

RESEARCH ARTICLE

Comparison of Two Step LEEP and Cold Conisation For Cervical Intraepithelial Lesions to Decrease Positive Surgical Margins

Taylan Senol*, Mesut Polat, Enis Ozkaya, Ates Karateke

Abstract

Purpose: To assess the success rates of two step loop electrosurgical excision procedure (LEEP) compared with conventional cold conization procedures for decreasing positive surgical margins. **Materials and Methods:** This study was conducted on 70 patients who underwent colposcopic evaluation in Zeynep Kamil Women and Children's Health Training and Research Hospital between 2013-2015 with indications of CIN 2/3 or persistent CIN 1 for more than 2 years. The study included age matched groups of patients with similar histopathological lesions who underwent cold conization (n=40) or LEEP (N=30). **Results:** Comparison of tissue characteristics between the two groups revealed significantly higher deepest depth and lower volume of tissue removed by the two step LEEP. Ectocervical positivity rate was similar between groups (1/39 versus 0/29, $P>0.05$), while endocervical surgical margin positivity rate was significantly higher in the cold conization group (9/39 versus 0/29, $P<0.05$). Surgical margin positive cases were significantly older than the cases with negative margins ($P<0.05$). **Conclusions:** Two step LEEP made it easier to reach the squamocolumnar junction in the endocervical region with lower blood loss and applicability in office settings. Our study suggests to use two step approach in cases with high grade and glandular CIN.

Keywords: Cervical intraepithelial neoplasia - loop electrosurgical excision procedure - cold conization

Asian Pac J Cancer Prev, 17 (7), 3317-3320

Introduction

Cervical cancer is the most commonly seen malignancy of female genital organs all around the world (Mahadevan et al., 1993; Debarge et al., 2003). Long duration of time is needed for cervical preinvasive lesions progress to cervical cancer. Bethesda system includes a well defined high grade squamous intraepithelial lesion which correspond to histopathological features of cervical intraepithelial neoplasia (CIN) 2/3 (Debarge et al., 2003; Tillmanns et al., 2006). Peak incidence of CIN lesions are observed in women 25-35 years of age (Kyrgiou et al., 2006). High percentage of lesions persist (70 %) or progress to higher degree lesions within 10 to 20 years period (McCredie et al., 2008; Castle et al., 2009). Surgical intervention should be considered for cases with CIN 2-3 or persistent CIN 1 lesions to prevent progression (Apgar et al., 2009). Treatment alternatives include loop electrosurgical excision procedure (LEEP), cold conization, cryotherapy and laser conization. As it is possible to obtain a satisfactory histopathological specimen after procedure, cold conization and leep are most commonly preferred procedures for cervical conization. According to the treatment guidelines, LEEP was proposed to be associated with lesser blood loss, lower

morbidity rates, lower obstetrics complications rate, lower cost without requirement for general anesthesia (Frega et al., 2013; Latif et al., 2014).

Whichever technique was preferred, a well planned patient follow up is crucial for disease prognosis. According to the studies that compared all these procedures, technique that allows excision of whole transformation zone followed by precise histopathological examination free from coagulation artefacts should be preferred. (Ramos et al., 2007). Data showed LEEP to result in favorable surgical, oncologic and obstetric outcomes for patients with cervical neoplasia (Sangkarat et al., 2014). Unsuccessful treatment and disease recurrence are mostly based on the technique used and patients individual risk factors. Some risk factors for lesion recurrence have been introduced in some studies that included age, grade of lesion, preoperative human papillomavirus (HPV) load, postoperative HPV status, positive surgical margin, number of positive margins, endocervical canal involvement and human immunodeficiency virus (HIV) positivity (Ramos et al., 2007; Malapati et al., 2011). Especially, the risk of recurrence increases in cases with residual squamocolumnar junction located at endocervical canal. Extend of cervical excision at endocervical and lateral borders during procedure was not standardized in the

Obstetric and Gynecology Department, Zeynep Kamil Training and Research Hospital, Istanbul, Turkey *For correspondence: taylan_senol@hotmail.com

literature, for this reason some clinicians prefer to apply second procedure to excise additional endocervical tissue for adequate endocervical canal evaluation (Prendiville et al., 1989). Some clinicians consider to decrease recurrence rates by application routine additional excisional procedure at endocervical border after conventional LEEP that increase possibility of making surgical margins free from lesions.

