



Contents lists available at ScienceDirect

## Taiwanese Journal of Obstetrics &amp; Gynecology

journal homepage: [www.tjog-online.com](http://www.tjog-online.com)

## Original Article

## The use of fibrin sealant (Tisseel) in laparoscopic excision of ovarian endometrioma



Yu-Cheng Liu, Yi-Chieh Li, Hsin-Hong Kuo, Chin-Jung Wang\*, Kai-Yun Wu

Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital at Linkou and Chang Gung University College of Medicine, Tao-Yuan, Taiwan

## ARTICLE INFO

## Article history:

Accepted 5 May 2016

## Keywords:

Endometrioma  
Fibrin sealant  
Laparoscopy  
Ovary  
Tisseel

## ABSTRACT

**Objective:** To evaluate the use of Tisseel, a 2-component fibrin sealant agent for the control of minor bleeding and repair of the ovarian defect at the end of laparoscopic cystectomy (LC) of endometriomas. **Materials and methods:** From January 2011 to December 2015, an observational study of all patients who underwent LC of endometrioma using Tisseel (group A) was performed. The demographic and operative data, including age, body mass index, operative indications, operative time, estimated blood loss, complications, and postoperative hospital stay duration were recorded. A contemporary cohort of patients, who underwent LC of endometrioma without Tisseel (group B) was also retrospectively compared.

**Results:** A total of 274 patients were recruited in this study (53 LCs with Tisseel and 221 LCs without Tisseel, respectively). Complete hemostasis was achieved in all patients. The mean size of main mass was significantly larger in the group A than in the group B ( $7.8 \pm 2.4$  cm vs.  $7.0 \pm 2.3$  cm,  $p = 0.033$ ) but the mean operating time, operative blood loss, febrile morbidity, and length of hospitalization were not significantly different between the two groups.

**Conclusion:** This preliminary series demonstrated the use of Tisseel in LC of endometriomas without any bipolar coagulation and/or suturing of ovarian tissue is clinically safe and feasible.

© 2017 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Conservative management procedures for ovarian endometrioma often include aspiration, fenestration, ablation, cystectomy, and ethanol sclerotherapy [1–3]. The excision of the entire cyst, with laparoscopy, is the most widely accepted approach for ovarian endometrioma management. Although the removal of the endometriotic tissues can improve fertility and reduce pain, studies have also revealed that the laparoscopic stripping procedure can also have other negative side effects [4,5]. The two major side effects of laparoscopic cystectomy are follicular depletion and thermal damage, which were results of cystic wall stripping and electro-surgical coagulation during hemostasis, respectively [5,6]. The careful attention to the surgical principle of not damaging the normal ovarian cortex and vessels (particularly at the hilum) can diminish the aforementioned hazards. However, the precise surgical procedures require skilled and experienced surgeons with ample training [7].

A variety of adhesive substances, such as cyanoacrylate glues, fibrin glue, and thrombin, can be applied during surgery or endoscopy for enhance hemostasis, suture support, and wound healing [8,9]. Fibrin sealant Tisseel (Baxter Healthcare Corporation, Deerfield, IL) is a product that consists of blood coagulation factors fibrinogen, factor XIII, thrombin, aprotinin (antifibrinolytic agent), and calcium chloride. It has been utilized in applications such as gastrointestinal, ophthalmic, urologic, gynecologic, ear, nose and throat surgery, thoracic and vascular procedures, and skin grafts [8–11]. Fibrin sealant can also support vascularization and fibroblast migration to achieve re-epithelialization, and thus augments wound healing [12].

With the beneficial effects reported in literature, the aim of our study is to present our institution's initial experience of using Tisseel in selected patients with laparoscopic cystectomy for ovarian endometriomas (LCOE) and compare the surgical outcomes of these patients with other LCOE patients who underwent bipolar electrocautery and suture.

