



Results of five year-follow up of patients treated with loop electrosurgical excisional procedure / cold-knife conization

Loop elektrocerrahi eksizyonel prosedür / soğuk konizasyon yapılan hastaların beş yıllık takip sonuçları

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ABSTRACT

Aim: Aim is to questioning the recurrence rate of Human Papilloma Virus (HPV) and cervical pathology after five year- follow up of patients treated with Loop Electrosurgical Excisional Procedure (LEEP)/Cold-Knife Conization. Due to cervical intraepithelial neoplasia so as to determine the competence of the surgical procedures. **Materials and Methods:** Retrospective analysis of 87 patients who attended between January 2011-December 2015, aged between 24-74 years, with the result of CIN I - II - III in their Pap smear tests, were included in. Demographic findings; age, parity, smoking, menopausal statue were recorded. The patients treated with LEEP/Cold-Knife Conization due to CIN I - II - III, were followed by co-test till 2020 and 5 year results were evaluated. **Results:** 87 patients were analyzed and the mean age of them was 35.1±1.71 (24-74). Parity 2.4±1.2 (0-11) and mean smoking was found to be 8 cigarettes/day (0-40/day). 67(77%) of cases were in premenapouse, 20 (23%) of them were in postmenapousal period. According to the colposcopy assisted cervical biyopsi results 45 (51.7%) cases were diagnosed as CIN I, 21 (24.1%) CIN II and rest 21 (24.1%) cases were found to be CIN III. Secondary surgery was needed due to positive surgical margin was recorded in 6 (6.8%) patients after LEEP. Routine annual follow-up was done. No abnormal cytologic Pap-smear result was recorded during these follow-ups. At the end of the 5 year follow-up; no recurrence was obtained from the co-test results. **Conclusions:** Our results put forth that HPV and cervical pathology could be eradicated after five year- follow up of patients treated with LEEP/Cold-Knife Conization if appropriate indications and techniques are applied.

ÖZ

Amaç: Loop Elektrocerrahi Eksizyonel Prosedür (LEEP)/soğuk konizasyon uygulanan servikal intraepitelyal neoplazi tanılı hastalarda, 5 yıllık takip sonrası servikal patoloji rekürrensini ve insan papilloma virus pozitifliğini ortaya çıkarmak, yapılan cerrahi tedavinin HPV'yi eradike etmekte yeterli olup olmadığını sorgulamaktır. **Gereç-Yöntem:** Retrospektif analize Ocak 2011- Aralık 2015 tarihleri arasında Pap smear test sonucu CIN I - II - III çıkan, 24-74 yaş arasında, kolposkopik biyopsi yapıp, HPV DNA genotip tayini olan 87 hasta dahil edildi. Olguların yaş, parite, sigara kullanımı, menopoz durumu gibi demografik özellikleri kaydedildi. CIN I - II - III nedeni ile LEEP veya konizasyon yapılan hastalar 2020 yılına kadar co-test ile yıllık takip edilip, 5 yıllık takip sonuçları değerlendirildi. **Bulgular:** İncelenen 87 hastanın yaş ortalaması 35,1±1,71 (24-74), parite 2,4±1,2 (0-11) ve sigara kullanımı ortalama 8 adet/gün (0- 40 adet/gün) olarak saptandı. Olguların 67'si (%77) premenopoz, 20'si (%23) postmenopoz dönemde idi. Kolposkopi eşliğinde alınan servikal biyopsi sonuçlarında 45 (%51,7) olguda CIN I, 21 (%24,1) CIN II ve 21 (%24,1) olguda CIN III tespit edildi. Yapılan LEEP sonrası 6 (%6,8) hastada cerrahi sınır pozitifliği nedeni ile ikinci cerrahi girişim yapıldı. Olgular rutin takibe yıllık olarak alındı. Takiplerde anormal Pap-smear sitoloji saptanmadı. Olguların 5 yıllık takip sonrası co-test sonuçlarında rekürrens saptanmadı. **Sonuç:** Bulgularımız CIN I - II - III saptanan olgularda, LEEP/soğuk konizasyonun uygun endikasyon ve uygun teknikle yapılmasının, HPV DNA ve CIN rekürrensini 5 yıllık takipler sonucu ortadan kaldırdığını göstermektedir.

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INTRODUCTION

Cancer is a serious problem with significant social and economic impacts on the human health. Despite advances in diagnosis, screening, and treatment, it still affects millions of people around the world, decreases the quality of life, and ranks second in death causes in the world. In studies, approximately 40% of humans will be diagnosed with cancer at some time in their lives and will need treatment (1,2).

Therefore, early diagnosis is of great importance. Cervical cancer ranks fourth in cancer in women, and

after the detection of the human papillomavirus (HPV) in its etiopathogenesis, it has regressed to 13th place in developed countries thanks to effective screening programs. It is one of the rare cancer types where prevention methods can be used effectively, thanks to its preventable risk factors and the existence of screening programs. In the primary prevention of cervical cancer, it is important to raise awareness of cervical cancer in society and to apply the HPV vaccine. For secondary prevention, routine screening is performed with a co-test in which Pap-smear test and HPV DNA analysis are performed together (3,4).



