

# Reducing blood loss at myomectomy with use of a gelatin-thrombin matrix hemostatic sealant

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**Objective:** To evaluate the hemostatic efficacy and handling of gelatin-thrombin matrix in abdominal myomectomy.

**Design:** Prospective and randomized trial.

**Setting:** University teaching hospital.

**Patient(s):** Women ( $n = 50$ ) with uterine fibroids with a uterine size equivalent to  $\geq 16$  weeks gestation.

**Intervention(s):** Gelatin-thrombin matrix (FloSeal Matrix; Baxter Healthcare Corp., Fremont, CA) was delivered to the site of the uterine bleeding during myomectomy.

**Main Outcome Measure(s):** Patient age, parity, number of myomas, operative time, blood loss, transfusion, intraoperative and postoperative complications, and length of hospitalization were evaluated.

**Result(s):** The average blood loss during surgery was  $80 \pm 25.5$  mL for the FloSeal group and  $625 \pm 120.5$  mL for the control group. Intraoperative blood transfusion was necessary in five patients from the control group. Postoperative blood loss was  $25 \pm 5$  mL for the FloSeal group and  $250 \pm 75$  mL for the control group. Length of the postoperative hospital stay was  $2.5 \pm 1.2$  days for FloSeal group and  $4.5 \pm 1.3$  for the control group. No major immediate or delayed complications were observed in either group.

**Conclusion(s):** Reductions in hemorrhage in FloSeal-treated women undergoing a myomectomy are encouraging, and provide evidence for the ability of gelatin-thrombin matrix to reduce blood loss when applied immediately and directly to bleeding uterine tissue. (Fertil Steril® 2009;92:356–60. ©2009 by American Society for Reproductive Medicine.)

**Key Words:** Myoma, myomectomy, FloSeal, hemostatic sealant

The standard treatment of symptomatic leiomyomas is hysterectomy for women who have completed childbearing and myomectomy for women who wish to preserve fertility. Myomectomy can be accomplished by laparotomy, laparoscopy, or hysteroscopy. Massive blood loss associated with the dissection of huge fibroids renders myomectomy a more technically challenging procedure than hysterectomy. A requirement for transfusion in up to 20% of cases after abdominal myomectomy has been reported in the literature, and in 2% of cases there is need for conversion of myomectomy to hysterectomy (1–3).

A number of interventions have been introduced to reduce bleeding during myomectomy (2, 3). Three categories of interventions can be identified: [1] interventions on uterine arteries such as laparoscopic uterine artery dissection, uterine artery embolization, pericervical mechanical tourniquet, and hormonal tourniquets such as vasopressin and terlipressin; [2] uterotonics such as ergometrine, oxytocin, misoprostol, and sulprostone; and [3] myoma dissection techniques, which include the use of laser and chemical dissectors such as

sodium-2-mercaptoethanesulfonate (mesna). Despite these procedures excessive hemorrhage during myomectomy remains a major challenge to gynecologic surgeons (2, 3).

Gelatin-thrombin matrix hemostatic sealant is a gelatin matrix of cross-linked bovine-derived gelatin granules and a bovine-derived thrombin component (4). The gelatin-thrombin matrix can be prepared immediately before use, as a highly viscous gel that can be applied with use of a syringe with a special applicator. Because the gelatin-thrombin matrix is hydrophilic, it adheres well to wet tissue in contrast to fibrin glue, acrylic acid, or gelatin-resorcin-formaldehyde, which need a dry surface. The large amounts of thrombin concentrated on the large surface area of the gelatin matrix and contact activation by gelatin lead to fast hemostasis (4). This effect is supported by the moderate swelling (about 10%–20%) of the gelatin-thrombin matrix after contact with blood or other body fluids. This gelatin-thrombin matrix is useful in cardiac (4), spinal (5), maxillofacial and plastic facial (6), rhinologic (7), brain (8), and urologic (9) surgery. However, little is known about its use in gynecologic surgery. The present prospective randomized study evaluated the hemostatic efficacy and handling of gelatin-thrombin matrix in myomectomy.

