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Improvement of Perioperative Outcomes in Major Gynecological and Gynecologic–Oncological Surgery with Hemostatic Gelatin–Thrombin Matrix

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Abstract. *Aim: To assess the impact of the use of intraoperative hemostatic gelatin-thrombin matrix (HM) (Floseal®, Baxter Healthcare) on transfusion rates and short-term perioperative outcomes in gynecological surgery. Patients and Methods: In this retrospective, single-center study, we evaluated data of 215 patients (83 cases and 132 controls) undergoing extensive gynecological surgery (e.g. oncological procedures) with and without intraoperative HM application. Results: Cases and controls did not differ according to age, preoperative hemoglobin (Hb) concentration, and Hb or C-reactive protein (CRP) levels at discharge. Patients receiving HM had significantly reduced operative (168 vs. 199 min, p=0.02) and hospitalization (9 vs. 14 days, p<0.001) times. The mean postoperative Hb drop (3.33 vs. 4.51 g/dl, p<0.001), and the mean postoperative increase in CRP (94.9 vs. 149.1 mg/l, p<0.001) were significantly less pronounced within the HM group. Despite more prevalent coagulopathy (48 vs. 31%, p=0.02), e.g. due to anticoagulant use (15.7 vs. 3%, p<0.001), patients treated using HM needed less frequent transfusions of packed red blood cells [odds ratio (OR)= 0.13, 95% confidence interval (CI)=0.07-0.24) and fresh frozen plasma (OR=0.51, 95% CI=0.24-1.05). In comparison to controls, the need for surgical revisions (OR 0.1, CI 95% 0.02-0.42) and intensive-care unit admissions (OR 0.15, 95% CI=0.08-0.30) was lower in patients treated with HM. Conclusion: To our knowledge, our study is the largest case–control study focusing on Floseal® use in gynecology. The use of HM was associated with significantly better short-term perioperative outcomes. Due to its local action, HM seems to be particularly useful in patients in which anticoagulant medication cannot be paused.*

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Intraoperative bleeding is a complication of gynecological surgery (1, 2). Increased perioperative blood loss (PBL) disrupts the operation, impairs organ exposure, contributes to prolonged surgical and hospitalization times, increases the need for transfusion, and negatively impacts therapy costs (1, 3). In non-oncological gynecological surgery, acute postoperative hemorrhage is the most frequent cause of returning to the operating theater (2). A PBL of more than 1 l complicates 15-40% of radical oncological operations, resulting in transfusion rates of 30-60% (4-6). In general surgery, intraoperative transfusion of only one to two units of packed red blood cells (PRBC) has been shown to significantly elevate the risk for surgical-site infection, pneumonia, sepsis and 30-day mortality (7). In gynecological patients, blood transfusions are clearly associated with increased surgical wound infections and composite morbidity and mortality (8). Additionally, a low perioperative hemoglobin (Hb) level and blood transfusions themselves may worsen the prognosis of pelvic cancers (9, 10). Typical intraoperative hemostatic maneuvers comprise of compression, sutures, clips and electrocoagulation. However, in some cases, conventional hemostasis can be insufficient (*e.g.* due to intraoperative coagulopathy), unsafe (*e.g.* due to proximity of structures sensitive to thermal damage) or impractical (*e.g.* diffuse bleeding area) (1, 11). Additionally, a subset of patients undergoing surgery have impaired hemostasis, *e.g.* due to use of oral anticoagulant. In the past two decades, an increasing number of topical hemostats, sealants and adhesives have been available to surgeons (1, 12). Hemostatic gelatin-thrombin matrix (HM) (Floseal®; Baxter Healthcare, Deerfield, IL, USA) is a locally