## Materials and methods

This study included 53 women (age range 21–42 years, median 31 years) with symptomatic ovarian endometrioma who

\* Corresponding author. Department of Obstetrics and Gynecology, Division of Gynecologic Endoscopy, Chang Gung Memorial Hospital at Linkou and Chang Gung University College of Medicine, 5, Fu-Hsin Street, Kwei-Shan, Tao-Yuan, Taiwan.  
E-mail address: [wang2260@gmail.com](mailto:wang2260@gmail.com) (C.-J. Wang).

underwent laparoscopic cystectomy and hemostasis with the aid of Tisseel performed by the authors (C.J. Wang) at Chang Gung Memorial Hospital from January 2011 to December 2015. The indications for surgery in these patients included pelvic pain and infertility. The selection criteria were women between the age of 21–45 years, who had dominant cystic sizes of equal or greater than 3 cm. Patients with suspected ovarian malignancy were excluded. Written informed consent was obtained from all subjects. All of the patients had bowel preparation in the morning of their surgeries. Intravenous cephalosporin prophylaxis was given before the procedure.

The Tisseel cohort was compared, retrospectively, to a contemporary cohort of patients who have underwent LCOE with bipolar electrocautery and suture without the aid of Tisseel. The study endpoints included median operative time, estimated blood loss (EBL), complications, and postoperative hospital stay duration.

The Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) was used to perform all statistical analyses. Descriptive statistics (mean  $\pm$  standard deviation) were used to summarize the patient's demographics and operation results. Continuous variables were compared with Student's *t*-test and categorical values with Pearson  $\chi^2$  analysis and Fisher's exact test. All probability values were two-sided. Significance level was accepted at probability below 5%. The study was approved by the Institutional Review Board of Chang Gung Memorial Hospital.

#### Operative procedures

All operations were performed with general endotracheal anesthesia in the dorsolithotomy Trendelenburg position. Both of the patient's legs were protected by elastic bandages, and a Foley catheter was inserted for constant urinary drainage. The LCOE was performed in accordance with the technique described by Yu et al. [7]. The following is a brief description of the procedure. Laparoscopic examination of the pelvis and lower abdomen was performed to determine the accessibility of the surgical field. Three or four trocars were used according to the complexity of the patient's pelvis. Disposable laparoscopic grasper, scissors, and suction-irrigator were used to perform various procedures such as holding, cutting, exploring, and dissecting. A sharp cortical incision was made with unipolar scissors and a cleavage plane was identified. The capsule of the endometrioma was then enucleated and stripped from normal ovarian tissue. At the end of the laparoscopic stripping procedure, the healthy ovarian tissue was carefully examined and was rinsed by saline to identify the bleeding areas. In the electrocautery and suture group, larger bleeders were coagulated using bipolar forceps with an electrosurgical bipolar unit (Elmed, Addison, IL). Complete hemostasis and approximation of ovarian defect were achieved using a 3–0 monofilament poligle-caprone 25 suture (Monocryl; Ethicon Inc., Somerville, NJ, USA) with a large curved needle following the principles of laparotomy. In the Tisseel group, Tisseel was applied on the inner ovarian surface defects with a Duploject Spray Set to achieve a uniform coating over the entire ovarian inner surface (Fig. 1). Thereafter, the edges of the ovarian defect were approximated with atraumatic forceps for 3–5 min. When complete hemostasis and approximation of ovarian defect were achieved, the peritoneal cavity was irrigated and lavaged until the purging fluid was clear (Fig. 2). The specimens were then removed from the abdomen using a disposable endobag for the purpose of avoiding contaminating the abdominal wall. All port sites were sutured with 3–0 polyglycolic acid suture at the level of the fascia to prevent herniation. The skin was approximated by sterile adhesive tape.

