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Safety and Efficacy of Gelatin-Thrombin Matrix Sealants (Floseal®) for Hemostasis During Liver Resection (with video)

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ABSTRACT

Background: The efficacy of gelatin-thrombin matrix sealants (Floseal®) for hemostasis has been well described in the field of cardiovascular surgery, but data supporting its safety and efficacy in liver surgery remains lacking.
Methods: The surgical outcomes of 83 consecutive patients in whom Floseal® was applied during hepatectomy were reviewed. The severity of bleeding before and after the application of Floseal® was graded according to the Validated Intraoperative Bleeding (VIBe) Scale.
Results: Floseal® was applied to 87 sites in 83 patients, and all the patient eventually achieved complete hemostasis. Complete hemostasis was achieved using the initial application (for 2 minutes) in 100% of the patients with VIBe grade 1, 76% of those with VIBe grade 2, 20% of those with VIBe grade 3, and 0% of those with VIBe grade 4. A multivariate analysis confirmed that the VIBe bleeding grade before the application of Floseal® (odds ratio, 36.0; P=0.002 per +1 point) was the only independent predictor for successful hemostasis with the initial 2 minutes after the application of Floseal®. No bleeding-related complications were observed during the study period in the present population.
Conclusions: Floseal® showed an acceptable hemostatic ability and could be safely used in patients undergoing liver resection.
Key words: hemostasis, hemostatic agent, liver surgery, laparoscopic surgery

INTRODUCTION

Intra- and postoperative bleeding is one of the most significant complications in all areas of surgery, with the potential to lead to substantial morbidity and mortality. Previous studies have reported that 5.7%-7.6% of patients in general and of those receiving solid organ surgery, including hepatectomy, develop bleeding-related complications, and more than 20% of patients are treated with blood product transfusion (1). Naturally, blood products are not only a limited resource, but also expensive. Therefore, the reduction of bleeding-related complications is needed from the perspectives of both patient safety and controlling healthcare costs (2,3).

The liver is a blood-rich organ that draws 0.8-1.2 liters of blood per minute; the amount of blood contained in the liver represents about 20% of that within the whole body (4). For that reason, the control of blood loss is a crucial problem, especially during hepatectomy (5-7). In addition to conventional

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hemostatic procedures including compression, suture, and coagulation with electrical cautery, several methods such as inflow occlusion (with/without outflow occlusion), maintaining a low central venous pressure, and the application of hemostatic agents (oxidized cellulose, fibrin sealant, etc.) have been used to reduce intraoperative blood loss (8-11). However, liver surgeons sometimes encounter incidental bleeding in complicated cases with severe liver damage, dense adhesions, or tumor invasion (12). Given that liver surgery is a technically demanding and high risk procedure, several choices of hemostatic methods are desirable to secure the safety of hepatectomy.

Floseal® (Baxter Healthcare Corporation, Fremont, CA 94555, USA) is a unique hemostatic agent that contains thrombin and bovine-derived gelatin granules (13). The effectiveness of Floseal® has been reported in the field of cardiac surgery, spinal surgery, gynecologic surgery, and urologic surgery (14). However, limited data is available supporting the safety and efficacy of the use of Floseal® during liver surgery (15).

Therefore, in the present study, we sought to investigate the safety and efficacy of the use of Floseal® during liver surgery through a video review of hemostasis and an evaluation of short-term postoperative outcomes.

METHODS

Study population

From a prospectively maintained clinical database in the Hepatobiliary-pancreatic Surgery Division, Toranomon Hospital, 83 consecutive patients in whom Floseal® was used during hepatectomy performed by a single surgeon (JS) between March 2021 and December 2021 were identified and studied in detail. This study was conducted in accordance with the ethical guidelines for clinical studies in Japan under the approval of the institutional review board of Toranomon Hospital (No. 1919).

Liver resection and use of Floseal®

Liver resection was performed using the clamp crushing method with a vessel-sealing device (LigaSure™ Exact Dissector, Medtronic, Minneapolis, USA, or HARMONIC® HD 1000i Shears, Ethicon Endo-Surgery Inc., Cincinnati, USA) under adequate inflow control (16). Although active bleeding during hepatectomy was basically controlled with coagulation, suturing, or the application of a non-absorbable filament, as appropriate, persistent or refractory bleeding, especially from the cut surface of the liver, was managed with the application of Floseal®.

