RESEARCH ARTICLE

Comparison of Recurrence Rates with Contour-Loop Excision of the Transformation Zone (C-LETZ) and Large Loop Excision of the Transformation Zone (LLETZ) for CIN

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Abstract

Aim: To compare recurrence rates of large loop excision of the transformation zone (LLETZ) with those of contour-loop excision of the transformation zone (C-LETZ) in the management of cervical intraepithelial neoplasia (CIN). Materials and Methods: The medical records of 177 patients treated consecutively by LLETZ and C-LETZ for CIN at Rajavithi Hospital between 2006 and 2009 were retrospectively reviewed. Results: Of the 87 women in the C-LETZ group, 2 cases (2.30%) had recurrence compared with 13 cases (14.4%) of the 90 women in the LLETZ group, the higher recurrence rate in the latter being statistically significant ($p<0.05$). Median times of follow up in the C-LETZ and LLETZ groups were 12 months and 14 months respectively ($p>0.05$). The C-LETZ group showed less intraoperative bleeding compared to the LLETZ group, but the rate of achievement of single specimens and positive margins were similar in the two groups. Conclusions: The present study demonstrated the superiority of C-LETZ over LLETZ in terms of efficacy; C-LLETZ is associated with a lower recurrence rate and also carries a smaller risk of intraoperative bleeding than LLETZ. The rotating technique still has a potential role in treating precancerous lesions of the cervix.

Keywords: C-LETZ - contour-loop excision of the transformation zone - LLETZ

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Introduction

Cervical excision is the mainstay of treatment of cervical intraepithelial neoplasia (CIN). Large loop excision of the transformation zone (LLETZ) is the most commonly used procedure and offers a safe, effective outpatient treatment of CIN (Boonlikit et al., 2008; Martin-Hirsch et al., 2013; Geneva: World Health Organization., 2014; Sangkarat et al., 2014). The disadvantages of LLETZ include the presence of residual dysplasia at the margins of the specimens, fragmentation of the specimen, and the risk of injury to the adjacent vaginal wall and thermal artifact (Montz et al., 1993; Ioffe et al., 1999; Wright Jr et al., 2003; Ghaem-Maghami et al., 2007; Boonlikit et al., 2008; Sangkarat et al., 2014).

A meta-analysis study of cervical excision for CIN has suggested that complete excision, in one fragment if possible, is preferable (Ghaem-Maghami et al., 2007). In this regard, the Fischer cone biopsy excisor, another method of excision using a rotating technique, was designed to minimize the disadvantages of LLETZ by increasing the support and stabilization of the excising stainless steel wire (Fischer et al., 1998). In addition, another similar technique, contour-loop excision of the transformation zone or C-LETZ (Utah Medical Products, Midvale, USA) has been used as an effective method for the treatment of CIN (Mints et al., 2006; Janthanaphan et al., 2009; Boonlikit and Yanaranop, 2012; Boonlikit and Thitisagulwong, 2012). The technique is similar to the Fisher excisor in that excision of specimens is performed by rotating, not passing. It can individualize the size of the cone and produce a one-piece specimen for histopathological assessment (Mints et al., 2006; Boonlikit and Thitisagulwong, 2012) which, as mentioned above, is a major advantage. A previous study showed that compared with cold-knife conization, C-LETZ is less traumatic, yields a comparable efficacy, and results in less morbidity (Janthanaphan et al., 2009). Evidence from meta-analysis suggests that there is no single surgical technique for treating cervical intraepithelial neoplasia which is clearly superior in terms of treatment failures or operative morbidity. Studies have been carried out to compare LLETZ with some alternative methods such as needle excision of the transformation zone (NETZ), but C-LETZ has not been included in any of these studies (Martin-Hirsch et al., 2013).

C-LETZ has been used in our institute for years as an alternative form of excision with clinical reports of success (Boonlikit and Yanaranop, 2012; Boonlikit and Thitisagulwong, 2012). In the present study, we review the clinical advantages of this procedure, and compare the recurrence rate of LLETZ with that of C-LETZ for CIN.

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Materials and Methods

After obtaining approval from our institutional review board, we retrospectively reviewed the medical records of 177 patients treated consecutively by LLETZ and C-LETZ for CIN at Rajavithi Hospital between 2006 and 2009. In this period, both C-LETZ and LLETZ were commonly performed as we were running randomized controlled trials comparing the two procedures between 2006 and 2007 (Boonlikit and Thitisagulwong, 2012). Therefore, more than half of the C-LETZ cases in the present study participated in that clinical trial. The rest of the cases were collected from operations in normal practice afterwards. Since there were more LLETZ cases in routine practice, the selected cases were those procedures which were performed in the same period as each case of the C-LETZ procedure.

