



Original Article

Efficacy of a topical gelatin-thrombin hemostatic matrix, FLOSEAL® , in intracranial tumor resection

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ABSTRACT

Background: Hemostasis plays an important role in safe brain tumor resection and also reduces the risk for surgical complications. This study aimed to evaluate the efficacy of FLOSEAL®, a topical hemostatic agent that contains thrombin and gelatin granules, in brain tumor resections.

Methods: We evaluated the hemostatic effect of FLOSEAL by scoring the intensity of bleeding from 1 (mild) to 4 (life threatening). We assessed the rate of success of hemostasis with 100 patients who underwent intracranial tumor resection. We also investigated the duration of the operation, the amount of intra- and postoperative bleeding, the number of hospital stays, and adverse events in patients who used FLOSEAL compared with those who did not use FLOSEAL.

Results: FLOSEAL was applied to a total of 109 bleeding areas in 100 patients. A total of 95 bleeding areas had a score of 1 and 91 (96%) showed successful hemostasis. Thirteen bleeding areas scored 2 and 8 (62%) showed hemostasis with the first application of FLOSEAL. The second application was attempted with five bleeding areas and four showed hemostasis. About 94% (103/109 areas) of bleeding points successfully achieved hemostasis by FLOSEAL. Moreover, FLOSEAL significantly decreased the amount of intraoperative bleeding and postoperative bleeding as assessed with computed tomography on 1 day postoperatively compared with no use of FLOSEAL. There were no adverse events related to FLOSEAL use.

Conclusion: Our results indicate that FLOSEAL is a reliable, convenient, and safe topical hemostatic agent for intracranial tumor resection.

Keywords: Brain tumor, FLOSEAL®, Intraoperative hemorrhage, Postoperative hematoma, Topical gelatin-thrombin hemostatic matrix

INTRODUCTION

In neurosurgical operations, most procedures involve a relatively limited space, especially in microscopic or endoscopic operations. Continuous bleeding easily obstructs the operative view in such operations, and this makes identifying the point of bleeding, which may cause damage to surrounding tissue with hemostasis, more difficult for surgeons. In neurosurgical operations,

hemostasis is essential for a clear operative field for safe resection.^[6,19] In addition, postoperative bleeding, even a small amount, may cause severe sequelae after the operation, which is not only disadvantageous for patients but also leads to a longer hospital stay.^[21]

In the past century, many hemostatic agents were introduced to improve the operation, such as bone wax, absorbable gelatin compressed sponges, oxidized regenerated cellulose, microfibrillar collagen hemostat, and fibrin glue. Recently, a novel hemostatic agent, FLOSEAL®, was introduced with Food and Drug Administration approval in 1999 and was included in insurance in Japan in August 2014. FLOSEAL is a topic hemostatic agent that contains thrombin and bovine-derived gelatin granules.^[24] Once FLOSEAL is applied at the area of bleeding, the granules swell and shield blood flow and provide a stable matrix called the tamponade effect. Compounded thrombin then facilitates forming a fibrin clot around the matrix that results in hemostasis.^[15] The effectiveness of FLOSEAL has been previously reported in various types of operations,^[1-4,6,9,11,13-15,16,20] and the use of FLOSEAL may shorten the time to achieve hemostasis.^[14] However, in neurosurgical operations, few previous reports have shown the utility of FLOSEAL,^[1,6] and no reports have evaluated its effectiveness objectively.

Therefore, in the present study, we investigated the effect of FLOSEAL by scoring bleeding before applying FLOSEAL after removal of brain tumors with operative videos and assessed the rate of successful hemostasis. In addition, with postoperative computed tomography (CT) scan images, we evaluated the amount of the postoperative bleeding and compared it with cases without FLOSEAL use. To the best of our knowledge, this is the first study to investigate the effect of FLOSEAL objectively in brain tumor resection.

