

CERVICAL CANCER SCREENING IN BOTSWANA: A ROLE FOR TELEMEDICINE

A. STATEMENT OF HYPOTHESIS AND SPECIFIC AIMS

A.1. Introduction

Women in sub-Saharan Africa often present with advanced stages of cervical cancer even though precancerous lesions are detectable via cervical screening techniques. This is the result of multiple factors, including lack of screening, lack of appropriate referral of women with cervical disease, as well as HIV-HPV (human papillomavirus) co-infection. In order to improve the availability of cervical cancer screening in Botswana, we propose a prospective case control study in which the principles of mobile telemedicine would be applied to cervical cancer screening, using simple visual screening techniques, such as the acetic acid test. Diagnoses made based on visualization of the uterine cervix after application of 4% acetic acid (control) made during live patient clinical encounters will be compared to (case) diagnoses for the same patient encounter based on photographic evaluation using the mobile telemedicine handset (photographic assessment with acetic acid - PIA). Percent agreement between diagnoses based on these two methods of evaluating the cervix will be analyzed in order to determine the efficacy and safety of using PIA in conjunction with mobile telemedicine as a tool for cervical cancer screening. Based on our results, we will develop educational training packets for health care workers in rural areas that will allow them to use this technology. This will help in the diagnosis, appropriate referral, and treatment of cervical dysplasia and cancer in women living in rural Africa with limited access to care.

A.2. Statement of Specific Aims

Specific Aim 1: To evaluate the accuracy and safety of remote diagnosis by physicians at tertiary care centers using photographic images of the cervix after application of 4% acetic acid (PIA) after transmission by mobile telemedicine handset. The diagnosis (1) made by an off-site gynecologist at a tertiary care center using PIA after transmission of photos using the mobile telemedicine handset will be compared to (2) diagnosis made by the on-site clinician during live patient encounter. Percent agreement between these pairs of diagnoses will be calculated.

Specific Aim 2: To evaluate the diagnostic reliability of photographic evaluation of the cervix after application of 4% acetic acid using a mobile telemedicine handset (photographic assessment with acetic acid - PIA) compared to conventional clinical assessment with visual inspection with 4% acetic acid (VIA). The diagnosis made by on site clinician (1) during live patient encounter with VIA will be compared with (2) the diagnosis made by the same clinician, now blinded to initial patient visit, using PIA. Percent agreement between these two diagnoses for each patient will be calculated.

Specific Aim 3: To determine the diagnostic accuracy, sensitivity and specificity characteristics, along with 95% confidence intervals, for the PIA test based on correlation with histopathology from Pap smear, HPV testing and/or biopsy results. We hypothesize that clinical impression based on either PIA or on site colposcopy and cervical exam will not significantly differ in terms of percent agreement with histology results. Based on previous studies examining the test performance of VIA testing, we expect the PIA test to have a sensitivity of approximately 70% and specificity of approximately

85% for detecting lesions of grade CIN1 or more severe dysplasia.³⁻⁶ Additional statistics, including positive and negative predictive values⁷, and the likelihood ratio⁸ for PIA will be also be calculated.

Specific Aim 4: To determine the prevalence of HPV infection in women presenting for cervical cancer screening in Botswana, as well to determine which specific HPV genotypes are detected most commonly in this population. We hypothesize that over 50% of women will be HPV positive and that types 16 and 18 will be most common.

B. BACKGROUND AND SIGNIFICANCE

B.1. Cervical cancer screening in Africa

Cervical cancer continues to be the leading cause of cancer mortality among women in the developing world.¹³ Prevention of cervical cancer depends on widespread screening, accurate diagnosis of precursor lesions, followed by appropriate triaging and implementation of therapy.¹⁴ In many African countries, there is no established program for mass screening, and when services are available, they are only offered in family planning clinics located primarily in large teaching hospitals in urban centers.¹² Additionally, the type of screening program which can be reasonably implemented in resource-poor nations is also an issue. Cervical cytology screening programs in the developing world have drastically reduced deaths due to cervical cancer, in the United States, for example, by 74% from 1955 to 1992,¹⁵ however, in rural areas of sub-Saharan Africa, initiatives which rely on cytology and colposcopy are not feasible due to relatively high cost, substantial need for infrastructure, trained personnel, and the prolonged time between when testing occurs and when results are available.¹⁶ Screening approaches which require minimal resources, which can be performed by providers at various levels of training, are better suited to implementation in these areas. One such approach is visual inspection with application of acetic acid (VIA).