Floseal® was directly applied to the bleeding point and gently held with a saline-moistened gauze for 2 minutes. If bleeding persisted after the initial application of Floseal® with 2 minutes of mild compression, additional Floseal® was applied to obtain adequate hemostasis.

Evaluation of bleeding grade

The severity of bleeding was graded according to the Validated Intraoperative Bleeding Scale (VIBe scale) (17). The VIBe scale grades are based on the visual field, qualitative description, and visual estimated blood loss. The VIBe scale grades are as follows: Grade 0 (no bleeding) corresponds to clinically insignificant and unremarkable bleeds, Grade 1 (mild) bleeds correspond to a general ooze that wells up over a 1-to-2-min period after blotting with gauze, Grade 2 (moderate) bleeds correspond to visible welling up after blotting that can be considered distracting to the surgical procedure, Grade 3 (severe) bleeds correspond to welling up immediately after blotting that require treatment before continuing with the surgery, and Grade 4 (life-threatening) bleeds are life-threatening and require immediate surgical treatment. In this study, the bleeding grades before the application of Floseal® and after the initial application of Floseal® (2 minutes) were evaluated to clarify the hemostatic power and efficacy of Floseal®. All operation videos of the 83 patients were independently reviewed, and the bleeding grades were scored by two HPB surgeons (SO and JS). Discrepancies between the two reviewers were resolved by consensus with the inclusion of the opinion of an additional reviewer (MM).

Statistical analysis

Standard statistical measures and procedures were used for the analysis. The risk factors for hemostatic difficulty were identified using a multivariate logistic regression analysis with backward elimination. Initially, all the factors were included in the model. Factors that showed no or limited statistically significant associations ($P > 0.1$) with each prognostic indicator adjusted for the remaining factors in the model were deleted from the model in a stepwise fashion. The factors tested were as follows: age, sex, body mass index, American Society of Anesthesiologist score > 2, under the administration of anticoagulant, Child-Pugh score,

indocyanine green retention rate at 15 min, METAVIR score status, VIBe scale grade before hemostasis, operation time, estimated blood loss, major hepatectomy, laparoscopic surgery, and METAVIR score status. The postoperative observation period was defined as the period from surgery until hospital discharge or transfer to a department other than the Department of Gastrointestinal Surgery, whichever came first. Major complications were defined as Clavien-Dindo morbidities >IIIa.

RESULTS

Baseline characteristics and surgical outcomes

The baseline characteristics and surgical outcomes are summarized in *table 1*. Among 83 patients, 15 patients had taken anti-coagulant/platelet agents preoperatively for various reasons. Among those people, 12 patients stopped taking those agents before the operation, whereas only three of those patients underwent hepatectomy under the administration of an antiplatelet agent. The median ICG-R15 value was 13.0%, and the Child-Pugh score was 5 in 52 patients (63%), 6 in 26 patients (31%), and 7 in 5 patients (6%), respectively. The median operation time was 197 minutes, and the estimated blood loss was 223 mL. Major hepatectomy and laparoscopic surgery were performed in 21 (25%) and 30 patients (36%), respectively.

Table 1 - Baseline characteristics and short term outcomes of the patients

	N = 83
Baseline characteristics	
Age	68 (34-86)
Male gender	60 (72%)
BMI	22.5 (17.1-32.0)
ASA score I/ II/ III	7 (8%)/ 62 (75%)/ 14 (17%)
Anticoagulant during hepatectomy	3 (4%)
Albumin (g/dL)*	3.9 (2.1-4.6)
Bilirubin (mg/dL)*	0.8 (0.2-2.0)
Hemoglobin (mg/dL)	12.9 (7.3-16.5)
Platelet count (104/mm3)*	19.1 (2.8-32.4)
Prothrombin (%)*	98.5 (75.6-121.6)
ICG-R15 (%)*	13.0 (2.4-70.7)
Child-Pugh Score 5/6/7	52 (63%)/ 26(31%) / 5(6%)
Status of liver fibrosis	49 (53%)/ 11 (13%)/
(METAVIR score) 0-1/ 2/ 3/ 4	3(4%)/ 11 (13%)
Procedures	
Pure laparoscopic hepatectomy	30 (36%)
≥2 segments resection	21 (25%)
Surgical outcomes	
Operation time*	192 (52-375)
Estimated blood loss*	217 (0-1364)
Any postoperative morbidities	18 (22%)
Major abdominal morbidities	5 (6%)
Length of observation period (days)	9 (3-108)

Figure represent median (range) unless indicated.
*Median (interquartile range)
Abbreviations: BMI, body mass index;
ASA, American Society of Anesthesiologist;
ICG-R15, indocyanine green retention rate at 15 minutes.