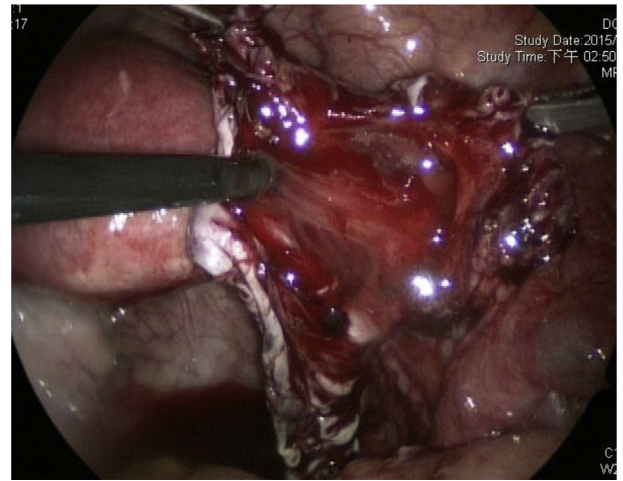


Fig. 1. Tisseel is applied on the inner ovarian surface defects with a Duploject Spray Set.



Fig. 2. Complete hemostasis and approximation of ovarian defect are achieved.

#### Results

In the study population ( $n = 53$ ), ten ovarian endometrioma were located on the right side, 21 on the left, and 22 on both sides. The mean diameter of the main ovarian mass was  $7.8 \pm 2.4$  cm, with range of 3–13.5 cm. The patient characteristics are summarized in Table 1. Mean operating time and EBL were  $100.7 \pm 47.5$  min (range: 40–260 min) and  $85.2 \pm 115.2$  mL (range: 5–550 mL), respectively. Post-operative hospital stay was  $1.9 \pm 0.5$  days (range: 1–3 days). No major complications including ureter injuries, bladder injury, or bowel injury occurred, and no patient required conversion to laparotomy. Histological examination of the resected tissue showed endometriotic tissue for all patients. One specimen was shown with atypical change, however, no malignant change was observed.

A cohort of patients who have underwent LCOE using bipolar electrocautery and suture during the same period was identified. The baseline demographic and operative data for these patients were extracted. The mean age of the cohort was  $34.0 \pm 6.0$  years (range: 18–45 years). The mean BMI was  $21.3 \pm 3.1$  kg/m<sup>2</sup> (range: 16.0–34.8 kg/m<sup>2</sup>). The mean operative time and EBL was  $91.0 \pm 42.8$  min (range: 25–292 min) and  $90.0 \pm 123.3$  mL (range:

**Table 1**

Baseline characteristics of enrolled patients who underwent laparoscopic cystectomy with (group A) and without Tisseel (group B).

	Group A (n = 53)	Group B (n = 221)	<i>p</i>
Patients			
Age (years)	32.1 ± 5.5 (21–42)	34.0 ± 6.0 (18–45)	0.034
Body mass index (kg/m <sup>2</sup> )	21.5 ± 3.4 (16.4–29.8)	21.3 ± 3.1 (16.0–34.8)	0.732
Nulliparous	40 (75.5)	139 (62.9)	0.084
Characteristic of masses <sup>a</sup>			
Right side	10 (18.9)	49 (22.2)	0.599
Left side	21 (39.6)	70 (31.7)	0.270
Bilateral sides	22 (41.5)	92 (41.6)	0.987
Main mass diameter (cm)	7.8 ± 2.4 (3.0–13.5)	7.0 ± 2.3 (3–15)	0.033
CA125 before operation (U/mL)	72.2 ± 57.6 (10.6–338.7)	81.2 ± 81.4 (10.0–648.9)	0.445
rASRM score	69.9 ± 30.3 (24–134)	76.4 ± 33.2 (16–150)	0.194
Indication to surgery <sup>b</sup>			
Pelvic pain	42 (79.2)	187 (84.6)	0.343
Infertility	14 (26.4)	52 (23.5)	0.659

CA125 = cancer antigen; rASRM = revised classification of the American Society for Reproductive Medicine.

Values are given as mean ± standard deviation or number (%).

<sup>a</sup> Determined with preoperative transvaginal pelvic ultrasonography.<sup>b</sup> Some patients were present with multiple indications.

5–800 mL), respectively. The mean length of hospitalization was 2.0 ± 0.7 days (range: 1–7 days). No intraoperative or acute postoperative complications were noted.

