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Original Research

Effectiveness of Oxidized Regenerated Cellulose-Based Haemostat (Surgicel®) for Monopolar Electrosurgical Conization and Its Risk Factors for Postoperative Rebleeding: An Observational Study

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Abstract

Background: Prompt detection and treatment of high-grade cervical intraepithelial neoplasia (CIN), namely, CIN3, are important for preventing malignant transformation. In most cases, such treatment is performed through conization, but minimally invasive procedures must also be considered. Therefore, we present a surgical method using a combination of monopolar electrosurgical conization (MESC) and oxidized regenerated cellulose-based haemostat (ORCH) (Surgicel®) and discuss its merits and risk factors. **Methods**: The medical records of 274 patients treated at our hospital from January 1, 2015, to December 31, 2021, were retrospectively reviewed. To detect risk factors for postoperative problems, we considered 2 indicators: postoperative recurrence and haemostatic suture for severe postoperative bleeding. We also focused on the following 10 representative factors for predicting significant risk for postoperative problems: (1) advanced age, (2) high BMI, (3) nulliparity, (4) smoking history, (5) long operation time, (6) intraoperative suture, (7) positive margin, (8) invasive squamous cell carcinoma (SCC), (9) no dysplasia, and (10) cervical glandular neoplasia (CGN). **Results**: Among the 274 patients, 19 instances of postoperative recurrence and 8 instances of haemostatic suture were detected. In a multivariate analysis of the 10 factors, we detected no significant impact except for "no dysplasia" on both indicators. This result indicated that our method had no specific risk and could provide a certain extent of usability. **Conclusions**: The combination of MESC and ORCH for the treatment of CIN3 could be performed effectively and safely with minimal intraoperative haemostatic suturing of the cut surface.

Keywords: monopolar electrosurgical conization; oxidized regenerated cellulose haemostat; cervical intraepithelial neoplasia; postoperative rebleeding; retrospective study

1. Introduction

Because untreated high-grade cervical intraepithelial neoplasia (CIN), namely, CIN3, has a cumulative incidence of transitioning to invasive cervical cancer of over 30% at the age of 30 years [1], prompt detection is important. In Japan, over 13,000 cases of CIN3 are reported to the Japan Society of Obstetrics and Gynaecology annually [2]. These cases are mostly detected by cytology screening and cervical biopsy. On the other hand, because cancer risk at 30 years can be decreased to less than 1% with adequate treatment [1], surgical treatment methods for CIN3, including cold knife conization (CKC), monopolar electrosurgical conization (MESC), laser conization and loop electrosurgical excision procedure (LEEP), have been improved. Additionally, because the incidence of CIN3 among reproductive-aged women (aged approximately 35 to 45 years) has increased in Japan [3,4], we have focused on not just the treatment effects—that is, the prevention of recurrence and positive resection margins—but also on the use of minimally invasive procedures. Among these representative operation methods, at our hospital, a simple MESC method is adopted. In this method, electrocoagulation and suturing of the cone bed are performed if needed to achieve homeostasis. Since the use of these procedures must be minimized to reduce the risk of cervical stenosis, we use oxidized regenerated cellulose haemostat (ORCH) (Surgicel®) to control bleeding from the cone bed. This tool can allow a relatively easy haemostatic procedure; however, it may also increase the risk of postoperative rebleeding. Therefore, in this study, we will introduce the merit of ORCH and simultaneously analyse all cases in our hospital. We elucidated factors that predicted the possibility of postoperative problems, in addition to the recurrence rate, which is generally regarded as important.

