

Three-Step Approach Versus See-and-Treat Procedure in Women with High Grade Squamous Intraepithelial Lesion or Atypical Squamous Cells Cannot Exclude High Grade Squamous Intraepithelial Lesion Cytology

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ABSTRACT

OBJECTIVE: The purpose of this study was to examine the correlation between histological findings in women with HSIL or ASC-H who have undergone loop electrosurgical excisional procedure with "Three-Step Approach" and "See-and-Treat Procedure".

STUDY DESIGN: A retrospective review was performed in 171 women with cytologically detected HSIL or ASC-H. Sixty five women with HSIL cytology and 35 women with ASC-H cytology were managed by "Three-Step Approach", 35 women with ASC-H and 36 women with HSIL cytology were managed by "See-and-Treat Procedure". Rates of histopathological findings were compared in two strategies with respect to previous cytology.

RESULTS: Fifteen women with ASC-H (42.9%), and 24 women with HSIL (68.5%) had CIN 2-3 at loop electrosurgical excisional procedure specimens in the "See-and-Treat" group whereas 14 women with ASC-H (38.8%), and 43 women with HSIL (66.2%) had CIN 2-3 at loop electrosurgical excisional procedure specimens in the "Three-Step Approach" group. There was no significant difference in the rate of CIN 2+ lesions when two strategies were compared in women with HSIL and ASC-H ($p=0.71$ and $p=0.72$, respectively). The overtreatment rates were 22.9% and 48.6% for HSIL and ASC-H cytology, respectively in the "See and Treat" group.

CONCLUSION: In the ASC-H group, the rate of CIN 2+ lesions is significantly high (51.4%). It seems rational to perform "See-and-Treat procedure" in the setting of ASC-H smears although the overtreatment rate seems to be high. Because of the rate of overtreatment, the "Three-Step Approach" seems to be more reasonable in women with ASC-H cytology who also have fertility concerns. After a cytological diagnosis of HSIL, "see and treat" approach seems to be a safe and time saving strategy.

Keywords: See and treat strategy, Cytology, Colposcopy

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Introduction

Loop electrosurgical excision procedure (LEEP) is a type of conization that is used not only to get a tissue diagnosis but also to treat appropriate patients. LEEP was first introduced by Prendeville as a new method of management for women with cervical intraepithelial neoplasia (CIN) (1). LEEP has been used for the diagnosis and treatment of CIN 2-3 that can be completely visualized at colposcopy.

The standard "Three-Step Approach" for high-grade squamous intraepithelial lesions (HSILs) includes colposcopy and colposcopy-directed biopsy, followed by LEEP or conization if CIN 2 or 3 was found (2).

The "See-and-Treat Procedure" has been introduced for lesions which give an impression of high grade CIN at colposcopy. In the "See-and-Treat Strategy", women with cytological abnormalities undergo colposcopy and LEEP at the same time while cervical biopsy step is skipped (3). This con-

viction is based on the cervical smear result and the colposcopic impression. Advantages of the “See-and-Treat Procedure” include a single visit to the hospital, fewer cost, and less emotional stress (4).

Several studies have assessed feasibility of the “See-and-Treat” strategy (5-8). The purpose of our study was to examine the correlation between histological findings in women with HSIL or atypical squamous cells cannot exclude HSIL (ASC-H) who have undergone LEEP with “Three-Step Approach” and “See-and-Treat Procedure”.

Material and Method

A retrospective review was performed in 171 patients with cytologically detected HSIL or ASC-H, who underwent LEEP with or without a prior cervical biopsy at a tertiary hospital between 2013 and 2015. The study protocol was approved by the local Institutional Ethical Committee. All patients signed an informed consent that allows the participating institution to use their clinical data.

