GENERAL GYNECOLOGY

The use of sealing hemostat patch (HEMOPATCH®) in laparotomic myomectomy: a prospective case–control study

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Abstract

Purpose Uterine myomas are the most common gynecological disease. In these cases, a myomectomy is performed traditionally laparotomically. However, alternatives have been widely used, including laparoscopic, endoscopic, and robotic surgery. During these techniques, diffuse parenchymatous bleeding remains one of the main intraoperative and postoperative complications and sometimes requires unplanned hysterectomies. Recently, hemostatic agents and sealants have been used to prevent excessive blood loss during surgical repair.

Methods We propose a prospective case–control study on the use of a sealing hemostat patch (HEMOPATCH®) on uterine sutures in laparotomic myomectomy. In the period between July 2016 and April 2017, 46 patients with symptomatic uterine fibromatosis underwent surgery. They were divided into two groups of 23 patients, with different treatments in the hemostatic phase of oozing bleeding. HEMOPATCH® is applied in group A, and spray electrocoagulation is applied in group B.

Results In group A, we achieve faster hemostasis ($p < 0.05$), than in group B. We report a significantly lower C-reactive protein value on the second and third days after surgery for group A compared to group B.

Conclusions HEMOPATCH®, during laparotomic myomectomy, is a valid alternative solution for obtaining rapid hemostasis and consequently intraoperative and postoperative bleeding. Furthermore, we suggest that a lower inflammatory peritoneal state is probably correlated with the barrier effect of the patch on the suture.

Keywords HEMOPATCH® · Sealing hemostat patch · Hemostatic agents · Laparotomic myomectomy · Hemostasis time

What does this study add to the clinical work

Hemopatch was effective and safe in laparotomic myomectomy, reducing intraoperative time to hemostasis (14 minutes) and a 23% reduction in intraoperative blood loss. Furthermore, in the treated group it reduces the post-operative peritoneal inflammatory state by performing a barrier effect and reducing the consequent formation of adhesions.

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Introduction

Uterine myomas are the most common gynecologic disease, with an incidence of 70 to 80% at 50 years of age and represent the first indication of hysterectomy in the USA [1]. Numerous surgical techniques are available for symptomatic uterine fibroids such as hysterectomy, myomectomy, myolysis, RMN-guided focused ultrasound surgery, and embolization of the uterine artery [2, 3]. Around 30–39% of hysterectomy are performed in the United States for symptomatic uterine fibroids, but this treatment could be inappropriate in young women who want to maintain fertility [4]. Myomectomy is an operation that allows you to remove individual myomas while preserving the uterus. It is traditionally performed laparotomically, however, during the last decades, endoscopic alternatives have been widely used including laparoscopic surgery, endoscopic and robotic surgery [3, 5]. The main step of myomectomy is the suture of the uterine incision, which requires an experienced surgeon. However, bleeding during myomectomy remains a major challenge

for all gynecological surgeons. The use of electrosurgery for uterine wall incision and hemostasis should be avoided because tissue necrosis could cause defective scarring and increase the risk of uterine rupture during subsequent pregnancy [6]. Intraoperative bleeding control requires precise and appropriate use of various primary hemostasis modalities, such as tampons, electrocoagulation, clips, and double-layer manual sutures [7]. Also, with these techniques, diffuse parenchymatous bleeding remains one of the main intraoperative and postoperative complications that require unplanned hysterectomies, with an overall incidence rate of 0.4% [8]. Recently, many hemostatic agents and sealants have been used to prevent excessive blood loss during surgical repair [9, 10]. This is the first prospective case–control study on the use of sealing hemostat patch, HEMOPATCH® (Baxter AG, Vienna, Austria), on uterine sutures in a laparotomic myomectomy, with the primary objective of assessing intraoperative bleeding and postoperative blood loss. Additionally, we want to evaluate the time needed to reach hemostasis using HEMOPATCH® and how much this new device influences operating time and the extent of peritoneal inflammatory insult and consequent adhesion formation.

Materials and methods

In the period between July 2016 and April 2017, 46 patients suffering from symptomatic uterine fibromatosis and older than 18 years of age were enrolled in the study. This study was carried out according to the guidelines of Good Clinical Practice and the Declaration of Helsinki (1996) and was approved by the Internal Review Board of the Campus Bio-Medico University Hospital Foundation, Rome.

The patients enrolled were informed of the possibility of using HEMOPATCH® during the surgical procedure and informed consent was obtained.

