Iranian Red Crescent Medical Journal

ORIGINAL ARTICLE

The Effect of BioGlue® on Cerebral Cortex in Experimental Rats

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Abstract

Background: BioGlue® is a newly introduced sealant applied by several cardiovascular surgeons to seal graft anastomoses. This study was carried out to determine the effect of a synthetic BioGlue® on the repair of meninges in comparison with contemporary bioadhesives.

Methods: A synthetic BioGlue® was provided by combining 45% human serum albumin and 10% glutaraldehyde. Forty Wistar female rats were randomly divided into 4 equal groups (Two case and two control groups). After craniotomy, dural incision was performed and the motor cortex was exposed. In the case group, the motor cortex was exposed to BioGlue® and in the control group, the incision was closed without application of BioGlue®. The rats were studied histpathologically after 5 and 14 days postcraniotomy.

Results: Synthetic BioGlue® caused an acute inflammatory response that resulted in a delayed gliosis in the superficial cerebral cortex, but the deep layers and adjacent areas of cortex were spared. Inflammatory changes and gliosis did not cause cell apoptosis or necrosis. Histopathological changes did not have any clinical significance as they were not accompanied by any neurological deficit or motor weaknesses and exposure to synthetic BioGlue® could not cause any clinically significant neurological deficit either.

Conclusion: The simplicity of producing this new synthetic BioGlue® and its relative low cost, compared to other similar glues, opens a new horizon to the use of this synthetic BioGlue® in the neurosurgical field.

Keywords: Cerebral cortex; Synthetic BioGlue®; Pathology; Rat

Introduction

Cerebrospinal fluid (CSF) leakage is still a troublesome complication in neurosurgical practice which might result in meningitis, low-tension headache and secondary pneumocephalus.[1] Watertight dural closure which does not allow CSF escape is not always easy or possible, especially in procedures in narrow spaces at the base of the skull.[1] Post-operative CSF fistula following neurosurgery is associated with increased morbidity and mortality too.[2] A wide variety of modalities are used for augmentation of dural closure, among which fibrin glue is the most popular.[1] BioGlue® is a newly introduced sealant applied by several cardiovascular surgeons to seal graft anastomoses. When applied, the glutaraldehyde molecules covalently cross-link the bovine serum albumin molecules to each other and to the tissue proteins at the repair area, providing a flexible mechanical seal independent of the body's clotting mechanism. This process is quick, reaching the maximal strength in two minutes.[3]

Glues and adhesives attach to a surface through a molecular attraction and their degradation products must be biocompatible.[4] The aim of this study was to determine the effect of a synthetic BioGlue® on the repair of the injured meninges in rat as an animal model.

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Received: May17, 2008 Accepted: October 12, 2008

Materials and Methods

Forty Wistar female rats (200-250 g) aged between 2-3 months old were randomly divided into 4 equal groups (two case and two control groups). The groups were studied for 5 and 14 days postcraniotomy. Each rat received 10 mg/kg of xylene and 90 mg/kg of ketamine intramuscularly for anesthesia. Knife no. 11 was used for a linear incision on the skin along the saggital suture line and the periosteum was removed to expose the saggital and coronal sutures. The operation site was below and posterior to the coronal suture. Using a dental drill, distal to the suture and toward the right side, a square shape craniotomy of 5 mm margins was made. The dura was exposed using knife no. 11 and a square incision of 4 mm width was made to expose the cortex. In the case group, synthetic BioGlue® was applied by sterile syringes. In the control group, no BioGlue® was used. The dura was then replaced on the cortex and the incision was closed using a 3-0 nylon suture. Post-operatively, the rats were visited daily and were checked for any neurological deficit, behavioral derangements and ominous signs of impending death.

