Article published online: 2024-06-07

Delayed Wound Healing Resulting from Inflammatory Process in Craniectomy Patients Treated with BioGlue: A Case Series with Literature Review

Methee Wongsirisuwan[1]

[1] Department of Neurosurgery, Rajvithi Hospital, Bangkok, Thailand

Asian J Neurosurg 2024;19:290–294.

Address for correspondence Methee Wongsirisuwan, MD, Department of Neurosurgery, Rajvithi Hospital, Bangkok 10400, Thailand (e-mail: mathee@hotmail.com).

Abstract

Background BioGlue is touted as a safe and effective sealant for various surgical procedures. This article describes five cases of delayed wound healing associated with the use of BioGlue after craniectomies.

Case Description Five patients of different genders and ages who had undergone craniectomy with BioGlue were presented to our medical center with wound dehiscence and purulent discharge. The first attempt to solve this problem by incision and drainage was unsuccessful. The removal of BioGlue is necessary to eliminate these problems.

Discussion The presence of wound dehiscence and aseptic cystic contents may indicate a chronic inflammatory process following the application of BioGlue. This problem usually occurs within a few months after wound closure. For rapid intervention, it is recommended to perform an incision and drainage and remove the BioGlue. The main risk factor is directly applying BioGlue to the skin, subcutaneous tissue, or titanium material.

Conclusion Neurosurgeons should exercise caution and be aware of a possible delayed chronic inflammatory process in surgical wounds associated with the use of BioGlue as a sealant, especially when the product is used without cranial coverage or in cases where it comes into direct contact with subcutaneous tissue or titanium material. To resolve this issue quickly, BioGlue should be completely removed at the first attempt at incision and drainage.

Keywords
- surgical wound
- inflammatory process
- craniectomy
- neurosurgery
- BioGlue

Introduction

BioGlue is a type of surgical adhesive used in surgical procedures to seal and adhere biological tissue. It mainly comprises of bovine serum albumin and glutaraldehyde, endogenous proteins in the biological system. It is used in various surgical procedures, for example, heart and lung operations, as well as other procedures that require the sealing or bonding of tissue. In neurosurgery, this technique for sealing dural tears aims to reduce the leakage of

article published online
June 7, 2024

DOI https://doi.org/10.1055/s-0044-1787673.
ISSN 2248-9614.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

cerebrospinal fluid (CSF). As stated by the manufacturer, there are inherent risks associated with the use of BioGlue, including the potential for infection, hypersensitivity, and inflammation. This study aims to evaluate the potential adverse effects of BioGlue during neurosurgical procedures. The report's documentation was in accordance with the SCARE 2020 criteria,[1] and the reporting was carried out in line with the PROCESS 2023 criteria.[2]

Cases Presentation

This study represents a consecutive retrospective review of 322 patients from a single academic hospital center who underwent brain surgery in which BioGlue was concomitantly applied as CSF leakage prevention sealant during surgery between January 2018 and December 2020. Of the 322 patients, 5 were retrieved and examined due to experiencing similar adverse effects following their surgeries. After a certain period following the surgeries, all patients experienced wound dehiscence and the presence of aseptic cystic contents. The demographic data and details of the surgeries and treatments are summarized in ►**Table 1**. In all cases, the dura was meticulously directly repaired to ensure a secure seal through suturing and the application of BioGlue. Additionally, titanium plates were utilized to cover the bony defect, while the bone flaps were not repositioned. It must be noted that every operation was performed by the author, who has more than 25 years of experience in brain surgery.

Case 1

A 56-year-old female patient with a history of trigeminal neuralgia surgery presented to the hospital with surgical wound dehiscence and purulent discharge following microvascular decompression surgery performed 30 days earlier. BioGlue was used to prevent CSF leakage, and a titanium plate was used to cover the skull defect. On examination, she was a healthy woman with no comorbidities.

The patient's postoperative course during hospitalization was uneventful, and there were no signs of immediate adverse outcomes, such as surgical site infection or inflammation, allowing her to be discharged from the hospital a few days after surgery. One month after the operation, she noticed a purulent discharge from the incision site. There were no obvious symptoms of pyrexia, discomfort, or pain. The only medical concerns were the dehiscence of the wound, the purulent discharge, and no signs of CSF leakage. Despite the absence of leukocytosis in the patient's blood tests, a simple wound dressing and a broad-spectrum antibiotic were administered. The exudate improved somewhat, but intermittent exudates continued to ooze from the wound, and the patient underwent wound exploration. Pus without foul odor collected in the layer between the scalp and the skull was removed and sent for further laboratory testing. An intact dura mater was found. A thorough irrigation with an antiseptic and an isotonic saline solution was performed. The wound was then closed, and the titanium plate was removed.