In this study, we tried to assess the success rates of two step LEEP compared to conventional cold conization procedure.

Materials and Methods

This study was conducted on the 70 patients who underwent colposcopic evaluation in Zeynep Kamil Women and Children’s Health Training and Research Hospital between 2013 and 2015 that indicated for CIN 2 or 3 and persistent CIN 1 for more than 2 years. Study included age matched groups of patients with similar histopathological lesions who underwent cold conization (n=40) or LEEP (N=30). Cold conization was performed under general anesthesia, patients in lithotomy position, first of all cervical transformation was discriminated by application of lugol solution, then a conical tissue that extended to the endocervical area was excised by scalpel. Leep conization procedure was also performed under general anesthesia, similar to the cold conization after lugol solution application, a loop electrode (ACEL0041 triangular electrode, Loktal Medical Electronics, Sao Paulo, SP, Brazil) that fit to the volume of cervix was used to remove conical tissue that included transformation zone and some part of endocervical canal from the cervix followed by additional tissue removal from endocervix by the use of other small loop with sharp corners (ACEL0027 quadrangular, Loktal Medical Electronics, Sao Paulo, SP,

Table 1. Comparison of Tissue Characteristics Between the Two Groups

		N	Mean	SD	P Value
Diameter (mm)	CC	39	26.8	7.1	< 0,05
	LC	29	17.6	3.3	
Depth (mm)	CC	39	10.6	1.8	< 0,05
	LC	29	11.8	2.5	
Volume(mm ³)	CC	39	8540.8	4927.9	< 0,05
	LC	29	3949.7	1810.9	

CC: Cold conization, LC: LEEP conization

Table 2. Summary of Histopathological Findings before Intervention

	Groups			P Value
	CC	LC	Total	
AGUS	0	1	1	> 0.05
ASCH	1	0	1	
HGSIL	23	19	42	
LGSIL	15	9	24	
Total	39	29	68	

CC: Cold conization, LC: LEEP conization, AGUS: atypical glandular cells of undetermined significance, ASCH: atypical squamous cells of undetermined significance, a high-grade squamous intraepithelial lesion is not excluded as a possibility, LSIL: low-grade squamous intraepithelial lesions, HSIL: high-grade squamous intraepithelial lesions.

Table 3. Ectocervical and Endocervical Margin Positivity Rates in Groups

		CC	LC	Total	P Value
EcCM	Neg	38	29	67	> 0.05
	Pos	1	0	1	
	Total	39	29	68	
EnCM	Neg	30	29	59	< 0.05
	Pos	9	0	9	
	Total	39	29	68	

EcCM: Ectocervical conization margin, EnCM: Endocervical conization margin

Table 4. Summary of Histopathological Findings after Intervention

	Groups		Total	P Value
	CC	LC		
CIN1	4	4	8	> 0.05
CIN2	16	4	20	
CIN3	19	20	39	
SCC	0	1	1	
Total	39	29	68	

CIN: Cervical intraepithelial neoplasia, SCC: Squamous cell carcinoma, CC: Cold conization, LC: LEEP conization

Brazil). All the tissue removed after procedures were sent to histopathological examination after formalin fixation. Maximum diameter and the depth of for each specimen were measured and presented as milimeters and volume of conical tissue was calculated ($\pi r^2.h/3$).

Results

Comparison of tissue characteristics between two groups revealed significantly higher deepest length and lower volume of tissue removed by the two step leep (Table 1). Groups had similar histopathological findings before intervention (Table 2). Ectocervical positivity rate was similar between groups (1/39 versus 0/29, P >0.05, Table 3), while endocervical surgical margin positivity rate was significantly higher in cold conization group (9/39 versus 0/29, P<0.05, Table 3). Distribution of histopathological findings after conization was summarized in Table 4. Surgical margin positive cases were significantly older than the cases with negative margins (37.5 vs. 44.7, P<0.05).

