

# Efficiency of TachoSil® to prevent postsurgical adhesion development on laparoscopic rat model

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**Abstract** The aim of this study was to evaluate the effectiveness of a fibrinogen and thrombin-coated hemostatic sponge (TachoSil®) in the prevention of postsurgical adhesions in a laparoscopic rat model and its histological effects on uterine and peritoneal parenchyma. Design was a prospective randomized blinded study. Setting was in International Laparoscopic Surgery Centre, Clermont-Ferrand, France. There were 100 sexually mature female Sprague–Dawley rats weighing 240 to 300 g and aged 6–8 weeks. A standardized severe surgical injury induced by scissors and 40-W bipolar coagulation in the rat uterine horn, corpus, and peritoneum was performed to induce

adhesion formation. After trauma, group 1 ( $n=50$ ) received no treatment and group 2 rats ( $n=50$ ) received TachoSil® applied on injured areas. Twelve weeks after the procedure, repeat laparoscopy was performed and adhesions were scored according to their extent and severity. A hysterectomy and a peritoneal biopsy in the injured area were achieved by laparotomy in order to investigate on a possible earlier effect of TachoSil® on the uterine and peritoneal parenchyma in 49 rats of each group. TachoSil® group adhesion scores showed a significant decrease on the three injured areas: peritoneum (12.96 vs. 21.66), uterine horn (7.22 vs. 15.20), and uterine corpus (5.88 vs. 34.52). TachoSil® group also demonstrated a major decline of uterine fibrosis and inflammation. This study revealed that TachoSil®, an absorbable biomaterial, can reduce postoperative adhesions after laparoscopic surgery on a rat model. TachoSil® also prevents thermo-induced injuries on uterine parenchyma (less fibrosis and less inflammation).

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## Introduction

Postoperative surgical adhesions in abdominal and pelvic surgery can have a major impact on patient's subsequent health [1]. These continue to be a significant cause of female infertility, bowel obstruction, chronic pelvic pain, and difficulties at the time of reoperation [2]. Almost 90% of abdominal adhesions seem to be due to surgical antecedents. Despite the development of many surgical techniques and the use of several products to prevent or minimize the formation of adhesions following surgery, at

least, 50% of patients still develop substantial adhesions [3]. The aim of our study was to evaluate the ability of a hemostatic sponge on the reduction of peritoneal and uterine adhesions in a laparoscopic rat model. TachoSil®, a particularly promising hemostatic agent, is a bioabsorbable fibrinogen and thrombin-coated hemostatic sponge manufactured by Nycomed Laboratory (Copenhagen, Denmark). We hypothesized that under conditions of inadequate hemostasis, it may contribute to decrease adhesion development in a laparoscopic rat model. TachoSil® may also prevent thermo-induced injuries on peritoneum and uterine parenchyma.

## Materials and methods

The bioabsorbable TachoSil® sponge is an equine collagen sponge coated with human fibrinogen and human thrombin (5.5 mg and 2.0 IU per cm<sup>2</sup>, respectively). These two components of the coating dissolve and partly diffuse into the wound surface at contact with physiological fluids like blood or lymph. A fibrinogen–thrombin reaction follows mimicking the last phase of blood coagulation leading to the conversion of fibrinogen into fibrin monomers. This spontaneously polymerize to a fibrin stable clot holding the collagen tightly to the wound surface, preventing bleeding and sealing the tissue.

The experimental design was a randomized, blinded, controlled, parallel-group study. The animals were treated in accordance with recommendations from the National Institutes of Health Guidelines for the Use of Animals in Research and were approved by the University Animal Care and Use Committee. Sexually mature female Sprague–Dawley rats, aged 6–8 weeks and weighing 240–300 g, were housed for a minimum of 1 week before surgery. The animals were maintained under standard laboratory conditions (temperature 20–22°C, relative humidity 50–70%, 12:12 h light/dark ratio) and were fed a standard laboratory diet and had free access to food and water before and after the operative procedures. In the event of a rat dying before the second operative procedure, the rat was replaced for laparoscopy in order to maintain the same number of rats in each group. Before each procedure, all instruments were sterilized by rubbing with 70% isopropanol. On the day of the surgery, each rat was anesthetized with a single intraperitoneal injection of pentobarbital at 0.08 mg/g (Nembutal, Sanofi Santé Animale, Brussels, Belgium) and was branded (metallic clip on ear and color marking on tail). Rats were placed in dorsal recumbent position, abdominal operative surface was shaved (electric shaver), and disinfection of the abdominal operative surface was carried out with dermic polyvidone (Viatrix, Mérieux, France).