In our practice, colposcopy and loop excision (C-LETZ and LLETZ) are always performed by gynecologic oncology staff and trainees. In the colposcopy clinic, patients eligible for treatment for CIN were scheduled to have their operations performed in the operative theater. All loop excision procedures were performed under local anesthesia using 2% mepivacaine hydrochloride with 1:100,000 units of adrenaline or a combination of 1 % xylocaine with 1:100,000 units of adrenaline. General anesthesia was used in rare cases where the patient was very anxious or when accessing the cervicovaginal area was very difficult. The LLETZ was performed using a 15, 20 or 25 mm loop depending on the extent of lesion, the age of the women, and parity. Radiofrequency Surgitron F.F.P.F generator (Ellman international, New York, USA) was used as a source of electrical energy. The generator was set to deliver 56-70 W for the cut mode and 34-38 W for the coagulation mode. The C-LETZ was performed using a 15×23 mm, 11×18 mm, 12×10 mm or 9×13 mm loop according to the extent of lesion, the age of the women, and parity. The C-LETZ was performed according to the following four-step sequence: (1) the electrode tip was placed at the cervical os, with the electrode arm in the 12 o'clock position; (2) ESU (electrosurgical unit) was activated and the C-LETZ plunged perpendicularly into the cervical tissue to its maximum depth (10-23 mm, depending on the C-LETZ electrode selected); (3) the C-LETZ electrode was swiftly rotated 360° around the transformation zone; (4) the electrode was removed together with the mini cone specimen. The use of an additional loop excision in the ectocervical or endocervical area to ensure adequate margin depended on the physician's personal judgement. Hemostasis after surgery was achieved, when necessary, by electrofulguration with a ball electrode and application of Monsel's solution. Intraoperative bleeding was categorized as *none*, *mild*, *moderate* or *severe*. *None* was defined as no bleeding or minimal oozing of blood that did not require any gauze. *Mild bleeding* was defined as slight bleeding that needed only one piece of gauze to halt it. *Moderate bleeding* was defined as bleeding that required more than one piece of gauze to stop it. *Severe bleeding* was defined as bleeding requiring any hemostatic intervention such as cervical suturing, vaginal packing, or blood transfusion. In all cases, after their operation, patients were sent to the recovery room and kept in bed for a few hours and then discharged from the hospital. From routine pathological data, the following histological outcomes were reported: (1) number of specimens obtained, (2) margin of specimen, (3) histology. Positive margin was defined as the presence of CIN at any site of the surgical margin. The first follow-up visit was scheduled for 2 weeks after the date of operation, and all postoperative complications were recorded at these visits. Postoperative infection was defined as any clinical sign of pelvic infection such as purulent vaginal discharge, cervicitis, endometritis or PID. All women underwent a postoperative examination after 4 to 6 weeks and were then followed up at 4-6 month intervals. Follow-up visits, except for the postoperative examination, included a speculum examination and Pap smear. If a patient had 2 consecutive negative Pap smears after the operation, she was referred back to the general gynecology clinic for yearly Pap smear. In the case of abnormal Pap smear, colposcopy was performed and management depended on colposcopic findings. The case was considered as recurrence if there was histologic evidence of CIN2/3. The data were analyzed using the statistical package for social sciences (SPSS Inc., Chicago, USA) version 17.0. Means, medians, and standard deviations were calculated for continuous variables, and frequency statistics were computed for categorical variables. Statistical analysis was performed with the X^2 test or the Fisher exact test for categorical data and Student's t-test for continuous data. Statistical significance was defined as $p<0.05$.

Results

A total of 177 women met the inclusion criteria for the present study with either C-LETZ (n=87) or LLETZ (n= 90). The mean age for the C-LETZ and LLETZ groups was 44.2±11.2 years and 40.9±12.8 years, respectively, so that the mean age of the LLETZ group was significantly lower than that of the C-LETZ group. The operations were performed by 8 gynecologic oncologists and trainees. Parity (8.04% vs 10.0%), and pretreatment cytology were similar in the two groups. There were more women with no histology from CDB in the LLETZ group (Table 1), and surgeons reported C-LETZ as being easier to perform than LLETZ. Table 2 shows the outcome of treatment. The C-LETZ group showed less intraoperative bleeding than the LLETZ group, but post-operative infection rate, rate of single pathologic specimen, histological diagnosis of the final specimen and the rate of positive margin of specimen were similar in the two groups. Regarding post treatment follow-up, median follow-up times in the two groups were not significantly different. Median time in the C-LETZ group was 12 months, range 3-43 months and median time in the LLETZ group was 14 months, range 2-55 months ($p>0.05$). Of the 87 women in the C-LETZ group, 2 cases (2.30%) had recurrence compared with 13 cases (14.4%) of the 90 women in the LLETZ group, and the higher recurrence in the LLETZ group compared to the C-LETZ group was statistically significant ($p<0.05$) (Table 3).