Bethesda terminology was used in the classification of cervical cytology. Colposcopic examination of the cervix was performed after applying 5% acetic acid to the ectocervix. The decision as to which treatment would be performed was made upon a particular physician’s preference. In the case of an inadequate colposcopic examination, defined as an incomplete visualization of the transformation zone, no visualization of the entire lesion, if present, or no correlation between cytological findings and the colposcopist’s impression, diagnostic excision was needed. For women with above mentioned characteristics, “See-and-Treat” strategy was chosen.

The patients were grouped as “See-and-Treat” group and “Three-Step Approach” group. In the “See-and-Treat” group LEEP was immediately performed during colposcopic examination and in the “Three-Step Approach” group LEEP was performed after colposcopy-directed biopsies. No patient among those who were going to get a “Three-Step” strategy was lost to follow-up, so that all patients who were intended for the “Three-Step Approach” completed the protocol.

LEEP was performed with local or general anesthesia and a standard LEEP device was used. The size of the LEEP de-

vice was chosen on the basis of the colposcopic findings during the procedure. LEEP specimens were oriented by a single suture at 12 o’clock position. After the procedure, hemostasis was obtained using diathermic coagulation.

Overtreatment was defined as treatment for no CIN or CIN 1 found during final histopathological analysis. We investigated the rate of overtreatment for both groups. Statistical analyses were performed using the statistical software package SPSS version 23.0 (SPSS, Inc., Chicago, IL). The data were expressed as counts and percentages. Statistical analysis was performed by Student’s t-test or chi-square (χ^2) test as indicated. The level of statistical significance was set at $p < 0.05$.

Results

The median age was 40.3 (26-65) in HSIL group and 41.6 (24-66) in ASC-H group. Cervical smear results showed HSIL in 100 (58.5%) cases, ASC-H in 71 (41.5%) cases. Seventy women underwent “See-and-Treat Procedure” while 101 women underwent “Three- Step Approach”.

Thirty-five women with ASC-H cytology and 36 women with HSIL cytology were managed by "See-and-Treat" strategy. Sixty-five women with HSIL cytology and 35 women with ASC-H cytology were managed by “Three-Step Approach” strategy (Table 1).

In the “See-and-Treat” group, 8 (22.9%) of women with HSIL and 17 (48.6%) of women with ASC-H were diagnosed as normal or CIN 1 based on LEEP findings. In the “Three-Step Approach” group, 17 (26.1%) of patients with HSIL and 19 (52.8%) of patients with ASC-H had normal histology or CIN 1 at LEEP specimens. Fifteen (42.9%) of patients with ASC-H, and 24 (68.5%) of patients with HSIL had CIN 2-3 at LEEP specimens in the “See-and-Treat” group. Fourteen (38.8%) of patients with ASC-H, and 43 (66.2%) of patients with HSIL had CIN 2-3 at LEEP specimens in the “Three-Step Approach” group. Invasive cervical cancer rates were 8.6% and 8.3% in cytologically ASC-H women treated with “See-and-Treat” and “Three-Step Approach” groups, respectively. Invasive cervical cancer rates were 8.6% in the “See-and-Treat” arm and 7.6% in the “Three-Step Approach” arm in women with a cytological diagnosis of HSIL (Table 1).

Table 1: Loop electrosurgical excision procedure results of women with ASC-H or HSIL cytology

	LEEP Results	See-and-Treat	Three-Step
ASC-H	Normal/CIN 1	17/35 (48.6%)	19/36 (52.8%)
	CIN 2-3	15/35 (42.9%)	14/36 (38.8%)
	Cervical cancer	3/35 (8.6%)	3/36 (8.3%)
HSIL	Normal/CIN 1	8/35 (22.9%)	17/65 (26.1%)
	CIN 2-3	24/35 (68.5%)	43/65 (66.2%)
	Cervical cancer	3/35 (8.6%)	5/65 (7.6%)

ASC-H: Atypical squamous cells cannot exclude HSIL, HSIL: High grade squamous intraepithelial lesion, LEEP: Loop electrosurgical excision procedure. CIN: Cervical intraepithelial neoplasia

The overtreatment rates were significantly different between HSIL (22.9%) and ASC-H (48.6%) cytology in the “See and Treat” group ($p < 0.05$).