A 5-mm abdominal incision under the xiphoid process permitting the introduction of a 14-G Veress needle (Tyco Healthcare, Norwalk, CT, USA) was performed. After safety tests, abdominal pneumoperitoneum was obtained with CO<sub>2</sub> gas at a pressure of 5 mmHg and a flow rate of 0.5 L/min with an automated insufflator (Electronic CO<sub>2</sub>-Endoflator®, Karl Storz, Tuttlingen, Germany) using pure CO<sub>2</sub> gas at room temperature. As soon as insufflation was achieved, the needle was removed, and a 5.5-mm transparent trocar with insufflation port (Vectec, Vichy, France) was introduced through the same incision, permitting the insertion of a 4-mm 10° endoscope connected to a single-chip video camera (Karl Storz Digicam) and a xenon light source (Karl Storz, Tuttlingen, Germany). Pneumoperitoneum was maintained at 5 mmHg and the rat was immobilized in Trendelenburg position. A second incision of 3 mm was performed in the right hypochondriac region under laparoscopic guidance, allowing the introduction of a 5.5-mm operative trocar with transparent cannula (Vectec, Vichy, France) for the introduction of instruments (laparoscopic scissors, atraumatic forceps, and bipolar coagulation). Another 8-mm incision was realized in the left hypochondriac region in order to introduce a 10-mm operative trocar with reduction device for 5 mm instrument (Vectec, Vichy, France) for the placement of the sponge. All trocars were fixed to the abdominal wall by a 2/0 monofilament nylon nonabsorbable suture (Monosof® 2/0, Tyco Healthcare, USA).

Rats were randomly assigned to two groups: group 1 (control group: without treatment) and group 2 (injured areas covered by TachoSil®).

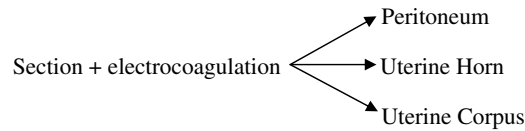
After complete inspection of the abdominopelvic cavity, visualization of the uterine horns required displacement of bowel with the grasping forceps. A standardized severe injury consisting in partial section of the uterine corpus, uterine horn (after randomization of the side), and denuding a 2-cm<sup>2</sup> area of the abdominal peritoneum sidewall (centered on a blood vessel) was performed with scissors. Then, an application of 40-W current for 2 s using bipolar forceps (Autocon 350®, Karl Storz) was carried out in order to coagulate the three operative sites in group 1 rats. In group 2 rats, after bipolar coagulation of the peritoneum and the uterine horn, a piece of TachoSil® (1×1.5 cm) was put into the injured areas. Thus, in this group, the uterine corpus was not electrocoagulated after section but benefited only from a piece of TachoSil® (Fig. 1).

Because CO<sub>2</sub> pneumoperitoneum is a cofactor of adhesion formation, it was maintained for a period of 30 min. In order to create a conventional laparoscopic surgery environment with 100% of carbon dioxide, a 26-G needle (20 mL/min) was inserted under laparoscopic guidance in the right iliac fosse (Becton Dickinson, Sandy, UT, USA). At the end of the procedure, the sutures around

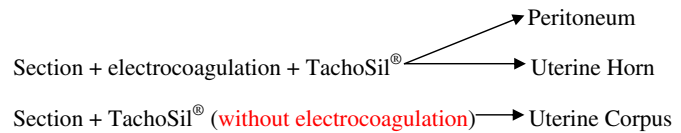
**Fig. 1** Operative proceeding steps

1) Laparoscopy

-Group 1: Control group (n=50):



-Group 2: TachoSil® group (n=50):



**12 weeks after**

2) Laparoscopic evaluation of adhesions (n=100) → Data documented on videotape

3) Laparotomy: Total hysterectomy → Histological analysis (n=99)

trocars were removed and CO<sub>2</sub> was allowed to escape spontaneously from the peritoneal cavity. The peritoneum was not sutured. The abdominal wall was nicked using undyed braided absorbable suture (Coated Vicryl® 3/0, Ethicon®, Johnson & Johnson). The rats were placed under a heating lamp for 2 h in order to avoid caloric loss resulting from anesthesia.

