Skull Base Cerebrospinal Fluid Leakage Control with a Fibrin-Based Composite Tissue Adhesive

Abstract—Cerebrospinal fluid (CSF) leaks can be responsible for significant patient morbidity and mortality. While the majority of leaks induced after head trauma will seal without intervention, spontaneous or surgically-induced leaks often require operative repair. Many modifications on standard surgical technique are available for repair of CSF fistulae, but none assures adequate closure. We have studied the efficacy of a novel fibrin-based composite tissue adhesive (CTA) for closure of experimentally-induced CSF leaks in rats. Fistulae were created in two groups of animals. Two weeks after creation of the leaks, the animals were sacrificed and analyzed for persistence of leak. A 58% leakage rate was noted in the control group ($n = 12$), and no leaks were noted in the experimental group closed after application of CTA to the surgical defect followed by skin closure ($n = 11$). Comparing the control group to the experimental group, results were statistically significant ($p = 0.015$). These data suggest that CTA may be effective as an adjunct for the closure of CSF fistulae. (*Skull Base Surgery*, 6(3):137–140, 1996)

Cerebrospinal fluid (CSF) leaks can be responsible for significant patient morbidity and mortality. Regardless of the cause, closure of CSF fistulae is mandatory, though frequently fraught with difficulty. Although the majority of post-traumatic CSF leaks will seal without the need for a secondary surgical procedure, spontaneous leaks and those occurring after skull base surgery will frequently require surgical intervention. The incidence of CSF leak after skull base procedures can be high, and closure may involve multiple surgical procedures because standard surgical techniques are frequently insufficient to assure fluid-tight closure. As an adjunct to primary suture repair, the use of vascularized grafts creates an additional barrier to CSF leakage and infection but is not always possible or successful. A material that could adequately seal small defects in the dural closure and remain occlusive until subsequent normal tissue reactions, such as fibrosis, permanently seal the defects would theoretically eliminate a great source of patient morbidity. Clinical studies of patients after extensive craniofacial and spinal procedures

whose dural repairs were supplemented with fibrin glue have suggested that the glues may be a valuable adjuvant for the management of CSF fistulae.¹ We therefore performed an in vivo study to assess the efficacy of a composite tissue adhesive as a CSF sealant.

MATERIALS AND METHODS

A novel fibrin-based tissue adhesive was tested: composite tissue adhesive (CTA) and thrombin. CTA is a collagen-fibrinogen-thrombin composite adhesive/sealant obtained from Cohesion Corporation, Palo Alto, California. Nominal protein content was 60 mg/mL. Thrombin and fibrinogen component formulations were mixed 1:1 v/v ratio via dual syringe applicator (Duploject™, Immuno AG, Vienna, Austria).

This in vivo study, based on the rodent model of Nishihira and McCaffrey,² modeled a large dural defect relative to skull size (Fig. 1). A large defect in the dura and

Figure 1. Schematic representation of rat model. (Modified from Nishihira S, McCaffrey TV: The use of fibrin glue for the repair of experimental CSF rhinorrhea. *Laryngoscope* 98:625-627, 1988.)

arachnoid membranes at the skull base was created and repaired by one of two methods. Two weeks after surgery the animals were sacrificed and the repairs tested for leakage. The 2-week time interval was chosen because tissue swelling and packing may maintain CSF closure in patients during the first week after surgery, and permanent closure is more likely if there is no evidence of leakage at 2 weeks. If leakage is apparent at this time, surgical intervention will be pursued.

A cutaneous incision was made along the center of the frontal nasal region of the skull. The tissue was reflected back to expose the anterior cranial fossa and nasal cavity. A unilateral defect was then made by drilling away the bone covering the ethmoid sinuses and anterior cranial fossa. The bony cleft separating the anterior cranial fossa from the ethmoid sinus was removed to allow free flow between the two chambers. The underlying dura and arachnoid membranes were resected, and the olfactory bulb and anterior aspect of the frontal lobe were removed (Fig. 2). The defect was repaired by one of two methods: 1) simple skin closure only, or 2) CTA covering the defect followed by skin closure. After 2 weeks, the rats were anesthetized and 0.2 mL of 5% fluorescein solution was introduced into the subarachnoid space through a burr hole created at the posterior portion of the cranium. After 2 hours, subjects were sacrificed, and the nasal bones anterior to the experimental defect were removed. The contents of the nose were then examined microscopically for the presence of the fluorescein dye. The experimental defect was not disturbed throughout this latter portion of

Figure 2. Photograph of experimental model showing cranial defect, residual frontal lobe (**), and opening into ethmoid sinus (*).

the experiment. After sacrifice, selected subjects not injected with dye were preserved in 10% neutral buffered formalin, decalcified with formic acid, sectioned, dehydrated, mounted on glass slides, and stained with hematoxylin and eosin for histopathologic evaluation.

RESULTS

The leakage rates at 2 weeks postoperatively are described in Table 1. A 58% leakage rate was observed for the control group (no packing and only skin repair), which was in contrast to previously described results (89%).² The experimental group treated with CTA and skin closure had no leakage evident. This, too, is in contrast with previously described results for fibrin sealant (FS) and packing in the same model (22%). Histopathologic findings at 14 days demonstrated CTA with colonization of implant with fibroblasts, capillaries, and macrophages (Fig. 3).