Inclusion criteria used were as follows: World Health Organization performance status 0 and 1, without contraindication to laparotomic surgery, signed informed consent, presence of intramural leiomyoma regardless of the relationship with the endometrium and serous (Leyomioma included in the study sec. FIGO Classification: Type 3, 4, 5, 6 and 2–5), presence of maximum 5 symptomatic uterine fibroids with a maximum diameter < 8 cm evaluated by pelvic transvaginal ultrasound (TVU), absence of adnexal pathology on preoperative ultrasound.

Exclusion criteria were the presence of subserosal, submucosal, or intraligamentous myomas (Leyomioma included in the study sec. FIGO Classification: Type 0, 1, 2, 7 and 8), previous laparotomic pelvic surgery, coagulation defects or concurrent anticoagulant therapy, liver disease, previous or present gynecologic neoplasms or psychiatric disease, body mass index (BMI) greater than

40, ongoing or recent history of pelvic inflammatory disease, and menopausal status. The patients were continuously enrolled when admitted to perform the surgical procedure. We divided the enrolled patients into two groups: group A patients who underwent laparotomic myomectomy with the HEMOPATCH® application and group B patients who underwent laparotomic myomectomy without the HEMOPATCH® application. The working group started by enrolling the first patient in group A and treating her with HEMOPATCH®, subsequently, the subsequent patient enrolled in group B were treated by conventional method (spray electrocoagulation, and, if necessary, a hemostatic suture with poliglecaprone 25) and the following enrolled patients are treated with the different technique compared to the last enrolled patient (alternating them eg: HEMOPATCH® and conventional method in a 1: 1 ratio) until the study period, reaching 23 patients per group. The preoperative evaluation included a complete history, physical and gynecologic examination, laboratory evaluation, electrocardiogram, chest radiograph, and pelvic US. The indication for surgery was symptomatic myoma (pelvic pain or menorrhagia) in all patients. Menorrhagia (heavy menstrual bleeding) was defined as bleeding lasting more than 7 days or the loss of more than 80 ml of heavy blood flow during the menstrual cycle. Pelvic pain was defined as symptoms of pelvic pressure, lower back pain, or both with and without increased urinary frequency, subjectively reported by patients, causing dysfunction in daily life. Women were advised of the risk of a hysterectomy if there was uncontrollable bleeding. Before surgery, patients were subjected to bowel preparation with laxatives, deep venous thrombosis prophylaxis with low molecular weight heparin (2 h before operation and postoperatively until complete mobilization). Short-term antibiotic prophylaxis was performed 2 h before surgery (cefazolin 2 g). No gonadotropin-releasing hormone analogs were administered prior to surgery. The surgical technique was performed under general anesthesia. The procedures were performed using standardized methods and the laparotomic intervention was started through one Pfannenstiel incision. In both groups, after myoma extraction, a continuous double-layer hysterorrhaphy using coated polyglactin 910 and a third layer with poliglecaprone 25 was performed. If extensive bleeding was seen in the incision, single stitches of poliglecaprone 25 were placed to achieve hemostasis in both groups. If only oozing bleeding was observed, HEMOPATCH® sealant was applied in group A according to the manufacturer's indications (applied dry on the uterine suture with a colored surface facing outwards and an unmarked surface in contact with the uterine wall (Fig. 1). A homogeneous pressure was applied using a dry gauze and the entire area was covered by sealant for two minutes, which favored
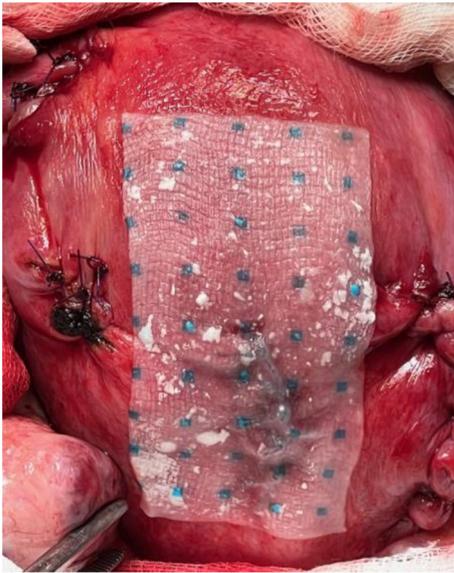
Fig. 1 HEMOPATCH on the surface of uterine wall

Fig. 2 Flow diagram

study of Ayachi, A. et al. [11]. The statistical value was established at $p < 0.05$.