A second-look laparoscopy was performed through the same incisions 12 weeks after the initial surgery to evaluate the incidence of postoperative adhesions and their severity. The results were documented on video tape (only surgical sites were evaluated) and assessed by two surgeons unfamiliar with the initial operative site, to prevent evaluator bias. The postoperative adhesions were scored according to their extent and severity using qualitative and quantitative parameters according to modified Mage's scoring system [4] (Table 1). The recorded films were screened (the two evaluators used the same monitor) in

front of a scanned millimeter graph A4 paper (21 × 29.7 cm) in order to create a spatial resolution similar to a pixelization. We compared the size of the adhesion with one of the forceps grasp which represents a fixed data (evaluation of a percentage). In the event of disagreement over surgeon's scores, the higher score was used in calculations.

Medians and ranges of the adhesion scores were calculated for each group and operative site separately. For the comparison of groups, insofar as each rat has three operative sites (peritoneum, uterine horn, and uterine corpus), we compared them 2 to 2. The median values were obtained including the sites without adhesion. The assigned score when no adhesions were detected was 1 for each operative site.

The final procedure consisted in hysterectomy with bilateral salpingo-oophorectomy and in peritoneal biopsy in the injured area, achieved by a median laparotomy in

**Table 1** Quantitative and qualitative evaluation of postoperative adhesions (modified Mage score)

Adhesion	Area 1/3	Area 2/3	Area 3/3
Filmy	1	2	4
Vascular vessels present, easily separable	4	8	16
Vascular vessels present, requiring sharp dissection	16	32	64

order to investigate on a possible earlier effect of the fleece-bound sealing system on the uterine and peritoneal parenchyma in 49 rats of each group (after hematoxylin erythrosin saffron coloration; Fig. 3). The evaluated uterine and peritoneal histological criteria were semiquantitative for inflammation, fibrosis, necrosis, vascular congestion, hemosiderin deposit (absence, 0; low, 1–15%; moderate, 16–49%; severe, 50–100%), and qualitative for granuloma (presence or absence). The histological study was performed by an experienced pathologist (C. Darcha). Euthanasia with CO<sub>2</sub> inhalation closed the procedure.

Statistical analysis was carried out using the Stat View System® (SAS-Institute, Cary, NC, USA). The comparison of adhesion scores was performed using a nonparametric Kruskal–Wallis test. The histological data were compared using chi-squared test. A statistical significant was considered for  $p < 0.05$ .

## Results

One hundred nineteen animals were used for the experiment, 100 rats undergoing a total of 298 procedures (200 laparoscopic and 98 laparotomic). Nineteen rats died until postoperative day 9 and were excluded from the analysis: Two died during the anesthetic induction before randomization, one peroperatively in group 2 (hemorrhagic complication during the placement of the first trocar), and 16 in postoperative period (all cases occurred before postoperative day 9). The number of animals dying in each group was respectively seven (14%) and nine (18%). No death occurred over postoperative day 9. In the end, 50 rats in each group were kept for the study.

The weight variation showed a mean increase of 50.3 g in group 1 and 45.5 g in group 2 during the observation period.

TachoSil® group adhesion scores showed a statistically significant decrease—26.06 vs. 71.38 ( $p < 0.0001$ ). The adhesion scores are presented in Table 2. The results revealed statistical significant lower scores on the three injured areas:

- Peritoneum—12.96 vs. 21.66 ( $p = 0.026$ )
- Uterine horn—7.22 vs. 15.20 ( $p = 0.0003$ )
- Uterine corpus—5.88 vs. 34.52 ( $p < 0.0001$ )

The adhesion scores according to the site are presented in Table 3. We have also noted that the numbers of injured areas presenting vascular adhesions requiring

**Table 3** Adhesion scores according to the operative site

	Control group	TachoSil® group
Peritoneum ( $p = 0.026$ )	21.66	12.96
Uterine horn ( $p = 0.0003$ )	15.20	7.22
Uterine corpus ( $p < 0.0001$ )	34.52	5.88

sharp dissection was significantly increased in group 1 (Figs. 2 and 3).

