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The use of novel hemostatic sealant (Tisseel®) in laparoscopic myomectomy: a case–control study

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Abstract
Background This is the first case–control study on the use of a fibrin sealant (Tisseel®) on uterine suture during laparoscopic myomectomy (LM), with the primary endpoint to evaluate the intraoperative bleeding and postoperative blood loss. In addition, we evaluated the time required to achieve hemostasis using Tisseel® and how much it can influence operative time.
Methods From December 2009 to January 2011, consecutive patients older than 18 years with symptomatic isolate intramural myoma with maximal diameter ≤6 cm and ≥4 cm and with a sonographically diagnosed free myometrium margin ≥0.5 cm were included in the study. We selected from our institute's database a group of consecutive patients with homogeneous features of the study group, who underwent laparoscopic myomectomy without Tisseel® application.
Results Fifteen women with symptomatic myoma were enrolled in the study (group A). Regarding the control group (group B), we selected a homogenous group of 15 patients with the same preoperative characteristics of the study group. Mean operative time was 47.7 min and 62.1 min, for groups A and B respectively ($p < 0.05$). Mean time required to achieve complete haemostasis was 195.5 s in group A and 361.8 in control group B ($p < 0.0001$). Mean estimated blood loss was 111.3 mL and 230 mL in groups A and B, respectively ($p < 0.05$). Mean hemoglobin decrease was 1.36 g/dL and 2.04 g/dL in groups A and B, respectively ($p < 0.05$).
Conclusions The use of Tisseel® during LM may represent a valid alternative solution for obtaining hemostasis, reducing intra- and postoperative bleeding. Furthermore, it may help the surgeon to obtain a rapid healing of the injured surfaces, probably reducing the use of electrocoagulation and traumatisms.

Keywords Laparoscopic myomectomy · Tisseel · Fibrin sealant · Hemostasis

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Several surgical approaches are available for the treatment of symptomatic uterine fibroids, such as hysterectomy, myomectomy, myolysis, magnetic resonance imaging-guided focused ultrasound surgery, and uterine artery embolization. Thirty percent of hysterectomies are performed for myomas, but uterine removal is inappropriate for young women who want to preserve fertility [1].

Myomectomy traditionally is performed by laparotomy [2]; however, during the past decades, a variety of endoscopic alternatives have come to be widely used for removal of myomas, including laparoscopic, hysteroscopic, and robotic surgery [3, 4]. Laparoscopic myomectomy (LM) is associated with lower haemoglobin drop, reduced operative blood loss, reduced hospital stay, diminished postoperative pain, and fewer overall complications than abdominal myomectomy. Moreover, no significant difference is found in terms of major complications, pregnancy, and recurrence rate [5]. However, the main operative step of laparoscopic myomectomy is the uterine suture, which requires an experienced surgeon [6]. Nevertheless, hemorrhage during myomectomy remains a major challenge to gynecologic surgeons, because uterine

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defect may be difficult to close because of its length, location, or bleeding [7]. The use of electrosurgery for uterine wall incision and hemostasis have to be avoided, because tissue necrosis could cause defective scarring and increase the risk of uterine rupture during subsequent pregnancy [8].

The laparoscopic control of intraoperative bleeding requires the timely and appropriate use of various primary hemostatic modalities, such as tamponades, electrocoagulation, clips, and manual oversewing [9–11]. Even with these techniques, diffuse parenchymatous bleeding has been difficult to manage laparoscopically, and it remains one of the major reasons for open conversion [12].

Recently, a lot of hemostatic agents and tissue sealants have been used with the goal to prevent excess blood loss and for reconstruction during surgical repair [13–18]. Several studies have evaluated the efficacy of these agents.

Initially, these agents have been described as suture support in patients with esophageal, gastric, colonic, and rectal anastomoses [19]. It has been reported as an adjunctive treatment for premature rupture of membrane repair, tubal reanastomosis, and embryo transfer [20–22]. In an animal model, fibrin sealant improved incisional integrity when added to the suture line of colonic anastomoses. Fibrin sealant augmented healing in both normal and peritonitis models as measured by suture line bursting pressures [6].

In gynecology, three previous articles have been published to demonstrate the adhesion-prevention effects of fibrin sealants after LM [23–25]. However, only one prospective trial has evaluated the efficacy of a hemostatic sealant when used during laparoscopic myomectomy [26].

