Rapid polymerizing fibrin glue from autologous or single-donor blood: preparation and indications

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A recipe for the preparation of a rapid polymerizing fibrin glue from single-donor or autologous blood products is presented. An in vitro investigation of different recipes with study of polymerization times, consistency, and in vitro survival of the product is described. The preparation in the operating room and the indications for clinical use of this glue in neurosurgery are discussed. The results of its use in a series of 38 patients is presented, including those undergoing surgery of the skull base, pituitary gland, cranial nerves, and the spine.

KEY WORDS • fibrin glue • fibrinogen product • adhesive • cerebrospinal fluid leak

Fibrin glue has not been popular in neurosurgery in the United States. This has been due to the lack of licensure of commercial products by the Food and Drug Administration owing to the risk of blood-borne diseases inherent in pooled fibrinogen products. Attempts at self-mixed preparations in the past have generally yielded runny mucoid products not suitable for use in environments moist with cerebrospinal fluid (CSF). The following recipe obviates this problem through production of a fibrin glue that polymerizes within several seconds of ejection from the syringe. This preparation is associated with minimal risk of transmissible disease because it is prepared from single-donor rather than pooled cryoprecipitate. Alternatively, the fibrin glue may be prepared from the patient's own blood, completely eliminating all risk.

Clinical Material and Methods

In Vitro Experiments

The fibrin glue was manufactured in two parts. Solution 1 consisted of single-donor (rather than pooled-source) cryoprecipitate obtained from the blood bank. The total volume obtained from each bag ranged from 10 to 15 ml. Solution 2 was bovine thrombin powder (Thrombostat, 20,000 U/vial).* Recipes were varied as follows to identify the formulation with the shortest polymerization time and optimum consistency.

* Thrombostat bovine thrombin powder manufactured by Parke-Davis, Morris Plains, New Jersey.

Thrombin powder was dissolved in 10% CaCl₂ solution (rather than the supplied diluent) to yield concentrations of 500, 1000, 1500, and 2000 U/ml. (Thrombostat already contains calcium in the dry form, but other brands of thrombin may not.) The ratio of Solution 1 to Solution 2 was varied in the proportions 3:1, 2:1, and 1:1. Each solution was drawn up into a syringe and ejected via a No. 23 needle. Total glue volumes in each trial ranged from 1.5 to 2 ml, and the product was ejected onto a plastic molded surface. Time zero was taken as the time of complete ejection. The end point of polymerization was marked when the fibrin glue would not run down a plane inclined 70° from horizontal. Between three and five replications were averaged to obtain a mean polymerization time for each specific recipe. The resulting product is illustrated in Fig. 1.

In Vivo Studies

The optimum glue recipe was identified in the in vitro studies as single-donor cryoprecipitate combined with thrombin in a 3:1 ratio in a concentration of 2000 U/ml. Fibrin glue was used in the surgical treatment of 38 patients. The option of autologous blood donation expressly for the purpose of glue preparation was offered when possible, but no patient exercised this option. If desired, this requires preparation at least 3 days prior to surgery. If a hospital does not have the mechanism in place for autotransfusion service, then the local Red Cross must be contacted to accommodate the patient's donation, and cryoprecipitation may then be performed. Single-donor cryoprecipitate from the blood bank was used in all patients in this series.
Rapid polymerizing fibrin glue

Fig. 1. Photograph showing a piece of fibrin glue held with forceps, demonstrating the rubbery consistency of the product.

Use of the fibrin glue was indicated in any case in which a dural defect could not be repaired in a watertight fashion, such as in some skull-base surgical procedures, and in routine closure of all transsphenoidal pituitary resections. It was also used as a sealant over bacitracin-soaked Gelfoam packing of paranasal sinuses and in occluding mastoid air cells in transpetrosal or wide lateral suboccipital procedures. This fibrin glue was used in a variety of other situations: all cases are summarized in Table 1.

Cryoprecipitate was requested from the blood bank 30 minutes prior to use to allow time for thawing. The actual mixing of the components in the operating room requires less than 5 minutes. The two solutions were drawn up in individual syringes (3 ml each) and ejected through No. 22 (3.5 in.) spinal needles (Fig. 2). The needle tips were approximated with a sterilized strip to facilitate mixing of the two components during the ejection process. The operative field should be aspirated as dry as possible before the glue is applied. The glue may be applied directly, and additional layers may be added after each has dried. Alternatively, the glue may be applied to Gelfoam or to cadaveric dura if desired. If CSF was evident welling up at the field margin after fibrin glue was applied, the glue was totally removed and all steps of the reconstruction and layering were repeated.

Results

In Vitro Experiments

The results of the in vitro experiments are displayed in Fig. 3, with polymerization time plotted against glue component ratios and thrombin concentration. The optimum preparation with the shortest polymerization time and firmest consistency utilized 2000 U/ml thrombin solution and involved a 3:1 cryoprecipitate:thrombin solution (Figs. 1 and 2). The glue has a rubbery consistency similar to a soft plastic.

