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Loop Electrosurgical Excision Procedure: Safety and Tolerability Among Human Immunodeficiency Virus-Positive Kenyan Women

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Abstract

Objectives—To estimate the safety, tolerability, and acceptability of loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia (CIN 2/3) in HIV-positive women performed by non-physician health care providers, in an HIV care and treatment clinic.

Methods—We carried out a prospective cohort study among women undergoing LEEP for biopsy-confirmed CIN2/3 at the Family AIDS Care and Education Services (FACES) clinic in Kisumu, Kenya. Women were followed up 4 weeks after the procedure and questioned for abstinence as well as presence and severity of side effects following the procedure. The results were analyzed using descriptive statistics and univariable and multivariable analysis.

Results—Among the 180 (91%) women who returned for a 4-week follow up after LEEP, 52% reported at least one postprocedure symptom, including bleeding, discharge, or pain. Using a Likert scale for severity of symptoms, 179 (99%) reported “very mild” to mild symptoms, while 1 (n=1%) participant described the symptoms as moderate. No participants reported severe symptoms. Mean CD4+ count was significantly higher among women who reported any symptoms compared to women who reported no symptoms post LEEP (419 cells/mm^3 vs. 349 cells/mm^3, $p < 0.05$), an association that remained significant after adjustment for antiretroviral treatment. The presence or severity of postprocedure symptoms did not differ among women who reported sexual activity (16%) less than 4 weeks after the procedure.

Conclusions—LEEP performed by clinical officers was well-accepted by HIV positive women and appears safe, resulting in minimal side effects, even among women with early resumption of intercourse.

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Introduction

Developing effective cervical cancer screening programs in resource-limited settings is of tantamount importance for providing comprehensive health care to the millions of HIV-infected women around the world. Cervical cancer is a major health burden in the developing world, where over 85% of cases occur (1). In Kenya, cervical cancer is the second most common cancer among women, with a crude incidence rate of 12.7 cases/ 100,000 women a year (2). The adult HIV prevalence rate in Kenya is estimated to be 7.1%, with the prevalence rate among women found to be higher at 8.4% (3). HIV has been shown to increase the risk for the development, progression and recurrence of Cervical Intraepithelial Neoplasia (CIN), the cervical cancer precursor (4).

A major factor in cervical cancer prevention is coupling accurate screening techniques with safe and effective treatment for CIN 2/3. Loop electrosurgical excision procedure (LEEP) has been shown to have several advantages over the alternative outpatient treatment for CIN2/3, cryotherapy. LEEP can treat women with larger or multiple cervical lesions, which are more common among HIV-infected women (5). LEEP has been shown to have a significantly higher overall cure rate than cryotherapy, especially among HIV-infected women (6). While LEEP has been well-studied and is the standard of care among HIV-infected women in resource-rich settings, studies in resource-limited settings, and specifically among HIV-infected women these settings are few (7,8). Further, safety of LEEP performed in resource-limited settings overall and among HIV-infected women has not been well documented (7).

In almost all reported studies of LEEP, physicians have performed the procedure. Kenya has a very high patient to doctor ratio, reported to be 308,878 to 1 in rural areas (9). Given the severe shortage of physicians, training midlevel HIV primary care providers to perform LEEP could help improve cervical cancer prevention among HIV positive women. While mid- level HIV primary care providers have been utilized to perform cyrotherapy (7), very few programs have looked into training this cadre of providers to perform LEEP.

We have recently reported on the low numbers of serious adverse events after LEEP performed in Kenyan primary care HIV treatment clinics by clinical officers, non-physician health care providers, as assessed by clinicians based on clinical data and patient files (10). Further factors influencing feasibility of the procedure include side effects and tolerability as well as compliance with instructions after procedure. Women are counseled to avoid intercourse for four weeks after LEEP. This is to avoid both an increased risk of complications from disruption of the healing wound, as well as a theoretical risk to their partner of increased transmission risk from increased HIV-1 genital shedding.

In this study, we sought to more closely estimate the safety, tolerability and acceptability of LEEP performed by clinical officers for CIN2/3 in HIV-infected women. In order to do this, we used patient response data to assess the rate of reported side effects and early return to intercourse following LEEP using a questionnaire administered to women four weeks after LEEP.