B.2. Visual inspection with application of acetic acid (VIA)

Visual inspection with application of 4% acetic acid (VIA) is a simple, inexpensive, practical alternative to cytology based screening programs, which has been projected to lead to a 25% reduction in lifetime risk of cervical cancer with just once in a lifetime screening by this method.¹⁷ Application of 4 or 5% acetic acid to the cervix causes dysplastic, neoplastic and certain types of normal epithelium to transiently appear white, with normal cervical squamous epithelium appearing pink.¹⁸ Abnormal white appearing areas can then be biopsied or treated with cryotherapy. Studies have shown that VIA is more sensitive but less specific than the Pap smear¹⁹, with estimated sensitivity of 66-99% or 55-90.1%, and specificity of 64-98% or 65-92.2% quoted in two independent studies.^{20, 21} One of the major drawbacks of VIA is that estimates of the accuracy of this method vary widely, with significantly higher sensitivity and specificity for detecting disease achieved by physicians compared to nurses administering VIA.²¹ Additionally, because VIA has the disadvantage of relative lack of specificity, it is thought that many women without actual cervical cancer precursors are being unnecessarily treated with ablative therapy.²⁴ The degree to which provider experience and training determines effectiveness of VIA as a screening tool highlights the potential value of developing a strategy for facilitating distant preceptorship and supervision for novice clinicians or non-physician health care providers, as well as providing consultation services to areas where physicians are not available.¹⁴ Mobile telemedicine technology has the potential to assist non-physician health care workers in interpreting VIA results.

B.3. Photographing the cervix - cervicography

Magnified visual inspection of the cervix with colposcopy provides increased sensitivity compared with VIA, and has proven to be extremely successful as a screening modality for cervical cancer. However, use of this technology in developing nations is severely limited by the cost of the colposcope and by the need for highly trained colposcopy providers. Therefore, development of a lower-cost method (also with increased specificity compared to VIA) to provide easily interpretable, magnified images of the cervix, would have the potential to increase effectiveness of cervical cancer screening in resource-poor areas. One such method of visual inspection of the cervix is cervicography, a technique first described by Staffl in 1981²⁵ in which the cervix is inspected through magnified photographic images. Cervicography has been shown in multiple studies to be a reliable method of detecting cervical cancer precursor lesions,^{5, 26 18 27 28 25} When compared directly to VIA, cervicography appears to have almost identical sensitivity, but have the advantage of being significantly more specific.⁵ Therefore, there has been growing excitement regarding the greater specificity of cervicography compared to VIA, and its potential for use in conjunction with VIA in cervical cancer screening programs.

The originally developed cervicography technique with resulting “cervigram” photographic images, were cumbersome, requiring photos to be developed before expert viewing, thus not allowing for real-time inspection.²⁴ More recently, a few promising studies have successfully developed digital cervical photography techniques.^{22, 29, 30 24} Digital cameras, with their advantageous portability, ease of use, and relative cost-effectiveness (as compared to colposcopy), have been shown to produce quality, high resolution images, which may be used to perform magnified examination of the cervix and vagina, and there is mounting evidence to suggest that digital camera-based assessment provides consistent and accurate assessment of lesions of the reproductive tract.³⁰ The mobile telemedicine Samsung SGH-U900 Soul phone with 5 megapixel camera handset technology is has the added advantage of not requiring internet connections or electricity, and allows images to be transmitted immediately, and be evaluated in realtime rather than in store-and-forward mode. This “simultaneous telemedicine” technology provides the opportunity for evaluation by an expert at a distant location while the patient is being evaluated in clinic.

B.4 HPV Testing

HPV testing is rapidly emerging as the gold standard for cervical cancer screening in terms of reducing incidence of advanced cervical cancer and deaths. Evaluation of test performance of effective, feasible and affordable early detection strategies for cervical cancer is a public health priority, and is invaluable to a community. HPV testing will not pose any additional harm or risk to the patient, and would 1) provide women enrolled in the study with a single round of HPV testing, and the knowledge of whether or not they are positive for high risk HPV. The HPV screening test was recently shown to most significantly reduce the numbers of advance cervical cancers and deaths, compared with Pap (cytology) testing or visual inspection with acetic acid (VIA)[\[1\]](#); 2) allow PIA results to be compared to HPV testing results, which are rapidly emerging as the gold standard for cervical cancer screening; and 3) collect data on the prevalence of HPV subtypes in Botswana, with major implications for the utility of currently available vaccines in decreasing the burden of cervical cancer in this population.

B.5. Significance

Telemedicine is a promising technology for screening and detection of cervical dysplasia and cancer. We propose that our mobile telemedicine technology will allow for safe and efficacious remote diagnosis by expert gynecologists. If remote diagnoses can indeed be made effectively and safely using mobile telemedicine, women can be appropriately triaged, with reduced referral delays, and decreased need for travel from remote sites for those women for whom mobile PIA has ruled out premalignant or malignant disease.¹⁴ Increasing the available cervical cancer screening services by using mobile telemedicine PIA has the potential to have a major impact on lessening the burden of cervical cancer.