MATERIALS AND METHODS

Patients

We evaluated 100 patients who underwent tumor resection by either craniotomy or an endonasal endoscopic operation. We included patients at the Department of Neurosurgery, Keio University School of Medicine, Tokyo, Japan, the Department of Neurosurgery, Japanese Red Cross Ashikaga Hospital, Tochigi, Japan, and the Department of Neurosurgery, Kawasaki Municipal Hospital, Kanagawa, Japan, between August 2017 and September 2018. Patients who fulfilled the following criteria were included in the study: (1) FLOSEAL (Baxter International Inc., IL, USA) was used in the operation for hemostasis after tumor resection; (2) FLOSEAL was washed out in 10 min after its application; and (3) preoperative written informed consent was obtained. This group of patients comprised the FLOSEAL group. Clinical information, including pre- and postoperative

images, operative time, amount of intraoperative bleeding, all events that occurred in hospital, blood collection data, and additional treatment, were obtained from the patients' medical records. This study was approved by the Institutional Review Board at Keio University School of Medicine and called "Evaluation of effectiveness of FLOSEAL® in brain tumor surgery" (Approval number: 20160439).

For a comparison group, we evaluated 100 patients who underwent tumor resection, by either craniotomy or an endonasal endoscopic operation at the Department of Neurosurgery, Keio University School of Medicine between April 2013 and May 2014, before FLOSEAL received insurance approval in Japan. This group of patients comprised the non-FLOSEAL group.

Validation of intraoperative bleeding severity scale

We evaluated the severity of intraoperative bleeding using a scale that has been described previously.^[10] Briefly, the score was ranked as 0 to 4 as follows: (0) no bleeding; (1) mild, oozing, or intermittent flow; (2) moderate, continuous flow; (3) severe, controllable spurting and/or overwhelming flow; and (4) life threatening, unidentified, or inaccessible spurting or gushing.

The scores were initially determined just before FLOSEAL was applied after removal of the tumor. We then evaluated whether hemostasis was successful after FLOSEAL was washed by irrigation for each FLOSEAL application. This scoring and evaluation were performed for every FLOSEAL application [Figure 1]. The second application sometimes needed to be performed to achieve hemostasis at the same bleeding point or at different points, and this was also

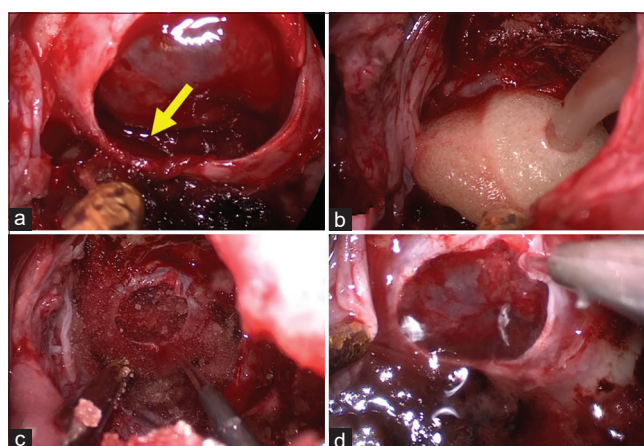


Figure 1: Hemostasis using FLOSEAL. A patient with pituitary adenoma underwent resection through endonasal endoscopic approach. (a) Moderate bleeding was observed from the cavernous sinus after tumor removal (yellow arrow), (b) FLOSEAL was applied to the bleeding, (c) FLOSEAL was washed by saline 2 min after its application, (d) complete hemostasis was achieved.

evaluated. For the second application at the same bleeding spot, the intensity of bleeding was reevaluated and scored.

Evaluation of the severity of intraoperative bleeding was performed by a neurosurgeon (E.I.) with an operative video and then another neurosurgeon (D.K.) confirmed the score.

Evaluation of postoperative bleeding

Postoperative bleeding in CT scan images with 5 mm in thickness taken at postoperative day (POD) 1 was analyzed by a three-dimensional system volume analyzer, SYNAPSE VINCENT (Fujifilm, Tokyo, Japan), and the volume of the bleeding was calculated. In these images, subdural hemorrhage or hemorrhage in the excised cavity, which was the target for hemostasis of FLOSEAL, was evaluated. Extradural hemorrhage, where FLOSEAL is not adapted, was excluded from this measurement.