applicable hemostatic agent, registered for support of local hemostasis when conventional hemostatic maneuvers are ineffective or impractical. It consists of a matrix of bovine-derived gelatin (cross-linked gelatin granules) and human thrombin. One application unit of Floseal® contains 2,500 IU thrombin in 5 ml or 5,000 IU thrombin in 10 ml (500 IU/ml). Floseal® is prepared by operating theater staff within 1-2 minutes and can be used for up to 8 h thereafter. Since contact with fibrinogen is essential for the action of thrombin, HM should be applied directly to the bleeding tissue, but never into blood vessels (12,13). After 2 min of action, all excess HM not incorporated into the clot is removed by irrigation (13). Floseal® is frequently used in many areas of surgery (*e.g.* visceral, cardiac and neurosurgery) (3, 14-16), but it is less known in gynecology (3). Excluding case reports with incidental HM use in conditions associated with intra-abdominal hemorrhage, such as ectopic pregnancy (17,18) or massive obstetric hemorrhage (19), we found only few studies – including our own preliminary report of 2012 – comparing HM use with conventional hemostasis in gynecological surgery (20-23).

The aim of the present study was to compare short-term perioperative outcomes, *e.g.* duration of surgery, duration of postoperative hospital stay, requirement for Intensive Care Unit (ICU), duration of ICU stay, surgical revisions ("back to the theater"), need for transfusions of PRBC and fresh frozen plasma (FFP), mean number of transfused PRBC and FFP units per surgery and per patient, mean postoperative Hb drop, minimal postoperative Hb concentration, and maximal postoperative rise of C-reactive protein (CRP) in patients with and without intraoperative HM application.

Patients and Methods

Patients and definitions. This was a retrospective single-center study, conducted at the St. Josefskrankenhaus, Academic Teaching Hospital of the University of Freiburg, Freiburg, Germany. The study period was January 1, 2008 to October 30, 2013. The study was approved by the Institutional Review Board of the University of Freiburg (Reference No. 194/12), and was registered with the German Clinical Trials Register (DRKS), a primary register of the WHO International Clinical Trials Registry Platform, trial number DRKS00004903. All major gynecologic surgeries (scheduled or emergent) with documented increased intra-abdominal bleeding for the study period were included. The term "major gynecologic surgery" was used for complex surgeries ("basic operation", *e.g.* hysterectomy, combined with additional steps, *e.g.* extensive hemostasis, lymphadenectomy, peritonectomy, or retroperitoneal preparation) or emergent surgical interventions due to acute intraabdominal hemorrhage (*e.g.* ruptured ectopic pregnancy, re-laparotomy for bleeding complication *etc.*). We defined "increased intra-abdominal bleeding" as any bleeding which could not be sufficiently managed with conventional hemostatic manoeuvres (sutures, clips *etc.*), resulting in measured or expected blood loss of more than 1 l, or any intra-abdominal bleeding leading to cardiovascular instability, or requiring transfusion of blood products. The PBL was defined as the blood loss within the whole perioperative (intra- and postoperative) period. Since the postoperative Hb change and Hb nadir are more objective parameter of PBLs than subjective blood loss estimation (24), we used Hb drop, Hb nadir, the need for transfusions and the total number of transfused blood products as surrogate markers for the overall PBL. Additionally, we used the preoperative Hb concentration as well as the Hb and C-reactive protein (CRP) levels at discharge for the purpose of patient characteristics and as indicators for comparability of case and control groups. The data were obtained by chart review. The "cases" were defined as all consecutive patients fulfilling the inclusion criteria in which Floseal® was used. "Controls" were defined as all patients fulfilling the inclusion criteria, but without HM use. With two exceptions (concomitant use of oxidized cellulose). Floseal® was the only hemostatic agent applied in cases. All HM applications were in accordance with the manufacturer's instructions. All oncological procedures were performed via laparotomy. All surgeons performing the operations were Board-certified. In all oncological surgeries, a gynecologic-oncological surgeon participated. All surgical reports were retrospectively checked by the first author for the correctness and plausibility of HM use. The indication for transfusion of blood derivatives was made on the basis of the national and institutional guidelines (25).

