial-arachnoid disruption. In three of these cases radiotherapy had also been given after the initial surgery. In a single patient who had undergone reoperation for a residual lumbar disc fragment after 18 months, the collagen sponge had formed a cleavage or dissection plane between the dura and epidural tissues.

**Microscopic Studies.** Histological changes could be analyzed from 1 day after implantation to as late as 56 months (Table 3). There were 38 specimens in the 1- to 3-day group. Red blood corpuscles were still present in the collagen sponge from the recent surgery. Isolated neutrophils were seen along the edges of the collagen sponge in only a single specimen from a patient who had sustained an intracerebral hematoma associated with a contaminated wound. More severe acute inflammation, sepsis, and gliosis were noted in an autopsy specimen from a patient who had undergone surgery 3 days prior to death for excision of a mycotic middle cerebral artery aneurysm secondary to infective endocarditis.

Of the 10 specimens in the 4- to 7-day period, early fibroblastic activity was seen in two specimens and

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**TABLE 2**

Clinical data on histological specimens obtained from 100 patients*

<table>
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<th>Pathology</th>
<th>No. Specimens</th>
<th>Surgical Procedure</th>
<th>No. Specimens</th>
<th>Source of Tissue Sample</th>
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* Specimens were obtained at reoperation or autopsy. In two of the cases two samples were obtained at reoperation.

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**Fig. 1.** Macroscopic views of collagen sponge taken at autopsy from two patients. **Left:** Collagen sponge and dura sampled 1 day following craniotomy for evacuation of an acute subdural hematoma. The collagen sponge (CS) is adherent to the edges of the dura (D) (**arrow**), forming a dural “seal.” The sponge has absorbed some blood from the area of surgery (**double arrow**). Original magnification \( \times 2.5 \). **Right:** Collagen sponge and underlying cerebral cortex sampled 40 days after surgery for an intracranial aneurysm. The inner surface of the sponge is smooth and shiny (**arrow**). No neomembranes or hemorrhages are apparent. The collagen sponge is firmly attached to the dura. In the underlying brain (B) no tissue reaction is visible. The pia-arachnoid layer is intact and adhesions have not formed. Original magnification \( \times 2 \).
resorption of red blood corpuscles had commenced. In the 8- to 14-day period 18 specimens were available. The bleeding associated with surgery had resolved in five cases. Early fibroblastic proliferation from the edges of the dura had penetrated the collagen sponge, using its fibers as a scaffold to lay down new collagen. Neocapillary formation within the collagen sponge was noted in one specimen. Neomembrane formation was not evident. There were no features of astrocytic proliferation, infection, tissue reaction, or gliosis in any of the subjacent brain sections sampled at 8, 11, or 12 days.

Sepsis was a complication in three of these cases. Acute inflammatory cells had penetrated the collagen sponge, but only close to the bacteria, in a specimen from a patient who had sustained a compound skull fracture following an axe injury. In the second patient, minimal polymorphonuclear cells were noted at the edges of the collagen sponge sampled during reoperation for a posterior fossa inflammatory mass. Finally, an acute inflammatory cell infiltration was noted in a specimen from a third patient who had undergone multiple operations for postsurgical hemorrhages following a traumatic episode.

Fibroblastic activity and neovascularization were well established at 15 to 30 days in 12 cases. Once again no neomembranes were seen in any of the specimens. A mild polymorphonuclear cell infiltrate was seen in the superficial layer of the collagen sponge in a single autopsy specimen (24 days) from a patient who had surgery for “contaminated” trauma in the adjacent dura.

Between 1 and 3 months, both the large and small fibers of collagen sponge were still identifiable, although an examination of eight cases showed that resorption of the latter had commenced. Marked fibroblastic activity (30 to 60 cells per high power field) and vascularization of the graft had continued. Graft encapsulation had not occurred (Fig. 2).