Discussion

There are several treatment approaches towards cervical intraepithelial lesions. Each treatment approach has its own advantages and disadvantages. There are some well defined disadvantages for LEEP to be difficulty in surgical margin assessment, its expense, sometimes thermal artefacts and it needs experience to perform while disadvantages of cryotherapy are absence of histological samples to be assessed and most of the time it is appropriate for the low grade lesions to be applied. (Martin et al., 1999). Majority of the clinicians now prefer to perform leep due to its availability in office settings and well tolerability by the patients. (Shin et al., 2009).

Whichever procedure is preferred, the aim of the procedure should be to remove all the transformation

zone and the squamocolumnar junction. Surgical margin positivity for the lesion after procedure is a major risk factor for recurrence. (Malapati et al., 2011). According to the previous study, recurrence rate was found to be 53.8 % in patients with positive surgical margin whereas 12.9% in patients with negative margins. (Maluf et al., 2004). According to the other studies from literature recurrence rates reported to be higher in cases with positive margins (Siriaree et al., 2006). Presence of lesions at the margins are associated with viral persistence and lack of information about the grade of residual pathology (Nam et al., 2009).

There have been several articles published in the literature that compared effectiveness of cold conization and the LEEP. (Ayhan et al., 2009; Shin et al., 2009). As we mentioned above, when cold conization and the leep were compared with regard to margin positivity, the rate of positive margins were reported to be between 5.7 and 19% in cases with HGSIL. (Park et al., 2007). According to the metaanalyses published on this issue, the rate was reported to be 6.24 %. (Zhu et al., 2015). Variable rates have been reported for conizations for CIN lesions, 7.2 to 42.5 %, mean value of positive margins rate according to the different reports was between 14.1 to 19 %. (Narducci et al., 2000). On the other hand some studies reported higher rates of endocervical margin positivity after LEEP in cases with adenocarcinoma in situ (ACIS) at endocervical region. (Kennedy et al., 2002). According to the four different randomized trials that compared two different approaches in terms of surgical margin positivity revealed insignificantly increased rates of positive surgical margins in cases underwent leep. (Duggan et al., 1999). Other two different study reported no difference between conization and LEEP with regard to positive margins and disease recurrence. (Latif et al., 2014). Study suggested to excise tissue that extends at least 15 mm deeper into the endocervical canal (Munro et al., 2015). Most of the studies reported the results of one step leep and therefore endocervical margin positivity has been reported to be major contributor for the success of LEEP in the literature (Costa et al., 2000). due to the comparable rates of surgical margin positivity between the two approaches and the aforementioned advantages of LEEP over cold conization, in order to decrease endocervical margin positivity rate, we conducted this study to assess the efficacy of second intervention. (Martin et al., 1999; Latif et al., 2014). In our study we tried to assess the success rate of leep in terms of margin negativity with its advantages of lower blood loss and easy to perform (Frega et al., 2013; Latif et al., 2014). Our data revealed higher rate of margin positivity in conization furthermore depth of cervical tissue removed during procedure was significantly higher in group with two step LEEP. However an old study did not show any difference between one and two step leep with regard to surgical margin positivity and the recurrence (Wright et al., 1992). But in their study age of the patients was not classified and most of the lesions were low grade lesions. On the other hand consistent with our study, Kim et al reported two step procedure to significantly decrease surgical margin positivity rate (Kim et al., 2009).