Changes in blood data, adverse events, and hospital stay

In general, at our institute, we check blood data at PODs 1 and 7. Therefore, for postoperative blood collection data, we evaluated changes in the values of each factor compared with the initial data in each group. FLOSEAL may cause infection, thrombosis, or postoperative hemorrhage, leading to postoperative anemia. Therefore, we evaluated maximum body temperature during the hospital stay, maximum C-reactive protein (CRP) levels, and the number of white blood cells (WBCs). In addition, we evaluated the number of days for hospital stay after the operations.

Statistical analyses

Statistical analyses were performed by the JMP program (version 12.0.1; SAS Institute Inc., Tokyo, Japan). All continuous data, such as age, tumor size, blood collection data, operative time, intraoperative hemorrhage, body temperature, hospital stay, and the amount of postoperative bleeding, were analyzed by *t*-tests between the FLOSEAL group and non-FLOSEAL group. For other data, such as sex, diagnosis, approach (open, microsurgery, or combined surgery), and the recurrence rate, were analyzed with the Pearson Chi-square test.

$P < 0.05$ was considered statistically significant for all statistical analyses.

RESULTS

Baseline patients' characteristics

The patients' characteristics are listed in Table 1. In the FLOSEAL group, there were 53 women and 47 men aged from 21 to 82 years (mean \pm SD: 57.46 ± 14.74 years). In the non-FLOSEAL group, there were 52 women and 48 men aged from 11 to 87 years (52.07 ± 16.04 years). Except for a

Table 1: Patients' characteristics in the FLOSEAL and non-FLOSEAL groups.

	FLOSEAL (n=100)	non-FLOSEAL (n=100)	P
Gender			
Male	47	48	
Female	53	52	0.887
Age (yo)			
-19	0	3	
20-39	13	18	
40-79	85	76	
80-	2	3	
Average	57.46 \pm 14.7	52.07 \pm 16.0	0.0142
Dx			
Meningioma	39	24	
Pituitary adenoma	23	18	
Glioma	16	18	
Schwannoma	7	17	
Metastasis	6	4	
Chordoma	3	8	
Others	6	11	0.0497
Size of tumor (cm)	3.39 \pm 1.58	3.16 \pm 1.42	0.279
Approach			
Open	68	70	
Endoscopic	31	28	
Combined	1	2	0.773
Recurrent tumor	24	36	0.0641
Initial blood test			
Cr (mg/dl)	0.7461 \pm 0.220	0.7290 \pm 0.175	0.544
Na (mEq/l)	140.8 \pm 2.86	141.6 \pm 2.37	0.024
K (mEq/l)	4.154 \pm 0.270	4.176 \pm 0.346	0.617
Cl (mEq/l)	104.2 \pm 3.10	104.9 \pm 2.60	0.100
LDH (IU/l)	196.8 \pm 44.2	174.2 \pm 42.6	< 0.01
AST (U/l)	22.14 \pm 8.12	20.82 \pm 9.23	0.284
ALT (U/l)	20.93 \pm 12.3	20.39 \pm 17.7	0.803
WBC (1000/ μ l)	6.076 \pm 1.97	5.918 \pm 1.62	0.536
Hb (g/dl)	13.36 \pm 1.20	13.57 \pm 1.52	0.286
Plt (1000/ μ l)	240.0 \pm 65.4	233.0 \pm 57.1	0.430
CRP (mg/dl)	0.2264 \pm 0.607	0.2100 \pm 0.500	0.835

yo: Years old, LDH: Lactate dehydrogenase, WBC: White blood cells

significant difference in the distribution of diagnosis, there were no significant differences in the patients' characteristics between the FLOSEAL and non-FLOSEAL groups, including tumor size or surgical approach. The subgroup "others" in diagnosis include craniopharyngioma, hemangiopericytoma, hemangioblastoma, fibroma, germ cell tumor, glomus tumor, and lymphoma, with one or two cases for each diagnosis.