Materials and Methods

This secondary analysis is part of a prospective cohort study of HIV-infected women undergoing surgical excision of biopsy-confirmed CIN2/3 to assess rates and predictors of CIN2/3 recurrence. The goal of this current paper is to present data on the safety, tolerability and acceptability of LEEP as measured at the four-week post-procedure follow-up visit. IRB approval was received from both collaborating institutions: University of California, San Francisco (UCSF) Committee on Human Research and the Kenya Medical Research

Institute (KEMRI) Ethical Review Committee. Eligibility criteria included HIV-infected women enrolled at the Family AIDS Care and Education Services (FACES) clinics in Kisumu, Kenya, who were between the ages of 25–65, either not on antiretrovirals (ARVs) or on ARVs for at least six months and able to provide informed consent. Those who declined to participate in the study were still offered LEEP per the clinic's protocol. Number of participants who declined LEEP were recorded along with reason for declining the procedure.

Baseline clinical demographics were collected from the electronic medical record at FACES for each woman at time of procedure, including age, CD4+ count, WHO stage, anti-retroviral therapy use and duration, hormonal contraception use and partner's HIV-status. LEEPs were performed by one of five clinical officers who had undergone didactic and practical training and received certification in the procedure (10). Training took place over a period of two to three months, and consisted of theoretical training, and then onsite training with supervision from a US trained gynecologist and/or medical officer. All clinical officers had to successfully perform 10 supervised LEEPs to achieve certification.

Colposcopy was performed immediately prior to each procedure. Information on lesion size and location, loop size and medications used during the procedure were recorded. The procedures were performed in "Blend" mode, a current that maximizes cut and cauterization to reduce intra-procedure bleeding. When necessary, excision was done with two passes to ensure that the entire lesion was removed. Monsel's solution was applied as needed after the procedure to control any immediate post-procedure bleeding. Specimens were evaluated by a pathologist for confirmation of CIN2/3 and to rule out more invasive lesions. Margin involvement and endocervical curettage specimens were also unable to be assessed due to both the multi-pass technique and laboratory limitations.

Women were instructed to remain abstinent until their four-week follow up visit at the clinic to avoid the risk of increased complications or the theoretical increased risk of transmission to partners. They were told to seek care from a clinician if they experienced heavy bleeding, fever, foul discharge or severe abdominal pain. Information on women who called or returned to clinic for adverse events was recorded.

At the four-week follow-up visit, a paper questionnaire was administered to participants by the study coordinator. They were asked if they had experienced any symptoms after the procedure, including bleeding, pain, foul discharge, and fever. A visual Likert scale was administered to assess severity of pain and bleeding symptoms. Participants were asked if their symptoms interfered with daily activities. They were also asked if they needed to seek medical attention after the procedure, and if so, if they received any additional treatment. The questionnaire also assessed abstinence rates. For those women who reported early resumption of intercourse, condom usage as well as discomfort or problems during intercourse post-procedure was assessed. Questionnaires consisted of mainly close-ended questions; however, participants were encouraged to expand on any of the items for which they had positive responses.

Statistical analysis was performed using STATA 11 (StataCorp LP, College Station, Texas). Univariable analysis using chi-square for categorical variables and t-tests for continuous variables as well as multivariable analysis using linear regression estimated association between clinical and demographic factors and presence of symptoms, as well as assessed association between abstinent rates and symptoms.

Results

Between April 2008 and December 2010, 265 HIV positive women had LEEP procedure for biopsy diagnosed CIN 2/3 at the FACES clinic in Kisumu Kenya. Of the 270 women with CIN 2/3 offered LEEP, 265 (98% (CI 97–99%)) agreed to undergo the treatment. Among those declining LEEP, two cited fear of the procedure, and one cited futility of the procedure as reasons for not accepting. Two others moved out of the area prior to follow up. Ten percent (27) (CI 7–15%) of women who underwent LEEP returned outside of their one-month follow up visit window, at which time study enrollment took place. Of the remaining 238 women, 197 (83% CI 77–87%) were eligible and agreed to enroll in the two-year prospective cohort study. Questionnaire results are available for 180 women.