Two patients in group A and 7 in group B required blood transfusion with packed red blood cells (2–4 units) because of heavy blood loss (>300 mL). Two (0.9%) patients developed a low-grade fever (<38.5°C) in group B. Both patients fully recovered after fluid challenge and antibiotic therapy with cefamezine 1 g every 6 h and gentamicin 60 mg every 8 h for 1 day. One patient in group A had postoperative urine retention and resolved after urinary catheterization for 1 day.

There were no significant difference, with respect to BMI, parity, EBL, cancer antigen 125 level before operation, and score of the revised classification of the American Society for Reproductive Medicine (rASRM) [13] (*p* > 0.05), that was observed when comparing the Tisseel cohort to their corresponding bipolar electrocautery and suture LCOE group (group B). Although the Tisseel cohort exhibited trends of less EBL and reduced length of hospitalization, the statistical analysis determined that there were no statistical significant differences. The complete data are listed in Table 2.

## Discussion

Removal of endometriotic tissues has been demonstrated to be an important procedure for the treatment of ovarian endometrioma [3]. Due to the many advantages over traditional abdominal methods, such as smaller incisions, reduced hospitalization duration, and faster recuperation, laparoscopic cystectomy for endometriomas has been now widely accepted.

The stripping technique of laparoscopic cystectomy, is to use grasping forceps to hold both sides of the cleavage plane, between mass wall and the normal ovarian parenchyma, and pull in opposite

directions to remove the ovarian endometriotic tissues. However, bleeding may occur during and after the procedure, especially in the region of ovarian hilum, and electrocautery is usually used to achieve hemostasis. In order to prevent potential thermal damage caused by electrocautery, hemostasis and reapproximation of the stroma and cortex with fine absorbable suture material are often recommended [14,15]. Although suturing can diminish the impact on ovarian reserve compared to desiccation [1,3,14–16], hemostasis and reconstruction of ovary by suture may still present concerns such as ischemic change and adhesion formation and reformation caused by the suture material after surgery. Therefore the ovarian defect left to heal by secondary intention is still the mainstay of the laparoscopic endometrioma surgery, unless the presence of persistent bleeding or poor apposition of ovarian tissue was observed [3,17].

Tisseel has been widely applied in a variety of surgical specialties for hemostasis, suture support, and the sealing or adhesion of tissue [8]. Owing to its hemostatic and sealing proprieties, Tisseel can provide bleeding control and approximation of ovarian defect simultaneously. Thus, the use of electrocoagulation and suture materials during LCOE can be reduced or even avoided.

Evidence from animal models (rats and rabbits) has revealed that after the use of fibrin-based materials can reduce postoperative adhesion formation [18]. Donnez and Nisolle reported the incidence of periovarian adhesions after laparoscopic cystectomy for ovarian endometrioma was significantly reduced when comparing patients who used fibrin glue and those without [19]. Takeuchi et al. reported a similar finding when comparing patients with laparoscopic removal of large ovarian endometrioma with fibrin glue approximation and patients who underwent laparoscopic resection with open ovarian capsule [20]. Studies that evaluated the adhesion-prevention effects of fibrin sealants, for patients that underwent laparoscopic myomectomy, also

**Table 2**

The Comparisons of outcome variables between patient cohorts that underwent laparoscopic cystectomy with Tisseel (group A) and without Tisseel (group B).

	Group A (n = 53)	Group B (n = 221)	<i>p</i>
Operating time (m)	100.7 ± 47.5 (40–260)	91.0 ± 42.8 (25–292)	0.148
Blood loss (ml)	85.2 ± 115.2 (5–550)	90.0 ± 123.3 (5–800)	0.797
Blood transfusion, n (%)	2 (3.8)	7 (3.2)	0.687
Complication, n (%)	1 (1.9)	2 (0.9)	0.477
Postop stay (days)	1.9 ± 0.5 (1–3)	2.0 ± 0.7 (1–7)	0.769

Values are given as mean ± standard deviation or number (%).



demonstrated that the use of fibrin sealant can decrease the formation of postoperative uterine adhesions [21,22]. However, an inconsistency was still observed in a rabbit model [23], and further trials are needed to confirm this inconsistency.