Patients with cervical intraepithelial lesions (CIN) are planned to be followed up and treated according to colposcopic cervical biopsy results. There are different approaches in the treatment and follow-up process of CIN I-II-III, which is frequently caught in the reproductive age. Removal or destruction of precancerous lesions prevents the risk of developing cervical cancer by 95% in the first eight years. With ablative treatments such as cryotherapy, laser ablation, excisional treatment such as cold conization, laser conization and Loop Electrosurgical Excisional Procedure (LEEP) can be applied. LEEP is an effective, cost-effective, frequently preferred, and widely used surgical procedure in which the cervical tissue is removed to a depth of 6-10 mm. Although evaluation of the surgical margin is better than other procedures in cold conization, it is less preferred due to the higher amount of bleeding and the need for general anesthesia. Although the surgical margin is negative, the probability of recurrence after treatment with both methods varies between 5% and 17% in a 20-year period (5,6).

The purpose of our retrospective study is to reveal the clinical pathology recurrence and HPV positivity after 5 years of follow-up in patients with CIN undergoing LEEP / cold conization and to question whether the surgical treatment performed is sufficient to eradicate HPV.

MATERIALS AND METHODS

Retrospective analyses of 104 patients who were admitted to our clinic with various complaints and whose pap smear tests resulted in CIN I - II - III among 10,832 tests between January 2011 and December 2015. These patients had not been diagnosed with cervical lesions before. 87 patients between the ages of 24-74 who underwent colposcopic biopsy and had HPV DNA genotype determination were included in the study. The remaining 17 patients were excluded from the study because no HPV-DNA result was found. Demographic characteristics of the patients such as age, parity, smoking, and menopausal status were recorded.

Co-tests were stored in ThinPrep solution (Cytoc's ThinPrep PreservCyt medium - Hologic USA), and HPV typing was performed using the Aptima Panther test (Thinprep 5000 processor Aptima® HPV 16 18/45 genotype assay - Hologic, USA). PAP smears were reported according to the modified Bethesda system. Aptima test used in our study; It is the test that scans 14 high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) HPV types with E6 / E7 mRNA. Type 16, type 18/45 were reported separately whilst the remaining 11 types were reported collectively.

In the colposcopy (Karl Kaps GmbH and Co.KG, Asslar / Wetzlar, Germany) performed by three specialist

physicians with more than 10 years of experience, a cervical biopsy was performed using 5% acetic acid and Lugol solution under 40x magnification. Paraffin blocks prepared from tissue samples were cut in 5-micron thickness and the preparations were stained with Hematoxylin-Eosin. The cuts were evaluated under a light microscope by the same pathologist who had 30 years of experience in the field. Cervical biopsy results performed with colposcopy were defined as chronic cervicitis, CIN I - II - III, and invasive cervical cancer. Patients who underwent conization due to CIN III and LEEP due to CIN I-II were followed up annually with PAP smear until 2020, and their 5-year follow-up results were evaluated. These follow-ups were made annually, and at the end of the 5th year, the co-test was repeated and the results were recorded. Approval was obtained from the local ethics committee for the study. Detailed information was given to the patients before each procedure and their consents were obtained. Research data were evaluated using the SPSS statistics 22.0 program. Quantitative variables were shown as mean \pm SD (Standard Deviation) - (Minimum / Maximum), while categorical variables were shown as n (%). The study was found ethically appropriate with the decision of the Ethics Committee of ATADEK, dated 28/01/2021 and numbered 2021-02/09.

RESULTS

Retrospective analyses of 87 patients who were admitted to our clinic with various complaints between January 2011 and December 2015, who were not diagnosed with cervical lesions before, and whose cytology results were CIN I - II - III and evaluated by co-test and colposcopic cervical biopsy was performed in our study. The distribution of the cases according to demographic data is shown in Table 1. In the results of a cervical biopsy taken with colposcopy, CIN I in 45 (51.7%) cases, CIN II in 21 (24.1%), and CIN III in 21 (24.1%) cases were detected. After LEEP, a second surgical intervention was performed in 6 (6.8%) patients because of surgical margin positivity, and the second procedure was always cold conization.

Patients who underwent LEEP or conization were followed annually with Pap-smear until 2020, and a 5th-year co-test was repeated. HPV DNA typing and colposcopic cervical biopsy results of the patients and the co-test results after 5 years of follow-up are given in Table 2. As a result, HPV DNA positivity and abnormal Pap-smear findings were not detected in all cases.

In our study, the most common HPV types were HPV type 16 with a frequency of 47.1% (41 cases), the other 11 HPV types with 21.8% (19 cases), and the third most common HPV type 18/45 with 12.6% (11 cases). In the

Table 1. Demographic characteristics of the patients (n=87)

Age	35,1±1,71 (24 - 74)
Parity	2,4±1,2 (0 - 11)
Smoking	8 pcs / day (0 - 40 pcs / day) 40 (%45,9)
Menopause status	
Premenopause	67 (%77)
Postmenopause	20 (%23)
Complaint	
Vaginal discharge	40 (%46)
Postcoital bleeding	20 (%22)
Irregular period	2 (%4)
Condyloma	5 (%6)
Control	20 (%22)
First coitus age	24,3±1,41 (14 - 40)
Contraception	
Condom	15 (%17)
Oral contraceptives	30 (%34)
Intrauterine device	20 (%22)
Injection	10 (%12)
Tubal ligation	5 (%6)
None	7 (%9)

Table 2. Comparison of HR-HPV DNA types with biopsy results.