Concerning the histological study, TachoSil® group demonstrates a major decline of uterine fibrosis and inflammation (respectively  $p = 0.0004$  and  $p = 0.0001$ ). More detailed in this group, we found a statistical significant reduction of uterine granuloma ( $p = 0.005$ ) and uterine hemosiderin deposit ( $p = 0.001$ ). On the other hand, there was a significant decrease of peritoneal granuloma in control group ( $p = 0.013$ ). However, there was no statistical significant difference affecting the other histological criteria between the two groups (peritoneal fibrosis:  $p = 1$ , peritoneal inflammation:  $p = 1$ , uterine necrosis:  $p = 1$ , peritoneal necrosis:  $p = 0.14$ , peritoneal hemosiderin deposit:  $p = 0.64$ , peritoneal vascular congestion:  $p = 0.68$ , and uterine vascular congestion:  $p = 0.17$ ).

## Discussion

The aim of this study was to evaluate the efficacy of TachoSil® to prevent any adhesion formation when severe peritoneal wounds are induced by scissors and bipolar coagulation during laparoscopy in a rat model and to analyze the impact of the fleece-bound system on uterine and peritoneal parenchyma. The choice of laparoscopic procedures was decided regarding to minimally invasive intraperitoneal manipulations and the quality of images obtained by the endoscope (“magnifying effect”) that allows a more accurate evaluation of the adhesions.

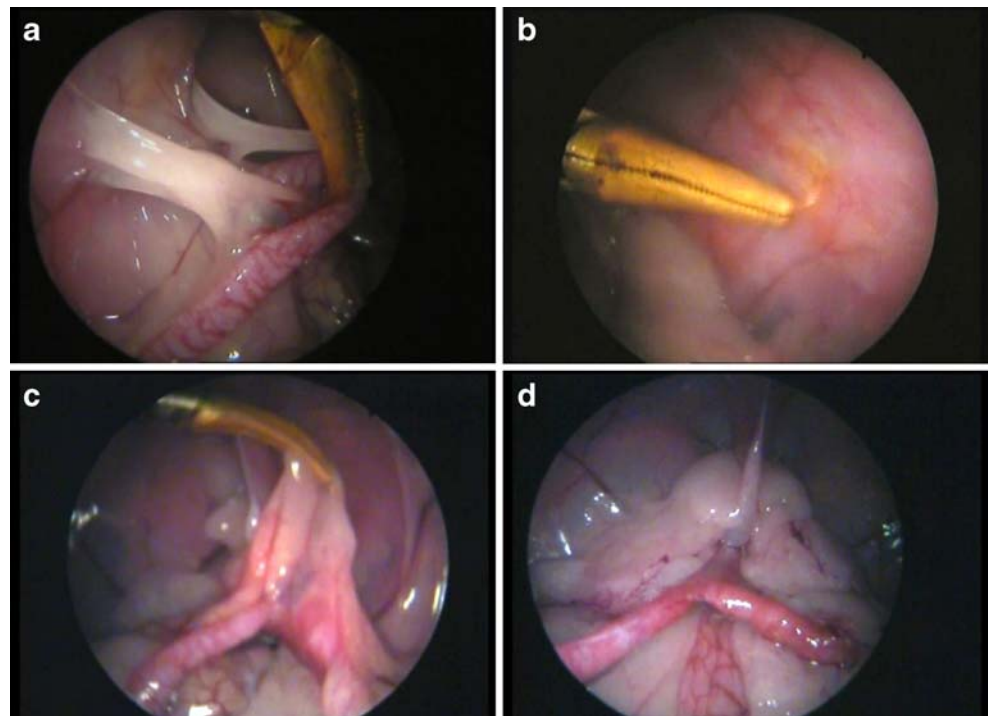
Bipolar coagulation is commonly used in clinical surgical practice in order to perform hemostasis and ablation of peritoneal lesions. The intensity of the current we used (40 W) in order to cause severe peritoneal injury corresponded to the power frequently used in clinical practice for the hemostasis. Roman et al. obtained adhesions to this level in all cases in a rat laparoscopic model [3]. Adhesiogenesis begins with the development of a fibrin matrix occurring for example during coagulation in suppressed fibrinolysis environment [5, 6]. The use of the