## MATERIALS AND METHODS

### Patients and Indications

From November 2006 through February 2008, 48 patients were enrolled in this randomized controlled trial. The mean

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age of all patients was 32 years (range 24–38 years). Entry criteria were symptomatic fibroids, a uterine size equivalent to  $\geq 16$  weeks of gestation, and a request to retain their uterus (myomectomy). Excluding criteria were a history of a bleeding disorder, concurrent anticoagulant therapy, a hemoglobin level of  $<10$  g/dL at the time of surgery, and premalignant endometrial histologic findings. In all cases, the diagnosis of uterine fibroids was based on clinical examination and three-dimensional ultrasound scan as previously reported (10).

Patients included in the present series were randomly assigned to the control group ( $n = 25$ ) or FloSeal (FloSeal Matrix; Baxter Healthcare Corp., Fremont, CA) group ( $n = 25$ ) according to a computer-generated sequence. Informed consent was obtained in all cases according to the local ethics committee criteria.

Patient age, parity, number of myomas, operative time, blood loss, intraoperative and postoperative complications, and length of hospitalization were analyzed with use of the Student's *t*-test and Fisher exact test. Data were presented as the mean  $\pm$  SD. A *P* value  $\leq .05$  was considered statistically significant.

### Surgical Procedure

All patients underwent abdominal myomectomy on the basis of the technique described by Acien and Quereda (11). The default skin incision was transverse suprapubic (Pfannenstiel incision). The uterus was exteriorized, and the bowels packed away with use of two large wet swabs. Diluted vasopressin (1:60) was injected into the myometrium around the myoma nodule and into the myoma tissue in both groups to decrease intraoperative bleeding. The operative technique comprised the incision on the most prominent part of the myoma (uterine incisions were made transversely to avoid the arcuate vessels), the use of a hooked clamp to hold the tumor, and a knife to peel it, without removing the apparent excess of myometrium or serosa.

Once the myomectomy was performed and before the uterine wounds were closed, in the FloSeal group the gelatin-thrombin matrix (FloSeal Matrix; Baxter) was immediately delivered to the site of the uterine bleeding via a single-barrel syringe and a special applicator tip according to the manufacturer's instructions. In the control group, isotonic sodium chloride solution was placed in the uterine bleeding site before closure.

Our primary end point was intraoperative blood loss. Therefore, this blood loss was estimated by calculating the blood volume of the suction machine and the weight change of gauze used during surgery. Secondary outcome measures included postoperative blood loss (assessed by surgical drains and changes in hemoglobin level), blood transfusion rates, and operative morbidity (pyrexia  $>38^{\circ}\text{C}$  in more than two occasions 6 hours apart, bowel obstruction, wound infection, wound hemorrhage, and venous thromboembolism).

### RESULTS

In all 50 patients myomectomies were completed successfully. Moreover, the two randomized groups were similar in baseline characteristics, including preoperative uterine size (Table 1).

The average blood loss during surgery was  $80 \pm 25.5$  mL (range 25–150 mL) for the FloSeal group and  $625 \pm 120.5$  mL (range 250–950 mL) for the control group ( $P < .005$ ) (Table 2). Moreover, intraoperative blood transfusion was considered necessary by the anesthetist in five (20%) patients from the control group and none in the FloSeal group, being obviously statistically significant ( $P = .0001$ ).

Average postoperative blood loss assessed by surgical drains at 48 hours was  $25 \pm 5$  mL (range 5–40 mL) for the FloSeal group and  $250 \pm 75$  mL (range 75–450 mL) for the control group ( $P < .005$ ) (Table 2). Moreover, postoperative fall in hemoglobin level at day 2 was  $0.5 \pm 0.2$  g/dL (range 0–1.2 g/dL) for the FloSeal group and  $2.8 \pm 0.9$  g/dL (range 0.8–4.9 g/dL) for the control group ( $P < .005$ ) (Table 2).

Average operating time was  $65 \pm 5.2$  minutes (range 45–95 minutes) for the FloSeal group and  $60 \pm 7.9$  minutes (range 40–100 minutes) for the control group. The average yield of fibroids per patient was  $3.2 \pm 1.2$  (range 1–15) for the FloSeal group and  $3.1 \pm 1.6$  (range 1–18) for the control group (Table 2). These differences were not statistically significant ( $P > .05$ ).