Commercial BioGlue® was provided in a simple formula of 10% glutaraldehyde and purified bovine serum albumin. To make a synthetic BioGlue®, 45% human albumin and 10% glutaraldehyde were mixed in a ratio of 4:1. To provide a 45% concentration of human albumin, a 20% human albumin (Blood Elements Products Research Center; BEPRC, Shiraz, Iran) was changed into powder by freeze and dry method. Nine grams of the powder was mixed into 20 ml of distilled water and sterilized by 45 nm microfilters. The albumin was also pasteurized using Menon *et al.*'s method.[5] The tensile and shear strengths were determined as described by Amirghofran *et al*.[6]

Ten rats in the study group (A) and ten in the control group (B) were sacrificed 5 days after the surgery. Ten rats in the study group (C) and 10 in the control group (D) were sacrificed after 14 days following the surgery. After opening the wounds, the right cortex was removed and fixed in 10% formalin in separate containers and sent for pathological study. The presence of any vascular congestion, inflammatory cells infiltration in deeper layers, dystrophic calcification, and the presence or the absence of any necrosis were recorded. Any inflammatory changes were analyzed in groups A, B, C and D. Histopathological changes in the cerebral cortex were demonstrated by the number of inflammatory cells per high power field (HPF), and labeled as mild, moderate or severe if 1-5, 6-10, or 11-15 cells per HPF were seen. The number of reactive astrocytes per HPF, and gliosis were recorded as mild, moderate or severe if 3-4, 5-6, or 7-8 reactive astrocytes were seen per HPD, respectively. Gliosis was shown by presence of reactive astrocytes in the tissue.

Results

Behavioral changes showed a decreased activity and drowsiness in all 40 rats on the first day post-operation which was completely reversed after 2 days. When compared to other laboratory animals not involved in this study, all rats had significantly identical behavioral patterns. This was not, however, checked by any standardized method and was, thus, based on the researchers' observation. Post-operative daily evaluation revealed no clinical weaknesses, and all the animals identically used their extremities easily and effectively.

Regarding acute inflammatory changes, group A had an average of 7.9±3.8 inflammatory cells per HPF in the superficial cerebral cortex compared to the control group (B) without any inflammatory cell infiltration and the difference was statistically significant (P=0.001). BioGlue® caused inflammatory reactions on the cerebral cortex in the acute phase after 5 days. Comparing groups A and B in relation to the severity of inflammation after 5 and 14 days, the inflammatory changes caused by BioGlue® in the cerebral cortex were not statistically different with time (P=0.21). Chronic inflammatory changes were seen in group C with an average of 5.6±3.8 cells/HPF compared to group D with no inflammatory cells infiltration in the cerebral cortex and the difference was statistically significant after 14 days (P=0.001), showing inflammatory changes by BioGlue® on the cerebral cortex until 14 days. The probability of infiltration of inflammatory cells in the deeper cerebral cortex was 30%, 0%, 10% and 0% in groups A, B, C and D, respectively. The difference was significant between the groups A and B (P=0.05), and C and D (P=0.04), but it was not significant between groups A and D (P=0.36). No dystrophic calcification was seen.

Gliosis was not seen in any of the four groups except group C which received BioGlue®, with an average of 3.9±1.9 reactive astrocytes per HPD. This shows that though cerebral cortex inflammation following BioGlue® application does not cause gliosis

in the acute phase (after 5 days) during time, it caused a significant gliosis (P=0.001). Synthetic BioGlue® caused an acute inflammatory response that resulted in a delayed gliosis in the superficial cerebral cortex, but the deep layers and adjacent areas of the cortex were spared. Inflammatory changes and gliosis did not cause any necrosis. Histopathological changes did not have any clinical significance as they were not accompanied by any neurological deficit or motor weaknesses and exposure to synthetic BioGlue® could not cause any clinically significant neurological deficit too. Figure 1 displays a mild chronic inflammation in the brain parenchyma. The moderate and severe inflammations were demonstrated in Figures 2, 3 and 4 showing a severe chronic inflammation in brain parenchyma with aggregation of lymphocytes around blood vessels. The presence of reactive astrocytes in the brain cortex is shown in Figure 5.

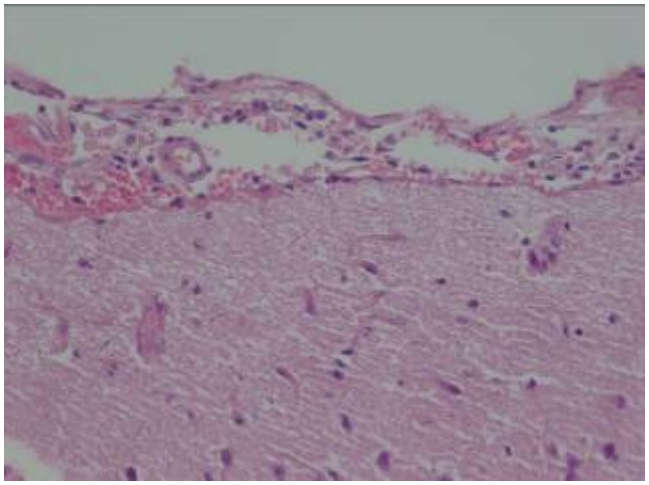

Fig 1: Mild chronic inflammation in brain parenchyma (H & E ×100)

