Special Article

VIA and Cryotherapy: Doing What's Best

Bandit Chumworathayi MD*, Kobchitt Limpaphayom MD**,
Somkeart Srisupundit MD***, Pisake Lumbiganon MD, MS*

** Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen*
*** Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University*
**** Department of Obstetrics and Gynecology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University*

Cervical cancer kills about 6,000 Thai women annually and has been for decades. The age-standardized incidence ratio (ASR) is 20.9 per 100,000 women-years. A multi-province survey by the Thai National Cancer Institute found that coverage of the previous cervical cancer screening program (i.e. the opportunistic Pap smear) was only 5%. Visual inspection with acetic acid (VIA) and cryotherapy, a secondary prevention program, could be a more practical approach for cervical cancer prevention, particularly in low resource, rural, and remote settings. The authors are expanding this program throughout Thailand (in conjunction with the use of the Pap smear when appropriate) with an 80% coverage target. Using both approaches in a complementary fashion should significantly reduce the incidence and mortality of cervical cancer among Thai women.

Keywords: *VIA and Cryotherapy, Cervical cancer prevention*

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Thailand's current population is 63 million. Forty percent of women are between 30 and 60 years of age. The nation comprises 76 administrative areas called "provinces", each with its own provincial health office responsible for approximately 1 million people.

Roi-et is a province in Northeast Thailand with a population of 1.2 million. It has one provincial general (secondary care) hospital and 14 district (primary care) hospitals. Each district usually has 5 to 10 sub-districts. Each sub-district has one health center (a primary health care setting) responsible for 5 to 10 villages. Each village has between 10 and 20 health volunteers serving between 100 and 200 dwellings: each is generally home to one large family. Health volunteers are the closest health personnel for villagers.

In the Tsunami of December 26, 2004, more than six thousand people died. The huge death toll, occurring over an hour was alarming. A consequence of the media attention has been the implementation of a warning system. By comparison, cervical cancer kills about the same number of women every year. The Age-Standardized incidence Ratio (ASR) is 20.9 per 100,000 women-years[1].

In developed countries, almost all cervical cancers can be prevented by early detection using the Papanicolaou (Pap) test and appropriate treatment. The Pap test is given to target women every year. The ASR in a country should therefore be as low as 3 to 5 per 100,000 women-years, if the national cervical cancer prevention program were to cover over 80% of all targeted women[2]. Since no comparable early detection and prevention of breast and colon cancers is possible, the authors are morally bound to ensure Thai women get this protection. Unfortunately, national policies for disease prevention in most developing countries, including Thailand, fail to achieve this objective.

The Thai National Cancer Institute surveyed many provinces and found that the coverage of the previous cervical cancer screening program (*i.e.* the opportunistic Pap smear) was only 5%[3]. In 2000, coverage was about the same (4.7%) for Roi-et[4], indicating the program was not effectively controlling cervical cancer in Thailand.

Correspondence to : Chumworathayi B, Department of Obstetrics and Gynecology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand. E-mail: bunchu@kku.ac.th

The Pap test has been used as a cervical cancer screening method in Thailand for 3 to 4 decades. Currently there are only about 150 cytoscreeners and 400 pathologists able to read Pap smear slides. To get 80% annual coverage of women between 30 and 60 years of age, 12 million Pap tests would have to be done annually. Even if coverage were reduced to 80% every 5 years, 2.4 million Pap test slides would have to be read annually. This is beyond the ability of the existing facilities and staff.

According to current incidence rates, were it possible to read all these slides, there would be an increase (of approximately 24,000 abnormal cases) needing colposcopy and further treatment each year. According to compliance statistics, 40% of these patients would not come for their follow-up colposcopic examination[5]. Ironically, since there are only 150 colposcopists in Thailand, and most are in Bangkok, such a high drop out rate would lessen the workload. Evidently, a more practical working approach is needed.

Visual Inspection with Acetic Acid (VIA) and cryotherapy

Since 1950, colposcopy has been used to identify the lesion(s) for women with an abnormal Pap test. The procedure usually includes washing the cervix with 3 to 5 percent acetic acid to identify pre-invasive lesions (cervical intraepithelial neoplasias). This allows biopsy of the most severe lesions to be performed under colposcopic vision. Most lesions can be seen by visual inspection (*i.e.* by the naked eye) with acetic acid washing.