In vitro survival studies demonstrated that the glue remains intact and retains the shape of the mold it is poured into for 5 days when stored uncovered at room temperature. After 5 days it desiccates and flakes. Longevity testing was also performed in which the glue was stored in a plastic flask under saline with a paraffin

<table>
<thead>
<tr>
<th>Surgical Procedure</th>
<th>No. of Cases</th>
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<tbody>
<tr>
<td>transsphenoidal resection of pituitary tumor</td>
<td>18</td>
</tr>
<tr>
<td>(includes intraop repair of CSF leak)</td>
<td>(5)</td>
</tr>
<tr>
<td>transsphenoidal resection of skull-base tumor</td>
<td>2</td>
</tr>
<tr>
<td>orbitozygomatic/frontal craniotomy for tumor</td>
<td>4</td>
</tr>
<tr>
<td>cavernous sinus aneurysm/tumor</td>
<td>3</td>
</tr>
<tr>
<td>microvascular decompression†</td>
<td>6</td>
</tr>
<tr>
<td>lumbar discectomy, CSF leak</td>
<td>2</td>
</tr>
<tr>
<td>bilat C-2 decompression-occipital neuralgia</td>
<td>1</td>
</tr>
<tr>
<td>anterior cervical discectomy, CSF leak</td>
<td>1</td>
</tr>
<tr>
<td>Chiari malformation/pseudomeningocele repair</td>
<td>1</td>
</tr>
</tbody>
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* CSF = cerebrospinal fluid.
† Involvement of the fifth, seventh, and ninth cranial nerves.

Fig. 2. Illustration showing the optimum recipe for fibrin glue preparation and method of delivery. The cryoprecipitate used should be from a single donor, not a pooled source. The two solutions are drawn up into separate syringes and ejected through needles with the tips fixed in approximation to facilitate mixing the solutions in the ejection process.

Fig. 3. Bar graph demonstrating the effect of varying thrombin concentrations and the ratio of cryoprecipitate on the polymerization time of the resulting fibrin glue. The ideal recipe is seen to be cryoprecipitate combined in a 3:1 ratio with 2000 U/ml thrombin solution. This produced a product with a mean polymerization time of 2.5 seconds.

TABLE 1

Summary of 38 cases with use of fibrin glue†
cover in order to better simulate in vivo conditions. The glue was inspected on a daily basis. It retained its shape and integrity until the 6th day, when it began to dissolve into the overlying solution.

In Vivo Studies

There have been no cases of postoperative CSF leakage in any of the 38 patients in whom this fibrin glue has served as part of the closure with reconstruction of the sellar floor, petrous/mastoid area, or skull base. The glue was used in the repair of intraoperative iatrogenic CSF leaks in five cases of transsphenoidal pituitary resection, and no CSF rhinorrhea has occurred during follow-up periods as long as 18 months. In all patients, a spinal drain was used as an adjunctive measure for several days (up to 72 hours) postoperatively. In only one case of a CSF leak was there failure of the glue; this operation was re-exploration of a recurrent lumbar herniated disc, and involved an early recipe of the glue based on 500 U/ml thrombin combined 1:1 with cryoprecipitate rather than the rapid polymerizing recipe used in the other cases. No complications or adverse effects from the glue were noted.

Discussion

A simple technique for the preparation of a fibrin glue from single-donor or autologous blood is described. An optimum recipe was established based on in vitro laboratory studies. This procedure minimizes the risk of blood-borne diseases that may be transmitted with higher frequency through the use of pooled donor products. The simplicity of this recipe allows glue to be ready in approximately 5 minutes. The commercially available products not licensed for use in the United States (such as Tissee1) generally require 30 to 60 minutes of mixing time and may need costly thermal agitators for use in their preparation; the substrate costs with these products may be as much as threefold higher. The simple formulation described here may prove substantially more economical both in mixing time and expense, while yielding a comparable product. The costs of the components at our institution total $31.50 to produce a fibrin glue volume of 20 ml (in the average case only several milliliters of glue is required).

The use of fibrin glue has been popular in cardiovascular surgery in conjunction with the use of prosthetic graft materials. Its utility in neurosurgery has already been demonstrated in numerous reports. The use of fibrin glue in neurosurgery is more widespread in Canada, Europe, and Japan, as compared to its very limited popularity in the United States. This is accounted for in large part by the lack of FDA licensure of commercial fibrinogen-containing products. The attempts at self-mixed substances often yield runny mucoid preparations that are not suitable for the often moist environment in which neurosurgeons would desire to use fibrin glue. However, the virtually instant polymerization of the recipe described here obviates this problem. The attributes of minimal expense, simplicity of preparation, relative safety, and rapid polymerization make this formulation desirable in a wide variety of neurosurgical contexts. The survival studies done in vitro suggest that the longevity of this preparation is probably adequate to allow the natural healing processes to advance and replace the glue. The author has found this substance to be reliable.

The use of fibrin glue as an aid in surgical closure may reduce the need for subsequent operative procedures for the delayed repair of CSF leaks that were not identified intraoperatively in procedures at high risk for CSF fistula formation. While there must be at least some minimal theoretical risk associated with the use of blood protein products in this manner, it is minimized with the use of single-donor cryoprecipitate. The recipe presented here can easily be made with absolutely no risk by using an aliquot of the patient's own cryoprecipitated blood. As more patients choose to donate their own blood in advance of elective surgical procedures, this option will become more convenient. It is hoped that this simple recipe and the above data might allow other neurosurgeons to make use of this inexpensive, expedient tool.

References

5. Revocation of fibrinogen licenses. FDA Drug Bull 8:15, 1978

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