In the initial blood test, sodium levels were lower and lactate dehydrogenase (LDH) levels were higher in the FLOSEAL group compared with the non-FLOSEAL group ($P = 0.024$ and $P < 0.01$, respectively), but mean values in both groups were within the normal range. There were no significant differences in any other factors between the groups.

Table 2: Success rate of hemostasis with severity of bleeding before application of FLOSEAL.

Score of bleeding	First try		Second try		Total	
	Number of bleeding spots	Number of cases hemostasis achieved	Number of bleeding spots	Number of cases hemostasis achieved	Number of bleeding spots	Number of cases hemostasis achieved
1: mild	95	91 (96%)	5	4 (80%)	100	95 (95%)
2: moderate	13	8 (62%)	0		13	8 (62%)
3: severe	1	0	0	0	1	
4: life threatening	0	0	0	0	0	0
Total	109	99 (90.8%)	5	4 (80%)	114	104 (91.2%)

Severity of intraoperative bleeding before hemostasis and the success rate

The severity of bleeding before the application of FLOSEAL and the success rate is shown in Table 2. Among the 100 patients in the FLOSEAL group, 109 times of hemostasis were attempted using FLOSEAL. After the first FLOSEAL application, within 95 areas of mild bleeding, 91 (96%) achieved successful hemostasis and eight of 13 areas of moderate bleeding (62%) achieved hemostasis, but one case of severe bleeding could not be stopped. A total of 99 (90.8%) bleeding points successfully achieved hemostasis. The second application of FLOSEAL was performed for five patients who could not achieve successful hemostasis with the first application. All of the five bleeding areas were scored as mild and 4 (80%) showed successful hemostasis. Hemostasis was attempted for a total of 114 times and 104 (91.2%) showed successful hemostasis, and 94.5% (103/109 bleeding area) of bleeding areas were controlled by FLOSEAL. The mean hemostasis time, from the application of FLOSEAL until washing out by saline, was 214 ± 89 s (104–533 s).

Operative time and intra- and postoperative bleeding

The duration of the operation and amount of intra- and postoperative bleeding in the FLOSEAL and non-FLOSEAL groups are shown in Table 3. There was no significant difference in the operative time between the FLOSEAL and non-FLOSEAL groups. However, the mean amount of intraoperative bleeding in the FLOSEAL group was significantly lower than that in the non-FLOSEAL group ($P = 0.043$). Head CT scans on POD 1 showed that the amount of postoperative bleeding in the FLOSEAL group was less than that in the non-FLOSEAL group ($P = 0.01$).

Changes in blood collection data, adverse events, and hospital stay

Blood collection data, adverse events, and hospital stay are shown in Table 4. K^+ levels at PODs 1 and 7 and CRP levels at POD 1 were significantly lower in the FLOSEAL group compared with the non-FLOSEAL group ($P < 0.01$, $P < 0.01$,

Table 3: Operative time and amount of intra- and postoperative bleeding in the FLOSEAL and non-FLOSEAL groups.

	FLOSEAL (n=100)	non-FLOSEAL (n=100)	P
Operative time (min)	365±155	356±195	0.698
Amount of bleeding (ml)	181.5±187	261.3±338	0.0426
Volume of postoperative hematoma (ml)	0.560±0.984	1.238±2.42	0.0100
Min: Minutes			

and $P = 0.029$, respectively). K^+ values in the FLOSEAL and non-FLOSEAL groups at POD 1 were within the normal range. There were no significant differences in any other factors between the groups.

With regard to postoperative infection, there were no significant differences in maximum body temperature after the operation, maximum CRP levels, and WBC count between the groups. CRP levels at POD 1 were significantly higher in the non-FLOSEAL group than in the FLOSEAL group ($P = 0.029$). There were no adverse events directly affected by FLOSEAL, although an operation for hematoma removal was performed in the non-FLOSEAL group for postoperative hemorrhage.