The simplified procedures for VIA is to wash the cervix with 3 to 5 percent acetic acid, wait for 1 minute and read it by a trained nurse. If there is any whitish plaque around the squamocolumnar area, the well trained nurse can treat this with a cryotherapy unit using liquid CO_2.

Ottaviano and La Torre (1982) examined the cervix of 2 400 patients, using the acetic acid test and the colposcope with the naked eye[6]. The physiologic transformation zone was clearly identified by the colposcope and naked eye in 1 568 of 1 594 (99%) of cases. Colposcopic examination was unsatisfactory in 108 of 264 (41%) of patients in whom the cervix was completely covered by normal squamous epithelium. An atypical transformation zone (ATZ) was identified by the naked eye as white epithelium in 98.4%, and as "suspicious" in 1.6% of 312 colposcopically-controlled cases. An unsatisfactory colposcopic examination occurred in 39 of 312 (12.5%) of patients with an ATZ. Final histologic diagnosis for the 312 ATZs was a benign lesion in 169 of 312 (54.2%), cervical intraepithelial neoplasia (CIN) grades 1 and 2 in 81 of 312 (26%), grade 3 CIN in 56 of 312 (17.9%), and preclinical invasive carcinoma in 6 of 312 (1.9%).

Ottaviano and La Torre concluded that the detection of intraepithelial or pre-clinical invasive cervical neoplasias should not depend on having a colposcope because any ATZ could be identified by the naked eye as "white epithelium" in 98.4%. By contrast, a colposcope is essential for the selection of CIN to be treated with ultraconservative therapy or colposcopically-directed conization.

The conventional Pap test has relatively low sensitivity (20-35%) but high specificity (90-95%)[7]. Megevand et al (1996) investigated VIA test performance and found it had a positive predictive value of 72.4% compared with 88.9% for the Pap test[8]. Sankaranarayanan et al (1999) reported that the sensitivity of the VIA test was 96% compared with 75% for the Pap test in women with severe dysplasia or more[9].

A study reported by the University of Zimbabwe/JHPIEGO (1999) showed that VIA had a sensitivity of 77% and a specificity of 64% compared to 44% and 91%, respectively, with the Pap test[10]. Denny et al (2000), from South Africa, reported a sensitivity of 67% and a specificity of 88%[11]. Belinson et al (2001) reported from China that VIA had a sensitivity of 71% and a specificity of 74%[12]. From these data, the authors conclude that the VIA test has a higher sensitivity but a lower specificity than the Pap test. However, for cervical cancer screening, sensitivity should be more important than specificity, particularly if the treatment of an abnormal test is relatively simple and not harmful.

VIA and Cryotherapy is appropriate for women between 30 and 45 years of age because: 1) the anatomical landmark "squamo-columnar" junction is easily visible; 2) if there are any pre-invasive cancer changes, they will be at this SCJ; and, 3) for women over 45 years of age the SCJ will generally be inside the cervical os, which is not easily visualized. In our training, the authors suggest nurse providers do the Pap smear for these women.

After a pre-invasive lesion is diagnosed, there are many treatment options available, including cryotherapy, cold-knife conization, laser conization, laser ablation, electrocautery, loop electrosurgical excision and total hysterectomy. Surgical treatments for cervical intra-epithelial neoplasia have been evaluated by Martin-Hirsch et al in a Cochrane review. The evidence

suggests that there is no obviously superior surgical technique for treating cervical intra-epithelial neoplasia[13].

Cryotherapy as a treatment of cervical intra-epithelial neoplasia is relatively inexpensive, safe and easy to learn when compared with other treatments. The procedure recommended in our training is a freeze-thaw-freeze (double-freezing) technique. With a CO_2 cryotherapy unit, the nurse puts the shallow cone-tip of the cryogun squarely on the cervix and does the first freezing for 3 minutes, de-freeze for 5 minutes then do a second freezing for 3 minutes. The one common side effect is a watery discharge per vagina for 4 weeks.

