Original Article

Gynecologic and Obstetric Investigation

Gynecol Obstet Invest 2015;80:21–25
DOI: 10.1159/000369391

Received: May 26, 2014
Accepted after revision: October 28, 2014
Published online: March 17, 2015

# A Pilot Study to Investigate the Efficacy of Fibrin Sealant (Tisseel®) in the Loop Electrosurgical Excision Procedure

Jin Hwi Kim Tae Chul Park Geum Ae Park Jae Yeon Song Yeon Hee Kim
Hee Joong Lee Sung Jong Lee Keun Ho Lee Soo Young Hur Jong Sup Park

Department of Obstetrics and Gynecology, School of Medicine, The Catholic University of Korea, Seoul, South Korea

**Key Words**
Loop electrosurgical excision procedure · Cervical intraepithelial neoplasia · Fibrin sealant

**Abstract**
***Aims:*** The objective of the current study was to evaluate the efficacy and feasibility of fibrin sealant (Tisseel®) in the loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia (CIN 2 or 3). ***Methods:*** We designed a single-blind, prospective, randomized study in 40 consecutive women undergoing LEEP for CIN 2 or 3 at our institute. Two milliliters of fibrin sealant (Tisseel) was applied to the uterine cervix of 20 women immediately after LEEP surgery (treatment group). We evaluated abdominal pain, vaginal bleeding, vaginal discharge and impairment in daily living after 1 week using visual analogue scale questionnaires and compared the results with those of 20 women who did not receive fibrin sealant (control group). ***Results:*** Among 40 women who returned for a follow-up 1 week after LEEP, 25 women (62.5%) reported at least one moderate to severe postprocedural symptom. The mean duration of moderate to severe vaginal bleeding and impairment in daily living during postoperative week 1 for the treatment group and the control group was 0.3 ± 0.80 versus 1.7 ± 2.36 days (p = 0.015) and 0.9 ± 1.37 versus 3.00 ± 2.62 days (p = 0.060), respectively. ***Conclusion:*** Intraoperative application of fibrin sealant (Tisseel) in LEEP can decrease postoperative vaginal bleeding and impairment in daily living.



## Introduction

Cervical cancer is still one of the most common gynecologic malignancies, especially in developing countries. As with other malignant diseases, prevention and early detection are very important in cervical cancer [1, 2]. Fortunately, a commercially available vaccine to prevent infection from the human papilloma virus and an effective screening system are available [1]. Using the screening test, we can find cervical intraepithelial neoplasia (CIN) 2+ lesions requiring treatment and, therefore, prevent cervical cancer effectively.

Treatment options for CIN can be divided into two main categories: procedures that ablate the abnormal tissue and procedures that excise the area of abnormality. Because ablative therapy does not produce a specimen for additional histologic evaluation, excisional therapy is preferred. The loop electrosurgical excision procedure


0378–7346/15/0801–0021$39.50/0

E-Mail karger@karger.com
www.karger.com/goi

Prof. Tae Chul Park, MD, PhD
Department of Obstetrics and Gynecology
School of Medicine, The Catholic University of Korea
222 Banpo-daero, Seocho-gu, Seoul (South Korea)
E-Mail amatchmad@gmail.com

(LEEP) has many advantages over other types of conization therapy that use cold knife or laser techniques [3–5]. It is an inexpensive, technically easy procedure, and healing can be achieved with minimal distortion and low complication rates as well as with good specimen quality [6].

Generally, LEEP is a safe procedure, but complications such as abdominal pain, abnormal vaginal discharge, postoperative bleeding and infection have been reported [3–6]. According to a recent report, the incidence of any of these symptoms after the procedure occurs in up to 52% of cases [7]. These symptoms make patients anxious and interfere in their daily activities.

Fibrin sealant, a two-component material consisting of concentrated fibrinogen and thrombin, is used in topical hemostats, sealants and adhesives. It is approved by the Food and Drug Administration for use in sealing, hemostasis and adhesion [8–10]. Tisseel® is commercially available in a convenient prefilled syringe and allows for efficient and versatile application on surgical wounds.

The objectives of this pilot study were: (1) to establish whether the fibrin sealant could decrease postoperative bleeding, discharge and pain; (2) to assess potential improvement in impairment in daily living, and (3) to assess treatment-associated complications such as hypersensitivity when using this sealant in LEEP surgery for CIN 2 or 3.

