ORIGINAL ARTICLE

Impact of visual inspection with acetic acid plus cryotherapy "see and treat" approach on the reduction of the population burden of cervical preinvasive lesions in Southeast Nigeria

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Abstract

Objective: The aim of this study is to determine the impact of visual inspection with acetic acid (VIA) plus immediate cryotherapy on the prevalence of VIA-detected cervical squamous intraepithelial lesion (SIL).

Methods: Women in four rural communities in Southeast Nigeria were screened with VIA. Women who tested positive to VIA were offered either immediate cryotherapy or large loop excision of the transformation zone based on predetermined eligibility criteria. Cervical biopsies were taken before cryotherapy and examined by consultant histopathologists. All participants were rescreened 1 year later. The main outcome measures were population prevalence of cervical precancers before and after intervention, cure rates, and over-treatment rates.

Results: A total of 653 women participated in the study. The prevalence of cervical SIL before the intervention was 8.9% (58/653). The prevalence 1 year later was 1.4% (9/649). This gave an 84.3% reduction in the population prevalence of SIL. The reduction in cervical SIL prevalence was statistically significant ($P = 0.0001$). The prevalence of high-grade SIL reduced significantly from 4.1% (27/653) preintervention to 0.5% (3/649) 1 year postintervention ($P = 0.0001$). This gave an 87.8% reduction in the population prevalence of high-grade SIL. Cryotherapy provided a cure rate of 87.9% (95% confidence interval: 76.82–94.33).

Conclusion: Population cervical cancer prevention using VIA plus immediate cryotherapy leads to significant reduction in the population prevalence of cervical SIL. This has the potential of being an acceptable supplement to cervical cytology for cervical cancer prevention in low-income populations.

Key words: Cervical cancer, cryotherapy, impact, see and treat, visual inspection with acetic acid

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Introduction

Cervical cancer is seen as a preventable disease. Prevention of cervical cancer hinges on two important interventions,

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namely, human papillomavirus (HPV) vaccination and screening and treatment of cervical precancers.[1] Screening for and treatment of cervical precancers have been practiced over the past several decades. High-income countries of the world have well-developed and well-implemented cervical cancer screening programs. Those programs are cytology-based, cost intensive, require well-developed health-care system and infrastructure, and well-educated female population. The above attributes are lacking in low-income countries of Sub-Saharan Africa. The burden of cervical cancer has continued to rise in Sub-Saharan Africa. Lack of well-organized and functional population-wide screening programs, increase in the incidence of sexually transmitted diseases like the human immunodeficiency virus and decrease in the age at sexual debut all contribute to the increasing burden of cervical cancer.[2]

The development of visual inspection with acetic acid (VIA) as an effective alternative to cervical cytology raised the prospects for halting the rising burden of cervical cancer in Africa and other low-income countries of the world. One of the peculiar advantages of VIA over cytology is the immediate results of the test, hence making it possible for immediate treatment to be offered, the so-called "see and treat" approach.[3] The World Health Organization (WHO) recommends "see and treat" VIA-based cervical cancer prevention method as an appropriate and effective alternative to the cytology-based prevention model for low-resource countries.[4] The recommendation came following a demonstration project by WHO in six African countries including Nigeria.[5] In the "see and treat" model, women who test positive to VIA can be treated immediately at same clinic visit with either cryotherapy or cold coagulation without any further confirmatory test. A major merit of this approach is that default to further confirmatory tests and treatment is completely avoided. These defaults have been reported to be significant challenges in low-income countries where as much as one-third of patients do not come for confirmatory colposcopy after a positive Pap smear cytology.[6]

The demonstration project by the WHO clearly demonstrated the feasibility and acceptability of this model in Africa. However, the diagnosis of cervical precancer in that study was based solely on VIA without any histological confirmation both in the pre- and post-intervention periods. This made it difficult to assess the actual impact of the intervention on the population prevalence of cervical squamous intraepithelial lesion (SIL). Therefore, the real-life impact of VIA-based "see and treat" model on the population prevalence of cervical SIL in low-resource countries remains unknown. This study aims to quantify the impact of a VIA-cryotherapy based see and treat model on the prevalence of cervical SIL in a rural African population. It is important to quantify this impact as it has the potential to stimulate the adoption of the model by resource-poor countries. To date, despite the recommendation by WHO, only a few countries have adopted the model as part of their national cervical cancer prevention program.