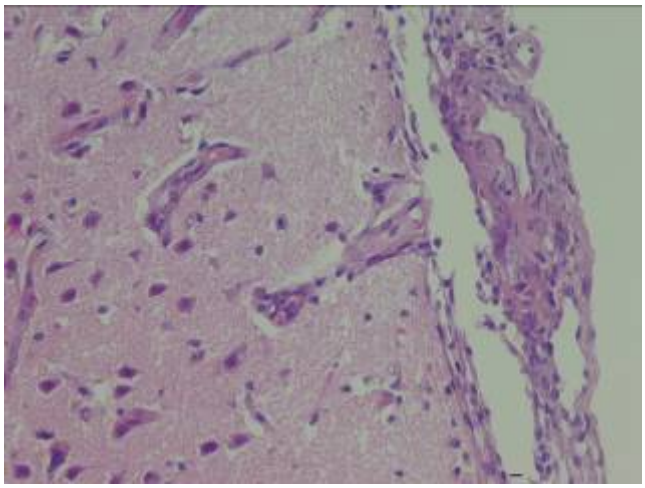

Fig 2: Moderate chronic inflammation in brain parenchyma (H & E ×100)

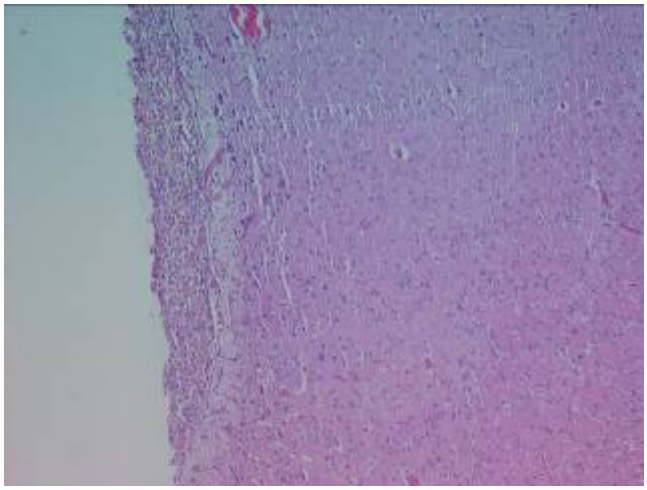

Fig 3: Severe chronic inflammation in brain parenchyma (H & E ×400)

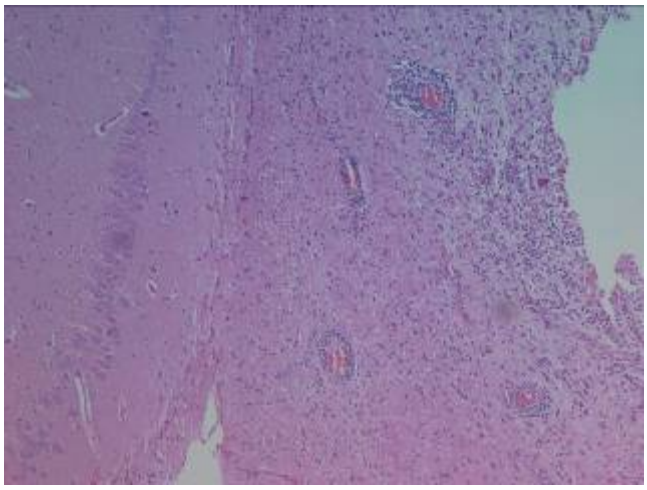

Fig 4: Severe chronic inflammation in brain parenchyma with aggregation of lymphocytes around blood vessels (H & E ×400)