This is the first case–control study on the use of a fibrin sealant (Tisseel®) on uterine suture during laparoscopic myomectomy, with the primary endpoint to evaluate the intraoperative bleeding and postoperative blood loss. In addition, we wanted to evaluate the time required to achieve hemostasis using Tisseel® and how much it can influence operative time.

Materials and methods

From December 2009 to January 2011, consecutive patients older than 18 years with symptomatic isolate intramural myoma with a sonographically diagnosed free myometrium margin (distance between the deeper part of the myoma and the endometrial cavity) $\geq$0.5 cm were included in the study. Inclusion criteria were: World Health Organization performance status less than 1; no contraindications to laparoscopic surgery; signed informed consent; presence of 1 symptomatic uterine myoma with maximal diameter $\leq$6 cm and $\geq$4 cm estimated by ultrasound (US); and absence of adnexal pathology on preoperative US examination. Only patients with single myoma were included to keep the groups as homogeneous as possible. Exclusion criteria were: presence of subserosal, submucosal, or intraligamentous myoma/s, previous laparotomic pelvic surgery, coagulation defects or concurrent anticoagulant therapy, liver disease, previous or present gynaecologic neoplasms or psychiatric disease, body mass index greater than 40, ongoing or recent history of pelvic inflammatory disease, and menopausal status.

Preoperative assessment included: complete history, physical and gynecologic examination, laboratory workup, electrocardiogram, chest radiograph, and pelvic US. The indication for surgery was symptomatic myoma (pelvic pain or menorrhagia) for all patients. Menorrhagia was defined as bleeding for more than 7 days or using more than ten pads or tampons per day during menstrual cycle. Pelvic pain was defined as symptoms of pelvic pressure, lower back pain, or both with or without increased urinary frequency, reported subjectively by the patients, causing dysfunction in daily life. Women were counselled about possibility of laparotomy if any part of surgery could not be completed laparoscopically and risk of hysterectomy if there was uncontrollable hemorrhage.

Before surgery, patients were submitted to mechanical bowel preparation, deep venous thrombosis prophylaxis with low molecular weight heparin (2 h before operation and postoperatively until complete ambulation). Short-term antibiotic prophylaxis was performed 2 h before surgery (cefazolin, 2 g). No gonadotropin-releasing hormone analogs were administered before surgery. Surgical technique was performed under general anesthesia.

All of the LM were performed in a standardized fashion under general endotracheal anesthesia by the same surgeon. Two 5-mm and one 10-mm trocar are placed in the lower abdomen. The uterine serosa and myometrium are coagulated with a monopolar laparoscopic hook and incised to expose the surface of the fibroid. The fibroid is grasped with a 10-mm tenaculum grasping forceps and extracted from of the surrounding myometrium by blunt dissection with the activated monopolar forceps step-by-step. Connective tissue bridges are coagulated additionally and cut with scissors to reduce blood loss. Fibroids are stored in the pouch of Douglas. The uterus is closed with interrupted intracorporeal two-layers suture (0-polyglactin, sharp curved needle). Fibroids are removed using morcellation with an electric morcellator and extracted through the 10-mm trocar. Clots are removed through repeated irrigation and suctioning. Tisseel® is applied on uterine suture by Duploject Spray Set to apply the solution uniformly on the whole suture.

Operative data, including time required to achieve complete hemostasis on uterine suture bleeding sites, intraoperative and postoperative complications, and length of hospital stay, were recorded. Blood loss was evaluated both by intraoperative estimated blood loss and by hemoglobin decrease (ΔHb). We estimated blood loss by using the following formula: estimated blood loss (mL) = the waste irrigation fluid volume (mL) minus the volume of used normal saline for irrigation (mL). Postoperative fever was defined as temperature increase greater than 38°C on two occasions at least 6 h apart, within 24 h, starting 24 h after surgery. Transvaginal pelvic US was routinely performed, in absence of symptoms, at hospital discharge. Follow-up examinations were performed, in absence of symptoms, at 1 and 12 months, including physical and gynecologic examination and pelvic US.

We selected from our institute's database a group of consecutive patients with homogeneous features of the study group, in terms of patients' characteristics and preoperative myoma characteristics, who underwent laparoscopic myomectomy without Tisseel® application. In these patients, complete hemostasis on uterine suture bleeding sites was obtained using bipolar forceps coagulation and with interrupted intracorporeal suture.