The JHPIEGO has integrated the cryotherapy treatment into the VIA screening program. The combination of screening and immediate treatment in a single visit reduces loss of follow-up. VIA and cryotherapy should be classified as a secondary prevention program, which could be a more practical approach for cervical cancer prevention in low resource (rural and remote) settings.

What have the authors done?

Training of service providers is the key to success of the program. A 5-day competency-based training of the 4 gynecologists who would be the clinical supervisors, was conducted in December, 1999, at Khon Kaen University. Then in January, 2000, a competency-based training for nurse service providers was conducted using the standard 10-day course of VIA and cryotherapy clinical skills training developed by JHPIEGO. Assurance of the program's quality and service providers' competency was done through regular supervisory visits by clinical supervisors.

In February, 2000, the authors implemented this single-visit approach combining VIA and cryotherapy in Roi-et province, a rural area in Northeast Thailand. The target population was women between 30 and 45 years of age.

Twelve competency-based trained nurses provided services in mobile (village health centre-based) and static (hospital-based) teams in four districts of Roi-et province, Thailand. Over 7 months, 5,999 women were tested by VIA. If they tested positive, after counseling about the benefits, potential risks, and possible side-effects, they were offered cryotherapy. The VIA test-positive rate was 13.3% (798/5 999), and 98.5% (609/618) of those eligible accepted immediate treatment.

Overall, 756 women received cryotherapy, 629 (83.2%) of whom returned for their first follow-up visit. No major complications were recorded, and 33 (4.4%) of those treated returned for perceived problems. Only 17 (2.2%) of the treated women needed clinical management other than reassurance about side-effects. Both VIA and cryotherapy were highly acceptable by the patients (> 95% expressed satisfaction with their experience). At their 1-year follow-up visit, the squamocolumnar junction was visible to the nurses, and the VIA test-negative rate was 94.3%[14].

The present study demonstrated that a single-visit approach with VIA and cryotherapy is safe, acceptable, and feasible in rural Thailand, and is a potentially efficient method of cervical-cancer prevention in such settings[14]. After the present study, the Thai Nursing Council has, with the approval of the Thai Medical Council, formally allowed registered nurses to do the VIA and cryotherapy after training under a physician's supervision.

What are the authors doing?

After the safety, acceptability, feasibility and program effectiveness (SAFE) demonstration project, the authors conducted 18 clinical skills (CS) workshops, 5 clinical training skills (CTS) workshops and 1 advanced training skills (ATS) workshop (data till March, 2005). There are now 244 trained nurses and 83 trained doctors in 10 provinces providing VIA and cryotherapy services. The authors are increasing the number of service providers and clinical trainers through standard training courses adopted from the 10-days CS and CTS courses of JHPIEGO. Expansion of the VIA and cryotherapy approach for cervical cancer prevention largely depends upon the effort of these personnel.

Why don't we train more pathologists and cytoscreeners?

Training sufficient numbers of pathologists and cytoscreeners to achieve the Pap smear program alone would be much more difficult and time-consuming (at least 1 to 3 years). Moreover, the Pap smear system is more complex and requires multiple-visits (including referrals). By contrast, the VIA and cryotherapy system needs only 3% to 5% acetic acid, a simple cryotherapy unit with CO_2 tank and the pelvic examination supplies. If the lesions are pre-invasive through VIA testing, trained nurses can treat 90% of patients by providing cryotherapy immediately. And, the most important reason is that VIA and cryotherapy can prevent the same number of cancer cases with a lower cost than Pap smear plus referral[15].

What will the authors do?

The present coverage of cervical cancer screening in Roi-et province is more than 60% of the women between 30 and 45 years of age[16]. This is the highest coverage a province has reached in Thailand.

By March, 2005, the authors have expanded the VIA and cryotherapy cervical cancer prevention program to 10 provinces (Roi-et, Nongkai, Yasothorn, Amnatcharoen, Ubonratchatani, Nakornratchasima, Suratthani, Nakornsithammaraj, Uttaradit and Chiang Mai); representing the Northeast, Northern and Southern regions of the country. This program uses both VIA and Pap. VIA is for women between 30 and 45 years of age with visible SCJ, and Pap is for women over 45 or without visible SCJ. The authors will expand the program until a cervical cancer prevention program is established in every province.