According to the institutional practice, the admission to the Intensive Care Unit (ICU) was based on the decision of the anesthesiologist at the end of the procedure, hence the particular indications were not further specified on the charts. Generally, admission to ICU was indicated for patients with complex surgeries, requiring multimodal pain management, respiratory support or showing cardiovascular instability (related or not to intraoperative bleeding), as well as for patients with severe pre-existing comorbidities or other risk factors.

Coagulopathies were divided into intraoperative or preoperative coagulopathy. Intraoperative coagulopathy was defined as any form of blood coagulation impairment first observed intraoperatively, mostly associated with but not limited to abnormal intra- or postoperative laboratory tests. As fulfilling the definition we also included intraoperative coagulopathy (*e.g.* dilutional coagulopathy) which was reported in the surgical report and adequately managed (*e.g.* FFP transfusion). Of note, an appreciable number of patients were unable to discontinue their use of anticoagulants (*e.g.* coumarin or heparin derivatives) during the perioperative period (*e.g.* due to severe cardiac comorbidity). These cases, operated on under ongoing anticoagulation, were classified as preoperative (pre-existing, drug-induced) coagulopathy. All patients in our cohort received antithrombotic prophylaxis postoperatively in the form of a daily subcutaneous injection of enoxaparin. Usual antithrombotic prophylaxis was not considered as coagulopathy.

Statistical methods. Values are given as means with standard deviation (SD) or rates (percentage), where appropriate. Frequency distributions for categorical variables were compared using chi-squared test (with Yates' correction where appropriate) or Fisher's exact test. Associations were summarized using odds ratios (OR) and corresponding 95% confidence intervals (CI) estimated from the models. The *t*-test was used for comparing groups. All *p*-values were two-sided and values less than 0.05 were considered statistically significant. The statistical analysis was performed with the software package Statistica 12 Test Version (Dell Inc., Tulsa, OK, USA), and the online calculator VassarStats: Website for Statistical Computation (26).

Results

Within the study period, we identified 220 eligible patients who underwent major gynecological surgery at the Department of Gynecology and Gynecologic Oncology, St. Josefskrankenhaus, Freiburg, Germany. Three patients did not meet the inclusion criteria for the case group because of prophylactic HM use during uncomplicated lymphadenectomy, and two patients were excluded from the control group because of a lack of information about their preoperative Hb level. Finally, the analysis included 83 cases and 132 controls.

The majority of procedures were oncological in both the HM (55.4%) and the control (65.2%) groups and the rate of oncological to non-oncological operations was comparable (p=0.15) in both cohorts. The detailed characteristics according to procedures and diagnoses are shown in Table I. Generally, both cohorts were comparable according to diagnoses and procedures, with a 1:1.5 case-to-control ratio. The mean age of cases and controls was 56.2 and 55.9 years, respectively (p=0.9). The HM and the control groups did not significantly differ in regard to preoperative Hb concentration (p=0.07), nor in Hb (p=0.053) and CRP (p=0.33) concentrations at discharge (see Table II). As demonstrated in Tables II and III, patients receiving Floseal® had significantly reduced operative (168 *vs*. 199 min, p=0.02) and hospitalization times (9 *vs*. 14 days, p<0.001). None of the patients in the HM group died within 30 postoperative days, while three perioperative deaths occurred in the control group. However, this difference was not statistically significant (p=0.29). Two out of 83 (2.4%) cases and 27 out of 132 (20%) controls needed re-laparotomy within 30 postoperative days (OR=0.1, 95% CI=0.02-0.42; p<0.001). Among patients needing surgical revision, bleeding complication was the reason for re-laparotomy in one out of two (50%) cases, and 26 out of 27 (96%) controls. Nine out of 11 controls (89%), and every second patient in the HM group (54%) needed ICU admission (OR=0.15, 95% CI=0.08-0.30; p<0.001). The mean duration of ICU stay, however, did not differ between cases and controls (p=0.11). The mean postoperative Hb drop (3.33 *vs*. 4.51 g/dl, p<0.001), and the mean postoperative CRP raise (94.9 *vs*. 149.1 mg/l, p<0.001) were significantly less pronounced in the HM group. HM patients less frequently needed transfusions of PRBC (22 *vs*. 68%; OR=0.13, 95% CI=0.07-0.24, p<0.001) and FFP (14 *vs*. 25% OR=0.51, 95% CI=0.24-1.05, p=0.09).