The Mann–Whitney test was used for nonparametric data. Statistical significance was set at a $p < 0.05$.

Results

Forty-four patients affected by uterine myomas were considered eligible and evaluated to be included in the study. Of these, 15 women with symptomatic myoma were enrolled in the study (study group A). Trial flow diagram is shown in Fig. 1.

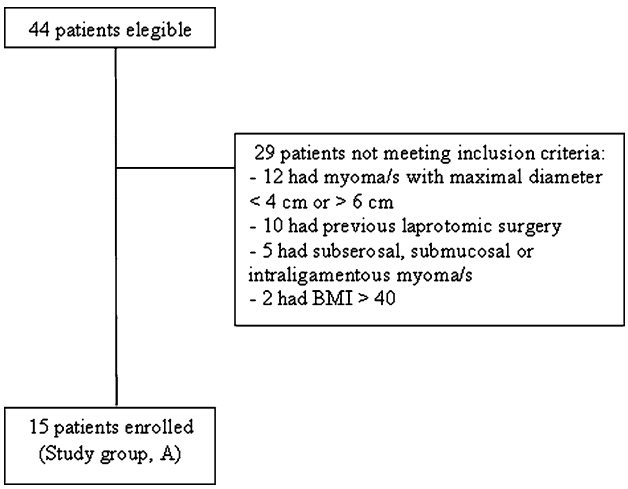

Fig. 1 Trial flow diagram

Regarding the control group (group B), we selected a homogenous group of 15 patients with the same preoperative characteristics as the study group. Patients' characteristics are shown in Table 1. Indications for surgery were menorrhagia or pelvic pain, or both; some patients had more than one indication (Table 1).

Size and location of myomas for each patient are shown in Table 2. In all patients, laparoscopic myomectomy procedure was performed without intraoperative complications. Operative characteristics are reported in Table 3.

Mean operative time was 47.7 min (standard deviation (SD), 15.4; 95% confidence interval (CI), 39.1–56.2) and 62.1 min (SD, 21.1; 95% CI, 50.4–73.8) for groups A and B respectively ($p < 0.05$). In particular, mean time required to achieve complete hemostasis was 195.5 s (SD, 40.9; 95% CI, 172.8–218.1) in group A and 361.8 (SD, 116; 95% CI, 297.5–426.1) in control group B ($p < 0.0001$).

Mean estimated blood loss was 111.3 mL (SD, 77.3; 95% CI, 68.5–154.1) and 230 mL (SD, 75.6; 95% CI, 128.7–212.4) in groups A and B respectively ($p < 0.05$). Mean weight of myomas removed were 122 g (SD, 61; 95% CI, 102–143.5) and 125 g (SD, 45; 95% CI, 101.9–143.3) in groups A and B respectively (p = not significant [ns]). No statistically difference was found as mean number and length of uterine incisions in the two groups. During laparoscopic procedures, no laparotomic conversions were reported in both groups. None of the patients required intraoperative blood transfusion. No intraoperative complications occurred.

Concerning postoperative features and complications (Table 4), only one (6%) patient required blood transfusion in group B and none in group A (p = ns). Mean hospital stay was 2.9 days (SD, 1.3; 95% CI, 2.2–3.6) for group A and 3.0 days (SD, 1.2; 95% CI, 2.3–3.6) for group B (p = ns).

Mean hemoglobin decrease was 1.36 g/dL (SD, 0.6; 95% CI, 1–1.7) and 2.04 g/dL (SD, 0.8; 95% CI, 1.6–2.5) in groups A and B respectively ($p < 0.05$). Three (20%) patients in group A developed febrile morbidity and two (13%) patients in group B (p = ns). In group B, one patient developed a nonechogenic complex mass that measured 6 cm, which was detected on the second operative day by pelvic US and diagnosed as pelvic hematoma. The patient was successfully treated with antibiotic therapy.

All patients returned to each follow-up examination. At the 12-month follow-up, no patient had developed myoma recurrence.