2. Materials and Methods

2.1 Data Collection

This study was reviewed and approved by the Human Ethical Committee of the University of Teikyo Hospital (trial registration number: 20-054-2). The deidentified medical records of 274 female patients who underwent MESC from January 1, 2015, to December 31, 2021, were reviewed retrospectively. To prevent postoperative bleeding, in all patients, we performed the following 3 procedures: (1) electrocoagulation of the cone bed by a monopolar electrosurgical device, appropriately adding suturing; (2) SURGICEL Absorbable Haemostat® (Johnson & Johnson K.K., Tokyo, Japan), a cotton-like ORCH, was attached to the cut surface just before the end of surgery; and (3) an intravenous administration of 1000 mg of tranexamic acid was given after surgery. Among these procedures, we mainly focused on Surgicel®, which is a cotton-like collagen. We decomposed one agent (2.5 cm $\times$ 5.1 cm) into approximately 10 sheets and filled these sheets into the cut surface. Proper attachment was checked by pelvic examination on the first postoperative day before discharge. In all cases, cytological tests and cervical biopsy were performed in the outpatient department before surgery, and definitive diagnosis and surgical margins of conization specimens were evaluated by histopathological examination after surgery. For each patient, we recorded the operation time, blood loss amount and additional clinical data, including age, body mass index (BMI), parity and smoking history. Postoperative surveillance was conducted by performing cytological tests at every visit, and patients with positive cytological test results underwent cervical biopsy. As indicators of the risk of our conization procedure, we extracted detailed data for patients who had the following factors: (1) postoperative recurrence, which was detected by cytological testing; and (2) haemostatic suture, defined as patients who underwent urgent suture haemostasis for treating severe haemorrhage in the emergency room after discharge. In total, 29 patients visited the hospital for urgent care, and these patients could have been regarded as having mild or severe haemorrhage. Apart from haemostatic suture, patients were treated with an intravenous administration of 1000 mg of tranexamic acid (13 patients), a tampon and/or gauze (26 patients) and microfibrous collagen (AVITENE™ (Japan Becton, Dickinson and Company, Tokyo, Japan)) (9 patients). However, we did not adopt this indicator since this group included several patients in which we could not distinguish between postoperative rebleeding and menstrual bleeding.

2.2 Analysis Methods

To identify risk factors predictive of postoperative problems, including recurrence and abnormal bleeding, we assessed the influence of the following ten factors: (1) patient characteristics, including advanced age ($\geq$50 years), high BMI ($\geq$25 kg/m^2), nulliparity, and smoking history; (2) long operation time, defined as cases in which the operation time exceeded 30 minutes; (3) intraoperative suture, defined as cases in which suturing was needed to stop bleeding from the cut surface; and (4) specific definitive diagnosis, including positive margin, invasive squamous cell carcinoma (SCC), no dysplasia and cervical glandular neoplasia (CGN). As indicators of difficult surgery, we adopted long operation time and intraoperative suture. The long operation time index was determined by the average of the 274 cases. The definitive diagnosis of CGN included the classification of atypical glandular cells (AGCs), adenocarcinoma in situ (AIS) and adenocarcinoma. To eliminate confounding factors, we divided the patients into two groups according to the existence or nonexistence of each factor and used a multivariate logistic regression analysis. These statistical analyses were performed using JMP version 12 for Windows (SAS Institute, Inc., Tokyo, Japan). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated to determine the strength of these correlations. $p <$ 0.05 was considered statistically significant. Other data are presented as the mean $\pm$ standard deviation.

3. Results

3.1 Patient Characteristics

Basic patient characteristics are shown in Table 1. The average patient age, BMI, parity, operation time and intraoperative bleeding were 39.6 $\pm$ 8.8 years, 21.3 $\pm$ 3.0 kg/m^2, 1.0 $\pm$ 1.0, 20.1 $\pm$ 7.9 minutes and 4.9 $\pm$ 38.5 mL, respectively. We collected intraoperative bleeding as a clearly countable amount in only 19 cases, since very little bleeding was detected in other cases. In these cases, we regarded intraoperative bleeding as 0 mL. The pathological findings detected before and after conization are summarized in Table 2. Among them, invasive SCC (13 cases), no dysplasia (22 cases), and positive margin (22 cases) were defined by pathological findings in surgical specimens. CGN was defined at least one diagnosis by cytological or histological diagnosis before or after conization. In 8 out of 274 cases, we needed to perform a suture procedure to stop active bleeding, and these patients visited the emergency department on approximately the 10th postoperative day (Table 3). Among them, 4 patients needed hospitalization, and one patient underwent suturing under general anaesthesia. In this patient, the laboratory test revealed a haemoglobin level decrease from 14.3 to 7.3 g/dL, and the patient needed to be hospitalized for 4 days.