Average length of the postoperative hospital stay was  $2.5 \pm 1.2$  days (range 2–3 days) for the FloSeal group and  $4.5 \pm 1.3$  days (range 3–7 days) for the control group (Table 2), being statistically significant ( $P < .05$ ). No major immediate or delayed complications were observed in either group of patients. Postoperative fever developed in only one patient in the control group. The patient was given treatment with cephalosporin (2 g/day) for 5 days and was discharged on the seventh postoperative day.

### DISCUSSION

Uterine fibroids are the most common solid tumors occurring in the female pelvis. Various prevalence rates have been quoted in literature, ranging from 20% to 50%, on the basis of hysterectomy specimens (3, 12). Generally, asymptomatic fibroids can be monitored simply through regular follow-up visits. However, myomectomy, by either an abdominal, a vaginal, a hysteroscopic, or a laparoscopic approach, should be considered for patients with symptoms or for those who have large or growing tumors and want to preserve fertility (3, 13). Because myomectomy can result in considerable blood loss, hemostasis at the time of surgery is paramount to the success of patient recovery (3). Methods to control bleeding and repair wounds have existed for many years (2, 3). Therefore, several methods to control blood loss in myomectomies are available, including the use of diluted vasopressin and analogues, misoprostol, oxytocin, chemical dissection

**TABLE 1****Baseline characteristics of the enrolled women.**

	FloSeal group	Control group	<i>P</i> value
No. of patients	25	25	
Mean age (y)	31.9 ± 5.6	32.1 ± 4.9	.851
Body mass index (kg/m <sup>2</sup> )	22.4 ± 3.7	23.3 ± 4.1	.532
Parity	0.5 ± 0.1	0.5 ± 0.2	.932
Symptom (%)			
Menorrhagia	78.2	76.9	.785
Pelvic pain	41.2	39.1	.769
Bladder or bowel disfunction	12.4	16.6	.359
Infertility	3.6	4.0	.816
Uterine size (wk)	18.2 ± 1.7	17.9 ± 1.4	.711

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with sodium-2-mercaptoethanesulfonate (mesna), midline uterine incision, tourniquets, autologous blood transfusion, hypotensive anesthesia, and GnRH agonists (2, 3, 12–19).

Recently, nonmechanical techniques to reduce blood loss during abdominal myomectomy were the subject of a Cochrane Library review (17). The review highlights the paucity of randomized data on the use of such techniques (17). Eight randomized control trials were included use of intra-myometrial vasopressin, intramyometrial ornipressin, vaginal misoprostol, oxytocin, chemical dissection with mesna, intramyometrial bupivacaine plus epinephrine, and the enucleation of the myoma by morcellation while it is attached to the uterus. A significant reduction in blood loss was observed with misoprostol (–149.00 mL, 95% confidence interval [CI] –229.24 to –68.76 mL), vasopressin and analogues (–298.72 mL, 95% CI –593.10 to –4.34 mL), and bupivacaine plus epinephrine (–68.60 mL, 95% CI –93.69 to –43.51 mL). On the other hand, there was no evidence of a decrease of intraoperative blood loss with use of myoma enucleation by morcellation or IV oxytocin administration (17).

Gonadotropin-releasing hormone agonists have been used to minimize blood loss by reducing uterine volume before surgery (3, 16). A Cochrane Library review evaluated the role of pretreatment with GnRH agonists before myomectomy (18). The review included 20 randomized controlled trials that compared GnRH agonists with no pretreatment or placebo (18). Preoperative and postoperative hemoglobin and hematocrit levels were significantly improved by GnRH agonist therapy before surgery, suggesting that pretreatment with a GnRH agonist before myomectomy is beneficial (18).

However, despite the use of one or more of these nonmechanical techniques to reduce blood loss during abdominal myomectomy, up to 31% of United Kingdom gynecologists reported the regular need for blood transfusions during myomectomy (19).