Safety and efficacy of Floseal®

Floseal® was applied in 83 patients. Major complications were observed in 5 patients (6%): bile leakage occurred in 2 patients, abscess formation occurred in 1 patient, perforation of the duodenum occurred in 1 patient, and cerebral infarction occurred in 1 patient. No bleeding-related complications occurred during the postoperative observational period in the present series.

The bleeding grades before the application of Floseal® were as follows: grade 1, 32 patients; grade 2, 45 patients; grade 3, 5 patients; and grade 4, 1 patient. *Figure 1* shows the percentage of complete hemostasis (i.e., grade 0) during the initial 2 minutes after the application of Floseal®. Although complete hemostasis was eventually achieved with a maximum of two applications of Floseal® in all the patients, complete hemostasis was achieved after only one application of Floseal® in 100% (32/32) of patients with grade 1, 76% (34/45) of patients with grade 2, 20% (1/5) of patients with grade 3 (1/5), and 0% (0/1) of patients with grade 4.

A multivariate logistic regression analysis confirmed that a VIBe scale grade of +1 point (odds ratio [OR], 36.06; 95% CI, 3.60-361.20; P = 0.002) was an independent predictor associated with the failure of

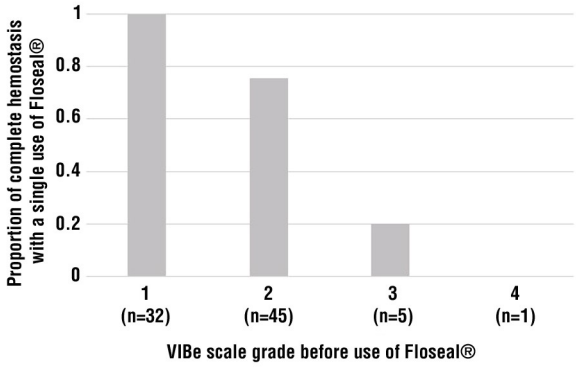

Figure 1 - The percentage of complete hemostasis (i.e., grade 0) after initial 2 minutes of application of Floseal®. Although complete hemostasis was eventually achieved within twice of application of Floseal® in every patient, complete hemostasis was achieved only with one time application of Floseal® in 100% (32/32) in grade 1, 76% (34/45) in grade 2, 20% (1/5) in grade 3 (1/5), and 0% (0/1) in grade 4.

Table 2 - Risk factors for difficulty of hemostasis

	P*	Coefficient†	SE	Wald chi-square	OR	95% CI
VIBe scale grade before hemostasis (per +1 point)	0.002	3.585	1.176	9.299	36.060	3.600-361.196
Laparoscopic surgery	0.055	-2.522	1.314	3.684	0.080	0.006-1.055

*Based on likelihood test adjusted for the other factors in the final model.
†Estimated coefficient for the variable and the associated standard error.
Abbreviations: SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval.

Note. Multivariate logistic regression was applied with a stepwise backward selection. Initially, all factors were included in the model. Then factors that showed no or limited statistically significant association (P > 0.1) with each prognostic indicator adjusted for the remaining factors in the model were deleted from the model in stepwise fashion. The 14 factors tested were as follows: age, gender, body mass index, ASA score > 2, history of hepatectomy, administration of anticoagulant, laparoscopic approach, resection of ≥2 hepatic segments, Child-Pugh Score, indocyanine green retention rate at 15 minutes, METAVIR score status, VIBe scale grade before hemostasis, operation time, and estimated blood loss.

complete hemostasis after one application of Floseal®, whereas a laparoscopic approach showed a tendency toward an increased probability of complete hemostasis (OR, 0.08; 95% CI, 0.01-1.06; P = 0.055).