Methods

The study was part of the "VIA see and treat" study and took place in Enugu and Imo States of Nigeria. The main study evaluated the outcomes, feasibility, and acceptability of population screening of cervical cancer using VIA and multiple modalities of treatment. The main study is in the process of being published.

The study took place from March 2011 to January 2014. The four communities that participated in the "VIA see and treat" study were selected through a multistage random sampling. One community, Nnarambia, was randomly selected out of the four communities for this study.

This was a "before and after" study. The intervention was VIA plus cryotherapy. The study was preceded by awareness creation and mobilization of the community. The community engagement approach was used to create awareness and determine the number of eligible women within the community.[7] This involved visits to women group meetings, community leaders and churches within the community. During these visits, educative information on cervical cancer and cervical cancer prevention were delivered to the women. These were given in the form of oral information and educative flyers on cervical cancer and cervical cancer prevention. During this period, information on the total number of eligible women for VIA screening based on predetermined criteria was collected. Eligible women were encouraged to visit the screening center during specified mass screening days during the study.

All eligible consenting women in the community were screened with VIA by trained providers, after giving a written informed consent. The providers were nurses and resident doctors who received special certified training on VIA. Women who tested positive to VIA and who are eligible for cryotherapy were offered immediate cryotherapy. Those who tested positive to VIA and who do not qualify for cryotherapy were offered large loop excision of the transformation zone (LLETZ). The main eligibility criterion for VIA screening was age between 30 and 50 years. Exclusion criteria for VIA screening included pregnancy, women <12 weeks postpartum, women with lesions suspected to be malignant, women with a history of hysterectomy and women who have been treated for cervical cancer previously. Eligibility for cryotherapy was based on three criteria which must all be met. These were VIA positivity, Type 1 transformation zone, and the lesion covers <75% of the ectocervix. Type 1 transformation zones are those in which the entire transformation zone can be

visualized without the aid of a cervical retractor. Cervical punch biopsies were done for all VIA-positive cases before cryotherapy was done. Multiple biopsies were taken from the worst acetowhite areas on the cervix. Specimen obtained from LLETZ and cervical punch biopsies were sent for histological examination by consultant histopathologists. All the biopsies were collected by a consultant Gynaecological Oncologist. No colposcopy was done before the biopsy. The histology was reported using the Bethesda classification. Cryotherapy was done using carbon dioxide gas. The double-freeze technique (3 min freeze one min thaw 3 min re-freeze) was used.

The participants were re-examined 1 year later with VIA by same providers. Persistent VIA-positive and new VIA-positive cases at 1 year were biopsied and treated with cryotherapy or LLETZ as appropriate. The main outcome measures were pre- and post-intervention prevalence of cervical precancers, cryotherapy cure rate for cervical precancers, and over-treatment rate of the "see and treat" model.

Data were analyzed with descriptive statistics and Z-test for comparison of proportions at 95% confidence level using SPSS version 15 and simple statistical software (IBM, Armonk, NY, USA). The value of $P < 0.05$ was considered statistically significant.

The study protocol was approved by the University of Nigeria Teaching Hospital Research Ethic Committee.

Results

The number of eligible women for VIA screening in the community was 677. A total of 653 eligible women were screened in the preintervention phase giving a response rate of 96.5%. The mean age of the participants was 43.6 ± 6.3 years. Five hundred and eighty-two (89.1%) women were married or divorced, and the mean parity was 4.3 ± 1.4. Table 1 shows the demographic characteristics of the participants. During the preintervention period, 71 (10.9%) women tested positive to VIA. Some 58 women were confirmed to have SIL by histology in the preintervention period. This gives a preintervention prevalence of SIL of 8.9% (95% confidence interval [CI]: 6.9–11.3) and an over-treatment rate of 18.3% (95% CI: 10.88–28.99). Sixty-four (90.1%) of the women who tested VIA positive were eligible for cryotherapy. Of these, 57 were confirmed to have SIL. Three women had lesions suspected to be cancerous. Of these, one was confirmed to be invasive cancer by histology. This gives a prevalence of 0.15% for invasive cervical cancer.