There was no significant difference in rates of CIN 2+ lesions when two strategies were compared in women with HSIL or ASC-H cytology ($p > 0.05$) (Table 2).

Among 65 women with HSIL managed with “Three-Step Approach”, LEEP results revealed CIN2 or CIN3 although colposcopy-directed biopsy results of 4 patients were normal or showed CIN 1. In this group, the probability of skipping a high grade lesion was calculated as 6.1%. There was no woman with ASC-H cytology whose biopsy was normal or CIN1 while LEEP resulted in CIN2-3.

Discussion

In 1990, Bigrigg and colleagues first described the outcome of a “See-and-Treat Protocol” and reported an overtreatment rate of 27.9% (3). In previous studies considering a “see-and-treat management”, a number of strategies were used to assess and treat a patient referred for colposcopy. This is the main reason why overtreatment rates in the literature range from 8.0% to as much as 83.3% (9-13). If “See-and-Treat Protocol” is applied only to women with a high-grade cervical smear result, the rate of overtreatment decreases dramatically. In the present study, we compared two management strategies (“See-and-Treat Procedure” versus “Three-Step Approach”) for women with ASC-H or HSIL cytology. There was no significant difference in rates of CIN 2-3 and cervical cancer when results were compared between two management strategies in women with HSIL or ASC-H.

The chance of unnecessary treatment increases in older women when compared with women younger than 40 years.

Women older than 40 years, whether the lesion is high grade or low grade, might be treated more easily than women younger than 40 years, because fertility is no longer an issue (14).

“See-and-Treat” strategy enables histological assessment and therapeutic excision carried out at the same visit. Despite this time saving implementation, the risk of overtreatment is one of the main criticisms associated with the “See-and-Treat” strategy (15). At present, both The American Society for Colposcopy and Cervical Pathology (ASCCP) and The National Health Service (NHS) of the United Kingdom in collaboration with The British Society for Colposcopy and Cervical Pathology (BSCCP) define overtreatment rate as the proportion of women whose excised specimens contained CIN 1 or less (16,17). NHS Cervical Screening Program (NHSCSP) 2010 and Cochrane Colposcopy and Cervical Cytopathology Collaborative recommend that the overtreatment rate should be less than 10% as a standard requirement (16,18). Using the “See-and-Treat strategy, we found 22.9% and 48.6% overtreatment rate in HSIL group and ASC-H group, respectively. In previous studies the overtreatment rates in HSIL cytology range from 3.0% to as much as 39.4% (7,19,20).

To date, there are only few data in the literature regarding with the overtreatment rates in women with ASC-H (21-24) (Table 3). After we exclude the study of Guducu et al. due to a very few number of patients, previous studies revealed overtreatment rates between 10.5% and 51.4%. Although the rate of overtreatment seems to be high in the ASC-H group in our study, the rates of CIN 2+ lesions is also significantly high. When our findings associated with “See and Treat” strategy are extrapolated to the population with ASC-H cytology, there seems to be an equilibrium between an overtreatment rate of 48.6% and a rate of 51.4% of CIN2+ lesions. Several studies demonstrated that women with ASC-H smears carried a sig-

Table 2: Rates of CIN 2+ Lesions when in “See-and-Treat and “Three-Step” Strategies

SMEAR	LEEP	See-and-Treat	Three-Step	Significance
HSIL	CIN 2+ Lesion	27/35 (77.1%)	48/65 (73.7%)	$p > 0.05$
ASC-H	CIN 2+ Lesion	18/35 (51.5%)	17/36 (47.1%)	$p > 0.05$

LEEP: Loop electrosurgical excision procedure, HSIL: High grade squamous intraepithelial lesion, ASC-H: Atypical squamous cells cannot exclude HSIL