There was no significant difference in the hospital stay between the FLOSEAL and non-FLOSEAL groups.

DISCUSSION

The effectiveness of FLOSEAL, which is a topical hemostatic agent containing a flowable gelatin bovine matrix and a human-derived thrombin component, has been shown in various types of operations^[1-4,6,9,11,13-15,16,20]. However, no reports have evaluated the effectiveness of FLOSEAL objectively in the neurosurgical field. In this study, we examined the ability of hemostasis of FLOSEAL by scoring the intensity of bleeding. In addition, we showed that the use of FLOSEAL reduced the amount of intra- and postoperative bleeding.

Table 4: Maximum body temperature, maximum WBC count, CRP, hospital stay, and blood collection data in the FLOSEAL and non-FLOSEAL groups.

	FLOSEAL (n=100)	non-FLOSEAL (n=100)	P
Maximum body temperature (C)	37.68±0.459	37.71±0.445	0.662
Maximum WBC (1000/μl)	13.02±4.01	12.03±3.60	0.0663
Maximum CRP (mg/dl)	3.819±3.75	3.230±2.91	0.216
Hospital stay (days)	11.96±4.32	13.19±4.75	0.084
Changes in blood test (1 POD)			
Cr (mg/dl)	-0.090±0.101	-0.0875±0.0769	0.844
Na (mEq/l)	0.0550±3.82	0.3020±3.90	0.652
K (mEq/l)	-0.1620±0.362	-0.300±0.383	<0.01
Cl (mEq/l)	1.086±3.86	1.337±4.11	0.669
AST (U/l)	4.980±20.7	2.800±12.7	0.370
ALT (U/l)	1.760±22.7	-1.690±13.4	0.193
WBC (1000/μl)	6.521±3.40	5.653±3.18	0.0637
Hb (g/dl)	-1.600±1.28	-1.616±1.31	0.931
Plt (1000/00/μl)	-26.45±34.6	-34.12±38.7	0.141
CRP (mg/dl)	1.922±1.49	2.578±2.45	0.029
Changes in blood test (7 POD)			
Cr (mg/dl)	-0.0685±0.132	-0.0883±0.0834	0.206
Na (mEq/l)	-1.085±3.28	-1.270±3.77	0.712
K (mEq/l)	-0.0290±0.344	-0.2330±0.517	<0.01
Cl (mEq/l)	-2.141±3.17	-1.946±4.27	0.718
LDH (IU/l)	-0.900±50.5	-0.2625±43.4	0.93
AST (U/l)	2.350±17.0	5.580±31.2	0.364
ALT (U/l)	14.38±31.9	18.54±51.6	0.494
WBC (1000/μl)	1.700±2.95	1.704±3.02	0.993
Hb (g/dl)	-1.716±1.38	-1.624±1.51	0.653
Plt (1000/00/μl)	33.24±50.4	26.44±43.3	0.307
CRP (mg/dl)	1.204±2.63	0.8004±1.30	0.173

POD: Postoperative day, LDH: Lactate dehydrogenase, CRP: C-reactive protein, ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, Hb: Hemoglobin

In our cohort, with the first FLOSEAL application, 91% of cases showed successful hemostasis. Although most of the intensity of bleeding was mild (95/109 bleeding spots), this success rate is similar to the previous reports.^[1,7,16] Oz *et al.* reported that the hemostasis rate was 95.5% in a total of 309 cases of cardiac, vascular, and spinal surgeries.^[15] Cappabianca *et al.* reported that the hemostasis rate was 96.6% among 29 cases of endoscopic endonasal extended approaches.^[1] Gazzeri *et al.* also reported that this rate was 94.9% in 214 cases of cranial, craniospinal, and spinal operations.^[7] FLOSEAL is effective in hemostasis, especially with diffuse bleeding or when bleeding points are hard to identify. In our study, although a high rate of hemostasis was achieved with bleeding scored as 1 (mild bleeding), the hemostasis rate was not high when bleeding was scored as 2 or 3 (only eight of 14 bleeding points achieved hemostasis). FLOSEAL has the potential to stop intensive bleeding,^[15] but in our cohort, this rate was not high enough. This may have been caused by the time taken to cover up FLOSEAL by a gauze sponge after application in a confined surgical space under microscopic or endoscopic surgery. FLOSEAL can be

washed out by bleeding when it is intense enough, during the time between the application and covering up. This may be a further issue to consider in the use of FLOSEAL in intracranial tumor resection.