3.2 Characteristics of Nineteen Patients with Postoperative Recurrence

To confirm the effectiveness of our treatment method, we examined 19 cases of recurrence diagnosed by follow-up cytological tests, including 8 cases of atypical squamous cells of undetermined significance (ASC-US), 2 cases of atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H), 6 cases of low-grade squamous intraepithelial lesion (LSIL), and 3 cases of high-grade squamous intraepithelial lesion (HSIL). Among these 19 cases, the definitive diagnosis after conisation included 14 cases of CIN3, one case of AIS, and 4 cases of no dysplasia. The average time between conization and recurrence was 304.2 $\pm$ 478.5 (31–1743) days. One patient chose to undergo laparoscopic hysterectomy, and no dysplasia was detected on postoperative histological examination. Other patients were diagnosed with no significant dys-

Table 1. Patient characteristics.

Patient characteristics	Avg. ± SD (Min–Max), Number
Total number	n = 274
Age (years)	39.6 ± 8.8 (24–79), n = 274
BMI (kg/m^2)	21.3 ± 3.0 (14.9–32.7), n = 274
Parity	1.0 ± 1.0 (0–4), n = 274
Nulliparity	n = 129
Smoking history	n = 50
Operation time (minutes)	20.1 ± 7.9 (9–81), n = 274
Operative bleeding (mL)	4.9 ± 38.5 (0–601), n = 274
Intraoperative suture	n = 62
Positive margin	n = 22
Postoperative recurrence	n = 19
Emergency room visit	n = 29
Haemostatic suture	n = 8
Emergency hospitalization	n = 6

Representative patient characteristics obtained from medical records are summarized in this table. For each item, we calculated averages and standard deviations, minimal and maximal values, and count data from medical records.

Abbreviations: Avg., Average; BMI, Body mass index; Min., Minimum; Max., Maximum; SD, Standard deviation.

plasia by cervical biopsy, namely, CIN2 or atypical glands were found. In 13 out of these 18 cases, we detected spontaneous negative conversion 296.0 ± 278.3 (49–993) days after a positive cytological test.

3.3 Predictive Factors of Postoperative Problems

To detect factors that significantly affected the frequency of postoperative problems, the aforementioned 10 factors were compared using multivariate analysis (Table 4). Significant impacts of no dysplasia on haemostatic suture, smoking history and no dysplasia on postoperative recurrence were detected. Although the following combination of factor and indicator did not show a significant impact, intraoperative suture showed a trend towards a higher possibility of postoperative recurrence ($p = 0.08$). These results indicate the possibility that our method had no specific risk and could provide a certain extent of usability.

4. Discussion

Conization of the cervix is a standard conservative treatment for patients with high-grade CIN to prevent progression to invasive cancer and preserve fertility. It is also an efficient diagnostic method for suspicious invasive carcinomas. Recently, various surgical methods, such as electrocautery, cryotherapy, laser ablation, CKC, MESC, and LEEP, have been applied [4]. At our hospital, MESC is used as a basic treatment and diagnostic method for cervical lesions because it is regarded as an acceptable alternative to CKC [5,6] and does not need specific tools such as those required for LEEP [7,8]. Additionally, since there is some evidence that haemostatic suturing has an adverse effect on blood loss, cervical stenosis and satisfactory colposcopy [9], we also tried to develop a new technique to treat intraoperative bleeding with minimizing suturing of the cone bed. In this process, by referring to some reports that identified the haemostatic effects of electrocoagulation and haemostatic agents [10,11], such as a fibrin sealant patch [12] or chitosan tampon [13], we used ORCH (Surgicel®) just before finishing the operation to minimize the use of haemostatic electrocoagulation and suturing. However, when haemostatic sutures are needed, cases might be regarded as difficult. Since, to the best of our knowledge, the application of combined of haemostatic electrocoagulation and ORCH during conization has not yet been published, we aimed to present the merits and risk of this procedure for the first time.