Results

82 patients affected by symptomatic uterine myomas were considered eligible and evaluated to be included in the study. 36 patients were excluded from the study: 15 for the presence of myoma > 8 cm, 8 for a positive history of abdominal surgery, 10 for the presence of more than 5 myomas, and 3 for BMI > 40. 46 patients met the inclusion criteria, of which 23 women were enrolled in the study group (group A) and 23 with the control group (group B). The trial flow diagram is shown in Fig. 2. The characteristics of the patients are reported in Table 1.

HEMOPATCH® was applied to all 23 patients in group A in the terminal phase of hemostasis after myometrial hysterorrhaphy. In group B, in all patients, hemostasis after myometrial hysterorrhaphy with conventional methods (spray electrocoagulation and if necessary, a hemostatic suture with poliglecaprone 25).

The average operative time was 79 min (standard deviation (SD) 26.7; confidence interval (CI) 95%, 67.4–90.6) and 93 min (SD 29.3; 95% CI 80.1–105.4), respectively, for groups A and B ($p > 0.05$). In particular, the mean time necessary to achieve complete hemostasis was 155.4 s (SD 37.4; 95% CI 139.3–171.6) in group A and 228.3 (SD 76.2; 95% CI 195.3–261.2) in control B ($p < 0.05$).(Table 2). The mean blood loss was 93.6 ml (SD 71.3; 95% CI 62.7–124.4) and 121.3 ml (SD 77.2; 95% CI 87.9–154.7), respectively, in groups A and B ($p > 0.05$). During these procedures, there were no uncontrollable hemorrhages that required a hysterectomy.

No patients required blood transfusion, or no complication occurred during surgery. (Table 2).

adequate adherence to the uterine wall). If only bleeding was seen in group B, we used the conventional method (spray electrocoagulation, and, if necessary, a hemostatic suture with poliglecaprone 25). Operative times were collected during surgery, including time to achieve complete hemostasis, intraoperative and postoperative complications, and length of hospital stay. Intraoperative blood loss was calculated by counting in the blood aspirated from the operating field in suction containers using the following formula: estimated blood loss (mL) = the volume of waste irrigation fluid (mL) minus the volume of normal saline used for irrigation (mL) and by weighing the surgical material contaminated with blood subtracting its dry weights. On the second and third postoperative days, we performed the PCR assay on all enrolled patients, with the aim of evaluating the peritoneal inflammatory status and the consequent risk of developing postoperative adhesions. Postoperative fever was defined as a temperature increase greater than 38 °C on two occasions at least 6 h apart, within 24 h, starting 24 h after surgery. At the time of discharge, pelvic TVU was performed in the absence of symptoms. Follow-up examinations were performed, in the absence of symptoms, at 1 and 12 months, including physical and gynecological examination and TVU. The ultrasound examinations were performed with a high-frequency transvaginal probe, by an adequately trained sonographer. During the ultrasound, the pelvic examination, performed at discharge, was assessed for the presence of a hematoma. In pelvic ultrasound evaluation, performed at 1-month and 12-month follow-up, indirect signs of pelvic adhesions were evaluated, with negative sliding sign by pressure with the transvaginal probe considering the
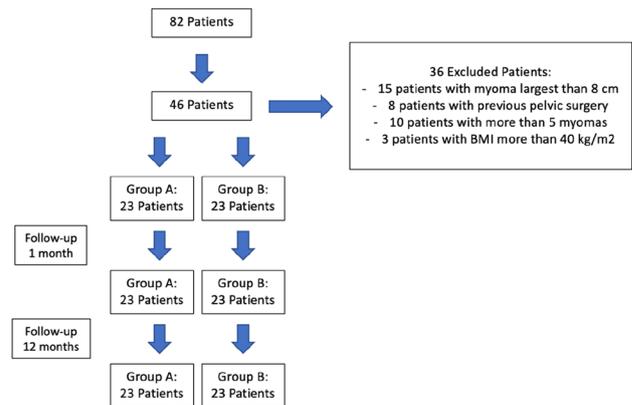
Table 1 Patients, indication to surgery, and preoperative myoma characteristics