## Patients and Methods

*Study Population*

Inclusion criteria were as follows: 20–55 years of age; biopsy-confirmed CIN 2 or 3; not pregnant, and informed written consent provided by the patient. Informed consent documents included information about the technique, safety considerations and reported morbidity. Individuals with current uterine bleeding or with known hypersensitivity to aprotinin were excluded.

The sample size was estimated, assuming a hypothetical 40% higher overall complication rate in patients who had LEEP without the fibrin sealant (control group) compared with those who received the fibrin sealant (treatment group; 80% power; type I error probability, 0.05). Theoretically, 20 patients were required for each group. Between December 2012 and March 2013, a total of 40 patients presented to the Uijeongbu St. Mary's Hospital, Uijeongbu, South Korea, for LEEP and were included in this study. Between December 2012 and March 2013, 40 patients were recruited (20 in the treatment group and 20 in the control group) and were assigned to LEEP with or without fibrin sealant.

*Fibrin Sealant*

Tisseel (Baxter Healthcare Co., Westlake Village, Calif., USA) is a prefilled dual-chambered syringe. Upon mixing sealer protein (human) and thrombin (human), soluble fibrinogen is transformed into fibrin, forming a rubber-like mass which adheres to the wound surface to achieve hemostasis and sealing or gluing of tissues. Tisseel mimics the final coagulation cascade step as it has all the relevant components to form a clot [11].

*Study Design*

This was a single-blind, prospective, randomized study involving 40 consecutive women undergoing LEEP for biopsy-confirmed CIN 2 or 3 at our tertiary referral center. After obtaining informed consent, 2 ml of fibrin sealant (Tisseel) was applied to the uterine cervix of 20 women immediately after LEEP surgery (treatment group). Before application, hemostasis was done completely using an electrocautery device. Blood and other fluids were wiped from the surgical wound surface (fig. 1). In the control group, hemostasis was also performed completely, but no fibrin sealant (Tisseel) was used. Patients were blinded to the use of the fibrin sealant.

Each patient was instructed to remain abstinent until their 1- and 5-week follow-up visit at the hospital to avoid risks of increased complications. Moreover, patients were asked to rate abdominal pain, vaginal bleeding, vaginal discharge and impairment in daily living using visual analogue scale questionnaires daily for the first week after surgery (no: no symptom; mild: mild symptom but no disability; moderate: moderate symptom with moderate disability; severe: severe symptom with severe impairment in daily living). When patients returned to the outpatient clinic, we evaluated the wound healing process by inspection through vaginal dressing and collected the questionnaires.

Informed written consent was obtained from every patient before surgery, and the study was approved by the institutional review board of our hospital. The details of the study design and protocol are summarized in figure 2.