DISCUSSION

In this study, the safety and efficacy of the use of the hemostatic agent Floseal® during a hepatectomy were investigated. The use of Floseal® was not associated with an increased incidence of bleeding-related complications after liver surgery. All grades of persistent/refractory bleeding were successfully managed using Floseal® in the present series, and a multivariate analysis confirmed that the initial bleeding grade before hemostasis was the only independent predictor for successful hemostasis after one application of Floseal®.

Several types of hemostatic agents have been introduced and used in liver surgery (18,19). However, because the hemostatic power and risk of infection-related complications differ among the available hemostatic agents, care should be paid when choosing a hemostatic agent, especially during complicated procedures including liver surgery. To date, the clinical use of Floseal® has been reported in gynecological surgery and cardiovascular surgery, and acceptable outcomes with a low incidence of adverse events and an acceptable efficacy of hemostasis have been observed (20,21); clinical evidence of the use of Floseal® in liver surgery, however, has not yet been established. Although one report on the hemostatic ability of Floseal® during liver surgery has been previously published, details such as patient background, postoperative complications, and difficulty factor for hemostasis were not reported (15). Thus, whether the use of Floseal® is safe during liver surgery has remained uncertain. Given that liver resection has unique complications, such as bile leakage, fluid collection, ascites retention, and bleeding-related complications associated with impaired coagulation ability, the efficacy and safety of Floseal® need to be clarified based on short-term clinical outcomes after hepatectomy.

In this context, the present outcomes are actually encouraging for the clinical use of Floseal® in liver surgery. The strengths of the present study include the following: 1) the efficacy of hemostasis was rated by two reviewers using an established bleeding scale, 2) details of the baseline patient characteristics and short-term clinical outcomes were clarified, and 3) factors associated with successful hemostasis were analyzed using a multivariate analysis. In fact, the management of persistent/refractory bleeding was successfully achieved using only Floseal® in all the patients included in the present analysis, and no evidence of an increased incidence of postoperative morbidity, especially bleeding-related complications, was seen. Interestingly, the pre-application bleeding grade was the only significant predictor of successful hemostasis using one application of Floseal®, and a laparoscopic approach showed a tendency toward an increased probability of hemostasis, probably because of the presence of pneumoperitoneal pressure. These outcomes are clinically reasonable, and it was surprising that successful hemostasis was achieved using Floseal® even for grade 3 or grade 4 bleeds.

Floseal® is a unique hemostatic agent containing thrombin and bovine-derived gelatin granules. Once Floseal® is applied at the bleeding point, gelatin granules swell and shield blood flow (i.e., tamponade effect); the compounded thrombin facilitates the formation of a fibrin clot around the matrix, resulting in hemostasis (13). Hemorrhage during hepatectomy is roughly classified into three types: arterial, portal, and venous. Since the blood pressure and hemodynamics

differ among these three types of bleeding, the required hemostatic powers also differ. An animal experiment revealed that direct injury to the portal vein or inferior vena cava with a scalpel, which results in grade 3 to 4 bleeding, was successfully stopped using Floseal®, and the reproducibility of these hemostatic powers has been confirmed in multiple trials using pigs (Supplemental Video, provided by Baxter Inc.; animal experiment approval number, IVT21-127). This hemostatic potential was clinically confirmed in the present study, and the reproducibility of the hemostatic power of Floseal® even in cases with higher grades of bleeding (i.e., grades 3 and 4) is encouraging.

The limitations of the present study include its retrospective nature and the limited number of patients in the study cohort. However, the present study analyzed the clinical outcomes of consecutive patients, and this preliminary series clearly demonstrated the potential efficacy and safety of Floseal® in liver surgery. Although a prospective, multicenter study is needed to further clarify the actual efficacy and safety of Floseal®, the present encouraging results warrant future studies comparing the hemostatic potential of Floseal® with other clinically available hemostatic agents.

CONCLUSION

In conclusion, Floseal® was safely used in patients undergoing liver resection, providing significant hemostatic efficacy. The present results may warrant future prospective studies, contributing to the improved safety of liver surgery in terms of adequate hemostasis.

Funding/Conflicts of interest

This study was supported by study grant from Okinaka Memorial Institute for Medical Disease. There is no conflict of interest to disclose.

Ethics of approval

This study was conducted in accordance with the ethical guidelines for clinical studies in Japan under the approval of the institutional review board of Toranomon Hospital (No. 1919).

Author's contributions

Satoshi Okubo and Junichi Shindoh contributed equally to this work

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