DISCUSSION

Cerebrospinal fluid leaks can develop spontaneously, by cranial trauma (2% to 40%) or from surgical procedures transecting the dura surrounding either the brain or spinal cord (2% to 30%).³⁻⁵ Relatively higher rates of

Table 1. Leakage Rates at 2 Weeks

	Leakage Rate
No closure	58% (7/12)
CTA	0% (0/12)

Figure 3. Hematoxylin and eosin-stained preparation at 14 days of CTA (*)-brain (**) interface. Note ingrowth of capillaries into CTA.

occurrence are noted in association with fractures of the frontal, ethmoid, and sphenoid sinuses, cribriform plate, mastoid and facial bones, and after transsphenoidal approaches for removal of pituitary tumors, as well as other surgical approaches to the skull base. In addition, in more routine intracranial surgery for various disease states, the inability to obtain a fluid-tight dural closure predisposes to postoperative CSF leaks which can lead to unwanted sequelae.

Meningitis is a common and potentially devastating complication which can occur after as many as 30% to 60% of postoperative leaks and has been reported in 20% of cases of CSF leakage after cranial trauma.⁶ Typical bacteria include *Pneumococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*. Clinically delayed onset of leakage is associated with meningitis complication rates of up to 57%.⁶ Pneumocephalus is another complication of dural opening and can predispose to the development of meningitis and the collection of loculated air under pressure, either of which can lead to death.^{3,6}

Cerebrospinal fluid leaks can be detected clinically by noting a clear, colorless, watery drainage from the nose or, in less obvious cases, by subarachnoid cisternogram using labeled technetium for qualitative assessment. Iodo-hexol cisternography with computed tomographic images taken in varying planes can specifically demonstrate the location of the leak. Standard treatment of post-traumatic CSF fistulae includes bed rest to lower CSF pressure and thereby facilitate spontaneous closure. Post-traumatic CSF leaks typically seal within 3 to 10 days, but may take longer. For cases failing to respond to this regimen, subsequent management includes antibiotic administration in conjunction with surgical closure and/or shunt placement

in instances when the source of CSF leak is obscure. Spontaneous or iatrogenically-induced leaks will generally require surgical intervention to assure closure. Surgical repair techniques require the localization of the leak followed by reconstitution of a "seal" which is established by primary suture of the dura and/or grafting with either muscle, pericranium, fat, or fascia. Cadaver dura preparations as well as artificial dura substitutes may be used. Theoretically, a vascularized graft after primary suture closure will provide the best chance of permanent closure.

Tissue adhesives or sealants have been used successfully. Cyanoacrylate and fibrin sealants may be used to augment standard surgical methods of dural repair. Despite tremendous adhesive strength and sealing properties, cyanoacrylates are no longer advised because necrosis of neurologic tissue has been observed.^{7,8}

Fibrin sealants have been used extensively in Europe since the late 1970s.⁹ These sealants are based on the final stage of coagulation, specifically the conversion by thrombin, Factor XIII and calcium ion of fibrinogen monomer into fibrin polymer to effect a hemostatic, adhesive clot. These are formatted into a two component system, analogous to a two part epoxy system. The first component consists of fibrinogen, Factor XIII, fibronectin, and plasminogen. The second consists of thrombin, calcium ion, and, optimally, an antifibrinolytic agent such as ϵ -amino-n-caproic acid or aprotinin.

Some clinicians report that the best sealing of CSF fistulae is obtained by dural suture supplemented by autologous fascia or pericranium graft and application of FS to cover the repair.³ However, there are no rigorously controlled clinical reports to date, and the effectiveness

over conventional closure means has not been quantified.^{1,10} In vivo and ex vivo studies have clearly demonstrated the potential advantage of FS in sealing CSF leaks. Nishihira and McCaffrey,² utilizing a rat rhinorrhea model, reported that FS and muscle packing worked best in sealing CSF leaks (22% leak rate vs 58% leak rate for FS alone and 33% leak rate for muscle packing alone). In an ex vivo human dura burst pressure study, Cain et al^{11,12} showed that FS increased burst pressure in conjunction with suture. Cyanoacrylate with sutures was significantly better; however, no burst resistance was noted when cyanoacrylate was used alone. In vivo rabbit and canine dural repair models showed that FS and suture had higher burst strength than suture alone for repairs up to 7 days postoperatively. However, FS showed marked inflammatory response and tissue necrosis.

Based on the experience to date, the concept of using a sealant to repair CSF leaks appears attractive, and there is a strong need for a safe, practical, and efficacious version. The properties of an optimized sealant would provide biocompatibility and a lack of toxicity. It should act as a stand-alone sealant with sufficient biological persistence until dural healing occurs. The material should facilitate, or at least not interfere with, normal wound healing. The effectiveness and assurance of a seal against CSF leakage would mandate a low fluid permeation rate through the material, as well as conformational stability. Sufficient mechanical and adhesive strength is necessary to deal with CSF pressure, especially if elevated above normal values. Ease of application is critical if the sealant is to be practicable.

Should these qualities be attainable with greater sealing efficacy than current methods, the cost-savings benefits would be greater because of reduced procedure time, reduced postoperative complications (eg, meningitis), avoidance of secondary surgical procedures, and overall reduced hospitalization. All currently available FS and cyanoacrylates fail to meet these requirements fully.

The goal of this study was to evaluate CTA as a stand-alone adhesive/sealant system for use in sealing small- to medium-sized dural defects which in turn would minimize or eliminate postoperative complications and reduce hospitalization time and related costs. Previous studies¹³⁻¹⁵ have suggested that CTA had improved handling qualities for use in sealing by increased viscosity and decreased variability in mechanical properties in comparison to standard fibrin sealants.¹⁶ In addition, CTA appeared to improve skin graft take when compared to FS or staple closure as determined by graft attachment strength over the course of 4 weeks and, based on these studies, appeared to be an excellent candidate as a CSF sealant.¹³

In the current study, CTA supplemented closure was superior to that of skin closure alone in preventing CSF leakage and, therefore, appears to possess the qualities required for an effective sealant. Further investigations are needed to quantify the CSF pressure necessary to effect repair failure.

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