Problems and solutions

In the past, an effective monitoring system for the coverage of cervical cancer screening program was not available. During the expansion of our VIA and cryotherapy program, a computer program was jointly developed by International Agency for Research on Cancer (IARC) and JHPIEGO to register all the cervical cancer prevention activities from the screening to final treatment. Later, a member of the authors team, Dr. Bancha Palanuwong, made it more user friendly. The modified version of the program is now used in some provinces and has proved effective for monitoring the cervical cancer prevention program.

The VIA and cryotherapy program in Thailand has been implemented by the Department of Health (DOH) and the Pap smear screening program by the Department of Medical Services (DOMS). Previously, no clear collaboration between the two programs occurred. In 2004, the DOMS had just organized a workshop for creating a Pap smear registry to monitor the coverage of Pap smear testing. In November, 2004, DOH and DOM organized a dissemination workshop together and concluded that the Pap test should be performed in areas where resources are available and VIA and cryotherapy should be considered in areas where the Pap test can not be effectively implemented. The ultimate goal is to have > 80% of women between 30 and 60 years of age screened for cervical cancer at least every 5 years[17].

Maintenance of the cryotherapy unit is essential for the long-term sustainability of this VIA and cryotherapy approach. The authors have therefore trained and set up maintenance teams in each region of the country.

Regardless of the screening methods (*i.e.* Pap test or VIA and cryotherapy), if the coverage increases, there will be more patients needing referrals for further evaluation and treatment. Facilities for further evaluation including colposcopy with or without tissue biopsy should be made available. Without these facilities, a cervical cancer control program will not be effective. In the initial phase of the screening, more patients with invasive cervical cancer will be detected and referred. The appropriate treatment though radical surgery, radiotherapy or chemotherapy should be prepared.

Why don't we think about using HPV vaccine and HPV testing now?

Human papilloma virus (HPV), one of the most common sexually transmitted infections (STIs), is the primary cause of cervical cancer [18]. For teenagers and young adults who have never had any sexual intercourse, prophylactic HPV vaccine without HPV DNA testing is suitable. However, there are 13 high-risk or oncogenic HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) but now there are only prophylactic HPV vaccine for types 16 and 18[19-21]. Although these vaccines have almost 100% efficacy, there is still questions about HPV infection that are not types 16 and 18. Five most common types of high-risk HPV (16, 18, 31, 33, or 45) account for 80% and types 16 or 18 infections account for only half of all high-risk HPV infections[22]. The authors estimate that it will take more than ten years for the development, low cost commercialization and recommendation by the national immunization plan committee of a new vaccine. The authors can not wait that long to decrease cervical cancer in Thailand.

For older women who have had sexual intercourse, HPV infection is a necessary, but not sufficient precursor to cervical cancer. While the cumulative lifetime incidence of HPV infection is 70% to 80% in many countries, the vast majority of women with HPV infection will not develop cancer. [23,24] This group of women should have a HPV DNA testing before getting HPV vaccines. If negative they should have a prophylactic vaccine, but if positive they should have a therapeutic or a combined one. Therapeutic vaccines are still in early stages of research and limited to viral load or persistence. Early phase human trials have shown that E6 and E7 proteins (HPV oncogenes), and some peptides derived from these proteins, are immunogenic in man[25]. These proteins can be safely delivered to patients with cervical cancer and precancer, using a range of adjuvants and delivery systems including

viral vectors, peptides and proteins. However, the cost-effectiveness and usefulness of this approach have not been clearly outlined and require further research. We can say that there currently is no cure for HPV infection, prevention is very difficult, and there is no clear way to predict which HPV-infected women are likely to develop cancer.

Both hybrid capture II (HC II) and polymerase chain reaction (PCR) techniques for detecting HPV DNA require transport of the sample (and use of a transport medium) to the laboratory, storage, and processing time in the laboratory. These requirements will have programmatic implications. While HPV is an objective test with rapid turnaround, the test results are not immediate. In addition, quality control mechanisms for HPV testing need further evaluation. These requirements currently use techniques that are too costly and difficult to implement in many low-resource settings. Therefore, further research is needed to develop HPV test technologies that are feasible for use in low-resource settings and that accurate in predicting a woman's risk of developing high-grade lesions and need for further testing. Ideally, an HPV diagnostic would require minimal supporting equipment and would provide inexpensive, accurate, and rapid detection.