C. RESEARCH DESIGN AND METHODS (refer to figure 1, page 5)

C.1. Study Settings

We plan to recruit subjects from among patients presenting to Princess Marina Hospital in Gaborone, Botswana, Africa for gynecologic evaluation. These women will be presenting either to Bontleng clinic for primary screening, or to the Women's Health Initiative clinic based on referral for abnormal PAP smear or VIA. At the Bontleng clinic, the patients will be assessed according to routine protocol by the nurse midwife in charge of cervical cancer screening. At the Women's Health Initiative clinic, patients will be assessed according to routine clinic protocol by the on-site gynecologist, Doreen Ramogola-Masire MD, Head of Women's Health Initiative Botswana-University of Pennsylvania-Partnership at Princess Marina Hospital, Gaborone and Nyangabgwe. At both sites, patients are evaluated for cervical dysplasia and/or cancer using reliable techniques including acetic acid visualization (VIA) and cytology based Papanicolaou smear; however, at the Women's Health Initiative clinic, evaluation may include colposcopy, with or without cervical biopsy and endocervical curettage (ECC), with pathologic and molecular evaluation. At each visit, the local on site gynecologist will visualize the cervix with a vaginal speculum, obtain Papanicolaou smear if clinically indicated, and then, after initial inspection of the cervix, swab the cervix, collecting a specimen for HPV testing. The HPV test will be an in vitro PCR hybridization assay that detects HPV types based on signal amplification, performed in the lab of Dr. Robert Burk at Albert Einstein College of Medicine. Next the gynecologist will apply 4% acetic acid to the cervix and vaginal fornices. In addition to routine clinical care provided by the nurse midwife or Dr. Ramogola-Masire, digital photographs of the cervix will be obtained for each woman being evaluated who is recruited to participate in the study, using the Samsung SGH-U900 Soul phone and utilizing mobile phone software created specifically for photographing the cervix for early cancer detection.

All photographs will be transmitted to Dr. Ann L. Steiner, MD, Clinical Associate Professor of Obstetrics and Gynecology, located at the tertiary care center, the Hospital of the University of Pennsylvania. These photos will then be evaluated through a process we have termed "photographic inspection of the cervix using acetic acid" or PIA. All cytology samples and cervical tissue from biopsies or curettage will be sent for routine processing and histopathologic diagnosis to Dr. M. Kayembe at the Botswana National Laboratory.

C.2. Study Design

In order to address the three specific aims, a prospective case control study will be performed involving women presenting for gynecologic evaluation and cervical cancer screening at the Princess Marina Hospital between July 1, 2009 and July 1, 2010.

C.3. Study Subjects

C.3.a. Eligibility Criteria

Subjects will be eligible for inclusion in the study if they: 1) are over 18 and 2) are either presenting to Bontleng clinic for cervical cancer screening or to the Women's Health Initiative clinic for further work-up of either an abnormal Pap smear result or abnormal VIA.

C.3.b. Exclusion Criteria

Since we are interested in examining lesions of the cervix for the purposes of cervical cancer screening or further evaluation, subjects who have conditions which would interfere with clearly visualizing the cervix, including heavy menses, severe cervicitis, or previous surgical removal of the cervix, will be excluded from this study. We will also exclude pregnant individuals. Since we are interested in examining the efficacy and safety of mobile telemedicine in identifying abnormal, "positive" PIA test results, indicating that a referral is needed, we do not wish to include women who are undergoing continuing treatment for known malignancy, or patients with any known previous history of cervical, endometrial, vulvar or ovarian cancer.

C.4. Study Outcomes

The primary outcome for the first aim of the study will be diagnosis reached by the off-site gynecologist based on photographic evaluation using cervical photos transmitted by the mobile telemedicine handset (photographic assessment with acetic acid - PIA). The primary outcome for the second aim of the study will be diagnosis reached by on-site clinician/gynecologist, blinded to initial patient visit, using PIA. The primary outcome for the final aim of the study will be HPV testing results, positive vs. negative, and HPV type detected.

C.5. Data Collection

Demographic, clinical and laboratory data will be collected at clinical visit (Table 1). Two photographs, at high and low magnification, will be taken of the uterine cervix after application of 4% acetic acid, using the telemedicine handset, the Samsung SGH-U900 Soul phone with 5 megapixel camera. Photographs will be taken utilizing mobile phone software created specifically for photographing the cervix for early cancer detection, a process we have termed "photographic inspection of the cervix using acetic acid" or PIA.