Both in the case and the control groups, intraoperative coagulopathy complicated an appreciable number of surgeries (32% and 28%, respectively; p=0.48). The high prevalence of patients with anticoagulant therapy which could not be stopped during the perioperative period in the HM group (16%) as compared to the controls (3%) was clinically important (p<0.001). Table IV is solely dedicated to the outcomes in patients with impaired hemostasis. In comparison to the controls, individuals with coagulopathy receiving HM intraoperatively significantly less frequently needed PRBC (40 *vs*. 93%; p<0.001) and FFP (27.5 *vs*. 51%; p<0.001) transfusions. They developed lower CRP levels postoperatively (p=0.002) and were discharged on average almost 6 days earlier (p=0.01). Despite coagulopathy, the surgical times were comparable (p=0.32) between cases and controls. Only one out of 40 patients in the HM group with coagulopathy but 14 out of 41 patients in the control group with coagulopathy developed complications necessitating re-operation (p<0.001).

We did not observe any adverse effects which could be attributed to HM use in our cohort.

Discussion

Surgical site bleeding can occur from identifiable vessels or as difficult-to-manage, massive capillary oozing, or as combination thereof (4, 11). Such bleeding and accompanying changes (*e.g*. secondary blood dilution) can initiate intraoperative coagulopathy, which in turn enhances bleeding. In a substantial number of cases (*e.g*. 8% of our whole cohort), surgery must be performed in patients with current anticoagulant use. The inability to achieve sufficient hemostasis can lead to suboptimal surgical results (*e.g*. suboptimal cytoreduction), unintended organ loss (*e.g*. hysterectomy), reoperation or even perioperative death. Generally, increased PBL is associated with prolonged duration of surgery, higher perioperative morbidity, delayed patient recovery, more frequent blood transfusions, and, in oncological patients, poorer long-term outcomes (1, 7, 8-10, 27). Perioperative blood transfusions can be associated with numerous immunological and infectious side-effects (28). Last but not least, the consequences and complications of PBL generate costs to the healthcare system. Therefore, there is an increasing trend towards restricted use of blood products and rising interest in more effective and safe intraoperative methods of hemostasis (1). A variety of hemostatic agents have been developed in the past two decades and an increasing use of hemostatic agents was noted (1, 12). Pro-hemostatic agents are roughly divided into three partially overlapping groups: *topical hemostats* promoting clot building at a bleeding source, *sealants* preventing vessel or tissue leakage, and *adhesives* which bond tissues. Topical hemostats consist mostly of a mechanical agent promoting clot formation (*e.g*. oxidized cellulose gauze, collagen sponge, gelatin), often in combination with the coagulation factors thrombin or fibrinogen (1, 12). Only two such products are offered in a flowable form, Floseal® (Baxter Healthcare, Deerfield, IL, USA) and Surgiflo® (Ethicon, Somerville, NJ, USA). Floseal® is a kit of bovine cross-linked gelatin with 2,500 IU or 5,000 IU of human thrombin,

Table I. *Patient characteristics*.