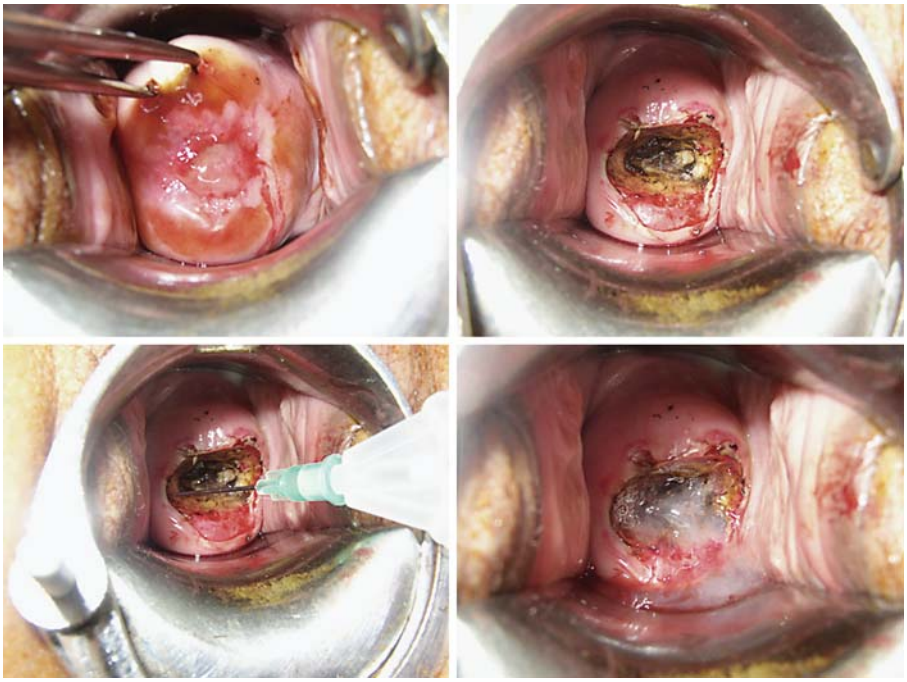
*Statistical Analysis*

Patients in the treatment and control groups were compared with respect to the mean duration of moderate to severe symptoms and the number of patients who complained of these symptoms during the first postoperative week using the Mann-Whitney U test. Logistic regression analysis was used to examine the relationship between variable clinical characteristics and moderate to severe vaginal bleeding. A p value $\leq 0.05$ was considered significant. Statistical analysis was performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, Ill., USA).

## Results

A total of 40 patients were considered eligible for this study. Twenty patients received 2 ml of fibrin sealant (Tisseel) after LEEP surgery (treatment group), and 20 received no fibrin sealant (control group). Table 1 lists the patients according to age, cone size and final cervical pathology. The patients varied in age from 27 to 55 years (mean 41.8 years). There was no statistically significant difference in age, cone size or final cervical pathology.

At the 1-week follow-up visit at the hospital, patient questionnaires were evaluated and significance was determined for the treatment group versus the control



Color version available online

**Fig. 1.** Two milliliters of fibrin sealant (Tisseel) was applied to the uterine cervix right after LEEP surgery (treatment group).

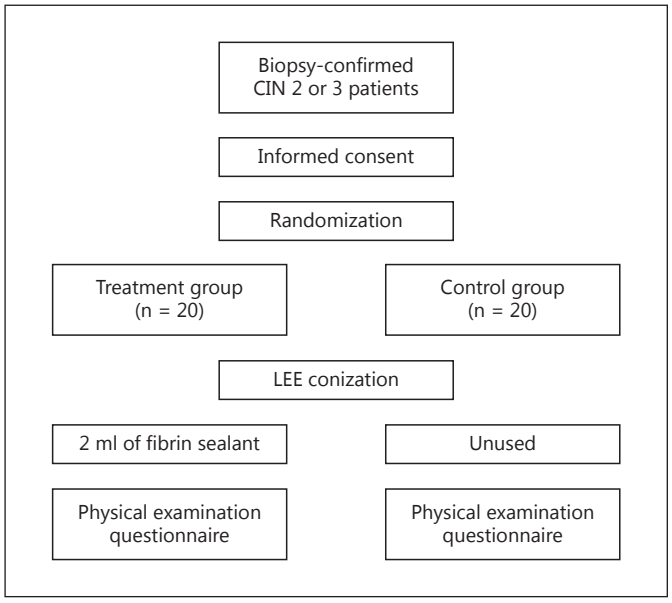



**Fig. 2.** Study design.

**Table 1.** Distribution of selected characteristics

| | Treatment group (n = 20) | Control group (n = 20) | p value |
|---|---|---|---|
| Age | 40.30±8.83 | 43.35±7.55 | 0.248 |
| ≤40 years | 10 (50.0) | 7 (35.0) | |
| >40 years | 10 (50.0) | 13 (65.0) | |
| Cone size | 4.71±1.65 | 4.62±1.98 | 0.872 |
| ≤4 $cm^2$ | 11 (55.0) | 11 (55.0) | |
| >4 $cm^2$ | 9 (45.0) | 9 (45.0) | |
| Pathology | | | |
| CIN 2 | 9 (45.0) | 9 (45.0) | 1.000 |
| CIN 3 | 11 (55.0) | 11 (55.0) | |

Data are means ± SD, or number of patients with percentages in parentheses.

group. The mean duration of time that patients of the treatment and the control group complained of moderate to severe vaginal bleeding and impairment in daily living during postoperative week 1 was 0.3 ± 0.80 versus 1.7 ± 2.36 days (p = 0.015) and 0.9 ± 1.37 versus 3.00 ± 2.62 days (p = 0.06), respectively (table 2). Three out of 20 (15.0%) patients in the treatment group complained of moderate to severe bleeding at least once during postoperative week 1. By contrast, 10 out of 20 (50.0%) patients in the control group complained of moderate to severe bleeding at least once. The difference between the groups was significant (p = 0.020) as determined by the Mann-Whitney U test (table 3). However, there was no significant difference in postoperative pain and vaginal discharge between the two