Six hundred and forty-nine women were screened in the postintervention phase. The postintervention VIA positivity rate was 1.7% ($n = 11$). Of these, only 9 women were confirmed to have SIL by histology. This gives a postintervention prevalence of SIL of 1.4% (95% CI: 0.7–2.7), and an over-treatment rate of 18.2% (3.99–48.85). Ten (90.9%) of the women who tested positive to VIA in the postintervention period were eligible for cryotherapy. The histology result of the only woman who had LLETZ in the postintervention period revealed chronic cervicitis. There was no case of suspected invasive cancer in the postintervention period. Table 2 shows the histological outcome of the VIA positive cases in the pre- and post-intervention periods.

The reduction of the prevalence of all SILs from the preintervention 8.9% to the postintervention 1.4% was statistically significant (Z-test: 5.7881; $P = 0.0001$) [Table 3].

Table 1: Sociodemographic characteristics of participants

Characteristic	*n* (%)
Age (years)	
30-39	252 (38.6)
40-50	401 (61.4)
Parity	
Nulliparous	59 (9.0)
Primiparous	84 (12.9)
Multiparous	510 (78.1)
Marital status	
Single	68 (10.4)
Married	551 (84.4)
Divorced	3 (0.5)
Widowed	31 (4.7)
Education	
No education	193 (29.6)
Primary education	261 (40.0)
Secondary	137 (21.0)
Tertiary	62 (9.5)

Table 2: Histological outcome of visual inspection with acetic acid positive cases

Histological outcome	Preintervention (*n*=71) (%)	Postintervention (*n*=11) (%)
Normal	6 (8.5)	0 (0.0)
Cervicitis	7 (9.6)	2 (18.2)
LSIL	31 (43.7)	6 (54.5)
HSIL	27 (38.0)	3 (27.3)

HSIL=High grade squamous intraepithelial lesion; LSIL=Low grade squamous intraepithelial lesions

Table 3: Prevalence of cervical precancer

Period	Positive for SIL (%)	Negative for SIL (%)
Preintervention (*n*=653)	58 (8.9)	595 (91.1)
Postintervention (*n*=649)	11 (1.7)	638 (98.3)

Two Tailed *Z*-test=5.7881, *P*=0.0001. SIL=Squamous intraepithelial lesion

Table 4: Prevalence of high grade squamous intraepithelial lesion

Period	Positive for HSIL (%)	Negative for HSIL (%)
Preintervention (n=653)	27 (4.1)	626 (95.9)
Postintervention (n=649)	3 (0.5)	646 (99.5)

Two-Tailed Z-test=4.4161, P=0.0001. HSIL=High grade squamous intraepithelial lesion

Similarly, the reduction of the prevalence of high grade SIL (HSIL) from the preintervention 4.1% to the postintervention 0.5% was statistically significant (Z-test: 4.4161; P = 0.0001) [Table 4].

The intervention of VIA plus immediate cryotherapy is associated with 84.3% and 88.9% reduction in the population prevalence of all cervical SIL and high-grade SIL, respectively, within 1 year.

Only 12.1% of the women with SIL (n = 7) during the preintervention period still had the lesion in the postintervention period [Table 2]. This gives a cure rate of 87.9% for cryotherapy in this study (95% CI: 76.82–94.33).

Discussion

This study presents some interesting findings that strongly supports the use of VIA-based see and treat cervical cancer prevention approach in resource-poor countries. The study is unique from previous studies on the subject matter because it provides definitive evidence from histopathological examinations of biopsy specimens from VIA positive cases.

The response rate of more than 96% shows a high acceptance of this model and provides yet another evidence in support of the community engagement approach in the cervical cancer prevention awareness campaign. A previous study from this setting reported similar large response in community mobilization for cervical cancer prevention using the community engagement approach.[7] This approach leverages on the influence of community gatekeepers to educate and mobilize women to utilize cervical cancer prevention services. The importance of this cannot be over-emphasized given the contributions of poor utilization of cervical cancer prevention services to the rising burden of cervical cancer in Africa.

Although the VIA positivity rate of about 11% in this study is similar to the overall rate of 10% reported by the WHO six-nation project, it is double the rate reported from Sagamu in Nigeria in the same WHO project.[6] The fact that histopathological result confirmed close to 90% of the VIA positive cases implies that the difference could not have been due to the higher false positive rate for VIA in this study. It could imply that the community in this study may have had a higher prevalence of HPV. HPV is the etiological agent in more than 99% of invasive cervical cancers. Chukwuali *et al.* in 2004, reported a prevalence of 12.2% for abnormal Pap smears from a similar setting in southeastern Nigeria.[8] The similarity between the VIA positivity rate in this study (11%) and the reported prevalence of abnormal Pap smears in the study setting by previous authors (12.2%) could suggest a similar efficacy between VIA and Pap smear in detecting cervical precancers.