She was prescribed a course of intravenous broad-spectrum antibiotics for 3 days. The purulent fluid's intraoperative culture and Gram stain analysis proved negative for pathogenic microorganisms. The patient was discharged with a prescription for a broad-spectrum antibiotic to be administered orally for 10 days. Ten days later, she presented with a recurrence of purulent discharge from the surgical wound incision site. Sepsis evaluation revealed no evidence of bacterial colonization, and she was transferred to the operating room for additional exploration. The intraoperative findings aligned with the results of the prior surgical intervention. The BioGlue was removed, and she was discharged on the seventh day following the surgical

Table 1 Summary of case presentations

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	56	34	85	42	21
Sex	F	M	F	M	M
Diagnosis	Trigeminal neuralgia	Vestibular schwannoma	Trigeminal neuralgia	Cerebellopontine angle meningioma	Trigeminal neuralgia
Operation	SOC with MVD	Craniectomy with tumor removal	SOC with MVD	SOC with tumor removal	SOC with MVD
Operative time (min)	65	215	54	75	89
First initial symptoms (since the operation)	30 days later	18 days later	10 days later	23 days later	248 days later
First presentation	Surgical wound dehiscence and purulent discharge	Surgical wound swelling	Wound dehiscence and purulent discharge	Wound dehiscence and purulent discharge	Wound dehiscence and purulent discharge
Management	1st: Wound dressing with antibiotic 2nd: I&D with titanium plate removal 3rd: BioGlue removal	Debridement with the removal of BioGlue, Gelfoam, and titanium plates	1st: Wound dressing 2nd: I&D with BioGlue and titanium plate removal	I&D with BioGlue and titanium plate removal	I&D with BioGlue and titanium plate removal

Abbreviations: F, female; I&D, incision and drainage; M, male; MVD, microvascular decompression; SOC, suboccipital craniectomy.

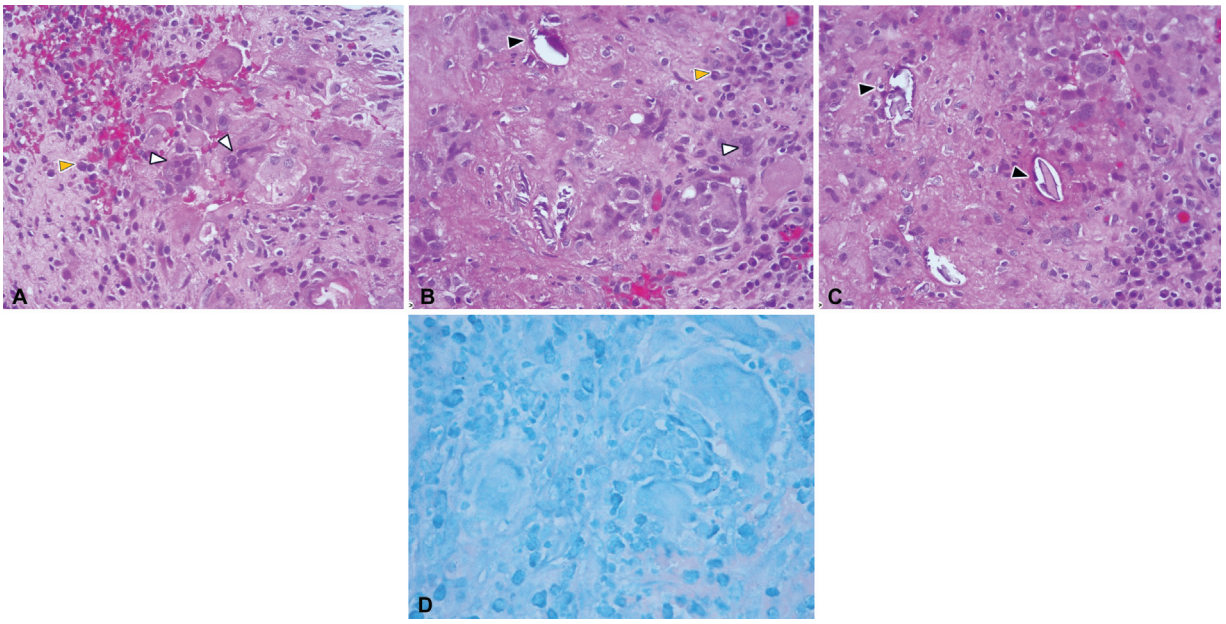

Fig. 1 (**A**–**C**) The histological stain indicated the presence of BioGlue as a chronic inflammatory mass (black arrowhead) surrounded by granulomatous inflammatory cells, multinucleated giant cells (white arrowhead), and histiocytes (orange arrowhead). (**D**) The acid-fast bacilli (AFB) stain revealed negative results for mycobacterium or other microorganisms.

procedure. The incision site demonstrated full recovery at 1- and 4-month postoperation visits.