Table 3: Overtreatment rates in women with ASC-H cytology

Authors	Year	Number of patients	Normal/ CIN 1	CIN 2-3/ Cervical Cancer	Overtreatment (%)
Kietpeerakool et al.	2009	58	16	42	27.5
Aue-Aungkul et al.	2011	35	18	17	51.4
Guducu et al.	2013	3	0	3	0
Kim et al.	2014	57*	6	51	10.5
Present study	2017	35	17	18	48.6

*: In this study, overtreatment rate includes 49 patients with “see and treat” approach and 8 patient with “three step” procedure, ASC-H: Atypical squamous cells cannot exclude HSIL, CIN: Cervical intraepithelial neoplasia

nificant risk of having high-grade cervical lesions (25,26). In this study, we found a 51.4% of CIN2+ lesions in women with ASC-H cytology. This finding reaffirms the necessity of pre-cautious evaluation in women with ASC-H smears. In conjunction with these data, it seems rational to perform “See-and-Treat procedure” in the setting of ASC-H smears although the overtreatment rate seems to be high. On the other hand, there was no patient with ASC-H cytology whose biopsy was normal or showed CIN 1 while LEEP resulted in CIN 2-3 in the “Three Step Approach” group. Considering the rates of overtreatment, the “Three-Step Approach” seems to be more reasonable in women with ASC-H cytology who also have fertility concerns.

Because of discordance between different authors, Srisuwan et al. suggested to review cytology reports by a second opinion before management to decrease the overtreatment rate (20). It is also known that narrowing the screening interval increases the risk of unnecessary treatment (14). Beside a high overtreatment rate, especially in resource-poor areas, where multiple visits are not feasible, “See-and-Treat” strategy would be a reasonable option. According to the World Health Organization, this is a simple, inexpensive and extremely effective method (27). Advantages of the “See-and-Treat” strategy include reducing the number of hospital visits and treatment time, fewer cost, less anxiety, and more accuracy in the diagnosis of high grade disease (3,14).

It is more important for a patient to reach immediately ultimate result because it is not easy to be calm for the patients while waiting the results. Balasubramani et al. found that women with HSIL were less anxious and more relieved having undergone the “See-and-Treat Procedure”; a delay in receiving treatment might have a negative influence on the emotional state of the patients (28). Additionally, approximately 25% to 70% of women with histologically proven HSIL are lost before completion of treatment (29,30). Gangli et al. showed that in women who are at a risk of being nonattendance, HSIL can be managed effectively using the “See-and-Treat” strategy (31).

Another contention about “Three-Step Approach” is the limited accuracy of colposcopy-directed biopsies (32). Some authors showed that a single colposcopic examination identifies CIN 2+ lesions in 53%-66% of women with HSIL (33,34). Because high-grade CIN can be missed at colposcopy, failure to detect cervical lesions by colposcopy in women with HSIL does not necessarily mean a high-grade CIN is not present. Li et al reported a 12.1% HSIL positive LEEP rate of women whose biopsies negative for CIN 2+ lesions (31). We found a 6.1% of CIN 2-3 rate in women with HSIL cytology whose colposcopy-directed biopsies were normal or showed CIN 1. We suggest that “See-and-Treat Procedure” would be a reasonable choice rather than “Three-Step Approach” to avoid failure for detecting high grade cervical lesions by col-

poscopy. Also Li et al. and some other authors suggested that LEEP becomes a necessary step, regardless of the outcome of the colposcopy-directed biopsies (13,19,31).

This study shows that the overtreatment rate is relatively low for women who were referred with a HSIL result and subsequently were found to have a high-grade colposcopic impression. We suggest “See-and-Treat Procedure” as the management strategy to be preferred for these patients. With this management strategy, delay in treatment, and noncompliance can be avoided as well as the probability of skipped lesions at colposcopy-directed biopsies.

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