Table 1. Patient Characteristics by Treatment Arm

			LLETZ (n=90)	C-LETZ (n=87)	p value
Age (years)			40.9±12.8	44.2±11.2	0.01
Nulliparous (%)	Yes		9 (10.0%)	7 (8.04%)	0.09
	No		81 (90.0%)	80 (91.9%)	
Referral cytology	ASC-US		6(6.70%)	6(6.90%)	0.7
	ASC-H		7 (7.80%)	5 (5.70%)	
	LSIL		8(8.90%)	7 (8.00%)	
	HSIL		60 (66.7%)	54(62.1%)	
	Invasive carcinoma		9 (10.0%)	15 (17.2%)	
Histology from colposcopically directed biopsy					
	No biopsy		27(30.3%)	8 (9.40%)	0.005
	LSIL	HPV	4 (4.50%)	9 (10.6%)	
		CIN1	13(14.6%)	11 (12.9%)	
	HSIL	CIN2	8 (9.00%)	11 (12.9%)	
		CIN3	30 (33.7%)	29(34.1%)	
		CIS	7 (7.90%)	17(20.0%)	
Surgeon	Staff		48(53.3%)	56(64.4%)	0.13
	Trainee		42(46.7%)	31(35.6%)	
Case	Standard (small lesion)		85(94.4%)	75(86.2%)	0.06
	Difficult (large lesion)		5(5.60%)	12(13.8%)	

Table 2. Outcome of Treatment from LLETZ and C-LETZ

			LLETZ (n=90)	C-LETZ (n=87)	p value
Intraoperative bleeding					
	None		14 (15.6%)	39 (44.8%)	<0.001
	Mild		66 (73.3%)	42 (48.3%)	
	Moderate		9 (10.0%)	5 (5.70%)	
	Severe		1 (1.10%)	1 (1.10%)	
Post-operative infection					
	Yes		1 (1.10%)	2 (2.29%)	0.53
	No		89 (98.9%)	85 (97.7%)	
No. of specimen	1		63 (70.0%)	69 (79.3%)	0.15
	2 or more		27 (30.0%)	18 (20.7%)	
Histology of specimen					
	Negative		5 (5.60%)	8 (9.20%)	0.43
	LSIL	CIN1	19 (21.1%)	14 (16.1%)	
	HSIL	CIN2	6 (6.70%)	2 (2.30%)	
		CIN3	28 (31.1%)	35 (40.2%)	
		CIS	30 (33.3%)	25 (28.7%)	
Invasive carcinoma			2 (2.20%)	3 (3.40%)	
Margin of specimen					
	Positive		46 (51.1%)	38 (43.7%)	0.32
	Negative		44 (48.9%)	49 (56.3%)	

Table 3. Comparison of Recurrence

		LLETZ (n=90)	C-LETZ (n=87)	p value
Recurrence	Yes	13 (14.4%)	2 (2.30%)	0.004
	No	77 (85.6%)	85 (97.7%)	
Time at follow up	Median	14	12	0.34
(month)	Mean (SD)	14.2±7.86	11.5±6.48	
	Min, Max	2, 55	3, 43	

Discussion

C-LETZ has been available for many years as a safe and effective method for the treatment of cervical precancerous lesions. In 2006, Mints et al. first reported the clinical value of this treatment. This first study revealed that the rate of complete excision based on histology was 86%. The histological quality of specimen obtained by C-LETZ was excellent as the resection margins and histological diagnoses were certain in 98% of cases, and in only 2% of cases the diagnosis was not clarified due to uncertain resection margins caused by thermal artifact; furthermore, a cure rate of 90% in the first six months was observed (Mints et al.,2006).

The first comparison of C-LETZ was reported in 2009 by the study of Janthanaphan et al. which was designed to compare the complications and success rate of C-LETZ with cold knife conization (CKC) in treating high grade lesion (HGL). The success rate and tissue size were not significantly different between the two groups while the operating time, blood loss, and post-operative infection were significantly less in the C-LETZ cases (Janthanaphan et al., 2009). Subsequently, a third study of C-LETZ regarding the thermal artifact of specimen was reported by retrospective review and histological reinterpretation of cases who had undergone LLETZ and C-LETZ. It was demonstrated that thermal artifacts, both in severity and extent, are not significantly different in specimens from LLETZ and C-LETZ (Boonlikit and Yanaranop,2012).