**Table 2.** Mean duration of time (days) that the patients complained about moderate to severe symptoms during postoperative week 1 in both groups

| | Treatment group (n = 20) | Control group (n = 20) | p value |
|---|---|---|---|
| Abdominal pain | 0.15±0.49 | 0.05±0.22 | 0.534 |
| Vaginal bleeding | 0.3±0.80 | 1.7±2.36 | 0.015 |
| Vaginal discharge | 1.0±1.48 | 1.9±2.51 | 0.752 |
| Disability in everyday life | 0.9±1.37 | 3.00±2.62 | 0.060 |

**Table 3.** Moderate to severe symptoms during postoperative week 1 in both groups

| | Treatment group (n = 20) | Control group (n = 20) | p value |
|---|---|---|---|
| Abdominal pain | 3 (15.0) | 1 (5.0) | 0.298 |
| Vaginal bleeding | 3 (15.0) | 10 (50.0) | 0.020 |
| Vaginal discharge | 8 (40.0) | 9 (45.0) | 0.752 |
| Disability in everyday life | 8 (40.0) | 14 (70) | 0.060 |

Data are number of patients with percentages in parentheses.

**Table 4.** Logistic regression analysis upon moderate to severe vaginal bleeding

| | OR | 95% CI | p value |
|---|---|---|---|
| Fibrin sealant treatment | 0.212 | 0.040–1.119 | 0.068 |
| Age >40 years | 3.348 | 0.655–17.101 | 0.146 |
| Cone size >4 $cm^2$ | 2.459 | 0.496–12.187 | 0.271 |
| Pathology CIN 3 | 0.453 | 0.092–2.235 | 0.331 |

OR = Odds ratio; CI = confidence interval.

groups (tables 2, 3). Although not statistically significant, impairment in daily living was more frequent in patients without fibrin sealant treatment.

Variables that correlated with postoperative vaginal bleeding were analyzed by logistic regression analysis (table 4). Fibrin sealant treatment reduced the risk of vaginal bleeding during postoperative week 1 (odds ratio 0.212; 95% confidence interval 0.040–1.119; $p < 0.068$).

There were no significant adverse effects related to the use of 2 ml of fibrin sealant immediately after LEEP surgery.

## Discussion

The aim of the present study was to investigate the efficacy of fibrin sealant (Tisseel) in LEEP. The results of the analysis showed that 2 ml of fibrin sealant applied to the uterine cervix immediately after LEEP surgery resulted in 0.3 ± 0.80 days of moderate to severe vaginal bleeding during postoperative week 1 in contrast to 1.7 ± 2.36 days in the control group (table 2). In addition, along with the decrease in postoperative vaginal bleeding, there was considerable improvement in the disability in everyday life (tables 2, 3). The results of the present study are consistent with those of earlier studies which reported that fibrin sealant has significant hemostatic effects in various surgical fields [12–16]. Furthermore, this study was the first prospective randomized study to demonstrate the potential hemostatic effects of fibrin sealant in LEEP for CIN 2 or 3.

Generally, LEEP is a very effective and safe procedure for cervical intraepithelial neoplasia (CIN 2 or 3). Bleeding shortly after surgery may be due to inadequate intraoperative hemostasis or a result of vasodilation after the vasoconstrictor solution wears off. Delayed hemorrhage may occur 1–2 weeks after surgery, which is related to dissolving sutures or erosion of a blood vessel during the healing process. The incidence of postoperative bleeding following LEEP is 0–8% [3–6, 17, 18]. However, most studies have focused on the incidence of serious bleeding requiring treatment such as suture or hospitalization. In fact, bleeding causing discomfort to the patient's daily life is more frequent. In a recent study, the incidence of any symptom, such as bleeding, vaginal discharge and abdominal pain after the procedure, is reported in up to 52% of cases [7].

Because LEEP is a relatively safe surgery, we focused on self-estimated symptoms that can lead to disability in everyday life and life-threatening complications. In our study, 14 patients (70%) in the control group complained of at least one symptom during the first postoperative week (table 4). Therefore, even if there are no life-threatening complications, we must make a ceaseless effort to find a method to improve the quality of life of patients. Because fibrin sealant has a role in topical hemostats, sealants and adhesives, we think that it is reasonable to apply it to the cervix after LEEP surgery. As a result, although the fibrin sealant could not reduce vaginal discharge and abdominal pain in this study, by reducing hemorrhage, the disability in everyday life of the patients was significantly improved.