**Table 2** Adhesion scores

	Control group	TachoSil® group
Adherence scores (overall scores; $p = 0.0035$ )	71.38 ( $p < 0.0001$ )	26.06 ( $p < 0.0001$ )



**Fig. 2** Postoperative laparoscopic views. **a** Parieto-uterine adhesion (uterine horn). **b** No adhesion. Note the peritoneal yellowish scar without adhesion replacing the injured area. **c** Severe adhesions of the uterine corpus. **d** Adhesion-free uterus



TachoSil combipatch in postoperative adhesion prevention could appear possible in this context. Forestier et al. observed that in a rabbit model, peritoneal burn damages decreased with the use of bipolar scissors comparatively to monopolar coagulation [7]. Mecke et al. demonstrated in a rat model that intra-abdominal adhesions were lower than in rats undergoing monopolar or CO<sub>2</sub> laser coagulation [8]. Laparoscopy is considered source of less adhesion than laparotomy, in agreement with several studies [9–13]. However, Elkelani et al. [14] confirmed that adhesiogenesis mechanisms were different after laparoscopy and laparotomy. For that purpose, CO<sub>2</sub> pneumoperitoneum appears like a cofactor in adhesion formation [9, 15]. Thus, we maintained the pneumoperitoneum for 30 min at the end of each laparoscopic procedure.

Adhesions that develop after abdominopelvic surgery are responsible for significant clinical and economic problems. The use of microsurgical principles and adhesion reduction devices represents the strategic mainstay of adhesion prevention [9, 16]. Several agents have been evaluated in order to reduce them but with inconstant and unsatisfactory results: barrier materials Interceed® (Gynecare-Ethicon, Somerville, NJ, USA) and Seprafilm® (Genzyme, Cambridge, MA, USA), for example, interposed between adjacent surfaces to avoid direct contact, solutions (crystalloids, hyaluronan-based gels, dextran, icodextrin) in attempt to keep adjacent peritoneal surfaces away (hydroflotation), and drugs such as heparin, corticosteroids, anti-inflammatory agents, and statins. It appears clearly that the ideal anti-adhesion agent might present some qualities: It must be biocompatible,

biodegradable, noninflammatory, nonimmunogenic, and nonsubject to rapid degradation.

TachoSil® has been used successfully in several indications. It represents a supportive treatment in surgery for the improvement of hemostasis, to promote tissue sealing and for suture support in vascular surgery when standard techniques are insufficient. Anegg et al. [17] reported an application in pulmonary resection: The use of TachoSil® resulted in a reduction in air leakage compared with standard techniques (significant reduction in both the time to chest drain removal and the period of hospitalization). Frena and Martin [18] showed an effective application of the sponge in improvement of intraoperative biliostasis to



**Fig. 3** Laparotomic view of severe adhesions between colon, uterus horn, and anterior abdominal wall

minimize the risk of postoperative fistula development occurring after hepatic resection. Tagliabue et al. [19] used TachoSil® in patients suffering from severe clotting disturbances in order to perform successful splenectomy and nephrectomy. Some other uses of the coated patch have also been reported: hepatic surgery (liver resection, liver transplantation), urologic surgery (kidney tumor resection, repair of recurrent vesicovaginal fistula), cardiovascular surgery (reduction of postoperative pericardial effusions after aortic tube grafts, in addition to stitches to facilitate mechanical and biologic suture in aortic arch aneurysm repair), digestive surgery (gastrointestinal anastomoses), and neurosurgery (management of cerebrospinal fluid leak after surgical removal of pituitary adenomas) [20–30].

In our study, the animals were reoperated 12 weeks after the initial surgery, corresponding to the period necessary for the hemostatic patch to be completely resorbed, according to the conclusions of Getman et al. who also demonstrated a preventive effect of TachoSil® to prevent pleural adhesions in an experimental rat model [31].