Compared with some previous large studies, the recurrence rate was approximately 6.9%. This result seemed superficially high, and there was the possibility that this technique showed a slightly poor treatment effect, although the possibility of involvement of positive surgical margins was relatively low [5,6,14]. However, since only one patient was diagnosed with CIN2, which might represent a very low recurrence rate compared to some past studies [15,16], our procedure might show a sufficient treatment effect. On the other hand, one weakness of this technique was detected; namely, the frequency of postoperative rebleeding was slightly higher than that reported in some past studies [5,6]. Therefore, the risks of this technique need to be evaluated in a multivariate analysis of several representative factors, however, one limitation was that we could not set the control group, since we used this technique for all patients and could not collaborate with colleagues at different hospitals. The main role of our hospital was daily clinical activities themselves. We could not clearly indicate the efficacy of ORCH as a haemostatic agent, and room for improving this technique remains. We also had the other limitation that we could not collect information on various factors, and the analysis for the two postoperative complications showed similarity. However, the most meaningful results of this analysis (Table 4) were the trends in the impact of intraoperative suture and no dysplasia on at least one of 2 indicators, including haemostatic suture and postoperative recurrence. These tendencies could be interpreted as indicative of atypical and difficult surgeries that might increase the possibility of postoperative problems, although long operation time, invasive SCC and CGN did not show differences in impact. Unlike some past studies [17,18], we also found that smoking history had a significant impact on postoperative recurrence. These results that our procedures are sufficiently safe. Since our procedure does not require special equipment, the combination of MESC and ORCH could be regarded as an efficient treatment method for high-grade CIN.

Table 2. Pathological findings.

Preoperative pathology				Postoperative pathology	
Cytology		Histology		Definitive diagnosis	
HSIL	n = 196	CIN 1	n = 1	CIN 1	n = 3
LSIL	n = 8	CIN 2	n = 22	CIN 2	n = 14
ASC-H	n = 23	CIN 3	n = 232	CIN 3	n = 198
SCC	n = 7	Carcinoma s/o	n = 19	CIN3/AIS	n = 5
ASC-US	n = 17			AIS	n = 7
AGC	n = 2			Invasive SCC	n = 13
AGC/HSIL	n = 11			No dysplasia	n = 22
AGC/ASC-H	n = 6			Dysplasia NOS	n = 12
AIS	n = 1				
Adenocarcinoma	n = 3				

For all patients, we performed cytological and histological examinations before surgery and histological examinations after surgery. The pathological findings detected before and after conization are summarized in this table. Cases that included two categories, for example, AGC/HSIL, were defined as cases in which two different types of cells or tissues were detected simultaneously on pathological examination.

Abbreviations: AGC, Atypical glandular cells; AIS, Adenocarcinoma in situ; ASC-H, Atypical squamous cells; ASC-US, Atypical squamous cells of undetermined significance; CIN, Cervical intraepithelial neoplasia; HSIL, High-grade squamous intraepithelial lesion; LSIL, Low-grade squamous intraepithelial lesion; NOS, Not otherwise specified; SCC, Squamous cell carcinoma; s/o, Suspected of.

Table 3. Characteristics of eight patients who underwent urgent treatment with postoperative haemostatic sutures.

Case number	1	2	3	4	5	6	7	8
Age (years old)	34	36	49	46	35	46	34	34
Parity	2	2	2	0	0	2	2	1
BMI (kg/m^2)	18.8	17.9	18.5	23.4	20.5	19.3	18.2	17.3
Smoking history	No	No	No	No	No	Yes	No	No
Operation time (minutes)	28	16	15	23	13	21	18	16
Bleeding (mL)	0	0	20	0	0	25	0	0
Intraoperative suture	Yes	No	Yes	No	No	No	Yes	Yes
Cytology (*1)	HSIL	HSIL	HSIL	HSIL	HSIL	HSIL	HSIL	HSIL
Histology (*2)	CIN 2	CIN 2	CIN 3	CIN 3	CIN 3	CIN 3	CIN 2	CIN 3
Definitive diagnosis (*3)	CIN 2	HSIL	CIN 3	No dysplasia	CIN3	CIN3	No dysplasia	CIN 3
Surgical margin	Negative	Negative	Positive	Negative	Positive	Negative	Negative	Negative
POD (*4)	16	8	12	14	14	11	9	9
Treatment period (*5)	3	1	4	1	2	2	3	2
Hospitalization period	0	0	4	0	0	2	2	2
Number of suture location	1	1	4 (*6)	1	3	3	NA	2
Hb decrease (g/dL)	13.7 to 9.6	NA	14.3 to 7.3	12.9 to 9.9	NA	11.4 to 10.4	NA	10.2 to 7.3

The characteristics of eight patients with haemostatic sutures are shown in this table.