Case 2

A 34-year-old male patient with well-controlled diabetes mellitus who had undergone a suboccipital craniectomy to remove a brain tumor presented 45 days after surgery. His condition and early postoperative course were similar to that of case 1. The patient's postoperative incision site had developed progressive swelling with a circumference of approximately 3 cm. He showed no signs of pyrexia, sepsis, or inflammation, and the wound showed no redness, erythema, or tenderness on palpation. A computer tomography scan of the brain was performed, which showed no signs of CSF leakage. Further wound exploration was then performed, and surgical observations were similar to the previously reported findings in patient 1. The wound was thoroughly debrided by irrigation with antiseptic and normal saline solution. Both BioGlue and the titanium plates were removed during the same procedure. The results of the pathological analysis confirmed the presence of a chronic inflammatory mass with granulomatous foreign body inflammation (►**Fig. 1B** and **C**) with dispersed multinucleated giant cells (►**Fig. 1A** and **B**) and histiocytes (►**Fig. 1A** and **B**). The official report after acid-fast bacillus staining also confirmed the absence of pathogenic microorganisms in the purulent exudate (►**Fig. 1D**). The patient achieved complete wound healing and remained asymptomatic throughout the 6-month posttreatment observation period.

Cases 3, 4, and 5

An 85-year-old woman and a 42-year-old and a 21-year-old man who had undergone posterior fossa surgery returned 10, 23, and 248 days after discharge, respectively. All had no medical history or comorbidities. Surgical wound dehiscence and purulent discharge were present in all cases. The purulent discharge persisted despite careful wound care and oral broad-spectrum antimicrobial therapy. In case 3, the patient was treated with a wound dressing for 10 days. However, the problem remained unresolved, leading to the decision to continue with incision and drainage (I&D). In cases 4 and 5, I&D was recommended as the primary intervention to alleviate the problem. The intraoperative findings were consistent with those described earlier. In case 5, BioGlue was still present in the surgical field even though the surgery had been performed 248 days ago. BioGlue was completely removed in each case. Biological tissues and fluids were evaluated for septic workup and pathologic examination, revealing chronic inflammation with no identifiable bacterial pathogens.

Discussion and Literature Review

BioGlue is frequently used in cardiovascular and neurosurgical procedures for rapid and effective tissue sealing. It has the remarkable advantage of eliminating the need for sutures or staples. This compound is claimed to be a biocompatible and biodegradable adhesive consisting mainly of bovine serum albumin and glutaraldehyde. Several medical reports have been published worldwide on the benefits of using BioGlue in various surgical procedures, including neurosurgery. Iino et al described a particular medical approach using BioGlue for the repair of ventricular septal tears tailored to a range of postinfarct myocardial pathologies.[3] Sidle et al concluded that the use of BioGlue is a safe and effective method for maintaining eyebrow position after endoscopic blepharoplasty.[4] Rathinam et al reported favorable results in the areas treated with BioGlue regarding reduced air leakage, reduced chest drainage

volume, shorter duration of chest drainage, and significant absence of complications.[5] In contrast, some medical reports have documented adverse events associated with using this product. Pasic et al reported complications of late wound healing following the use of BioGlue as a hemostatic sealant in cardiac surgery.[6] Babin-Ebell et al reported a case of cardiac tamponade and pericardial effusion after repair of a left ventricular tear with BioGlue and pledget sutures.[7] Another study in the literature by Luthra et al cautioned against the use of BioGlue and discussed its potential adverse effects, which include primary hypersensitivity, allergic reactions, immune reactions, foreign body reactions, and glutaraldehyde-related side effects. These adverse reactions are thought to be due to glutaraldehyde, a typically highly toxic liquid.[8] Another medical article warning of the negative effects of BioGlue was written by Subasi and Guclu. Their research indicated that a surgical procedure on the nasal septum resulted in segmental cartilage injury from BioGlue.[9] Singh et al reported wound complications following BioGlue application and recommended primary drainage, debridement, and removal of all BioGlue residues.[10] Singh and Wales cautioned against the use of BioGlue for hemostasis due to its adhesive and sealing properties. They said surgeons should exercise caution and administer minimal amounts to avoid adverse outcomes.[11]

