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Konizasyon Sonrası Pozitif Ve Negatif Cerrahi Sınırı Olan Hastalarda Hematolojik Parametrelerin Karşılaştırılması

Comparison Of Hematologic Parameters In Patients With Positive vs. Negative Surgical Margins After Conization

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ÖZ

Giriş: Tam kan sayımı parametrelerinin soğuk konizasyon sonrası cerrahi sınır pozitifliğini predikte etmesindeki faydasının değerlendirilmesi.

Gereç ve Yöntemler: 2009 – 2013 yılları arasında biyopsi tanısı yüksek grade skuamöz intraepitelyal lezyon olup soğuk konizasyon uygulanan hastalar retrospektif olarak incelendi. 63 cerrahi sınır pozitif hasta çalışma grubu (Grup 1) ve 168 cerrahi sınır negatif hasta kontrol grubu (Grup 2) olmak üzere toplamda 231 hasta çalışmaya dahil edildi. Pozitif cerrahi sınırlar ile yaş, koni boyu, koni derinliği, koni çapı ve tam kan sayımı parametrelerinin ilişkisi değerlendirildi.

Bulgular: Hastaların ortalama yaşı 41.9'du. Grup 1'deki bütün hastaların konizasyon sonrası patoloji sonucu yüksek grade skuamöz intraepitelyal lezyondu. Grup 2'deki 5 hastanın konizasyon sonrası patoloji sonucu mikroinvaziv karsinom, 108 hastanın yüksek grade skuamöz intraepitelyal lezyon, 35 hastanın düşük grade skuamöz intraepitelyal lezyon ve 20 hastanın patoloji sonucu ise normal olarak raporlandı. Grup 1'deki 52 hastaya tekrar eksizyonel prosedür veya basit histerektomi uygulandı. Bu hastaların 24'ünde rezidüel hastalık saptandı. Her iki grup arasında nötrofil/lenfosit oranı, platelet/lenfosit oranı ve ortalama platelet volümü açısından istatistiksel olarak anlamlı bir farklılık saptanmadı (Sırasıyla p=0.7, p=0.96 ve p=0.81).

Sonuç: Nötrofil/lenfosit oranı, platelet/lenfosit oranı ve ortalama platelet volümü soğuk konizasyon sonrası pozitif cerrahi sınırı predikte etmede faydalı olarak gözükmemektedir.

Anahtar Kelimeler: Cerrahi sınır, nötrofil/lenfosit oranı, ortalama platelet volümü, platelet/lenfosit oranı,soğuk konizasyon

ABSTRACT

Aim: To evaluate the utility of complete blood count to predict positive surgical margins after cold knife conization (CKC).

Material and Methods: Woman who underwent CKC because of biopsy - proven high-grade squamous intraepithelial lesions (HSIL) between 2009 and 2013 were retrospectively analyzed. Out of 231 woman in total, primarily referring 63 surgical margin positive women were included as the study group (Group 1), 168 surgical margin negative women were selected as the control group (Group 2). The relation between the positive surgical margins and age, height of cone, depth of cone, diameter of cone, complete blood count parameters was assessed.

Results: The mean age of the patients were 41.9 years. The conization result of all patients' in Group 1 was HSIL. The conization results of Group 2 were microinvasive carcinoma, HSIL, low-grade squamous lesion (LSIL) and no residual disease for 5, 108, 35 and 20 patients, respectively. 52 women in Group 1 underwent either repeat excisional procedure or simple hysterectomy and 24 of them showed residual disease. There was no statistically significant difference in regard to neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and mean platelet volume (MPV) occurred between two groups (p=0.7, p=0.96 and p=0.81 respectively).

Conclusion: Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio and MPV do not seem to be useful in predicting positive surgical margins after CKC.

Keywords: Cold knife conization, mean platelet volume, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, surgical margin

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Introduction

High-grade squamous intraepithelial lesion (HSIL) is one of the preventable pre – invasive disease of the cervix. The recommended management of biopsy-proven HSIL leads to decreased incidence of cervical cancer (1). In cases where the lesion cannot be completely removed, it may lead to positive surgical margins. Involvement of surgical margins on pathological examination is an established risk factor for recurrence and persistence of cervical intraepithelial neoplasia (CIN) (2). On the other hand, patients who underwent a repeat surgical operation may experience difficulties in getting pregnant or maintaining pregnancy (3).

