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Loop Electrosurgical Excision Procedure and Cold Knife Conization: which is the best? A large retrospective study

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ABSTRACT

Objective. This study was performed to compare Loop Electrosurgical Excision Procedure (LEEP) and Cold Knife Cone (CKC) biopsy in the treatment of Cervical Intraepithelial Neoplasia (CIN) in terms of oncological outcome, effectiveness, and safety.
Materials and Methods. In this retrospective observational study with a follow-up of 24 months patients with CIN at diagnosis were enrolled between January 2016 and July 2019. The primary outcome included: persistent disease rate, recurrent disease rate and cone biopsy positive margins. As secondary end point, we evaluated surgical time, bleeding within 24 hours, infections related to the procedure and cone size.
Results. Ninety- six women were enrolled: 60 in LEEP group and 36 in cold knife conization group. Women undergoing LEEP procedure had similar primary oncological outcome without any statistical difference than those undergoing CKC (persistent disease 6 (10%) *vs* 2 (7.6%), recurrent disease 5 (8.3%) *vs* 4 (11.1%), positive margins 12 (20%) *vs* 7 (19.4%). Secondary endpoint included post-operative bleeding within 24 hours with a significant difference between two groups (4 (6.6%) in LEEP group and 8 (22.2%) in CKC group, p = 0.026). The remaining outcome measures, surgery time (200-215 sec.), cone size (0.86-1.57 cm^3) and post-operative infections, have no significant differences.
Conclusions. The surgical conization techniques evaluated gave encouraging and balanced results in terms of oncological outcome, but the LEEP technique should be considered as the primary technique for the treatment of CIN due to its simplicity of execution, cost reduction and less postoperative complications.

INTRODUCTION

Cervical cancer is the fourth most common cancer in women worldwide [1]. Cervical intraepithelial neoplasia (CIN) is a premalignant lesion of cervical cancer, and it is classified by histology as CIN 1, CIN 2 or CIN3 [2]. The CIN1 category applies to histopathologically low-grade cervical squamous intraepithelial lesions (L-SIL), whereas CIN2 and CIN3 are often joined together and apply to high-grade cervical squamous intraepithelial lesions (H-SIL). For the past 30 years screening programs, using cytology combined with human papilloma virus testing, have markedly decreased the incidence of death due to cervical cancer [3-6]. As recommended by the 2019 ASCCP Risk-Based Management

Consensus, while observation is preferred to treatment for CIN 1, excisional treatment is preferred to ablative treatment for histologic HSIL (CIN 2 or CIN 3) [7, 8]. According to 2014 WHO guidelines, there are three principal treatments for CIN: cryotherapy, large loop excision of the transformation zone (LLETZ, or LEEP), and cold knife conization (CKC) [9]. Conization of the cervix is the excision of a cone shaped portion of the cervix to remove a cervical lesion and the entire transformation zone. These procedures could be a potential risk for future pregnancies. Some studies show an increased risk of preterm delivery, low birth weight and p-PROM (premature prelabor rupture of membranes) in pregnancies after conization compared to untreated women [10-14]. Although CKC has been the traditional procedure for CIN, LEEP has been the most used method for CIN due to its several advantages, including shorter operative time, ease of performance, and low cost [15-17]. There are few randomized controlled trials to definitively prove the superiority of LEEP procedure over cold knife conization (CKC) [18]. This study compares the two procedures evaluating the disease recurrence rate and the residual disease rate after 24 months follow-up, the positivity of the cone margins, the surgical times and the early post-operative complications, with the aim of clarifying the aspects related to surgical procedures, in order to be able to guide the choice of specialist.