Several reports have highlighted the benefits of using BioGlue as a hemostatic and sealant in neurosurgical procedures. Kumar et al used BioGlue in several neurosurgical procedures and documented no adverse effects associated with its use. It has been claimed to be an effective adjunctive measure for dural closure as it prevents CSF leakage and is easy to use.[12] According to Dusick et al, BioGlue is a valuable tool for preventing CSF leaks after transsphenoidal surgery.[13] Although there are numerous reports on the benefits of using BioGlue in neurosurgical procedures, adverse effects have also been associated with its use. According to the abstract by Gaberel et al, BioGlue appears to increase the likelihood of surgical site infection in patients who have undergone craniotomy, especially when combined with a synthetic dural graft. It is suggested that the use of BioGlue may trigger a significant inflammatory response, leading to wound dehiscence and subsequent bacterial colonization, creating an optimal environment for bacterial proliferation.[14] BioGlue was used by Abuzayed et al as an additional measure to close the dural defect in L5-S1 disk surgery. On the second postoperative day, the patient was presented with progressive sciatica, and magnetic resonance imaging revealed a mass lesion at the surgical site. The patient required urgent surgical intervention, and a mass of BioGlue was found to be compressing the spinal nerve roots.[15] In a comprehensive analysis of the use of bioadhesives in neurosurgery, Qiu et al pointed out the limitations and potentially unfavorable consequences associated with the use of bioadhesives, including the mass effect on adjacent neural structures, systemic allergic reactions, air embolism, compression of cranial nerves, infection, and the development of new aneurysms.[16]

The results of this case series study suggest that the use of BioGlue as a sealant to achieve a watertight dural closure may be associated with problems in surgical wound healing. All patients had similar medical characteristics, such as wound dehiscence and purulent discharge from a previously healed wound. In addition to purulent discharge, there was an absence of erythema, heat, or pain associated with the wound, which are pathognomonic features of the infectious process. In all patients, this problem occurred within a few months of wound closure, except for case 5, where BioGlue was still present even though surgery had been performed 62 weeks earlier. This observation in patient 5 is reminiscent of the report by Yuen and Kaye,[17] in which the presence of BioGlue at the site of dural repair was still noted 2 years after application. A literature review related to the adverse effects of BioGlue in neurosurgical procedures can be seen in ►**Table 2**.

A simple I&D procedure without the removal of BioGlue is insufficient to solve this problem. Histopathologic examination will confirm that this condition is due to a chronic

Table 2 Summary of literature review related to adverse effects of BioGlue in neurosurgical procedures

Investigator	Ref. number	Total number of patients in the study	Neurosurgical procedure	Adverse effect of BioGlue
Kumar et al, 2003	12	0 of 210	- Transsphenoidal surgery - Craniotomy - Laminectomy	No
Dusick et al, 2006	13	0 of 124	- Transsphenoidal surgery	No
Gaberel et al, 2011	14	30 of 661	- Craniotomy	Surgical site infection, especially when combined with a synthetic dural graft
Abuzayed et al, 2010	15	1 of 1	- Laminectomy	Mass lesion after dural defect closure
Qiu et al., 2019	16	Not available	- Endovascular embolization - Dural closure - Transsphenoidal surgeries	Mass effect on neural structures, systemic allergic reactions, air embolism, infection, etc.
Yuen and Kaye, 2005	17	1 of 1	- Dural repair in laminectomy case	Persistent of BioGlue two years after application

inflammatory process, as evidenced by granulomatous multinucleated giant cells and histiocytes. Assessment of sepsis will show the absence of an increase in white blood cells and the presence of bacterial pathogens.

In this study, in addition to the documentation of the aseptic cyst, which presented as an inflammatory process and which is most likely related to the use of BioGlue, as previously reported in the medical literature, two potential risk factors that may contribute to this problem in the surgical site were revealed: the direct application of BioGlue to the skin or subcutaneous tissue and its direct contact with Gelfoam or a titanium plate. In the author's experience, who has used BioGlue in numerous neurosurgical procedures, some complications have occurred when BioGlue has been in direct contact with the skin or overlying subcutaneous tissue. The author has not observed complications in cases where the skull covered the BioGlue.

Despite the facts discovered in this study, there are some limitations to consider. First, this is a retrospective study, so some uncontrollable factors, such as underlying comorbidities, may alter the outcome. Second, this study was conducted at a single center, resulting in limited participants. Another limitation is that the same surgeon performed the surgeries. Different surgeons may change the outcome if the study is conducted at a multicenter center.