The FLOSEAL group had less blood loss during the operation and less postoperative bleeding compared with the non-FLOSEAL group. A reduction in intraoperative bleeding by FLOSEAL has been reported in various fields of operations,^[4,16] including neurosurgical operations.^[5] This could result in less risk for patients having a blood transfusion or having coagulation intolerance due to blood loss. In addition, less intraoperative bleeding may be related to a clear surgical field. In neurosurgical operations, a clear surgical field is important for safe tumor resection, which eventually leads to less risk for patients having operative complications. Our finding of a reduction in postoperative bleeding in the FLOSEAL group is consistent with the previous reports in orthopedics or adenotonsillectomy.^[9,11,23] As a result of reduced postoperative bleeding, patients may have little risk for reoperation for postoperative hemorrhage or for having complications.

Table 5: Comparison of prices of representative hemostats in Japan.

Product	Distributor	Price (yen)
FLOSEAL	Baxter	13,000/g
Gelfoam	Pfizer	1166.9/sheet
Spongel	LTL PHARMA	756.6/sheet
SURGICEL Absorbable Hemostat	Johnson and Johnson	1752.8/sheet
BOLHEAL	TEIJIN PHARMA	11,609.8/ml
Beriplast	CSL Bering	12,081.1/ml
Tachosil	CSL Bering	11,138.9/sheet
Integran	Koken	13,000/g
AVITENE	ZERIA Pharmaceutical	13,000/g

Perioperative bleeding increases morbidity, mortality, and medical costs.^[8,21] Controlling perioperative bleeding by FLOSEAL may also result in a shorter hospital stay.^[4,9,16] A lower risk of complications in patients and a shorter hospital stay would lead to reduced medical expenses.^[22] In addition, due to its potential ability of hemostasis, the previous study showed that the use of FLOSEAL alone for hemostasis in spinal surgery would lead to cost saving compared with the use of other topical hemostatic matrixes or combination of hemostats, including FLOSEAL.^[12,17,18] In our cohort, the hospital stay was not significantly different between the FLOSEAL and non-FLOSEAL groups. However, the FLOSEAL group tended to have a shorter hospital stay than did the non-FLOSEAL group ($P = 0.084$). For addition, to provide more appropriate evidence, studies that compare among FLOSEAL and other available hemostats in the aspect of medical cost are needed. For reference, Table 5 is as list of hemostatic agent prices in Japan.

FLOSEAL application can cause infection, inflammation, and anemia. In our cohort, except for the finding that CRP levels at POD 1 were higher in the non-FLOSEAL group than in the non-FLOSEAL group, there was no significant difference in blood collection data or body temperature. Additional adverse events related to FLOSEAL were not observed.

In the present study, FLOSEAL provided reliable, convenient, and safe hemostasis in intracranial tumor resection, especially at a limited operative field. FLOSEAL should be added as an option for hemostasis when traditional methods fail to achieve hemostasis.

CONCLUSION

This study showed a high rate (91%) of hemostasis using FLOSEAL after intracranial tumor resection. In addition, FLOSEAL use reduced the amount of postoperative bleeding and there were no adverse events related to FLOSEAL. Our results indicate that FLOSEAL is a reliable,

convenient, and safe topical hemostatic agent in intracranial tumor resection.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms.

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Nil.

Conflicts of interest

We received a research grant from Baxter International Inc., but this company was not involved in this study.

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