MATERIALS AND METHODS

This retrospective observational study was performed at the Maternal and Child Health and Urological Sciences Department, Policlinic Umberto I hospital, Sapienza University of Rome, between January 1, 2016, and July 31, 2020. The study was approved by our Internal Review Board. Informed consent was obtained from all participants. All women with intraepithelial cervical neoplasia confirmed by a cervical cytological testing and colposcopically directed biopsies of the portion, were enrolled. Inclusion criteria were as follows: age over 18 years old, a positive biopsy for L-SIL or H-SIL and a signed informed consent. Exclusion criteria included concomitant HIV (Human Immunodeficiency Virus) infection, pregnancy, a personal history of conization, concomitant oncological disease and the use of an anticoagulant medication. All treatments were performed with local anesthesia (lidocaine 1%, 10 mg/ml) and intraoperative colposcopy. In both techniques, hemostasis was achieved with diathermocoagulation with a ball electrode. Two surgeons performed the conization with the same surgical skills. Patients were scheduled for a visit, 4-6 weeks apart, with a follow-up of 24 months, receiving cervical cytological testing, colposcopy and/or cervical biopsy. The first post-operative check-up was performed up to 6 months after surgery, considering any disease found at follow-up as persistence of the disease. Persistent disease was defined as the diagnosis of CIN within 6 months after the procedure; recurrent disease was defined as diagnosis of CIN 6 or more months after initial treatment. The resection margin was considered as positive or negative based on the presence or absence of abnormal cells at the margin of the cone. Secondary endpoints included post-operative bleeding within 24 hours assessing with necessity or not of vaginal gauze at the end of procedure. Vaginal gauze allows you to control bleeding within 24 hours by evaluating its possible complete imbibition by blood and potential bleeding after its removal. Other secondary endpoints of this study were: cone size calculated as volume (approximate as a pyramid) of the cone specimen, surgical time was measured in seconds from the start of excision until diathermocoagulation hemostasis ended and post-operative infections after 24 hours after treatment were evaluated by necessity of hospitalization or antibiotics. Data were summarized using standard descriptive statistics. All calculated P-values were 2-sided and P-values < 0.05 were considered statistically significant. Analyses were performed using the IBM-Microsoft SPSS version 25.0 for Windows.

RESULTS

The study population included one hundred twenty patients affected by cervical intraepithelial neoplasia or carcinoma in situ. Nine patients refused enrollment and fifteen decided to perform hysterectomy. A total of 96 women were included in our study: 60 were performed loop electrosurgical excision procedure (LEEP) and 36 a cold knife conization (CKC). All patient characteristics and the severity of lesions were comparable between the two groups (**Table 1**). The original diagnosis before surgery was for group A: L-SIL/CIN1, 15 (25%), H-SIL/CIN2-3, 41 (68.3%), microinvasive cervical cancer (pT1a1), 4 (6.7%); and for group B: L-SIL/CIN1 6 (16.6%), H-SIL/CIN2-3,

25 (69.4%), microinvasive cervical cancer (pT1a1), 5 (13.8%). **Table 2** shows a comparison of the primary and secondary outcomes. Specifically, we compared disease recurrence, residual disease and positive margins as primary outcome measures and surgical time, cone size and post-operative complications as secondary endpoint. The disease recurrence monitoring in a range of 6 months to 24 months were 5 cases (8.3%) and 4 (11.1%), the residual disease monitoring up to 6 months were 6 cases (10%) and 2 (7.6%) and the positive margins were 12 (20%) and 7 (19.4%) in LEEP group and CKC group, respectively. All primary outcomes did not statistically differ between groups. As secondary endpoint, procedure time in seconds: 200 (170-230) and 215 (185-245). A statistically significant difference was found in post-treatment hemorrhages within 24 hours. In detail, in the LEEP group 4/60 (6.6%) women had a post-treatment bleeding needed vaginal tamponade and in CKC group 8/36 (22.2%) women reported the same complications (p = 0.026). Cones are larger in cold knife conization, without any statistical significance (1.57 cm3 in CKC and 0.86 cm3 in LEEP group). No post-operative infections requiring hospitalization or antibiotics were found during this study.

DISCUSSION

Many studies have compared the two techniques of conization in terms of difficulty of execution, timing, costs, complications, and efficacy [19-23]. In a recent meta-analysis, the risk of post-operative bleeding within 24 hours in CKC compared to LEEP was not statistically significant (RR 1.05, 95% CI, 0.50-2.21, p = 0.90) [18]. In our study, post-operative bleeding was found to be less after LEEP, with a statistical significance that could suggest the preferential use among this conization technique, thanks to less blood loss and less discomfort of the patient. Many studies have evaluated risk of residual disease and recurrent disease [24-26]. The risk of residual disease is around 6.1% in patients treated with CKC and 11.2% in patients treated with LEEP (RR 0.54, 95%CI, 0.30-0.96, p = 0.04) [18, 27, 28]. The residual rate of cervical lesions in patients with positive margins who underwent a second surgery after the initial LEEP was 45.5% [29]. In this study, the residual disease is greater in LEEP treatment according to the literature, but the difference between procedures is not statistically significant. According to Hurtado-Roca meta-analysis, prevalence of relapse after cold cone treatment was 2.0% and 7.1% in patients treated with LEEP and there was not statistically significant difference in the risk of disease recurrence between patients treated for CIN with cold cone compared to LEEP (RR 0.32, 95% CI, 0.09-1.14, p = 0.08) [18]. In a retrospective multi-institutional study, among the measures analyzed, the only one associated with an increased risk of recurrence after conization is the persistence of HPV and women with HPV vaccination have a lower risk of relapse of the disease, even if not statistically different [30, 31]. In our study the relapse rates are similar between the two techniques: in the group treated with CKC we observed 4 cases during follow-up, while in the group of patients treated with LEEP 5 cases were observed, which represent 11.1% and 8.3% respectively. In a recent review, women with multiple HR-HPV infection have a significant risk factor for severe cervical lesions [32]. In a retrospective multi-institutional study, patients with high grade HR-HPV-negative cervical dysplasia have more favorable outcomes than patients with documented HR-HPV infection [33]. Furthermore, deregulation of some genes such as NR2F6, LOXL2 and DMBT1, could lead to unfavorable oncological