Discussion

Laparoscopic myomectomy is now considered the best treatment option for symptomatic women with uterine fibroids who wish to maintain their fertility. Compared with laparotomy, laparoscopic myomectomy has the advantages

Table 1 Patients, indication to surgery, and preoperative myoma characteristics

	Group A	Group B	*p* value
Patients			
Age, year (median, range)	35.2 ± 6.9 (95% CI 31.8–38.2)	35.5 ± 8.4 (95% CI 30.8–40.1)	ns
Nulliparous	5 (33%)	3 (20%)	–
Body mass index (mean ± SD)	25.3 ± 6.3 (95% CI 22.4–28.2)	26.2 ± 4.4 (95% CI 23.7–28.6)	ns
Indication to surgery[a]			
Menorrhagia	9 (60%)	10 (66.7%)	–
Pelvic pain	7 (46%)	9 (60%)	–
Characteristic of myomas[b]			
Intramural	11	13	–
Intramural/subserosal	4	2	–
Myoma size, cm (mean ± SD)	4.6 ± 0.7 (95% CI 4.2–5)	4.8 ± 0.7 (95% CI 4.4–5.2)	ns

[a] Some patients have more than one indication

[b] At preoperative transvaginal pelvic ultrasonography

ns not significant; *SD* standard deviation; *CI* confidence interval

Table 2 Size and location of every myoma for all patients

Patient	Group A		Group B	
	Size of myomas (cm)	Location	Size of myomas (cm)	Location
1	6	IM	4	IM
2	4	IM/SS	6	IM
3	4	IM	5	IM
4	5	IM/SS	6	IM
5	4	IM	5	IM/SS
6	5	IM	5	IM
7	4	IM	4	IM/SS
8	5	IM	4	IM
9	4	IM	4	IM
10	4	IM	5	IM
11	5	IM/SS	5	IM
12	5	IM	4	IM
13	4	IM	5	IM
14	4	IM/SS	5	IM
15	6	IM	5	IM

IM intramural; *IM/SS* intramural/subserosal

Table 3 Operative characteristics and complications

	Group A	Group B	*p* value
Patients	15	15	–
Operative time (min) (mean ± SD)	47.7 ± 15.4	62.1 ± 21.1	<0.05
Time to achieve complete hemostasis (sec) (mean ± SD)	195.5 ± 40.9	361.8 ± 116	<0.0005
Intraoperative blood loss (mL) (mean ± SD)	111.3 ± 77.3	230 ± 75.6	<0.05
Length of uterine incisions	2.9 ± 0.8	3.1 ± 1	ns
Weight of myoma (g) (mean ± SD)	122 ± 61	125 ± 45	ns
Intraoperative blood transfusion	0	0	–
Laparotomy conversion (n)	0	0	–

ns not significant; *SD* standard deviation

of small incisions, short hospital stay, less postoperative pain, rapid recovery and good assessment of other abdominal organs [27].

However, several studies have shown that relevant operative blood loss represents one of the most frequent complications that may occur during laparoscopic myomectomy [28–30]. The main operative step for surgeons during laparoscopic myomectomy is to perform a correct uterine suture [6].

The laparoscopic control of intraoperative bleeding requires the timely and appropriate use of various primary hemostatic modalities, such as tamponades, electrocoagulation, clips, and manual oversewing [9–11]. Even with these techniques, diffuse parenchymatous bleeding has been difficult to manage laparoscopically, and it remains one of the major reasons for open conversion [12].

Recently, nonmechanical techniques to reduce blood loss during abdominal myomectomy were the subject of a Cochrane Library review [31]. The review highlights the paucity of randomized data on the use of such techniques. Eight randomized, controlled trials (RCTs) included the use of intramyometrial vasopressin, intramyometrial ornipressin, vaginal misoprostol, oxytocin, chemical dissection with mesna, intramyometrial, and bupivacaine plus epinephrine.

Table 4 Postoperative features and complications

Data	Group A	Group B	*p* value
Postoperative features			
ΔHb, g/dL (mean ± SD)	1.36 ± 0.6 (95% CI 1–1.7)	2.04 ± 0.8 (95% CI 1.6–2.5)	<0.05
Blood transfusion, *n* (%)	0 (0%)	1 (6%)	ns
Hospital stay, days (mean ± SD)	2.93 ± 1.3 (95% CI 2.2–3.6)	3 ± 1.2 (95% CI 2.3–3.6)	ns
FU (mo)	12	12	–
Recurrences	0	0	–
Complications, *n* (%)			
Fever	3 (20%)	2 (13%)	ns
Pelvic hematoma	0 (0%)	1 (6%)	ns
Wound infection	1 (6%)	0	ns
Lower abdominal pain	0	1 (6%)	ns