Hemostasis is blood clot formation at the site of vessel injury. It is a complex interaction between platelets, plasma proteins, and coagulation and fibrinolytic pathways. Platelets are activated at the site of injury and provide the initial

**TABLE 2****Surgical parameters after myomectomy.**

	FloSeal group	Control group	<i>P</i> value
Operating time (min)	65 ± 5.2	60 ± 7.9	.173
No. of myomas per patient	3.2 ± 1.2	3.1 ± 1.6	.335
Intraoperative blood loss (mL)	80 ± 25.5	625 ± 120.5	.001
Blood transfusion (%)	0	20	<.001
Postoperative blood loss (mL)	25 ± 5	250 ± 75	.001
Postoperative hemoglobin fall (g/dL)	0.5 ± 0.2	2.8 ± 0.9	.005
Hospital stay (d)	2.5 ± 1.2	4.5 ± 1.3	.005

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hemostatic response. The clotting cascade involves the sequential activation of fibrin lattices that reinforce the platelet plug.

Hemostatic agents and tissue sealants are used routinely to prevent excess blood loss and in reconstruction during surgical repair (4–9). FloSeal, a novel hemostatic sealant composed of thrombin and a gelatin matrix, has become commercially available since it was approved by the US Food and Drug Administration in 1999 (4–9).

FloSeal matrix hemostatic agent is composed of thrombin and a gelatin matrix that is manufactured by extracting collagen from bovine corneal tissue. The collagen then undergoes gelatinization and cross-linking/stabilization with glutaraldehyde. This compound is then ground to 500- to 600- $\mu$ m particles. The thrombin component is of bovine origin and is supplied as a sterile freeze-dried powder that is reconstituted in 0.9% sodium chloride and mixed with the gelatin matrix in the operating room just before use (4–9). The preparatory time is approximately 1 minute, and, once completed, the mixture is usable for 2 hours.

Both FloSeal components work independently to promote clot formation at the bleeding site. The granular nature of the compound conforms to the wound's shape. The granules swell 10% to 20%, causing tamponade in the wound bed on contact with blood or other fluid. This reduces bleeding and provides a matrix on which a clot can form. On the other hand, the thrombin activates platelets and factor V, VII, and XII and promotes the conversion of fibrinogen to fibrin. Fibrin traps the granular matrix, which promotes stability of this complex. Absorption of the gelatin complex typically occurs 6 to 8 weeks after application (4–9). The unique property of this product is the requirement for the presence of blood at its application site for activation (4–9).

The volume of blood lost during abdominal myomectomy correlated with the size and location of the myomas (16, 20). Myomas are often surrounded by large, supporting blood vessels that originate in the surrounding myometrium (16, 21). Recently, a new theory that relates the vascular system development with these tumors has been proposed (21): the small myomatous foci compress the preexisting blood vessels and induce their regression, leading to the formation of transiently avascular regions inside such tumors. Subsequently, the density of blood vessels increases in the direct surrounding of the myoma, and, as it grows in size, new blood vessels penetrate the tumor from its periphery where “the vascular capsule” is being formed, and originate the vascular network observed inside the larger myomas. This concept does not agree with the earlier suggestion (22) that the arterial pattern of a myoma represents an expansion of the preexisting supply to that area of the myometrium. However, it does correspond with the recently proposed model of angiogenesis in growing tumors (23). Hence, the frequent bleeding in the myometrial bed after the myomas are removed (myomectomy) is now explained by this vascular distribution surrounding the myomas.

Abdominal myomectomy may be considered a reasonable option for women with very large uterine size who desire to retain their uterus (16). A study of 91 women with uterine size greater than an equivalent of 16 weeks gestation (range 16–36 weeks) reported no conversion to hysterectomy (24). This is consequent with the results of the present study, where abdominal myomectomies were accomplished in all cases.

An average intraoperative blood loss of 540 mL was reported in a review of abdominal myomectomies for uterine sizes exceeding 14 weeks gestation despite the use of different nonmechanical techniques to reduce blood loss during surgery (16). This is similar to the blood loss in our control group. However, the FloSeal group presented a significant reduction in the intraoperative bleeding. Furthermore, the intraoperative blood transfusion rate and the postoperative blood loss were also significantly reduced in the FloSeal group. Moreover, the average length of postoperative hospital stay was also significantly reduced in the FloSeal group.

Reductions in hemorrhage in FloSeal-treated women undergoing a myomectomy are encouraging and provide evidence for the ability of gelatin-thrombin matrix to reduce blood loss when applied immediately and directly to a bleeding uterine tissue.

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