Recently, Angioli et al. report their experience of using a 2-component (collagen granules and thrombin) topical hemostatic agent, FloSeal (Baxter Healthcare Corporation, Deerfield, IL), to obtain hemostasis and preserve ovarian function during LCOE [24]. FloSeal possesses broader applications, from capillary oozing to arterial and spurting bleeding, and provides more effective hemostasis than Tisseel. However, Tisseel is also unique from FloSeal by the fact that it can provide tissue gluing as well as wound healing support. With respect to preventing periovarian adhesion formation, Tisseel might be more suitable than FloSeal for use in LCOE.

One of the limitations of our study is that it is a retrospective study, and we did not have any documentation of markers of ovarian reserve to compare the difference of ovarian damage in the 2 groups. In a prospective randomized study by Song et al. that compared ovarian reserve in hemostasis by hemostatic sealant versus by bipolar coagulation during laparoscopic ovarian cystectomy, the hemostatic sealant group exhibited lesser decline of post-operative serum anti-Müllerian hormone levels than the bipolar coagulation group [25]. However, Song's study used FloSeal and not Tisseel as bleeding control. The effect of Tisseel in similar applications will require further prospective investigations.

In conclusion, these preliminary results suggest that Tisseel can be used, instead of bipolar coagulation and suture, in the laparoscopic excision of ovarian endometrioma. Further in-depth, and more well-designed studies are needed to confirm the possible ovarian damage and adhesion formation caused by bipolar coagulation and suture, and the use of Tisseel for bleeding control and approximation of ovarian defect in patients undergoing laparoscopic stripping of endometrioma.

## Conflicts of interest

The authors have no conflicts of interest relevant to this article.

## Acknowledgments

This research was supported in part by grant CPRPG3E2111 (to Chin-Jung Wang) from the Chang Gung Memorial Hospital at Linkou, but this study was not sponsored by any surgical device company.