In our study population, most of the surgical margin

positive cases were over 40 years of age and majority of the cases were postmenopausal, this result led us to conclude that two step LEEP approach was more effective in cases with invisible transformation zone due to advanced age and menopausal status (Zhu et al., 2015). According to the study by Shin et al, surgical margin positivity rate was found to be higher in cases over 45 years of age (Shin et al., 2009). with advancing age cervical tissue and the vaginal fornices start to shrink and be smaller, so that it may interfere with the successful excision of enough cervical tissue. Excision of tissues at deeper part of endocervix with higher longitudinal length with smaller base by two step leep has advantages over other techniques in advanced aged women with small cervix to obtain negative margins. Our data revealed favorable results with two step leep, especially in women over 40 years of age. And according to our experience it is difficult to determine the depth of tissue removed during cold conization due to the higher hemorrhage that deteriorates tissue exposure.

Studies in the literature on surgical margin positivity compared the volume and weight of tissue removed after two different procedures and values were found to be higher in group with cold conization. Fifty percent bigger and 100 % heavier tissues removed by cold conization compared to LEEP. (Fanning et al., 2002). In our study we found significantly higher tissue volume removed by cold conization compared to leep. According to some studies, volume of tissue removed by conization was associated with preterm labor risk (Sozen et al., 2013). Furthermore metaanalyses on this issue revealed significantly higher rates of preterm birth after cold or laser conization compared to LEEP (Bruinsma et al., 2011). Besides its obstetrical advantages in young population, two step LEEP make it easier to reach the squamocolumnar junction at endocervical region with lower blood loss and it is applicable in office settings. Our study suggests to use two step approach in cases with high grade and the glandular skip lesions.

Retrospective nature and the low number of study population are major drawbacks in our study, further prospective studies on larger group of patients are needed to clarify feasibility of this approach and identify appropriate candidates.

References

- Apgar BS, Kittendorf AL, Bettcher CM, et al (2009). Update on ASCCP consensus guidelines for abnormal cervical screening tests and cervical histology. *Am Fam Physician*, **80**, 147-55.
- Ayhan A, Boynukalin FK, Guven S, et al (2009). Repeat LEEP conization in patients with cervical intraepithelial neoplasia grade 3 and positive ectocervical margins. *Int J Gynecol Obstetrics*, **105**, 14 -7.
- Bruinsma FJ, Quinn MA (2011). The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. *Br J Obstetrics Gynaecol*, **118**, 1031-41.
- Castle PE, Schiffman M, Wheeler CM, et al (2009). Evidence for frequent regression of cervical intraepithelial neoplasia-grade. *Obstet Gynecol*, **113**, 18-25.
- Costa S, Nuzzo MD, Terzano P, et al (2000). Factors associated