Characteristic	Cases (HM)	Controls	*p*-Value
Number of patients	83	132	
Mean age (years) (SD)	56.2 (17.4)	55.9 (15.8)	0.9[t]
Patient characteristics according to procedure			
Oncological procedures	46/83 (55.4%)	86/132 (65.2%)	0.15
Non-oncological procedures	37/83 (44.6%)	46/132 (34.8%)	
Procedure type[a,b]			
Hysterectomy (simple or radical)	39	82	0.03
Salpingoophorectomy (bilateral or unilateral)	31	63	0.14
Pelvic lymphadenectomy	27	53	0.27
Para-aortic lymphadenectomy	18	29	1.0
Omentectomy	18	32	0.66
Tumor debulking with retroperitoneal preparation	10	19	0.62[Y]
Partial bowel resection or repair of bowel laceration	10	25	0.18
(Partial) peritonectomy	12	21	0.78
Partial bladder resection or repair of bladder laceration	2	12	0.09[F]
Hemostasis in upper abdomen (liver, diaphragm, spleen)	3	1	0.3[F]
Extensive adhesiolysis	15	13	0.08
Emergent laparotomy due to intra-abdominal hemorrhage (*e.g.* ruptured EP, postoperative hemorrhage)	17	12	0.02
Conservative myomectomy[c]	8	3	0.02[F]
Operative therapy of severe postpartal hemorrhage (including peripartal hysterectomy)	4 (0/4)[c]	10 (7/10)	0.42 (0.069[F])
Patient characteristics according to diagnoses			
Oncological diagnoses			
Primary ovarian cancer	17	29	0.79[Y]
Primary endometrial cancer	8	22	0.15[Y]
Primary cervical cancer	9	17	0.65[Y]
Other intra-abdominal malignancy (relapsed, metastatic and other cancer)	12	18	0.86[Y]
Non-oncological diagnoses			
Scheduled surgery for benign reasons with massive intraoperative bleeding	16	24	0.84[Y]
Mergencies due to intra-abdominal hemorrhage (*e.g.* postoperative hemorrhage, ruptured EP)	21	22	0.12[Y]

If not otherwise indicated, *p*-values were calculated using chi-squared test. SD: Standard deviation, EP: ectopic pregnancy; [t]*t*-test, [Y]after Yates' correction, [F]Fisher exact probability test. [a]Abdominal surgery unless otherwise indicated, [b]procedures may be cumulative, [c]abdominal or laparoscopic.

resulting in 5 ml or 10 ml or ready-to-use HM, respectively (12, 13). Surgiflo® consists of 6 ml porcine gelatin which can be mixed either with 2-5 ml saline solution or with 2,000 IU lyophilized human thrombin, resulting in 8-11 ml ready-to-use hemostat (12, 29). The flowable consistency and portionability allow application to irregular and diffuse bleeding surfaces (12, 30).

In the field of gynecological surgery, excluding our own preliminary data of 2012 (21), we identified only one comparison of 25 cases and 25 controls focusing on Floseal® use and PBL (20). In abdominal conservative myomectomy, HM use was associated with decreased PBL and lower transfusion rates (20). According to other endpoints, Floseal® has been shown to reduce bleeding and to increase the chance of organ preservation in tubal and non-tubal ectopic pregnancies (17, 18). Cases of effective HM use in massive obstetric hemorrhage have been reported (19). By measuring serum anti-Müllerian hormone levels after adnexal surgery, Sönmezer *et al*. (22) and Song *et al*. (23) found less decline in ovarian reserve as compared to use of bipolar thermal hemostasis.

In the present study, we analyzed the largest cohort of gynecological patients with intraoperative Floseal® use so far, treated in one institution according to a similar surgical algorithm and with uniform perioperative (*e.g.* anesthesiological) management. Our results demonstrated a significant improvement of numerous short-term perioperative outcomes after HM use. Fewer transfusions, complications and re-operations, as well as faster recovery were benefits relevant both to patients as well as to the healthcare system. Although a formal cost-utility analysis was not the aim of the present study, several outcomes (*e.g.* reduced surgical times, fewer ICU stays, shorter hospitalization, lower utilization of blood products) were clearly translated into reduced hospital costs. These findings and conclusions concur with results obtained in other

Table II. *Differences in short-term perioperative outcomes between case and control groups.*