## References

- [1] Vercellini P, Vendola N, Bocciarelli L, Colombo A, Roggoni MT, Bolis G. Laparoscopic aspiration of ovarian endometriomas. Effect with postoperative gonadotropin releasing hormone agonist treatment. *J Reprod Med* 1992;37: 577–80.
- [2] Hsieh CL, Shiao CS, Lo LM, Hsieh TT, Chang MY. Effectiveness of ultrasound-guided aspiration and sclerotherapy with 95% ethanol for treatment of recurrent ovarian endometriomas. *Fertil Steril* 2009;91:2709–13.
- [3] Jadoul P, Kitajima M, Donnez O, Squifflet J, Donnez J. Surgical treatment of ovarian endometriomas: state of the art? *Fertil Steril* 2012;98:556–63.
- [4] Somigliana E, Ragni G, Benedetti F, Borroni R, Vegetti W, Crosignani PG. Does laparoscopic excision of endometriotic ovarian cysts significantly affect ovarian reserve? Insights from IVF cycles. *Hum Reprod* 2003;18:2450–3.
- [5] Busacca M, Vignali M. Endometrioma excision and ovarian reserve: a dangerous relation. *J Minim Invasive Gynecol* 2009;16:142–8.
- [6] Hachisuga T, Kawarabayashi T. Histopathological analysis of laparoscopically treated ovarian endometriotic cysts with special reference to loss of follicles. *Hum Reprod* 2002;17:432–5.
- [7] Yu HT, Huang HY, Soong YK, Lee CL, Chao A, Wang CJ. Laparoscopic ovarian cystectomy of endometriomas: surgeons' experience may affect ovarian reserve and live-born rate in infertile patients with in vitro fertilization-intracytoplasmic sperm injection. *Eur J Obstet Gynecol Reprod Biol* 2010;152:172–5.
- [8] Dunn CJ, Goa KL. Fibrin sealant: a review of its use in surgery and endoscopy. *Drugs* 1999;58:863–86.
- [9] Petersen B, Barkun A, Carpenter S, Chotiprasidhi P, Chuttani R, Silverman W, et al. Tissue adhesives and fibrin glues. *Gastrointest Endosc* 2004;60:327–33.
- [10] Angioli R, Plotti F, Ricciardi R, Terranova C, Zullo MA, Damiani P, et al. The use of novel hemostatic sealant (Tisseel) in laparoscopic myomectomy: a case-control study. *Surg Endosc* 2012;26:2046–53.
- [11] Kim K, Park SI, Kim BJ, Kim MH, Choi SC, Ryu SY, et al. Efficacy of fibrin sealant in reducing hemorrhage after a loop electrosurgical excision procedure. *Gynecol Obstet Invest* 2012;74:1–5.
- [12] Jeschke MG, Finnerty CC, Shahrokhi S, Branski LK, Dibildox M. Wound coverage technologies in burn care: novel techniques. *J Burn Care Res* 2013;34:612–20.
- [13] Revised American Society for Reproductive Medicine classification of endometriosis: 1996. *Fertil Steril* 1997;67:817–21.
- [14] Fedele L, Bianchi S, Zancanato G, Bergamini V, Berlanda N. Bipolar electrocoagulation versus suture of solitary ovary after laparoscopic excision of ovarian endometriomas. *J Am Assoc Gynecol Laparosc* 2004;11:344–7.
- [15] Coric M, Barisic D, Pavicic D, Karadza M, Banovic M. Electrocoagulation versus suture after laparoscopic stripping of ovarian endometriomas assessed by antral follicle count: preliminary results of randomized clinical trial. *Arch Gynecol Obstet* 2011;283:373–8.
- [16] Pellicano M, Bramante S, Guida M, Bifulco G, Di Spiezio Sardo A, Cirillo D, et al. Ovarian endometrioma: postoperative adhesions following bipolar coagulation and suture. *Fertil Steril* 2008;89:796–9.
- [17] Muzii L, Bianchi A, Croce C, Mancini N, Panici PB. Laparoscopic excision of ovarian cysts: is the stripping technique a tissue-sparing procedure? *Fertil Steril* 2002;77:609–14.
- [18] Clark RA. Fibrin sealant in wound repair: a systematic survey of the literature. *Expert Opin Invest Drugs* 2000;9:2371–92.
- [19] Donnez J, Nisolle M. Laparoscopic management of large ovarian endometrial cyst: use of fibrin sealant. *J Gynecol Surg* 1991;7:163–6.
- [20] Takeuchi H, Awaji M, Hashimoto M, Nakano Y, Mitsuhashi N, Kuwabara Y. Reduction of adhesions with fibrin glue after laparoscopic excision of large ovarian endometriomas. *J Am Assoc Gynecol Laparosc* 1996;3:575–9.
- [21] Takeuchi H, Kitade M, Kikuchi I, Shimanuki H, Kumakiri J, Kinoshita K. Adhesion-prevention effects of fibrin sealants after laparoscopic myomectomy as determined by second-look laparoscopy: a prospective, randomized, controlled study. *J Reprod Med* 2005;50:571–7.
- [22] Tsuji S, Takahashi K, Yomo H, Fujiwara M, Kita N, Takebayashi K, et al. Effectiveness of antiadhesion barriers in preventing adhesion after myomectomy in patients with uterine leiomyoma. *Eur J Obstet Gynecol Reprod Biol* 2005;123:244–8.
- [23] Peacock KE, Hurst BS, Marshburn PB, Matthews ML. Effects of fibrin sealant on single-layer uterine incision closure in the New Zealand white rabbit. *Fertil Steril* 2006;85(Suppl 1):1261–4.
- [24] Angioli R, Muzii L, Montero R, Damiani P, Bellati F, Plotti F, et al. Feasibility of the use of novel matrix hemostatic sealant (FloSeal) to achieve hemostasis during laparoscopic excision of endometrioma. *J Minim Invasive Gynecol* 2009;16:153–6.
- [25] Song T, Lee SH, Kim WY. Additional benefit of hemostatic sealant in preservation of ovarian reserve during laparoscopic ovarian cystectomy: a multicenter, randomized controlled trial. *Hum Reprod* 2014;29:1659–65.