	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 (39%)	10 (44%)	–
Pelvic pain	7 (30%)	9 (39%)	–
Fertility	2 (9%)	1 (4%)	–
Pelvic pressure	4 (1%)	3 (13%)	–
Frequent urination	1 (4%)	0 (0%)	–
Characteristic of myomas[b] (FIGO class.)			
Intramural alone (Type 3–4)	11	13	–
Intramural/subserosal alone (Type 5–6)	4	2	–
Hybrid alone (Type 2–5)	2	4	–
Combination of myoma type	6	4	–
Myoma size, cm (mean ± SD)	4.6 ± 0.7 (95% CI 4.2–5.0)	4.8 ± 0.7 (95% CI 4.4–5.2)	ns

ns Not significant

[a]Some patients have more than 1 indication

[b]At preoperative transvaginal pelvic ultrasonography

Table 2 Intraoperative data

	Group A	Group B	p value
Operative time, minutes (mean ± SD)	79 ± 26.7	93 ± 29.3	ns
Hemostasis time, seconds (mean ± SD)	155.4 ± 37.4	228.3 ± 76.2	< 0.005
Intraoperative blood loss, ml (mean ± SD)	93.6 ± 71.3	121.3 ± 77.2	ns
Intraoperative blood transfusions, n	0	0	–
Hysterectomy conversions, n	0	0	–

ns not significant, *SD* standard deviation

Table 3 Postoperative data

	Group A	Group B	p Value
Hemoglobin drop, (Hb) (g/dl) (mean ± SD)	3.14 ± 1.1 (IC 95% 2.7–3.6)	3.55 ± 1.1 (IC 2.7–3.6)	ns
Blood transfusions, n (%)	1 (4.5%)	1 (4.5%)	ns
PCR 2° day (mg/L)	42.9 ± 25.3	67 ± 34.9	< 0.05
PCR 3° day (mg/L)	55.4 ± 44.3	92.4 ± 53.7	< 0.05
Hospital stay (days) (mean ± SD)	3.6 ± 0.7 (IC 95% 3.2–3.9)	3.5 ± 0.9 (IC 95% 3.1–3.9)	ns
Follow-up (months)	12	12	–
Relapse	0	0	–
Fever	2 (8.7%)	3 (13%)	ns
Pelvic hematoma	2 (8.7%)	3 (13%)	ns
Wound infection	1 (4.3%)	0 (0%)	ns
Pelvic pain	2 (8.7%)	2 (8.7%)	ns
TVU-negative sliding sign 1-month	2 (4%)	6 (13%)	ns
TVU-negative sliding sign 12-months	3 (7%)	9 (20%)	ns

SD Standard Deviation, *ns* not significant, *TVU* transvaginal ultrasound

Postoperative characteristics and complications (Table 3), only one patient (4%) required a blood transfusion in group A and one in group B (p = ns). The average hospital stay was 3.6 days (SD 0.7, 95% IC 3.2–3.9) for group A and 3.5 days (SD, 0.9, 95% CI 3.1–3.9) for group B (p = ns). The mean drop in hemoglobin was 3.14 g/dl (SD 1.1, 95% CI 2.7–3.6) and 3.55 g / dl (SD 1.4; 95% CI 2.9–4.2) in groups A and B, respectively (p > 0.05). The mean dose of CRP on the second postoperative day was 42.9 mg / L (SD, 25.3) and 67 mg / L (SD 34.9), respectively, in groups A and B (p < 0.05). The mean CRP dose on the third postoperative day was 55.4 mg/L (SD, 44.3) and 92.4 mg/L (SD 53.7) in groups A and B, respectively (p < 0.05). Two patients in group A and three in group B developed a postoperative fever. Two patients in group A and three in group B developed a pelvic hematoma, identified by the US during hospitalization. The patients were successfully treated with wide-spectrum antibiotic therapy.

The evaluation of the sliding sign using transvaginal ultrasound that was performed during the follow-up visit one month later reported a negative sliding sign 2 (4%) for group A and 6 (13%) for group B with a result not statistically significant (p = 0.24; 95% CI). Re-evaluation of the sliding sign using transvaginal ultrasound in the 12-month follow-up visit reported a negative sliding sign of 3 (7%) for group A and 9 (20%) in group B with a not statistically significant result (p = 0.09; 95% CI). All patients returned for a follow-up visit and, in the twelfth month, no patient had a recurrence of a myoma.