Factor	Cases (HM) (n=83)	Controls (n=132)	*p*-Value
Surgical time (minutes)	167.9 (101.3)	198.7 (83)	0.016
Postoperative hospitalization time (days)	9.1 (5.2)	14.3 (9.9)	<0.001
Intensive care unit (ICU) admission: Yes/no	45/83 (54.2%)	117/132 (88.6%)	<0.001
Days in ICU, whole cohort	1.5 (2.1)	3.4 (3.7)	<0.001
Days in ICU per ICU patient	2.8 (2.1)	3.8 (3.7)	0.11
Re-operations within 30 days: Yes/no	2/83 (2.41%)	27/132 (20.45%)	<0.001[Y]
Deaths in the postoperative period (30 days)[a]	0/83 (0%)	3/132 (2.3%)	0.29[F]
Preoperative hemoglobin concentration (g/dl)	12.7 (1.7)	12.2 (1.8)	0.07
Postoperative hemoglobin nadir (g/dl)	9.3 (2.2)	7.7 (2.1)	<0.001
Postoperative hemoglobin change (g/dl)	3.3 (2)	4.5 (2.1)	<0.001
Hemoglobin concentration at discharge (g/dl)	10.6 (1.7)	10.1 (1.5)	0.053
PRBC transfusion: Yes/no	18/83 (21.7%)	90/132 (68.2%)	<0.001
Number of transfused PRBCs per operation	0.64 (1.5)	2.6 (3.4)	<0.001
Number of transfused PRBC per patient[b]	2. 9 (1.9)	3.8 (3.5)	0.31
FFP transfusion: Yes/no	12/83 (14.5%)	33/132 (25%)	0.09
Number of transfused FFP units per operation	0.49 (1.4)	1.4 (3.4)	0.02
Number of transfused FFP units per patient[b]	3.4 (1.9)	5.6 (4.6)	0.13
Maximal postoperative CRP rise (mg/l)[c]	94.9 (83.5)	149.1 (100.4)	<0.001
CRP at discharge (mg/l)[d]	29.4 (36)	37.8 (63.8)	0.33

Values are given as rates (percentage) or means (standard deviation). Comparisons of means were carried out using *t*-test; comparisons of proportions using chi-squared test [with Yates correction ([Y]) where appropriate], or by Fisher exact probability test ([F]). HM: Hemostatic matrix; PRBC: packed red blood cells; FFP: fresh frozen plasma; CRP: C-reactive protein. [a]All three patients developed postoperative bleeding complications requiring blood transfusions. Two patients received two consecutive re-laparotomies for intra-abdominal hemorrhage, respectively, and one patient underwent six surgeries resulting from anastomotic leakage and burst abdomen. The immediate causes of death were aspiration pneumonia in one case, and sepsis in two other cases. [b]Cumulative number for whole hospital stay (including revision surgeries). [c]Available for 67 cases and 121 controls. dAvailable for 67 cases and 119 controls.

surgical disciplines (15). One of the most striking observations in our cohort (see Table IV) was that within the subgroup with coagulopathy, despite significant fewer blood transfusions, patients treated with HM recovered faster and were discharged earlier. Of note, coagulopathy or history of bleeding disorder were exclusion criteria in the studies of abdominal myomectomy (20) and of thyroid surgery (16). There are only few studies concerning the specific advantages of HM use in patients with coagulopathy. HM provides local restoration of hemostasis at the bleeding site, independently of and without influencing systemic coagulation. Hammes *et al*. used HM to stop gastrointestinal bleeding in anticoagulated pigs (31). Landi *et al*. observed that the use of both available HMs (Floseal® and Surgiflo®) enhanced the effectiveness of bleeding control in patients using antiaggregant or anticoagulant drugs who underwent spinal surgery (32). Del Verme *et al*. used HM in patients with intraparenchymal hemorrhage on anticoagulant or antiplatelet therapy. They reported "excellent", "safe" and "reproducible" results both in terms of decreased bleeding and patient outcome (33). In the field of gynecological surgery as far as we are aware our observations are unique.