The transition from the cervical SIL to invasive cervical cancer is usually slow, sometimes up to between 10 and 18 years. Furthermore, it is established that only a proportion of cervical precancers eventually progress to invasive cervical cancer. These two factors could explain the gap between the 8.9% prevalence of cervical SILs and 0.15% prevalence of invasive cervical cancer in this study.

The prevalence of high-grade intraepithelial lesion (HSIL) in this study was 4.1% in the 1st year and 0.5% in the 2nd year after intervention. The high baseline prevalence of 4.1% could reflect the prevalence of persistent HPV infection in this community. It might be interesting to study the determinants of persistent HPV infection in this community.

In contemporary practice, low grade cervical intraepithelial lesions (LSIL) do not require treatment at first diagnosis, it is included in this study because VIA is not discriminatory between LSIL and HSIL. Hence, in practice, it is recommended to treat all VIA positive cases. The high prevalence of HSIL in this study suggests that many cases of LSIL might have persisted and progressed to HSIL, thus further justifying its inclusion in the analysis of this study. The significant reduction in the population prevalence of HSIL within 1 year found in this study is noteworthy, as it reflects the degree of population protection from invasive cervical cancer.

VIA-based see and treat model of cervical cancer prevention in this study brought about an 81% reduction in the population prevalence of cervical precancers. This is a very significant effect. This finding sets this study apart from previous studies on the subject matter. The WHO six-nation project measured only the VIA positivity pre- and post-intervention without histological confirmation, hence could only extrapolate on the real effect of this model with regards to reduction in the burden cervical precancers. Cervical precancer is a suitable end point in this situation. The implication of this finding is that resource-constrained areas of Africa can use the VIA-based see and treat the model as part of the population cervical cancer prevention measures. The advantages of this include the elimination of the need for repeat visits for follow-up and the attendant loss to follow-up. The loss to follow-up is an established

impediment to cervical cancer prevention in Africa.[6] This model has been shown to be more cost-effective in previous studies from this setting.[9] Cost is a significant cause of low uptake of cervical cancer prevention services in Nigeria. Both cryotherapy and LLETZ have been reported to be feasible and acceptable treatment options in VIA-based see and treat cervical cancer prevention approach in rural Nigerian communities, even in situations of mass screening exercises.[10]

Another important advantage of VIA and cryotherapy is that both can be performed by nonphysicians as demonstrated in this study and elsewhere. This means an increased potential for the services to be extended to remote rural areas with very limited availability or even outright nonavailability of physicians. It is noteworthy that there was no case of invasive cancer observed in the VIA-positive women, even among those considered ineligible for cryotherapy. The over-treatment rate recorded in this study is similar to that reported by earlier studies.[9] The rate appears acceptable in view of the fact that the treatment is tolerable, safe, and acceptable. Furthermore, the risk-benefit ratio weighs so much in favor of treatment.

Cervical precancer screening alone may not be all the answer to cervical cancer prevention as it is only a secondary prevention approach. A comprehensive approach will include vaccination with HPV Vaccine, as well as effective screening and treatment for cervical precancers.[1]

The findings of this study have useful applicability in the fight against cervical cancer as the study was done on real-time population. It is feasible to obtain similar results using the processes of community engagement as was employed in this study.

Conclusion

VIA-based see and treat approach to cervical cancer prevention is associated with significant reduction in the population burden of cervical SILs. The approach is feasible, cost effective and acceptable for large scale population prevention programs. Low-resource countries of the world may find it useful to include this model to complement the standard cytology-based screening in population-based cervical cancer prevention programs.

Limitations of study

This study is not without limitations. The sensitivity of VIA after cryotherapy is unknown. If the sensitivity is limited, it could have missed out some VIA positive cases postintervention. However, it is documented that the anatomy of the cervix returns to normal 6 months after cryotherapy.

The histology specimen was read by only one specialist histopathologist. There is the possibility of misclassification of the results which could have led to overestimation of the prevalence of HSIL, thereby overestimating the impact of the intervention on the population.

Although this study was not designed to directly evaluate the sensitivity of VIA, the histologic confirmation of most VIA-positive women in this study suggests the limited sensitivity of the procedure. This at variance with previous reports on the sensitivity of VIA.

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Conflicts of interest

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