It is well known that many cancers develop from sites of infection, chronic irritation, and inflammation. Inflammation influences each single step of tumor genesis, from tumor initiation to promotion and metastatic progression (4). Neutrophils and lymphocytes are closely correlated with local inflammation and immune responses, respectively. Recently, neutrophil-to-lymphocyte ratio (NLR) and platelet-to- lymphocyte ratio (PLR) have been introduced as associated with prognosis in various cancer types (5,6).

Mean platelet volume (MPV), which can be easily evaluated by hematological analyzers, is a convenient marker of platelet functions and activation. It shows the average size of platelets and reflects the platelet production rate and stimulation (7). The presence of platelets is increased by pro-inflammatory cytokines released by cancer cells through the promotion of megakaryocyte proliferation (8). It is also known that alterations of MPV can also be used as an indicator of disease severity in many of the systemic inflammatory diseases (9).

Nevertheless, NLR, PLR and MPV as a marker of positive surgical margins after cold knife conization (CKC) have not been studied in the literature before. In the present study, we examined whether NLR, PLR and MPV are suitable as diagnostic markers for the detection of positive surgical margin after CKC.

Material And Methods

This retrospective study was conducted in the Gynecologic Oncology department of Zekai Tahir Burak Women's Health Research and Education Hospital, between October 2009 and October 2013. The data of the cases were collected from hospital records. The ethics committee of our institution approved the study. Cervical cytology and histopathology results obtained by colposcopic biopsy before the procedure were recorded in all cases. Women who underwent CKC because of biopsy- proven HSIL were obtained. Patients who underwent Loop Electrosurgical Excision Procedure were excluded from the study.

Exclusion criteria for the present study were hematologic disorders, usage of anticoagulants or drugs that may interfere with CBC results, presence of an active infection at the time of surgical intervention, recurrent transurethral resection with intravesical therapy, prior blood transfusion, and the presence of other cancer types.

Conization was performed by incising through the anterior lip of the cervix at the 12 o'clock position, on a plane parallel to the axis of the cervical canal. As the standard procedure, the hemostatic sutures were applied lateral margins of the cervix using no. 0 polyglactin (Vicryl; Ethicon, Cincinnati USA); endocervical curettage was applied and the base of the CKCs were cauterized using a high-voltage spray mode. Conization specimens were marked with a suture at 12 o'clock before sending to pathological examination to define the location of the lesions. The horizontal (Cone diameter) and vertical (Cone height) diameters reported in pathology results. The depth (Cone depth) of the specimens was also obtained from the pathology reports. These diameters were all measured after formaldehyde fixation. The surgical margins were considered as positive if the lesion was cut-through or closer than 1 mm to the margin. The management options of the patients with positive margins were repeat conization, simple hysterectomy, or radical hysterectomy with pelvic lymph node dissection. Specimens of repeat operations were reviewed for the presence of residual disease.

According to final histopathological analysis, the study patients were divided into groups. Out of 231 woman in total, primarily referring 63 surgical margin positive women were included as the study group (Group 1), 168 Surgical margin negative women were selected as the control group (Group 2). All were evaluated according to standard complete blood count (CBC) results. The hemoglobin levels, white blood cells (WBC), absolute neutrophil count, absolute lymphocyte count, absolute monocyte count, absolute eosinophil count absolute basophil count, absolute platelet count, and mean platelet volume (MPV) were employed as parameters of interest. The neutrophil-lymphocyte ratio (NLR) was defined as the absolute neutrophil count divided by the absolute lymphocyte count; similarly, the platelet-lymphocyte ratio (PLR) was defined as the absolute platelet count divided by the absolute lymphocyte count.