Subjacent brain sections in an autopsy specimen at 40 days showed no astrocytic or inflammatory reaction. A mild inflammatory cell infiltrate and a foreign body giant cell reaction, however, had occurred in response to the vicryl sutures.

At 4 to 6 months, incorporation of the collagen sponge into the dura had occurred and the sponge was almost fully collagenized with an abundance of fibroblasts in evidence. Although resorption of small fibers had progressed, the larger fibers were still reasonably visible. In two cases reoperation for recurrent gliomas had been necessary at 7 months and at 10 months. Mild astrocytic pro-

**Discussion**

A large variety of artificial and biological products have been extensively evaluated as dural grafts. Most appear to resist infection, have sufficient strength to hold sutures to prevent CSF leakage or to close CSF fistulae, but evoke varying degrees of tissue reactions when tested, mainly in experimental models. With the exception of lyophilized dura mater and lyophilized pericardium, detailed in vivo histological studies in humans have rarely been performed. Compact synthetic materials are still being developed for duraplasty. There has been a surge of interest in collagen-derived products for the repair of dural defects and attention in increasingly being directed at the biological and physical properties of graft materials.

Concern with respect to the safety of dural grafts from septic complications has been addressed in several reports. In general, these grafts do not seem to influence wound infection rates. However, because collagen sponge is a porous graft, this issue was particularly addressed in this study. Although the study was not fully randomized, the incidence of wound infections in the study group compared well to that in a control cohort in which collagen sponge was not used. This applied even when comparisons were made with respect to contaminated surgery. The overall wound infection rate in our group.
Accidental surgical dural tears have been documented in up to 12% of patients undergoing laminectomy for degenerative spinal disorders, especially during removal of a thickened, adherent fibrous ligamentum flavum; these tears are often difficult to repair.52 We have found that collagen sponge is extremely useful in this situation provided that a meticulously layered wound closure is performed. In addition, there is some promise that collagen sponge may be useful in preventing epidural fibrosis. Further clinical and human histological studies are required, although these may prove difficult.

Watertight dural closure, even that augmented with fibrin glue, was attempted by Shaffrey, et al.,51 in the repair of established CSF fistulae. As many as one-third of the fistulae closed in a delayed manner aided by CSF diversion. This apparently allowed sufficient time for natural fibroblast-initiated repair to occur. Although our study was not randomized and involved only a small group of patients, no statistical difference emerged when our data were compared to the identical use of pericranium.

In the past, researchers involved in chemical processing of collagen products pursued a perhaps obsessive quest to enable grafts to hold sutures. This resulted in degradation of the collagen and induced severe inflammatory responses; thus collagen products fell into disrepute.25,30 The treatment of bovine collagen with glutaraldehyde has minimized the immunogenicity, making collagen eminently suitable for development as dural replacement material.54 Although isolated concern was voiced in the United Kingdom over the transmission of bovine spongiform encephalopathy across species barriers from bovine products, so far there has been no evidence of transmission of this disease to humans. It appears that transmission of this infection across species barriers, a problem mainly restricted to the United Kingdom and perhaps Western Europe, requires high doses and long exposure. In addition, collagen sponge is manufactured and processed in the United States of America, making this risk even more remote.7,10,24

The histological analyses in this study of 102 implanted specimens in 100 patients form one of the most extensive in vivo evaluations of a dural replacement graft so far reported. Our histological analyses examined in detail human tissue responses (brain and meninges) to a dural graft at various time periods not only throughout the early stages, but also at much later stages.

Fibrin, derived from blood in the surgical field, plays an important early role (in lieu of sutures) in maintaining the graft in situ until fibroblasts, associated with the supporting blood vessels, proliferate into the graft. This may explain why, not just with this method, only partial success is achieved in stopping CSF leaks immediately after repair of CSF fistulae. Time is also required, and on occasion lumbar CSF drainage may need to be instituted, before fibroblasts finally repair the dura in a watertight manner.