In 2012, the first randomized controlled trial comparing C-LETZ versus conventional LLETZ was reported. The results showed that C-LETZ had a higher rate of obtaining a single pathologic specimen, and it removed more cervical tissue than LLETZ. The incidence of incomplete excision and complications seemed to be similar in the two groups (Boonlikit and Thitisagulwong, 2012). Regarding efficacy, however, no study comparing C-LETZ with LLETZ has been reported. The present study demonstrates for the first time that C-LETZ is very effective in the management of CIN compared with LLETZ. Even though the number of difficult cases tended to be higher in the LLETZ group than in the C-LETZ group, the success rate of 97.7% was very high and significantly better than LLETZ which achieved 85.6%. The success rate of LLETZ in the present study is slightly lower than that reported in another previous study, where it ranged from 91-98% (Martin-Hirsch et al., 2013) but similar to the study from the same institute which previously reported a LLETZ success rate of 86.8% (Boonlikit et al., 2008). The excellent outcome of C-LETZ is consistent with a previous study (Mints et al., 2006).

The reason for the improved outcome in the C-LETZ group may be related to a number of factors. Previous studies revealed the important finding that C-LETZ removed more cervical tissue compared with LLETZ (Boonlikit and Yanaranop,2012; Boonlikit and Thitisagulwong, 2012). One comparative study showed that the specimen size from cold knife conization and C-LETZ were similar (Janthanaphan et al., 2009,) and a randomized controlled trial reported heavier specimen weight from C-LETZ compared to that of LLETZ (Boonlikit and Thitisagulwong, 2012). In the authors' opinion, one of the possible explanations would be related to physicians' choosing a too-large C-LETZ electrode size and misdirected overtreatment for curative purposes. This was probably related at least in part to their relative lack of experience in using this alternative technique. However, if the size of specimen was the major reason

for the improved success rate then the high complete excision rate would have accounted for this regard as there is an increase in treatment failures associated with involved margins following excisional treatment (Wright Jr et al., 2003; Ghaem-Maghami et al., 2007; Boonlikit et al., 2008; Martin-Hirsch et al., 2013; Sangkarat et al., 2014). However, the larger specimen in the previous study of C-LETZ was not associated with a lower incidence of positive margin (Boonlikit and Thitisagulwong, 2012). Likewise, in the present study, there was no difference in the rate of positive margin in the two groups, and therefore it was unlikely to be the reason for the superior success rate of this technique. The reason for the better outcome from C-LETZ needs to be studied further. Although previous randomized controlled trials have concluded that, compared to LLETZ, C-LETZ has a higher rate of obtaining a single pathologic specimen (Boonlikit and Thitisagulwong, 2012), in our series, there was no difference in the rate of achieving a single pathologic specimen between two groups. This is probably related to the frequency of use of the "top-hat" technique in the LLETZ group.

In the present study, the frequency of intraoperative bleeding was lower in the C-LETZ cases, and the characteristics of the particular ESU used in each group may explain this variation. Radiofrequency ESU provides excellent cutting but very little coagulative effect (Hurwitz et al., 1993). In a study by Ferris et al. (Ferris et al.,1994), comparing the various types of ESU in terms of electrical specification and performance characteristics, it was found that the performance of the Ellman ESU was categorized as average for cutting and just fair for fulguration whereas the Finesse ESU was rated better for both cut and coagulation modes. This, rather than the characteristics of the procedure itself, may account for the lower amount of intraoperative bleeding in C-LETZ. However, there was no difference in the frequency of severe bleeding and this finding corresponds well with a previous study (Boonlikit and Thitisagulwong, 2012) .

As with any retrospective study, we encountered many confounding factors and limitations in the course of our research. First, its retrospective nature precludes standardization of protocol: the ESU settings used were variable and the procedures were performed by physicians of different skill levels. Selection of each technique depended on the physicians' preference. The intraoperative bleeding was defined by using the qualitative grading; consequently, the results may be unreliable and this grading is not comparable to other studies recording the amount of bleeding in ml. Moreover, postoperative bleeding could not be assessed and reported because of lack of adequate data.

In conclusion, the present study is the first to demonstrate the superiority of C-LETZ over LLETZ in term of success rates and recurrence. The rotating technique still potentially has a role in treating precancerous lesion of the cervix: it is easy to learn and handle, and the risk of intraoperative bleeding is low and less than that of LLETZ. These findings indicate that the C-LETZ technique is very promising. A large clinical trial comparing success rates is needed to clarify this matter.

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