Discussion

Myomectomy is a surgical procedure for patients with bleeding or compressive symptoms and/or for patients with large and/or growing leiomyoma that want to preserve fertility [4]. The main intraoperative step for all surgeons during abdominal myomectomy is to perform correct uterine suture [12]. Because myomectomy can result in considerable blood loss, intraoperative bleeding control requires the sudden and appropriate use of various modes of primary hemostasis, such as tampons, electrocoagulation, clips, and double-layer manual sutures [13]. Even with these techniques, diffuse parenchymatous bleeding has been difficult to manage, and it remains one of the main reasons for hysterectomy conversion [8]. Recently, a Cochrane Library review analyzed non-mechanical techniques to reduce blood loss during abdominal myomectomy [13]. Eight randomized controlled trials (RCT) included the use of intramyometrial vasopressin, intramyometrial ornipressin, vaginal misoprostol, oxytocin, and chemical dissection with sodium-2-mercaptoethanesulfonate (mesna), intramyometrial and bupivacaine

plus epinephrine, although the evidence was limited by the paucity of RCT. A significant reduction in blood loss was observed with misoprostol (149.00 mL; 95% CI 229.24–68.76 ml), vasopressin and analogs (298.72 mL; 95% CI 593.1–4.34 ml) and bupivacaine plus epinephrine (68.6 mL; 95% CI 93.69–43.51 ml). Gonadotropin-releasing hormone agonists have been used to minimize blood loss by reducing uterine volume before surgery [3, 14]. In addition, a Cochrane Library review evaluated the role of pretreatment with GnRH agonists before myomectomy, including 20 RCTs, comparing GnRH agonists versus placebo or without pretreatment [15]. The result was that pretreatment with GnRH agonists before surgery increased hematocrit and hemoglobin levels, suggesting that their use before myomectomy is beneficial.

A novelty introduced in recent years concerns the use of topical hemostats to facilitate this phase during surgery.

HEMOPATCH® is a sealing hemostat patch that has been widely used in different surgical fields, such as neurosurgery as dural sealant in cranial and spinal procedures, in pancreatic surgery to prevent postoperative pancreatic fistula after distal pancreasectomy or in urology to support the surgeon in achieving local hemostasis during partial nephrectomy or in cardiac surgery [16–19]. Its application in gynecology has not been evaluated by prospective studies, so we cannot make direct comparisons, except for the use of other topical hemostats, such as Floseal® in ovarian cystectomy, Tisseel® and Floseal® in laparoscopic myomectomy, and retrospective studies on hysterectomy for benign pathology [20, 21]. HEMOPATCH® consists of a collagen matrix and a biocompatible dye. The collagen pad is derived from the bovine dermis and optimized to be soft, thin, pliable, and of high liquid absorption capacity. The active side of the collagen pad is coated with a layer of functionalized N-hydroxylSuccinimide PolyEthylene Glycol (NHS-PEG), which is a rapid protein-reactive monomer that seals the damaged surface and induces hemostasis binding to the -NH2 group of the tissue [22].

Ours is the first study to our knowledge, that involves the use of HEMOPATCH® in gynecology during myomectomy. Concerning the hemostatic effects of HEMOPATCH® data emerging from our study, they are consistent with those reported by Raga et al., who have conducted a prospective randomized trial to evaluate the efficacy of a gelatin-thrombin matrix hemostatic sealant (FloSeal®) during myomectomy [20]. They reported a significant reduction in intraoperative blood loss (80 mL ± 25.5 in the FloSeal® group versus 625 mL ± 120.5 in the control group; p < 0.005), 0% in the blood transfusion of the FloSeal® group blood transfusion (p < 0.001), reduction in postoperative blood loss (p < 0.005), and less postoperative hemoglobin decrease (p < 0.005), and hospital stay (p < 0.005) in the FloSeal® group.

Another case–control study conducted by Angioli et al. evaluated the use of a fibrin sealant Tisseel® in laparoscopic myomectomy and showed a statistically significant reduction in intraoperative blood loss in the Tisseel® group ($p < 0.05$) and a reduction in hemoglobin decrease ($p < 0.05$), which were significantly lower in the study group [21].