The use of sutures is further minimized by using an onlay graft, which reduces not only operative time but, more importantly, the risk of an additional foreign body giant-cell reaction.31 Foreign body giant-cell reactions, which are known to occur in response to grafts containing vicryl,34,35,40,49 were seen only in response to vicryl sutures
Collagen sponge for duraplasty

used to hitch the dura. Collagen sponge, because it is inert, does not incite foreign body giant-cell reactions or chronic inflammatory cell responses and has a distinct advantage over other collagen products, such as bilayered human collagen, collagen vicryl, or collagen-coated vicryl.27,35,49

A striking feature was the ease with which early fibroblasts were able to penetrate directly into the collagen sponge. This was facilitated by the large pores or the sponge-like structure of the collagen sponge. The proximity of fibroblasts to the collagen sponge fibres suggests that the latter acts as a scaffold for the deposition of new collagen. These findings are very similar to those of the animal studies previously reported.37 Furthermore, collagen itself is known to have a chemotactic interaction with fibroblasts, which can promote rapid recolonization of the collagen implant by the host's tissues.20,45

Parizk and colleagues'3 observed in 1988 that the compact structure of xenogenic pericardium limited fibrolastic migration to the filamentous edges or to the holes made by the suturing needle. Two years later Laun, et al.,28 raised the question of the role of graft porosity in effecting dural repair, but conclusive evidence was lacking. The pattern of fibroblastic proliferation into the collagen sponge, which can be seen as early as 5 days and is well established by 15 days, provides sufficient evidence that porosity of the graft is indeed an essential feature in effecting dural repair. This porosity, we believe, also minimizes the risk of graft encapsulation because dural repair can proceed “through” the graft and not “around” it as has been the case with more compact and generally synthetic materials.22,37 Indeed, with these materials, ultimate sealing of the dural defect against the CSF relied on an encapsulating neomembrane formed by fibroblasts.48 The neocapillaries, which proliferate from the dural edges, also proceed, together with the fibroblastic response, into the collagen sponge. This is probably why the treacherous friable neomembranes, which are prone to bleed,1,3,6,42,53 are unlikely to occur with collagen sponge, making the risk of secondary hemorrhage virtually nonexistent. It was not surprising that glial fibroblastic scars were only seen in patients following parenchymal brain tumors, which often required repeat operations, and in patients with gliomas also associated with radiotherapy. Meningocerebral adhesions will occur if there are breaches in the pia-arachnoid layer regardless of the choice of dural repair techniques.11,22,29,30,40,44,47,50

The absence of neutrophils, lymphocytes, or giant cells in the collagen sponge, or indeed in the host meninges (except in relation to bacteria or foreign body contamination), and the lack of astrocytic proliferation in the brain, both in the early periods and over the entire 5-year period, clearly demonstrate that collagen sponge is immunologically well tolerated by humans. This agrees with the empirical observations of the senior author (JRvD), who has used collagen sponge for this purpose over a 15-year period.

Conclusions

In general neurosurgical practice, watertight dural closure does not always appear to be essential to prevent CSF leakage from wounds. Perhaps emphasis should be placed instead on the subsequent meticulously layered wound closure and the early detection or prevention of hydrocephalus. The collagen sponge structure promotes proliferation and ingrowth of fibroblasts, and provides a scaffold for their rapid migration, making it an ideal dural substitute. Porosity appears, in fact, to be an important prerequisite for successful dural repair. It is probable that these properties heavily outweigh the criticism of “lack” of watertight closure.

Collagen sponge is resistant to secondary infection and, in our experience, can be used safely in surgery even with contaminated wounds. In our study meningocerebral adhesions only occurred when severe pia-arachnoid disruption had occurred. Collagen sponge is also beneficial as an onlay graft if brain swelling is anticipated, particularly in the posterior fossa.

Disclosure

The authors have no proprietary interest in collagen sponge or the company that manufactures it.

Acknowledgments

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