Conclusion

Every neurosurgeon should consider the potential for a delayed chronic inflammatory process in surgical wounds associated with the use of BioGlue as a sealant, particularly when this product is used without cranial coverage or when it comes into direct contact with subcutaneous tissue or titanium material. To prevent delayed sterile cyst formation, using BioGlue with a minimal volume is recommended to fulfill its sealing properties. To solve this problem immediately, BioGlue should be completely removed during the first I&D attempt. In cases where the diagnosis of infection or inflammation is unclear, it is recommended that tissue and fluid samples be taken for definitive diagnosis. However, as mentioned above about the limitation of this study, further randomized controlled trials with large sample sizes and large multicenter studies are needed to confirm this hypothesis.

Ethical Approval

This case series is registered by the hospital's Ethics Committee (number 133/2566) and it was carried out following the principles of the Helsinki Declaration.

Conflict of Interest

None declared.

References

1 Agha RA, Franchi T, Sohrabi C, Mathew G, Kerwan ASCARE Group. The SCARE 2020 guideline: updating consensus surgical CAse REport (SCARE) guidelines. Int J Surg 2020;84:226–230

2 Mathew G, Sohrabi C, Franchi T, Nicola M, Kerwan A, Agha RPROCESS Group. Preferred reporting of case series in surgery (PROCESS) 2023 guidelines. Int J Surg 2023;109(12): 3760–3769

3 Iino K, Yamamoto Y, Ueda H, Takemura H. Two-patch technique with BioGlue for ventricular septal rupture resulting from acute anterior myocardial infarction. JTCVS Tech 2022;13(13):83–86

4 Sidle DM, Loos BM, Ramirez AL, Kabaker SS, Maas CS. Use of BioGlue surgical adhesive for brow fixation in endoscopic browplasty. Arch Facial Plast Surg 2005;7(06):393–397

5 Rathinam S, Naidu BV, Nanjaiah P, Loubani M, Kalkat MS, Rajesh PB. BioGlue and Peri-strips in lung volume reduction surgery: pilot randomised controlled trial. J Cardiothorac Surg 2009;4(04): 37

6 Pasic M, Unbehaun A, Drews T, Hetzer R. Late wound healing problems after use of BioGlue for apical hemostasis during transapical aortic valve implantation. Interact Cardiovasc Thorac Surg 2011;13(05):532–534

7 Babin-Ebell J, Bougioukakis P, Urbanski P, Froehner S, Diegeler A. Foreign material reaction to BioGlue® as a possible cause of cardiac tamponade. Thorac Cardiovasc Surg 2010;58(08): 489–491

8 Luthra S, Theodore S, Tatoulis J. Bioglue: a word of caution. Ann Thorac Surg 2008;86(03):1055–1056, author reply 1056–1057

9 Subasi B, Guclu E. The effects of using Bioglue in nasal septal surgery. Ear Nose Throat J 2021;100(07):516–521

10 Singh A, Wyatt M, Clarke M, Wales L. Late sterile abscess formation in carotid endarterectomy following use of BioGlue: a word of caution. EJVES Short Rep 2017;37(37):12–13

11 Singh A, Wales L. Late sterile cyst formation following use of Bioglue in carotid endarterectomy. EJVES 2019;58(06):e128

12 Kumar A, Maartens NF, Kaye AH. Evaluation of the use of BioGlue in neurosurgical procedures. J Clin Neurosci 2003;10(06): 661–664

13 Dusick JR, Mattozo CA, Esposito F, Kelly DF. BioGlue for prevention of postoperative cerebrospinal fluid leaks in transsphenoidal surgery: a case series. Surg Neurol 2006;66(04):371–376

14 Gaberel T, Borgey F, Thibon P, Lesteven C, Lecoutour X, Emery E. Surgical site infection associated with the use of bovine serum albumine-glutaraldehyde surgical adhesive (BioGlue) in cranial surgery: a case-control study. Acta Neurochir (Wien) 2011;153 (01):156–162

15 Abuzayed B, Erman H, Inan M, Aydin S, Sanus GZ. Acute mass formation of Bioglue after spinal dural repair: a Glue-oma case report. Neurosurg Q 2010;20(04):253–255

16 Qiu L, Qi See AA, Steele TWJ, Kam King NK. Bioadhesives in neurosurgery: a review. J Neurosurg 2019;133(06):1928–1938

17 Yuen T, Kaye AH. Persistence of Bioglue in spinal dural repair. J Clin Neurosci 2005;12(01):100–101