Research suggests that HPV DNA testing has potential as a primary screening method among women aged 30 and older (like VIA target group, that is 30-45 years-old). Among these women, the sensitivity of a single lifetime HC II test for detection of high-grade dysplasia has been 80 to 90 percent (higher than for cytology), and specificity has ranged from 57 to 89 percent[26-28]. The test also has a high negative-predictive value. In addition, HC II may be more effective than conventional cytology or visual inspection with acetic acid for screening postmenopausal women. When used to detect HSIL, however, the test is only moderately specific, particularly among women younger than age 30. Women with positive test for carcinogenic types of HPV may experience great anxiety about developing cancer, despite being at very low risk. This issue must be taken into account when considering initiating HPV testing.

Conclusion

Cervical cancer is still a major women's health problem in Thailand despite availability for many decades of the Pap smear early detection program. This indicates the logistical failure of the cervical cancer prevention program by Pap smear. Strong research evidence shows that VIA has good performance for cervical cancer screening and that cryotherapy is effective for the treatment of pre-invasive cervical lesions. The authors have demonstrated that VIA and cryotherapy in a single visit approach is safe, acceptable and feasible in the rural and remote areas of Thailand. The authors are expanding this program throughout the nation, in conjunction with the appropriate use of Pap smear, with the target of achieving 80% coverage of targeted women. This should reduce the incidence and mortality of cervical cancer among Thai women.

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การตรวจคัดกรองมะเร็งปากมดลูกด้วยวิธี VIA แล้วรักษาด้วยวิธี Cryotherapy ทำให้ความครอบคลุมดีขึ้น

บัณฑิต ชุมวรฐายี, กอบจิตต์ ลิมปพยอม, สมเกียรติ ศรีสุพรรณดิฐ, ภิเศก ลุมพิกานนท์

สตรีไทยเสียชีวิตจากโรคมะเร็งปากมดลูกถึงปีละประมาณ 6,000 คน และเป็นเช่นนี้มาหลายสิบปีแล้ว อุบัติการณ์ของโรคนี้เมื่อปรับตามกลุ่มอายุ [age-standardized incidence ratio (ASR)] เท่ากับ 20.9 ต่อสตรี 100,000 คน-ปี การสำรวจในหลายจังหวัดโดยสถาบันมะเร็งแห่งชาติของประเทศไทยพบว่า ความครอบคลุมของโครงการตรวจคัดกรองมะเร็งปากมดลูกในประเทศไทยก่อนหน้านี้ (ซึ่งก็คือการตรวจแพปเสมียร์เมื่อสตรีมีโอกาสมาพบแพทย์เพื่อรับการตรวจภายใน) มีเพียงร้อยละ 5 ของกลุ่มประชากรเป้าหมายเท่านั้น การตรวจคัดกรองมะเร็งปากมดลูกด้วยวิธี VIA (visual inspection with acetic acid) แล้วรักษาด้วยวิธี cryotherapy ซึ่งเป็นการป้องกันทุติยภูมิ สามารถเป็นแนวทางที่เหมาะสมกว่าในการป้องกันมะเร็งปากมดลูก โดยเฉพาะในสถานที่ที่มีทรัพยากรจำกัดและห่างไกลความเจริญ กรมอนามัยกำลังขยายโครงการป้องกันมะเร็งปากมดลูกด้วยวิธีนี้ออกไปทั่วประเทศไทย (โดยยังคงใช้ร่วมกับการตรวจแพปเสมียร์ในบางกรณีที่เหมาะสมเท่านั้น) โดยมีเป้าหมายเพื่อให้ได้ความครอบคลุมถึงร้อยละ 80 ของกลุ่มประชากรเป้าหมาย (สตรีอายุ 30-45 ปี) ด้วยความหวังว่า แนวทางนี้จะสามารถลดทั้งอุบัติการณ์และอัตราการเสียชีวิตจากโรคมะเร็งปากมดลูกในสตรีไทยลงได้อย่างมีนัยสำคัญในอนาคต