Table 1. *Patients characteristics.*

	LEEP N = 60	Cold knife conization N = 36	p
Age, mean ± SD	41.8 ± 13.6	43 ± 12.8	NS
BMI, mean ± SD	26 ± 2	26 ± 2	NS
Smoke, n (%)	22 (36.6%)	15 (41.6%)	NS
E/P, n (%)	13 (21.6%)	8 (22.2%)	NS
L-SIL/CIN1, n (%)	15 (25%)	6 (16.6%)	NS
H-SIL/CIN2-3, n (%)	41 (68.3%)	25 (69.4%)	NS
Microinvasive cervical cancer, n (%)	4 (6.7%)	5 (13.8%)	NS

SD: standard deviation; BMI: body mass index; E/P: estroprogestinic therapy; L-SIL: low-grade cervical squamous intraepithelial lesions; H-SIL: high-grade cervical squamous intraepithelial lesions; CIN: cervical intraepithelial neoplasia.

Table 2. *Primary and secondary outcome measures.*

	LEEP N = 60	Cold knife conization N = 36	p
Residual Disease: (monitoring: up to 6 months)	6 (10%)	2 (7.6%)	NS
Disease Recurrence (monitoring: range 6 months to 24 months)	5 (8.3%)	4 (11.1%)	NS
Positive Margins, n (%)	12 (20%)	7 (19.4%)	NS
Bleeding within 24 hrs, n (%)	4 (6.6%)	8 (22.2%)	0.026
Cone size (cm^3), mean	0.86	1.57	NS
Surgery time (sec), mean ± SD	200 ± 30	215 ± 30	NS
Post-operative infections	0	0	NS

LEEP: Loop Electrosurgical Excision Procedure; CKC: Cold Knife Conization, SD: standard deviation.

outcomes in patients with cervical cancer [34]. A multicenter study has confirmed that preoperative conization could play a protective role in the risk of disease recurrence in patients with an early stage cervical cancer (IB1) [35]. The positivity of the histological margins does not seem to be correlated with the type of technique used and our study also confirmed this finding [17, 24-26]. In this prospective, it would be interesting to assess a fragility score able to predict morbidity and mortality for these procedures, as has been done in other cancers [36, 37]. In this way, we could broaden the approach for gynecological cancers [38]. About cone sizes, despite the small size of the cone, the LEEP technique provides a sample that is adequate for histological analysis and allows optimal colposcopic surveillance than CKC [17]. A randomized trial recommends the use of the LEEP technique for CIN 2-3 lesions with no evidence of microinvasion at the preoperative evaluation and in small extension of endocervical lesions, because pathological evolution and thermal artefacts are less important in the management of the disease. CKC technique should be preferred when endocervical extension is massive and microinvasion cannot be ruled out [25]. Post-operative infections are not related to the type of technique used and we have not had any cases requiring hospitalization [39]. Furthermore, LEEP procedure is usually performed in an outpatient low-cost clinic setting, while CKC procedure is usually performed under anesthesia in a hospital setting with significantly higher costs [40].

CONCLUSIONS

This study provides data showing the safety of the two techniques in terms of oncological outcome. The LEEP technique should be considered as the primary technique for the treatment of CIN due to its simplicity of execution, cost reduction and less postoperative bleeding. Our data are reassuring but the relatively small number of patients means the results should be confirmed in larger groups of patients.

COMPLIANCE WITH ETHICAL STANDARDS

Author contributions

V.G., P.M.: Conceptualization. A.G., O.O.: Supervision. A.V., G.S., T.G.D., V.T.: Writing - original draft preparation. A.G., O.O., A.M., M.M.: Review and editing. All authors have read and agreed to the published version of the manuscript.

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Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

A written informed consent was obtained from all subjects.

Data sharing

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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