Table III. *Impact of hemostatic matrix (HM) use on transfusion rate, re-operation and intensive care unit admissions.*

Parameter	Cases (HM)	Controls	OR	95% CI
PRBC transfusion	18/83	90/132	0.13	0.07-0.24
FFP transfusion	12/83	33/132	0.51	0.24-1.05
Revision surgery	2/83	27/132	0.1	0.02-0.42
Intensive care unit admission	45/83	117/132	0.15	0.08-0.30

PRBC: Packed red blood cells; FFP: fresh-frozen plasma; OR: odds ratio; 95% CI: 95% confidence interval.

We used CRP, an acute-phase protein increasing in response to both infectious and non-infectious exposures *e.g.* tissue damage, as a rough follow-up parameter for the degree of postoperative systemic inflammation. Significantly lower CRP levels in the study group indicated a generally lower degree of inflammation in patients receiving HM. The shortcoming of this approach is, however, that we did not separately analyze patients with and without postoperative infections.

Reported complications following HM use in different areas of surgery are rare and generally do not outweigh the benefits

Table IV. *Differences in short-term perioperative outcomes restricted to the subgroup of patients with coagulopathy (40 cases and 41 controls).*

Factor	Cases (HM)	Controls	*p*-Value
Any coagulopathy	40/83 (48.2%)	41/132 (31.1%)	0.017
Acute intraoperative coagulopathy (*e.g.* dilutional)	27/83 (32.5%)	37/132 (28%)	0.48[Y]
Preoperative coagulopathy (*e.g.* drug-induced)	13/83 (15.7%)	4/132 (3%)	0.002[Y]
Age (years)	62.6 (16.8)	54.6 (19.5)	0.06
Surgical time (minutes)	177.2 (118.1)	201.4 (98)	0.32
Postoperative hospitalization time (days)	11.3 (5.6)	17.1 (12.8)	0.01
ICU admission: Yes/no	31/40 (77.5%)	38/41 (92.7%)	0.07[F]
Days in ICU, whole cohort	2.5 (2.4)	4.6 (4.6)	0.01
Days in ICU per ICU patient	3.3 (2.2)	5 (4.6)	0.07
Reoperations within 30 days: Yes/no	1/40 (2.5%)	14/41 (34.2%)	<0.001[F]
Preoperative hemoglobin concentration (g/dl)	12 (1.8)	11.7 (2.1)	0.46
Postoperative hemoglobin nadir (g/dl)	7.96 (1.8)	6.8 (2.4)	0.02
Postoperative hemoglobin change (g/dl)	4 (2.2)	4.8 (2.6)	0.13
Hemoglobin concentration at discharge (g/dl)	9.9 (1.7)	9.6 (1.56)	0.34
PRBC transfusion: Yes/no	16/40 (40%)	38/41 (92.7%)	<0.001[Y]
Number of transfused PRBCs per operation	1.2 (1.9)	4.5 (4.5)	<0.001
Number of transfused PRBC per patient[a]	3.5 (1.97)	6.1 (5.4)	0.14
FFP transfusion: Yes/no	11/40 (27.5%)	21/41 (51.2%)	0.03
Number of transfused FFP units per operation	1 (1.9)	3.3 (5)	0.008
Number of transfused FFP units per patient[a]	3.6 (2)	6.1 (5.4)	0.14
Maximal postoperative CRP rise (mg/l)[b]	121.6 (79.5)	191.9 (109.6)	0.002
CRP at discharge (mg/l)[c]	36.2 (37)	55.9 (101.9)	0.27

Values are given as rates (percentage) or means (standard deviation). Comparisons of means are calculated using *t*-test; comparisons of proportions are calculated using chi squared test [with Yates correction (Y) where appropriate], or by Fisher exact probability test (F). ICU: Intensive care unit; HM: hemostatic matrix; PRBC: packed red blood cells; FFP: fresh frozen plasma. [a]Cumulative number for whole hospital stay (including revision surgeries). [b]Available for 37 cases and 38 controls. [c]Available for 38 cases and 36 controls.