The Kolmogorov-Smirnov test was used to determine the distribution of the variables. The median value (min – max) was used in variables without normal distribution. The Mann-Whitney U-test was used for continuous variables without normal distribution. The difference in the categorical variables was assessed using the Chi-square test. All statistical analyses were performed with the SPSS software version 23.0 (SPSS, Inc., Chicago, IL). A p value < 0.05 was considered to indicate statistical significance.

Results

In total 231, 63 (27%) women in Group 1 and 168 (73%) women in Group 2 were followed-up. The age, preceding cervical cytology, and cone size (diameter, height, and depth) are shown in Table 1.

Table 1: Demographic and pathologic characteristics of the study population

	Margin negative (n=168)	Margin positive (n=63)	p
Preceding Cytology			
Normal	2 (1,2%)	-	0.38
ASC-US	20 (11,9%)	3 (4,8%)	
ACS-H	9 (5.4%)	4 (6,3%)	
LSIL	15 (8,9%)	4 (6,3%)	
HSIL	122 (72,6%)	52 (82,5%)	
Age	40,5 (20-69)	43 (29 – 71)	***0.02***
Cone diameter (cm)	3 (1,5 – 5,5)	3 (2 – 4,5)	0.5
Cone height (cm)	2,5 (1 – 4)	2,5 (1- 3,5)	0.14
Cone depth (cm)	1,5 (0,5 – 2,6)	1,35 (0,5 – 2,5)	0.27

Median age was significantly higher in Group 1 (p=0.02). There were no statistically significant differences detected within hematologic parameters and NLR, PLR, MPV levels between the groups (Table 2).

Table 2: Hematologic parameters of the study population

	Margin negative (n=168)	Margin positive (n=63)	p
Hemoglobin (g/dL)	13,7 (8,5 – 15,9)	13,4 (8,8 – 17,1)	0.6
WBC (/uL)	7430 (3650 – 14110)	7730 (3390 – 14900)	0.48
Neutrophil (/uL)	4300 (2030 – 10100)	4590 (1340 – 13500)	0.37
Lymphocyte (/uL)	2250 (900 – 5200)	2320 (800 – 4370)	0.72
Monocyte (/uL)	490 (110 – 980)	490 (60 – 930)	0.63
Eosinophil (/uL)	110 (0 – 550)	110 (0 – 470)	0.63
Basophil (/uL)	30 (0 – 300)	20 (0 – 300)	0.19
Platelet (/uL)	266000 (125000 – 584000)	278000 (153000 – 439000)	0.95
NLR*	1,9 (0,87 – 5,57)	2,05 (0,78 – 13,5)	0.7
PLR†	119,93 (32,47 – 277,14)	120 (61,11 – 214,18)	0.96
MPV (fL)	10 (7 – 13)	10 (7 – 12)	0.81

* Neutrophil-to-lymphocyte ratio

† Platelet-to-lymphocyte ratio

The conization result of all patients' in Group 1 was HSIL. The conization results of Group 2 were microinvasive carcinoma, HSIL, low-grade squamous lesion (LSIL) and no residual disease for 5, 108, 35 and 20 patients, respectively. 52 (82.5%) of the patients with positive cone margins underwent repeat excisions; 29 of them underwent simple hysterectomy, while the remaining 23 of them underwent reconization. Residual disease was identified in 24 (46%) patients at repeat operation. Residual pathology was cancer in 5 patients. Groups with or without residual disease were similar with respect to age, cone size (diameter, height, and depth) and hematologic parameters (Table 3).

Table 3: Clinical characteristics of women with residual disease negative compared to that of women with residual disease positive diagnosed after cold knife conization