*1: This index shows the result of cytological examination before surgery.

*2: This index shows the result of histological examination before surgery.

*3: This index shows the result of histological examination after surgery.

*4: This index shows the day the patient visited the emergency room for postoperative rebleeding.

*5: This index shows the total number of days at the hospital for the treatment of postoperative rebleeding, including the hospitalization period.

*6: In this case, we performed haemostatic sutures in the 4–5, 5–6, 8–9, and 6–7 o'clock positions of the cone bed under general anaesthesia in the operating room.

Abbreviations: BMI, Body mass index; CIN, Cervical intraepithelial neoplasia; Hb, Haemoglobin; HSIL, High-grade squamous intraepithelial lesion; POD, Postoperative day.

Table 4. Identification of influencing factors for postoperative problems.

Factors	Haemostatic suture		Postoperative recurrence	
	OR (95% CI, Number)	p value	OR (95% CI, Number)	p value
No dysplasia (n = 22)	4.1 (0.8–21.6, n = 2/8)	0.04	3.5 (1.1–11.7, n = 4/19)	0.027
CGN (n = 30)	NA (NA, n = 0/8)	0.4	0.4 (0.1–3.4, n = 1/19)	0.5
Positive margin (n = 22)	1.7 (0.2–14.2, n = 1/8)	0.42	1.4 (0.3–6.4, n = 2/19)	0.22
Intraoperative suture (n = 62)	2.1 (0.5–9.1, n = 3/8)	0.28	2.1 (0.8–5.6, n = 7/19)	0.055
Invasive SCC (n = 13)	NA (NA, n = 0/8)	0.65	NA (NA, n = 0/19)	0.39
Smoking history (n = 50)	0.6 (0.1–5.3, n = 1/8)	0.72	3.7 (1.4–9.7, n = 8/19)	0.0048
High BMI (n = 31)	NA (NA, n = 0/8)	0.41	0.4 (0.1–3.2, n = 1/19)	0.31
Nulliparity (n = 129)	0.4 (0.1–1.8, n = 2/8)	0.19	0.4 (0.1–1.1, n = 5/19)	0.1
Advanced age (n = 33)	NA (NA, n = 0/8)	0.23	1.4 (0.4–5.1, n = 3/19)	0.84
Long operation time (n = 19)	NA (NA, n = 0/8)	0.36	NA (NA, n = 0/19)	0.17

A multivariate analysis of 274 patients with MESC was performed to examine the influence of 10 representative factors that were collected from medical records. The number of patients with each factor, the ORs and 95% CIs for the occurrence of surgical complications and the p-values are shown in this table.
Abbreviations: BMI, Body mass index; CGN, Cervical glandular neoplasia; CI, Confidence interval; NA, Not available; OR, Odds ratio; SCC, Squamous cell carcinoma.

5. Conclusions

By identifying risk factors for postoperative problems, the combination of MESC and ORCH for the treatment of high-grade CIN could be performed effectively and safely while minimizing intraoperative haemostatic suturing of the cut surface.

Author Contributions

WI collected and analysed the data and wrote the manuscript. AT and ON supervised the whole study. AT, AO, MH, AS, RM and HT performed medical care on the subjects. AF and ON determined the methods of the operation and supervised all medical procedures. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This retrospective study was approved by the Institutional Review Board of Teikyo University. The study registry number, registry name and registration date are as follows: 20-054-2, clinical outcomes of surgery, chemotherapy and radiotherapy for gynaecological malignant tumours: retrospective analyses, 2021/5/31. Written informed consent was obtained from the patients for the publication of this report.

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Conflict of Interest

The authors declare no conflict of interest.

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