Furthermore, the formation of adhesions and the risk of rupture during delivery at the uterine suture site represent supplementary common complications of abdominal myomectomy. In this context, it is important to consider that inadequate hemostasis and the consequent uncontrolled deposition of fibrin are widely believed to contribute to adhesions [23, 24]. Therefore, achieving accurate hemostasis has always been an essential target of reproductive surgeons, to prevent adhesions that could impact the patient's fertility. Therefore, the reduction in intraoperative and postoperative bleeding due to the hemostatic effect of HEMOPATCH® related to the ability to rapidly and tightly adhere to persistent oozing bleeding, reducing the uncontrolled deposition of fibrin, could probably contribute to the reduction in postoperative adhesion rate by determining a physical barrier between the uterine incision and adjacent viscera [25]. We observed significantly lower PCR values on the 2nd and 3rd day postoperative for group A compared to group B suggesting a lower inflammatory peritoneal state probably correlated to the barrier effect of the patch on the suture. In the literature, HEMOPATCH® has shown its efficacity in liver surgery in providing hemostasis and preventing the formation of adhesions between the adjacent cut surfaces [26]. HEMOPATCH® does not cause adhesions unlike other hemostatic devices based on regenerating oxidative cellulose, which acts with a reduction in pH and the consequent formation of adhesions due to the inflammatory process of acid pH [27, 28]. Regarding adhesions in our follow-up patients, we did not have symptoms directly related to adhesions, such as chronic pelvic pain, without a statistically significant difference between the two groups. However, the group using HEMOPATCH® reported fewer indirect signs of postoperative adhesions (negative sliding sign) on the TVU in both follow-up at 1 month and 12 months, indicating that it may offer a real barrier effect in adhesion formation after laparotomic myomectomy. This result reached near statistical significance ($p = 0.09$), which probably would have been achieved with a larger patient sample. Regarding other complications that are reported in the literature with the use of the most common hemostatic means, HEMOPATCH® has a good safety profile on the most common complications of topical hemostatic agents: pelvic abscess and small bowel obstruction.

In terms of pelvic abscesses in gynecological procedures using hemostats, we have the largest retrospective cohort study available that examined 17.960 patients who underwent hysterectomy regardless of the surgical approach [29]. Harris et al., in this study, did not show an association between the use of topical hemostatic agents and the incidence of pelvic abscess, but only when stratified by surgical approach, topical hemostatic agents were associated with an increased pelvic abscess in the robotic hysterectomy group [29]. Additionally, Anderson et al. found an increased risk of pelvic abscess when using topical hemostatic agents such as gelatin-thrombin matrix, as well as with oxidized regenerated cellulose [30].

The second most common complication that uses topical hemostatic agents is small bowel obstruction [29]. Unlike gelatin-thrombin matrices, HEMOPATCH® does not include this complication. When this complication occurred, it was found that the intestine was directly in contact with gelatin-thrombin matrices, and intestinal biopsies revealed the presence of giant cells of a foreign body [29, 31].

Moreover, using HEMOPATCH® in our series, we avoided the extensive use of electrosurgery for the uterine wall and hemostasis, thus improving the resistance of sutures, reducing the risk of complications (hematomas, inflammatory abscesses, dehiscences, and adhesions). On the other hand, tissue necrosis could cause defective scarring and increase the risk of uterine rupture during subsequent pregnancy [32].

Finally, in terms of postoperative results, we did not observe statistically significant differences in mean operating time, blood transfusions, hospital stay, or percentage of recurrences and complications. Therefore, we have observed that HEMOPATCH® is a simple aid that can be applied in surgery to support the most common suture materials, without affecting the percentage of relapses and complications.

We have observed that HEMOPATCH® is an easy-to-use, harmless product that can be used in surgery as a valid support for the most common suture materials, without influencing recurrence and a very low complication rate.

Among the limiting factors of the study, we can certainly include that it is not a randomized trial that reports the experience of a single center and a low number of patients enrolled. A further weakness is the indirect evaluation of adhesions, which can only be performed indirectly through semeiology and ultrasound and not through a subsequent laparotomic and/or laparoscopic control, precisely due to its prospective design at 12 months of follow-up. The last critical point is that every study in surgery is based on the skill of the operator and as such the reproducibility of the results in centers different from ours could be different.

Conclusion

The use of HEMOPATCH® during laparotomic myomectomy may represent a valid alternative solution to obtain hemostasis and reduce intraoperative and postoperative

bleeding. Furthermore, it may help the surgeon obtain rapid healing of the damaged surfaces, reducing the use of electrocoagulation and surgical sutures on the uterine serosa to achieve optimal hemostasis. Additionally, we suggest a lower inflammatory peritoneal state probably correlated with the barrier effect of the HEMOPATCH® on the suture. Other randomized trials are needed to confirm these preliminary data.

Declarations

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