	Residual disease negative (n= 28)	Residual disease positive (n= 24)	p
Age	42 (29 – 70)	44 (31-71)	0.98
Cone diameter (cm)	3,2 (2 – 4,5)	3 (2 – 4)	0.08
Cone height (cm)	2,8 (1- 3,5)	2,5 (1,5 – 3,5)	0.07
Cone depth (cm)	1,5 (0,5 – 2,5)	1,25 (0,5 – 2,5)	0.97
Hemoglobin (g/dL)	13 (10,8 – 17,1)	13,4 (8,8 – 16,6)	0,72
WBC (/uL)	7215 (4100 – 14900)	8125 (4900 – 10510)	0,70
Neutrophil (/uL)	4435 (2400 – 13500)	5145 (2380 – 7300)	0,37
Lymphocyte (/uL)	2425 (1000 – 4100)	2150 (800 – 3770)	0,27
Monocyte (/uL)	465 (100 – 930)	510 (300 – 730)	0,85
Eosinophil (/uL)	100 (0 – 360)	120 (0 – 470)	1
Basophil (/uL)	20 (0 -300)	25 (0 -100)	0,81
Platelet (/uL)	270500 (153000 – 439000)	303500 (156000 – 410000)	0,84
NLR*	2 (1,26 – 13,50)	2,13 (1,13 – 6,63)	0,12
PLR†	116,74 (62,37 – 212,86)	128,63 (61,11 – 214,18)	0,23
MPV (fL)	10 (7- 12)	10 (7 – 12)	0,48

* Neutrophil-to-lymphocyte ratio

† Platelet-to-lymphocyte ratio

Discussion

According to our knowledge, this is the first study investigating the relationship between NLR, PLR, MPV, and positive surgical margin after CKC. Our study showed that NLR, PLR and MPV are not useful hematologic parameters to detect positive surgical margin after CKC.

A complete blood count is a cheap, easy and practical measure that may provide information about inflammatory markers. The combination of cellular inflammatory markers, particularly NLR, PLR, and MPV, can constitute significant markers of clinical outcome in various malignancies (5,6,11). Also in a previously published study by Hammes et al. (12) reported that macrophages are closely related to CIN persistence and progression. In the absence of macrophages, neutrophil infiltration increases, replacing the function of macrophages, which can induce the progression of CIN to cervical neoplasia (13). Unlike neutrophils, lymphocytes act as components of host defense against tumor cells (14). Hence, a high NLR may indicate a larger HSIL size, and this may imply a positive surgical margin after CKC. To date some authors have been demonstrated a correlation between the increase of NLR and cervical cancer invasiveness (15,16). In our study, higher NLR values were observed in positive surgical margin patients without reaching clinical significance.

PLR is a novel marker for host systemic inflammation (17). In epithelial ovarian cancer, PLR and NLR can predict outcomes and PLR seems to be a better prognostic predictor for survival than NLR (18). In addition, an association between PLR and uterine malign lesions was demonstrated (19). Zhang et al. (20) demonstrated that PLR is correlated with tumor size in cervical cancer. Beside the prognostic and inflammatory role of PLR, also MPV is considered to reflect the level of platelet activity and inflammation (21). Recent studies confirmed that low levels of MPV are associated with high-grade inflammatory diseases and reverse in the course of anti-inflammatory therapy (22). Oge et al. (23) demonstrated significantly higher levels of MPV in advanced – stages endometrial cancer. In this study, there were no differences between the two groups in terms of PLR and MPV levels.

As a secondary outcome, hematologic parameters were evaluated to predict residual disease after CKC with positive surgical margins (Table 3). In the previous studies, endocervical curettage positivity, volume of disease ≥50%, and multiple quadrant disease were reported as predictors of residual disease (24,25). In our study, similar hematologic parameters were observed between the two groups.

The strengths of the current study lie in its single center nature. Also our study has the advantage that CKC procedures were performed by experienced surgeons, which may lead to similar cone sizes between two groups. In addition many systemic conditions, which may influence NLR, PLR and MPV levels, excluded from the study.

However, we should underline some limitations associated with our study. The retrospective nature of the study cannot exclude any bias. Different HPV subtypes, which might have caused different sizes of squamous intraepithelial lesions (10), were not defined in our records. Number of involved quadrant at conization specimen, which might have predicted residual disease, was not defined in the pathology reports. Despite above limitations, we think that our study contributes to the limited body of knowledge on this topic.

Conclusion

In conclusion, this study showed that there were no correlation between NLR, PLR, MPV and positive surgical margins after CKC. Even though NLR, PLR, MPV seems unfeasible to be used as a predictive parameters for positive surgical margins after CKC, factors affecting NLR, PLR, MPV levels should be considered along with the need for comprehensive studies including larger patient populations.

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