SD standard deviation; *FU* follow-up; *ns* not significant; *CI* confidence interval

A significant reduction in blood loss was observed with misoprostol (149.00 mL; 95% CI 229.24–68.76 mL), vasopressin and analogues (298.72 mL; 95% CI, 593.1–4.34 mL), and bupivacaine plus epinephrine (68.6 mL; 95% CI, 93.69–43.51 mL). However, evidence is limited from a few RCTs that misoprostol, vasopressin, bupivacaine plus epinephrine, tranexamic acid, tourniquet, and mesna may reduce bleeding during myomectomy [31].

Gonadotropin-releasing hormone agonists have been used to minimize blood loss by reducing uterine volume before surgery [1, 32]. A Cochrane Library review evaluated the role of pretreatment with GnRH agonists before myomectomy [33]. The review included 20 RCTs that compared GnRH agonists with no pretreatment or placebo. 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.

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 [13]. In addition, some studies [34–36] have demonstrated that GnRH agonist pretreatment resulted in blurring the cleavage plane between the myoma and the myometrium increased difficulty in shelling out pretreated myomas. Moreover, the induction of a period of hypoestrogenism before myomectomy seems to favor short-term recurrence of uterine myomas, limiting the efficacy of surgery [37].

Hemostatic agents and tissue sealants are used routinely to prevent excess blood loss and for reconstruction during surgical repair [14–18, 38]. Several studies have been conducted to evaluate the hemostatic effect of these agents [39–41].

Tisseel® is a novel hemostatic sealant made of two components: a freeze-dried cryoprecipitate containing fibrinogen, Factor XIII, and fibronectin, and an aprotinin solution dissolved with calcium chloride ($CaCl_2$). Both components, opportunely mixed, are applied on the surface to be treated, where they consolidate giving rise to the formation of a fibrin clot with high hemostatic and sealing properties. Factor XIII plays a first-class role in the process, because not only does it make the glue more homogeneous and resistant, it also favors the formation of covalent links between tissue collagen and fibrin. When applied on tissue surfaces, fibrinolysis occurs and the glue is substituted by fibrotic tissue, facilitating repair. Its adhesive and hemostatic properties have been demonstrated in a number of experimental studies and clinical trials [31, 42, 43]. Tisseel®, thanks to its hemostatic, adhesive, and tissue healing properties, is widely used in all surgical fields as an auxiliary tool for the commonest suture materials, improving their resistance and reducing the risk of complications, such as hematomas, dehiscences, and adhesions [44–46].

Until now, three articles have been published that demonstrate the adhesion-prevention effects of fibrin sealants after LM [23–25]. However, only one prospective trial has evaluated the efficacy of a hemostatic sealant when used during laparoscopic myomectomy [26]. This is the first case–control study on the use of a fibrin sealant (Tisseel®) on uterine suture during laparoscopic myomectomy with the goal to evaluate intraoperative bleeding, postoperative blood loss, and time required to achieve hemostasis.

In our series, there was a statistically significant reduction of intraoperative blood loss (111.3 mL ± 77.3 vs. 230 mL ± 75.6 in groups A and B respectively; $p < 0.05$) and hemoglobin decrease (1.36 g/dL ± 0.6 vs. 2.04 g/dL ± 0.8 in groups A and B respectively; $p < 0.05$), which were significantly lower in the study group.

Concerning the hemostatic effects of Tisseel®, data emerging from our study are consistent with those reported by Raga et al. [26], who have conducted a prospective, randomized trial to evaluate the efficacy of a gelatin-thrombin matrix hemostatic sealant (FloSeal®) during myomectomy. They reported a significant reduction in intraoperative blood loss (80 mL ± 25.5 in FloSeal group vs. 625 mL ± 120.5 in control group; $p < 0.005$), blood transfusion (0% in FloSeal group vs. 20% in control group; $p < 0.001$), postoperative blood loss 25 mL ± 5 in FloSeal group vs. 250 mL ± 75 in control group; $p < 0.005$), postoperative hemoglobin decrease 0.5 g/dL ± 0.2 in FloSeal group vs. 2.8 g/dL ± 0.9 in control group; $p < 0.005$), and hospital stay 2.5 days ± 1.2 in FloSeal group vs. 4.5 days ± 1.3 in control group; $p < 0.005$). Furthermore, adhesions formation and risk of rupture during delivery on uterine suture site represent

supplementary common complications of laparoscopic myomectomy.