At the four week follow up visit, 52%, (CI 45–60%) of participants (n=94) reported experiencing any symptom after the procedure; 23% (CI 17–30%) (n=42) reported foul discharge, 16% (CI 31–46%) (29) reported bleeding and 14% (CI 10–20%) (26) reported pain. No participant reported fever. Among the women reporting symptoms, 99% (CI 97–100%) (n=179) characterized them as ”very mild” to “mild”, with only one participant reporting moderate symptoms of bleeding and pain. Only 1.7% (CI 0.3–5%) (n=3) reported that these symptoms interfered with their daily activities. 2.8% (CI 0.8–6.3%) (n=5) had seen a clinician for any of these symptoms. Most of these women (80%, CI 28–99%), N=4) received treatment; 3 received treatment for sexually transmitted infection while 1 received pain relief.

Baseline clinical and demographic characteristics were examined for correlation with post-procedure symptoms (Table 1). Women who reported symptoms had a significantly higher mean CD4+ count compared to women who reported no symptoms post LEEP (419 cells/mm^3 vs. 349 cells/mm^3, $p < 0.05$). This association remained significant after adjusting for ARV using linear regression ($p<0.001$).

Only 16% (CI 11–22%, n=29) of women reported early resumption of intercourse prior to their 4-week follow-up visit. Of these women, the majority, 76% (CI 56–90%) (n=22) reported having sex within the second or third week. Seventy-nine percent (CI 60–92%, n=23) of these women reported using a condom during sex. Seventeen percent (CI 5.8–36%, n=5) reported having bleeding or discomfort after sex. No difference in reported symptoms was found between women who had remained abstinent and women who did not remain abstinent (Table 2). Intercourse without a condom was not significantly associated with experiencing post-LEEP bleeding, discomfort or foul-smelling discharge (Table 3). Women who reported symptoms also had a significantly higher CD4+ count compared to women who did not report symptoms (567 cells/mm^3 vs. 270 cells/mm^3, $p <0.05$). However, this association did not remain significant in when adjusting for ARV use in linear regression ($p = 0.30$). While not significant, those who reported symptoms were less likely to be on ARVs than those who reported no symptoms (73.7% vs. 100%, $p = 0.08$). Of the women with early resumption of intercourse and reported symptoms, 32% (CI 13–57%) reported that their partners were HIV negative, while 42% (CI 20–67%) reported partners had unknown status.

Since undergoing LEEP, two women have reported becoming pregnant. Both pregnancies had no complications and children were born at full-term.

Discussion

LEEP performed by clinical officers had a high acceptance rate and appears to be safe and tolerable to HIV-positive women. When assessing safety, there were no reports of major side effects from any of the women up to four weeks post procedure. About half of the women reported some minor symptoms, but only five participants sought further medical

care, and only three reported that these interfered with their daily activities. These results concur with other studies that also reported low adverse effects rates after LEEP in HIV negative women in low resource settings (11) and add insight into the growing body of literature around safety of the procedure in HIV positive women in similar settings.

Particularly important is that our report shows no difference in side effect rates for LEEP performed by trained clinical officers compared to the side effect rates reported in studies of LEEP performed by physicians working in teaching facilities (12). As providers look to scale up cervical cancer screening and treatment programs in resource limited settings utilization of mid-level health care providers presents an important opportunity and viable solution for providing cervical cancer screening and prevention services in areas where traditional surgical providers are scarce.

Our reported abstinence rate was 84%, which was reassuring that such a large number of patients were able to comply with instructions given post procedure. Also reassuring was that those who were not abstinent were not associated with more symptoms compared to those who remained abstinent. As women are not always able to negotiate sex with their partners (13), it is reassuring that this vulnerable population does not appear to be at higher risk for worse outcomes. Our abstinence rate is higher than a previously reported 4 week post procedure abstinence rate of 50% for women undergoing cryotheraphy in South Africa (14). It should be noted that the majority of participants reported partners who were either HIV-negative or of unknown status. It is possible that the high reported abstinence rate was related to fear of the theoretical increased transmission of HIV after the procedure. However, this has not been explored in the literature.

Given that many participants had partners who reported an HIV negative or unknown status partner, further examination needs to be completed assessing the risk of HIV-transmission by women with early resumption of intercourse. Limited studies have reported increased HIV-1 genital shedding in women with CIN (15) and after treatment for cervical dysplasia (16). Further research examining HIV-shedding after LEEP procedure needs to be completed to fully assess the risk posed by LEEP procedure on HIV-shedding and HIV female-to-male transmission.