(12, 14-16). The manufacturer's instructions contains warnings that "Floseal® matrix contains thrombin made from human plasma", and therefore "may contain infectious agents, such as viruses" (13). Additionally, "gelatin-based hemostatic agents may serve as a nidus for infection and abscess formation" (13). Increased adhesion formation after HM application was observed in a rat model (34). In human gynecology, cases of small bowel obstruction (35), local eosinophil-rich inflammatory response (30) or intra-abdominal granulomata (36) have been reported. However, in the reported cases, an inappropriate use of HM may be discussed. For instance, Shashoua *et al*. described caseating giant cell granulomata following Floseal® application "to the cervical stump for adhesion prevention" during laparoscopic supracervical hysterectomy (36), although HM is not an anti-adhesive barrier. In other reports, the authors directly stated that it was not known if the manufacturer's recommendation to remove excess Floseal® had been followed (30, 36). Our data indicate a favorable safety profile of HM. Nevertheless, as potential adverse effects can occur, the application of HM should always outweigh the potential harm of bleeding or transfusion and the surgeon should follow the instructions for use.

A further matter of concern is the possible impact of local thrombin application on cancer development. The manufacturer states that long-term animal studies to evaluate the carcinogenic potential of Floseal® matrix have not been performed (13). In ovarian cancers – whose first-line treatment requires extensive surgery with high bleeding potential – thrombin has been shown to stimulate the growth of cancer cells in vitro (37). In our opinion, as long as the application of HM is restricted to the bleeding surface and all of the thrombin from HM is incorporated into the clot, the pro-cancerogenic action of HM will remain rather speculative.

The limitations of our study result from its retrospective design. The first source of bias was the individual decision of the surgeon to apply HM according to the clinical scenario and not per randomization or per strict protocol. However, assuming that some HM applications could take place during more difficult surgeries with more bleeding, the significantly better outcomes in the HM group are even more interesting. Additionally, subtle changes in surgical performance over time (*e.g.* more differentiated use of conventional hemostatic maneuvers due to a learning curve) are not exactly measurable, and their contribution to PBL in individual surgeries cannot be quantified. In any event, since the final results obtained in a total of 215 patients did not substantially differ from the preliminary data of 87 patients (21), a

selection bias or changing surgical habits during the study period were not likely to have influenced the use of HM.

A further source of bias in retrospective studies can be the control group. Fortunately, both cohorts had similar characteristics according to diagnoses and procedures. The proportion of oncological to non-oncological and of emergent to scheduled surgeries did not significantly differ within the whole cohort. In both groups, similar requirements for discharge were followed in the study period, which is reflected by similar Hb and CRP levels at discharge irrespective of perioperative course.

Our intention was the evaluation of the HM use under 'real-world' conditions, with additional focus on patients with intraoperative coagulopathy. Therefore, in this study, we did not limit our analyses to more homogenous subgroups (*e.g.* radical oncologic surgeries), or to specific procedure types (*e.g.* only hysterectomies). However, such focused observations could be useful in forthcoming studies.

Although we recognize the retrospective design as a shortcoming of our study, we do not think that a prospective randomized study comparing HM against no hemostats would be ethically justifiable, given the obvious benefits afforded by HM use (14). We believe that further studies should focus on comparing different hemostats under different clinical scenarios or in regard to specific procedure types, under medical, economical and safety aspects [similar to (32)]. The results of the present study and of earlier case series, however, support the conclusion that HM is a helpful tool for gynecologic surgeons, provided it is used correctly.

In conclusion, as far as we are aware, this is the largest case–control observation of HM (Floseal®) application in gynecological surgery to date. In our study, the intraoperative use of HM was associated with shortened surgical and hospitalization times, less postoperative anemia and fewer blood transfusions, as well as a reduced number of re-operations and ICU stays. Since Floseal® enhances local clot building at the bleeding site without affecting the systemic hemostasis, it seems to be particularly suitable for patients whom perioperatively should continue therapeutic anticoagulant use.

Conflict of Interest

Baxter Healthcare supported travel costs and participation at educational meetings of RW. CJ and JF declare that they have no conflict of interest in regard to this study.

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