HR-HPV DNA	CIN I (n=45)	CIN II (n=21)	CIN III (n=21)	Postoperative first 5 years
Negative	16 (% 35.5)	0 (% 0)	0 (%0)	87 (% 100)
Type 16	15 (% 33.3)	14(% 66.6)	12 (% 57.1)	0 (% 0)
Type 18/45	6 (% 13.3)	3 (% 14.2)	2 (% 9.5)	0 (% 0)
Other 11 Type	8 (% 17.7)	4 (% 19)	7 (% 33.3)	0 (% 0)

HR-HPV DNA: High risk oncogenic HPV DNA, CIN: Cervical Intraepithelial Lesion

remaining 16 patients, HPV DNA analysis was negative, and all of these cases were in the group with CIN I. No abnormal Pap-smear or co-test results were found in any of the patients, regardless of the surgical technique used during follow-up.

Although short and long-term complications were not encountered in both surgical techniques, spontaneous pregnancy developed in the first three months after conization in 3 of the cases. These cases gave birth at term without the need for cerclage.

DISCUSSION

With the presence of HPV for cancer formation, it is thought that certain risk factors either increase the rate of exposure to the virus or the viral persistence accelerates the carcinogenic process. More than 70% of women are exposed to HPV at some time in their lives and it is known that more than 70% of them are between the ages of 15-24 (7,8).

Although the diagnosis rate of CINs has increased due to the long pre-invasive period and effective screening programs, the expectation of fertility at the age of

diagnosis in most patients leads to the avoidance of radical surgical procedures. The goal of CIN treatment is to eradicate the transformation zone. The most common surgical methods for this are LEEP and cold conization. However, excessive removal of tissue from the cervix may cause cervical insufficiency in patients who are young and did not give birth. Therefore, it should be performed with appropriate indications and appropriate technique. In our study, spontaneous pregnancy developed in the first three months after conization in 3 of the patients in both surgical techniques and there was no need for cerclage.

In our study, 5-year follow-up results after LEEP / cold conization were evaluated. This evaluation was carried out by retrospective analysis of 87 patients whose cervical histology result was positive for CIN and high-risk HPV DNA scanning results, whose diagnosis was confirmed by cervical biopsy under colposcopy.

There was no recurrence in the follow-up period of 51 months after LEEP in 31 CIN III cases by Bryson et al. Therefore, they claim that LEEP treatment is safe, and that a second treatment is not required in patients with negative margin (9).

Likewise, in the study conducted by Reich et al. on 4417 patients with histologically detected HGSIL and negative surgical margin after conization, HGSIL recurrence was detected in only 15 cases after 18 years of follow-up. The recurrence time is on average 8.9 years, and no recurrence was observed in the remaining 99.7% group (10).

In accordance with the literature, HPV DNA positivity and pathology recurrence were not detected in all cases in our retrospective analysis. We think that the reasons for this are the close monitoring of the cases, supporting them with food supplements and 95% of the smoking group quitting smoking. We think that there is a possibility of recurrence when the follow-up period of our cases is extended. Therefore, longer follow-up results are needed.

On the other hand, in the study of Kim et al., 39.7% margin positivity was found in those who had conization with LEEP, and residual disease was found in 16.7% of margin negative cases. This indicates that there may be residual disease also in margin negative cases and care should be taken in terms of patient follow-up (11).

There is no consensus on the follow-up of patients who underwent conization due to CIN, but patients with positive surgical margins and high-risk HPV-infected patients should be followed up more frequently. In addition, all patients are recommended to follow-up for at least 10 years and cytological screening is considered to be sufficient for follow-up. Because, histological cervical intraepithelial neoplasia was not found in any of the cases with normal cytology (12).

In the study of Azodi et al., the comparison of conization techniques was made and they revealed that the margin positivity is seen at the least rate in the cold conization technique (13).

In accordance with the literature, we performed the second surgical intervention as cold conization due to the positivity of surgical margins in 6 (6.8%) patients after LEEP. Surgical margin positivity was not found in any of the patients who underwent cold conization as primary surgery.

In the study of Günay et al., the success rate of surgical margin negativity was similar with LEEP and cold conization technique. Our study was also found similar to the literature (14).

However, we think that the limiting factors of the study are that our evaluations are based on the results obtained from a single center, the HPV DNA typing is only looked at 16, 18 and 45, other oncogenic HPV types are not genotyped, and the number of patients is limited. In addition, 5-year follow-up of the cases is not

sufficient in terms of recurrence. With longer follow-up, it may be possible to detect both high-risk HPV DNA positivity and histopathological recurrence. Therefore, larger prospective randomized controlled studies are needed.

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