The on-site clinician/gynecologist, at the time of live patient encounter, will determine based on visual inspection after application of 4% of acetic acid (VIA) alone, whether the patient's cervix is (1) normal or (2) abnormal, requiring additional diagnostic or therapeutic interventions. Subsequently, the on-site gynecologist, blinded to the initial live patient encounter, will be asked to assess the digital cervical photographs (photographic assessment with acetic acid – PIA), and to determine whether the cervix appears (1) normal, constituting a "negative" PIA test (no referral needed), or (2) abnormal, constituting a "positive" PIA test (referral needed). An abnormal PIA will be defined as photographic evidence of opaque, well-circumscribed aceto-white areas proximal to the squamo-columnar junction and/or external os³². A normal or negative PIA test will be any result not fulfilling the above positive definition.

The cervical photographs will be transmitted to the gynecologist at the tertiary care center via the Samsung SGH-U900 Soul phone mobile telemedicine handset, and the outside gynecologist, blinded to

the results of the live patient encounter, will be asked to provide the same assessment given by the on-site gynecologist based on photographs alone: whether the cervix appears (1) normal, constituting a “negative” PIA test (no referral needed), or (2) abnormal, constituting a “positive” PIA test (referral needed), using the criteria described above.

Samples collected from cervical smear for HPV testing will be sent to the lab or Dr. Robert Burk at Albert Einsetting School of Medicine for HPV testing. Samples will be labeled only with the patients study number and will be destroyed at the completion of the study.

Finally, tissue samples in the form of Papanicolaou smears, endocervical curettage (ECC) and cervical biopsies will be obtained as clinically indicated. Definitive histopathologic diagnosis will be determined for each of these tissue samples. Results of Pap smears will be reported according to the 2001 Revised Bethesda System. The cut-off for positive results ascertained from Pap smears will be cervical intraepithelial neoplasia grade 1 (CIN1, including HPV changes) or worse (i.e. CINII, CINIII, and invasive cancer). Normal or non-neoplastic histopathologic results from Pap smear and related testing will constitute a negative result. Colposcopic diagnosis of high grade squamous intraepithelial lesions (HSIL), in the absence of a cervical biopsy or pap result, will be considered as true positive HSIL.³²

C.6. Data Analysis

Subjects characteristics will be described overall and by 1) normal vs. abnormal VIA, 2) normal vs abnormal PIA and 3) normal vs abnormal pap smear. Categorical variables will be summarized by frequencies and proportions and continuous variables will be summarized by means, medians and standard deviations. Transformations to normality will be applied as necessary.

Percent agreement including 95% confidence intervals for each pair of diagnostic impressions:

- 1) diagnosis made by off- site gynecologist based on PIA in comparison to on-site gynecologist using VIA
 - 2) diagnosis made by on-site gynecologist using PIA in comparison to on-site gynecologist using VIA and
 - 3) diagnosis made by off-site gynecologist based on PIA in comparison to on-site gynecologist using PIA.
- Pairwise comparisons will also be made between the on-site and off-site gynecologists' diagnostic impressions using PIA for all diagnostic sub-variables listed in Table 3. Pairwise comparisons will also be made between evaluation and conclusions from PIA vs. live patient encounter.

Comparisons of percentages of abnormal vs. normal using VIA vs PIA will be performed using the McNemar's test. The kappa statistic will be used to measure reproducibility between PIA and VIA.

The accuracy of the clinicians' diagnoses based on either live patient encounter or PIA will be determined by comparison to the gold standard of histopathologic diagnosis based on pap smear and tissue biopsy to determine the accuracy of cervical evaluation using mobile technology.

Additionally, we will determine the sensitivity and specificity characteristics along with 95% confidence intervals for the PIA in comparison to VIA as well as pap smear. Additional statistics including positive and negative predicative values for the PIA will also be calculated.

C.7. Sample Size

	SE
Kappa	5% 7.5% 10%
70%	357159 90
80%	251112 63

90% 13259 33

Table 1: Sample sizes for detecting varying agreements and SE of estimate.

We assume the sensitivity of VIA to be 63.5-76.7%, specificity of 64.1-67.3%, positive predictive value of 22.7% and negative predictive value of 89.5% with the prevalence of cervical cancer of 15% among women in Botswana. Based on detecting an agreement (kappa) of at least 80%±7.5% between any diagnostic test and the histopathologic gold standard, we would require a total of n=112 subjects.

Additionally, in order to have 95% confidence intervals for abnormal diagnoses with a range of ±7.5%, we would require n=110 subjects.

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[1] Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh AM et al. HPV screening for cervical cancer in rural India. N Engl J Med 2009;360:1385-94.