- with cone margin involvement in CIN patients undergoing conization-equivalent electrosurgical procedure. *Acta obstetrica et gynecologica Scandinavica*, **79**, 586-92.
- Debarge VH, Collinet P, Vinatier D, et al (2003). Value of human papillomavirus testing after conization by loop electrosurgical excision for high-grade squamous intraepithelial lesions. *Gynecol Oncol*, **90**, 587-92.
- Duggan BD, Felix JC, Muderspach LI, et al (1999). Cold-knife conization versus conization by the loop electrosurgical excision procedure: a randomized, prospective study. *Am J Obstetrics Gynecol*, **180**, 276-82.
- Fanning, J, Padratzic J (2002). Cold knife conization vs. LEEP. Are they the same procedure? *J Reproductive Med*, **47**, 33-5.
- Frega A, Sesti F, De Sanctis, et al (2013). Pregnancy outcome after loop electrosurgical excision procedure for cervical intraepithelial neoplasia. *Int J Gynecol Obstetrics*, **122**, 145-9.
- Kennedy AW, Biscotti CV (2002). Further study of the management of cervical adenocarcinoma in situ. *Gynecologic Oncol*, **86**, 361-4.
- Kim K, Kang SB, Chung HH, et al (2009). Value of second pass in loop electrosurgical excisional procedure. *J Korean Med Sci*, **24**, 110-3.
- Kyrgiou M, Koliopoulos G, Martin-Hirsch P, et al (2006). Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet*, **367**, 489-98.
- Latif NA, Neubauer NL, Helenowski IB, et al (2015). Management of adenocarcinoma in situ of the uterine cervix: a comparison of loop electrosurgical excision procedure and cold knife conization. *J Lower Genital Tract Disease*, **19**, 97-102.
- Mahadevan N, Horwell DH (1993). Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful followup, not retreatment. *Br J Obstet Gynaecol*, **100**, 794-5.
- Malapati R, Chaparala S, Cejtin HE (2011). Factors influencing persistence or recurrence of cervical intraepithelial neoplasia after loop electrosurgical excision procedure. *J Lower Genital Tract Disease*, **15**, 177-9.
- Maluf PJ, Adad SJ, Murta EFC (2004). Outcome after conization for cervical intraepithelial neoplasia grade III: relation with surgical margins, extension to the crypts and mitoses. *Tumori*, **90**, 473-7.
- Martin-Hirsch PL, Paraskevaidis E, Kitchener H (1999). Surgery for cervical intraepithelial neoplasia. *Cochrane Database Syst Rev*, **3**.
- McCredie MR, Sharples KJ, Paul C, et al (2008). Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncol*, **9**, 425-34.
- Munro A, Leung Y, Spilsbury K, et al (2015). Comparison of cold knife cone biopsy and loop electrosurgical excision procedure in the management of cervical adenocarcinoma in situ: What is the gold standard? *Gynecologic Oncol*, **137**, 258-63.
- Nam K, Chung S, Kim J, et al (2009). Factors associated with HPV persistence after conization in patients with negative margins. *J Gynecologic Oncol*, **20**, 91-5.
- Narducci F, Occelli B, Boman F, et al (2000). Positive margins after conization and risk of persistent lesion. *Gynecologic Oncol*, **76**, 311-4.
- Park JY, Lee SM, Yoo CW, et al (2007). Risk factors predicting residual disease in subsequent hysterectomy following conization for cervical intraepithelial neoplasia (CIN) III and microinvasive cervical cancer. *Gynecologic Oncol*, **107**, 39-44.
- Prendiville W, Cullimore J, Norman S (1989). Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. *BJOG: An Int J Obstetrics Gynaecol*, **96**, 1054-60.
- Ramos MC, Pizarro DLB, Michelin MA, et al (2007). High-grade cervical intraepithelial neoplasia, human papillomavirus and factors connected with recurrence following surgical treatment. *Clin Experimental Obstetrics Gynecol*, **35**, 242-7.
- Sangkarat S, Ruengkachorn I, Benjapibal M et al (2014). Long-term outcomes of a loop electrosurgical excision procedure for cervical intraepithelial neoplasia in a high incidence country. *Asian Pac J Cancer Prev*, **15**, 1035-9.
- Shin JW, Rho HS, Park CY (2009). Factors influencing the choice between cold knife conization and loop electrosurgical excisional procedure for the treatment of cervical intraepithelial neoplasia. *J Obstetrics Gynaecol Res*, **35**, 126-30.
- Siriaree S, Srisomboon J, Kietpeerakool C, et al (2006). High-grade squamous intraepithelial lesion with endocervical cone margin involvement after cervical loop electrosurgical excision: what should a clinician do? *Asian Pac J Cancer Prev*, **7**, 463.
- Sozen H, Namazov A, Cakir S, et al (2013). Pregnancy outcomes after cold knife conization related to excised cone dimensions. A retrospective cohort study. *J Reproductive Med*, **59**, 81-6.
- Tillmanns TD, Falkner CA, Engle DB, et al (2006). Preoperative predictors of positive margins after loop electrosurgical excisional procedure-cone. *Gynecol Oncol*, **100**, 79-84.
- Wright Jr TC, Gagnon S, Richart RM, et al (1992). Treatment of cervical intraepithelial neoplasia using the loop electrosurgical excision procedure. *Obstetrics Gynecol*, **79**, 173-8.
- Zhu M, He Y, Baak JP, et al (2015). Factors that influence persistence or recurrence of high-grade squamous intraepithelial lesion with positive margins after the loop electrosurgical excision procedure: a retrospective study. *BMC Cancer*, **15**, 1.