Interestingly, our study found that a higher CD4+ count was associated with an increase in reported positive symptoms. One possibility for this finding could be that women with a higher CD4+ count could have a better immune response so were more likely to have an inflammatory response to the procedure compared to women with a lower CD4+ count. Another possibility could be that a higher CD4+ count is associated with better overall health status and thus these women might have been more likely to engage in activities that resulted in more symptoms. This association deserves further investigation, especially as more women become enrolled in HIV care in sub-Saharan Africa who both have higher CD4+ counts, and who have improvement of CD4+ counts with access to antiretroviral therapy (ARVs).

Our study is limited in that the results are self-reported, and only reflect four-weeks post procedure. While this reflects the immediate sequelae post procedure, it does not allow us to comment on any longer term adverse events, such as preterm birth rates (17). While we are able to comment on the number of women who have since gotten pregnant and their outcomes, a more formal analysis of long-term reproductive outcomes remains to be performed.

Our study findings demonstrate that LEEP can be performed with minimal adverse effects, even with non-compliance to abstinence stipulations, in HIV positive women by mid-level health care providers. With the growing evidence that LEEP can be performed safely, with

minimal sequelae in HIV positive patients, the next step is to examine the efficacy of treatment by LEEP for prevention of recurrent CIN2/3 and invasive cervical cancer alongside scale-up of cervical cancer prevention services.

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Table 1

Baseline characteristics of 180 HIV positive women who reported presence or absence of symptoms over a 4 week period after loop electrosurgical excision procedure (LEEP) for CIN2/3

Characteristic	Women who reported symptoms post LEEP* N = 94	Women who reported no symptoms post LEEP N = 103	P-Value
Mean Age (years) ± SD	32.8 ± 0.5	33.2 ± 0.7	0.65
CD4 count/mm^3, mean, SD	419 ± 28.7	349 ± 20.9	0.05
WHO stage (%) 1 2 3 4	24.2 27.5 34.1 14.3	17.4 33.7 36.1 12.8	0.65
Anti-Retroviral Therapy use, N (%)	78.7	87.2	0.13
Duration of ARV use (%) < 3 months 3–6 months 6–12 months > 1 year	25.5 8.8 11.8 53.9	27.9 7.0 22.1 43.0	0.22
Hormonal Contraception use, N (%)	25.8	20.9	0.5
Size of Loop used (%) <1 × 1 cm 1–2 cm > 2 cm	1.8 92.7 5.5	2.1 89.6 8.3	0.5
Lesion greater than 2.5 cm (%)	11.6	14.3	0.65

* Positive symptoms were defined as bleeding, pain, fever, foul smelling discharge

Table 2

Reported symptoms of 180 HIV positive women who were and were not abstinent over a 4 week period after LEEP for CIN 2/3

Symptoms (% yes)	Women who reported abstinence N = 151	Women who had sex < 4 weeks after the procedure N = 29	P-Value
Did you have any of the following after your procedure…			
-Bleeding	14.6	24.1	0.20
-Pain	12.6	24.1	0.12
-Fever	0	0	
-Foul Smelling Discharge	21.2	34.5	0.12
-Any of the above	49.7	65.5	0.12
Did any of these symptoms interfere with your daily activities?	1.3	3.5	0.50
Severity of Symptom*:			
Bleeding: very mild – mild	100	96.6	0.16
Bleeding: moderate	0	3.4	0.16
Pain: very mild – mild	100	96.6	0.16
Pain: moderate	0	3.4	0.16
Bleeding/pain: severe-very severe	0	0	N/A

* Fisher's exact test

Table 3

Characteristics of 29 HIV positive women who had sex less than four weeks after LEEP who reported presence or absences of symptoms

Characteristic	Women who reported symptoms post LEEP N = 19	Women who reported no symptoms post LEEP N = 10	P-Value
% who did not remain abstinent in the first month	20.2	11.6	0.12
- Mean CD4 count	567 ± 75.9	270 ± 41.3	0.05
- ARV use (%)	73.7	100	0.08
- Age	31.6 ± 1.1	31 ± 1.5	0.74
- % condom use	68.4	100	0.07
- % who reported discomfort during intercourse	26.3	0	0.13