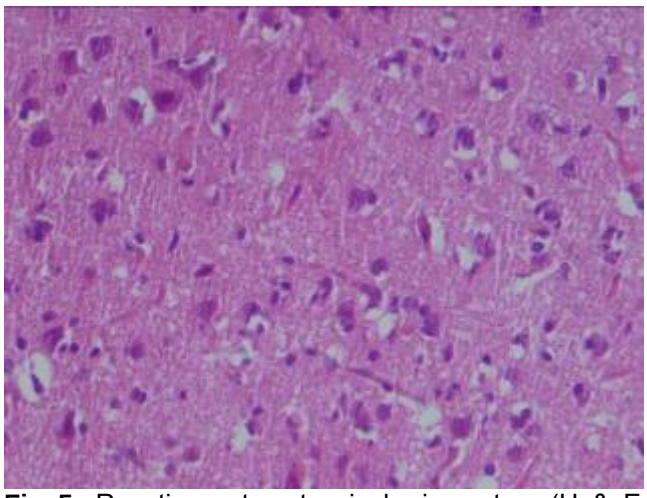

Fig 5: Reactive astrocytes in brain cortex. (H & E ×400)

After 20 seconds, the tensile strength was 65% in the BioGlue® group which is relatively fast and in 2 minutes, the maximum strength was observed. The tensile strength was 833±46 g/cm^2 and the shear strength 276±21 g/cm^2.

Discussion

BioGlue® is recently added to the list of synthetic tissue sealants used in surgeries. A paramount property of an adhesive is its strength.[6] The glue polymerizes very fast providing a "weld" at the site of repair.[3] The BioGlue® was also used as a surgical sealant in cardiopulmonary and neurosurgical operations.[2,7-9] BioGlue® has been also used in the treatment of high anal fistulas.[10] As commercially prepared fibrin sealants become more widely available, the number of patients and surgeons benefiting from improved surgical outcomes is also set to increase.[10] Fibrin sealants are the most effective tissue adhesives currently available, and they are biocompatible and biodegradable.[11] The use of fibrin sealants in addition to sutures has a direct effect on hemostasis and blood loss. Fibrin sealants also reduce the volume of the fluid drained and air leakage postoperatively in the head, neck, and thoracic surgery and in some cases result in a reduced length of hospital stay. The use of fibrin sealant as suture support can also reduce the number of sutures and the length of operations for intricate or complex procedures.[12] Autologous fibrin glue has the protective advantages of transmission of viral diseases and immunological reactions.[13]

There are controversies on the repairing effect of BioGlue®. In Spain, the plug of BioGlue® was expelled from the tract accompanied by purulent drainage but no patient required emergent reoperation for acute postoperative sepsis.[14,15] Based on some preliminary experiences, BioGlue® was no more offered as an option to patients with anorectal fistulas.[16,17] Fisher *et al.* (2008) applied BioGlue® sealant but did not notice any reduction in the incidence of pancreatic fistula following pancreas resection[3] but Amirghofran *et al.* illustrated the safety of BioGlue® in cardiovascular surgery.[6]

In our study, the tensile and shear strengths of the BioGlue® is comparable to the results of Amirghofran *et al.*, showing the effectiveness of the BioGlue®.[6] Comparing groups A and B in relation to the severity of inflammation and the inflammatory changes by BioGlue® in the cerebral cortex did not differ with time. Other studies reported inflammation but the pathological findings did not reveal any granulomatous responses[6,7,18] demonstrating the safety of BioGlue®.

In all groups, vascular congestion was noticed in the cerebral cortex while this change may not be related to the BioGlue®. The contact of BioGlue® to the cerebral cortex caused a superficial inflammatory reaction, but no significant damage was visible in the deeper cerebral cortex. We showed that the contact of synthetic BioGlue® with the cerebral cortex may cause inflammatory reactions in the cerebral cortex after 5 days post-operation and may continue until the 14th day. This reaction caused late gliosis that may be observed on day 14th. However, these inflammatory changes and gliosis are localized and did not involve deeper cerebral regions and did not cause any cell necrosis. In addition, these pathological changes did not have any clinical importance because they were not accompanied by any neurological deficit or motor weaknesses.

Based on this study, the relative simplicity in production of this new synthetic BioGlue® and its relative low cost compared to other similar glues, opens a new horizon to the use of this synthetic BioGlue® in the neurosurgical field.

Acknowledgements

We thank the Office of the Vice-Chancellors for Research of Shiraz University of Medical Sciences for financial support.

Conflict of interest: None declared.

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