In this context, is important to consider that inadequate hemostasis and the consequent uncontrolled deposition of fibrin is widely held to contribute to adhesions [47–49]. Thus, the attainment of meticulous hemostasis has been an essential tenet of reconstructive reproductive surgeons for many years. For this reason, the properties of fibrin sealants, as well as their widespread deliverability, make them viable candidates for use in adhesion prevention, although their use may at first seem counterintuitive.

Thus, the reduction of intraoperative and postoperative bleeding due to the hemostatic effect of Tisseel® seen in our study, reducing the uncontrolled deposition of fibrin, could probably contribute to reduce the rate of postoperative adhesions. In fact, several studies in animals and humans have supported the use of fibrin-based materials for adhesion prevention [50, 51].

As mentioned before, until now, only three articles have been published that evaluate the adhesion-prevention effects of fibrin sealants in patients undergoing LM [23–25].

The one conducted by Takeuchi et al. [24] has demonstrated that the use of fibrin sealants significantly reduces adhesions formation after myomectomy. According to their results, fibrin gel effectively prevents uterine wound adhesions and de novo adnexal adhesions after LM, with a postoperative adhesions rate of 34.5% and 62.5% for the fibrin gel and control groups respectively ($p < 0.005$).

Moreover, by using Tisseel® in our series we avoided the use of electrosurgery for uterine wall and hemostasis. On the other hand, tissue necrosis could cause defective scarring and increase the risk of uterine rupture during subsequent pregnancy [9]. Tisseel®, because of its hemostatic and sealing proprieties, allows minimizing the use of electrocoagulation and improves the suture resistance, reducing the risk of complications (hematomas, inflammatory abscess, dehiscences, and adhesions) [52–54].

In addition, in our series we have observed a statistically significant advantage for the Tisseel® group in terms of operative time (Table 3). In particular, the time required to achieve complete hemostasis was significantly lower in the group with Tisseel®. On the contrary, Raga et al. [26] reported no statistically significant difference in average operative time between the FloSeal® group and control group (65 ± 5.2 and 60 ± 7.9 min respectively).

The differences between our study and the study conducted by Raga et al. are probably due to the different inclusion criteria used in the trials. In fact, Raga et al. included patients with one or more fibroids. They did not consider the myoma diameter but the only uterine size, which had to be equivalent to ≥16 weeks of gestation. In addition, they included patients with every kind of myoma regardless of their location. Instead, in our study we included patients with only one symptomatic uterine myoma, with maximal diameter ≤6 cm and ≥4 cm estimated by US, and we excluded patients with subserosal, submucosal, or intraligamentous myoma/s. Myoma dimensions and location are important factors, which may significantly influence operative time [55], thus these features must be considered and analyzed to avoid bias.

Another parameter not considered by Raga et al. is the length of uterine incision. We have measured and analyzed it to obtain two homogeneous groups and because the time required to suture uterine incisions is likely connected to their length. Thus, the different inclusion criteria could explain the finding of a statistically significant reduction in operative time only in our study and not in the one conducted by Raga et al.

Ultimately, concerning postoperative features (Table 4), there was no statistically significant difference in blood transfusion rate, hospital stay, recurrence rate, and complications. Thus, we have observed that Tisseel® is an easy-to-use, harmless product that can be used in surgery as a valid support for the commonest suture materials, without influencing recurrence and complication rate.

In conclusion, the use of Tisseel® during LM may represent a valid alternative solution for obtaining hemostasis, reducing intraoperative and postoperative bleeding. Furthermore, it may help the surgeon to obtain a rapid healing of the injured surfaces, reducing the use of electrocoagulation and traumatisms. Randomized trials are needed to confirm this preliminary data.

Disclosures Drs. Roberto Angioli, Francesco Plotti, Roberto Ricciardi, Corrado Terranova, Marzio Angelo Zullo, Patrizio Damiani, Roberto Montera, Federica Guzzo, Giuseppe Scaletta, and Ludovico Muzii have no conflicts of interest or financial ties to disclose.

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