Because our study was a pilot study, the small study population was a major limitation. In addition, this study

was conducted in a single-blind setting because we could not produce adequate placebo. We will conduct further studies with a large number of patients using a prospective design based on this study. In addition, to investigate the association with disease recurrence, a longer follow-up period is required.

In conclusion, we believe that fibrin sealant (Tisseel) is an efficient, safe and effective hemostatic agent which plays a role in LEEP for CIN 2 or 3.


## Acknowledgments

This work was supported by the 2012 research fund of the Catholic Clinical Research Center, The Catholic University of Korea, Seoul, South Korea.


## Disclosure Statement

The authors declare that there are no conflicts of interest.

## References


1 Hoppenot C, Stampler K, Dunton C: Cervical cancer screening in high- and low-resource countries: implications and new developments. Obstet Gynecol Surv 2012;67:658–667.

2 Khorasanizadeh F, Hassanloo J, Khaksar N, Mohammad Taheri S, Marzaban M, et al: Epidemiology of cervical cancer and human papilloma virus infection among Iranian women – analyses of national data and systematic review of the literature. Gynecol Oncol 2013;128:277–281.

3 Gunasekera PC, Phipps JH, Lewis BV: Large loop excision of the transformation zone (LLETZ) compared to carbon dioxide laser in the treatment of CIN: a superior mode of treatment. Br J Obstet Gynaecol 1990;97:995–998.

4 Keijser KG, Kenemans P, van der Zanden PH, Schijf CP, Vooijs GP, Rolland R: Diathermy loop excision in the management of cervical intraepithelial neoplasia: diagnosis and treatment in one procedure. Am J Obstet Gynecol 1992;166:1281–1287.

5 Wright TC Jr, Gagnon S, Richart RM, Ferenczy A: Treatment of cervical intraepithelial neoplasia using the loop electrosurgical excision procedure. Obstet Gynecol 1992;79:173–178.

6 Hallam NF, West J, Harper C, Edwards A, Hope S, Merriman H, et al: Large loop excision of the transformation zone (LLETZ) as an alternative to both local ablative and cone biopsy treatment: a series of 1,000 patients. J Gynecol Surg 1993;9:77–82.

7 Woo VG, Cohen CR, Bukusi EA, Huchko MJ: Loop electrosurgical excision procedure: safety and tolerability among human immunodeficiency virus-positive Kenyan women. Obstet Gynecol 2011;118:554–559.

8 Alving BM, Weinstein MJ, Finlayson JS, Menitove JE, Fratantoni JC: Fibrin sealant: summary of a conference on characteristics and clinical uses. Transfusion 1995;35:783–790.

9 Spotnitz WD, Burks S: Hemostats, sealants, and adhesives: components of the surgical toolbox. Transfusion 2008;48:1502–1516.

10 Spotnitz WD: Fibrin sealant: past, present, and future: a brief review. World J Surg 2010; 34:632–634.

11 Tisseel – full prescribing information. 2012.

12 Vaiman M, Eviatar E, Segal S: Effectiveness of second-generation fibrin glue in endonasal operations. Otolaryngol Head Neck Surg 2002;126:388–391.

13 Pryor SG, Sykes J, Tollefson TT: Efficacy of fibrin sealant (human) (Evicel) in rhinoplasty: a prospective, randomized, single-blind trial of the use of fibrin sealant in lateral osteotomy. Arch Facial Plast Surg 2008;10:339–344.

14 Neuss H, Raue W, Koplin G, Schwenk W, Reetz C, Mall JW: A prospective randomized trial: the influence of intraoperative application of fibrin glue after radical inguinal/iliacal lymph node dissection on postoperative morbidity. Eur J Surg Oncol 2009;35:884–889.

15 Papacharalabous EN, Giannopoulos T, Tailor A, Butler-Manuel SA: Intraoperative haemostasis with new fibrin surgical sealant (Quixil) in gynaecological oncology. J Obstet Gynaecol 2009;29:233–236.

16 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.

17 Mor-Yosef S, Lopes A, Pearson S, Monaghan JM: Loop diathermy cone biopsy. Obstet Gynecol 1990;75:884–886.

18 Oyesanya OA, Amerasinghe CN, Manning EA: Outpatient excisional management of cervical intraepithelial neoplasia. A prospective, randomized comparison between loop diathermy excision and laser excisional conization. Am J Obstet Gynecol 1993;168:485–488.