The first aim of our experiment was to determine a possible efficiency of hemostatic fleece to prevent postoperative adhesions in a laparoscopic rat model. TachoSil® group adhesion scores show a statistically significant decrease on the peritoneum, the uterine horn, and the uterine corpus. The fleece-bound sealing system shows an ability to prevent postoperative adhesions in this laparoscopic rat model. More detailed, the adhesion scores were higher for the peritoneum than the uterine corpus and the uterine horn. The uterine corpus was not electrocoagulated but only cut and the effect of TachoSil® appears more beneficial in absence of coagulation, probably due to the preservation of the tissue vascular system.

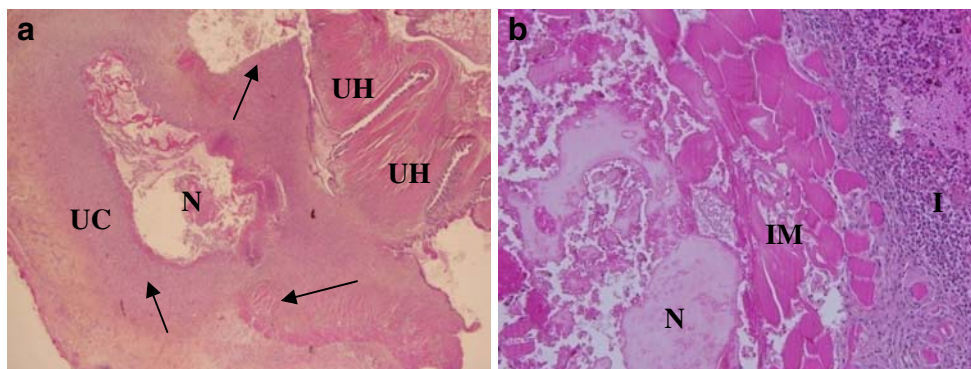
The second aim of our study was to evaluate a possible earlier effect of TachoSil® on uteroperitoneal parenchyma. Indeed, in clinical practice, the use of bipolar coagulation is very common to perform, for example, a myomectomy. Thus, it is responsible for thermo-induced injuries which can cause postoperative adhesions and parenchymal weakness with subsequent consequences. Agdi and Tulandi advocated a sparing use of electrocautery in surgical

management of uterine fibroids to prevent extensive myometrial injuries which can jeopardize myometrial healing and predispose to uterine dehiscence or rupture during pregnancy and labor [32]. In this study, TachoSil® was revealed as a tissue protector insofar as we found a statistically significant decrease of uterine fibrosis and inflammation. However, there was no difference concerning the peritoneal fibrosis and inflammation in groups 1 and 2 because of the use of bipolar coagulation on it (Fig. 4). There was a significant decrease of peritoneal granuloma in control group ( $p=0.013$ ) for the same reason. We conclude that the use of TachoSil® in place of bipolar coagulation, especially when the surgical procedure appears particularly hemorrhagic, can offer two advantages: an efficient non-deleterious hemostasis and a potential prevention of adhesion formation by means of shunning the bipolar coagulation. Fedele et al. suggested that bipolar electrocoagulation of the ovarian parenchyma after laparoscopic stripping of an endometriotic ovarian cyst adversely affects ovarian function [33]. Li et al. recently investigated, in a clinical study, the impact of electrocoagulation on ovarian reserve after laparoscopic excision of ovarian cysts. Thus, electrocoagulation is associated with a statistically significant reduction in follicular reserve, which seems partly a consequence of the damage to the ovarian vascular system [34]. TachoSil® might be used in place of it in order to permit a follicular and fertility saving.

## Conclusion

These results confirm that TachoSil® has anti-adhesion effects on a laparoscopic rat model. TachoSil® also prevents thermo-induced injuries on uterine parenchyma (less fibrosis and less inflammation). The next step will be to corroborate these data on clinical investigations before extrapolation. Moreover, it seems interesting to study the impact of the fleece-bound sealing system on the ovarian parenchyma in order to show the preventive effect of thermo-induced injuries resulting from electrocoagulation used during ovarian cystectomy.

**Fig. 4** Histological views.  
**a** Uterus  $\times 20$ : severe inflammation and necrosis resulting of use of electrocoagulation. UH uterine horn, UC uterine corpus, N necrosis, arrows inflammation.  
**b** Peritoneum  $\times 200$ : severe injuries. N necrosis, I inflammation, IM injured myocytes



**Conflict of interest** There is no actual or potential conflict of interest in relation to this article.

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