International Journal of Science and Research (IJSR)
ISSN: 2319-7064
ResearchGate Impact Factor (2018): 0.28 | SJIF (2018): 7.426

Use of Acetic Acid in the Trace of Papiloma Human Virus in the Uterine Column

Use of acetic acid in the detection of papillomavirus in the cervix

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Abstract: ***Cervical cancer is still an important cause of morbidity and mortality in Brazil despite access to the Pap smear. The relationship between HPV Human Papilloma Virus and cervical cancer is undeniable; in almost 100% of neoplastic lesions, the presence of the virus is confirmed. Objective: To verify the efficiency of the acetic acid test followed by visual inspection acetic acid (VIA), in the detection of pre-clinical signs of HPV in the cervix; comparing the prevalence of positive HPV results to the acetic acid test with the prevalence of the same virus positivity in Pap smears (PAP). Method: After collection of the cervical material for PAP, the neck was embroidered with 5% acetic acid and visual inspection was performed after 1 minute; the colos that presented aceto-white zones were considered positive. For Pap, the results that accounted for "Low Grade Intraepithelial Lesion" and "Grade I Intraepithelial Neoplasia" were considered positive. Results: A total of 248 Pap smears plus the VIA test were evaluated and all cases with an aceto-white area in the cervix were submitted to colposcopy and biopsy. As a control, the PAP results from the same women were used. The prevalence of positivity for the VIA test was significantly higher than in the PAP results. Conclusion: The prevalence of positivity for the VIA procedure was 10% versus 1.6% in the Papanicolaou results. This difference was considered significant (x2 = 17.86 - P = 0.0001), but the evidence of lesions detected by the VIA test in the biopsies performed was 38.5%.***

Keywords: Human Papilloma Virus, Test of acetic acid. Tracking, Cancer of the uterine cervix

1. Introduction

Cervical cancer is still a major public health problem in the world today, especially in developing countries. In Brazil, it is the second most common cancer among women, second only to breast cancer [1]. Although the Papanicolaou test in the 1930s can effectively prevent this neoplasm, many women still contract it and a large number die, resulting in a considerable social cost.

In the 1970s, Harald Zur Hausen, of the German Research Center, studied the relationship between cervical cancer and some types of human papillomavirus (HPV). The results of this study had a great impact on the investigations on the prevention of cervical cancer and provided Professor Zur Hausen or Nobel Prize in Medicine [2]. Today, it is a fact that most cases of cervical cancer are linked to the previous presence of HPV.

However, it would be desirable to ally the Papanicolaou with a procedure that could detect pre- clinical lesions of HPV. The detection of the virus, and even more, its identification would be ideal for the true prophylaxis of cervical cancer since it has already been demonstrated that about 99% of the cases of cancer of the cervix have the causing agent HPV [3, 4].

There are approximately 200 types of viruses identified as HPV, but some of them are only designated as cancer triggers in the cervix (types 16 and 18, mainly); others (especially 6 and 11) are present in the majority (70%) of the condylomatous lesions of the female and male anogenital region[5]. Eventually this virus is identified in the cervix by the Pap smear, from the cervical smear, but this test has no specificity for HPV detection.

The *Screening Guidelines for the Prevention and Early Dete ction of Cervical Cancer*, published by the American Society in 2 012[6], advocates *co-testing*, ie the HPV test in the routine preventive exam, in addition to *Pap- test*, for women *aged* 30 to 65 years. This test is possible when using Papanicolaou in a liquid (*thin-Pap-test*).

Unfortunately, this procedure is still incipient in Brazil and practically inaccessible in the public health network, due to the high labor cost.

There are other methods for HPV screening, including alternative and simple technology methods, and among these procedures is visual inspection after the use of 5% acetic acid.[7] One of the direct inspection techniques former (in English *direct visual inspection* or DVI) were used in the 30 's, introduced by Schiller [8] and were abandoned in the next decade, with the emergence of cytology, thanks to Georg Papanikolaous studies.

It is estimated that soon after the onset of sexual life, contact with HPV is already occurring; However, the permanence of this virus, which occurs in one-third of infected women, combined with the specific conditions of each will determine the progress to precancerous lesions and cervical cancer [9].

It has already been shown by some authors that the use of acetic acid in solutions of 3-5% can help in the detection of cancer precursor lesions in the cervix [7, 9], determining areas aceto-white on the surface examined, attributed to pre-clinical lesions of the infection by HPV.

Acetic acid has a mucolytic action and acts causing cellular dehydration and coagulation of the intranuclear proteins, reducing the transparency of the epithelium, and the intensity of aceto-bleaching is directly proportional to the severity of the lesion [10]. It allows immediate reading of the result, allowing the elaboration of a therapeutic care plan at the first visit, reducing the number of treatment dropouts [8, 11]. It is a low cost method, simple and easy to learn.

The purpose of the present study is to expand the detection of HPV in genital cancer prevention consultations, allowing intervention in time to avoid the evolution of this virus to cervical cancer.

The objectives of the study were as follows:

- Verifytheefficiencyof the 5% Acetic Acid test, followedby direct observation (VIA = *visual inspection acetic acid)* to detect preclinical signs of the Human Papilloma Virus (HPV) in the cervix in routine preventive gynecological examination in Basic Health Unitsof Sorocaba.
- To compare the prevalence of results compatible with the presence of HPV in women who underwent the VI A test with the prevalence of this result obtained in Papsmears alone

In this study, it is considered a positive result that charged "intraepithelial lesion Low grade (including cytopathic effect HPV and neoplasia cervical intraepithelial Grade I - CIN I), terminology such proposed in the document" Pipes Clinical compared to the results of the Papanicolaouexam" from the Oncocentro Foundation of São Paulo.[12]

2. Method

1) Location, Casuistry, Procedures

The study was conducted with users of five Basic Health Units of Sorocaba, components of the Regional Health East and who showed a greater demand for Pap smears in a previous evaluation. Data collection began in September 2013 and was completed in June 2014.

Prior to data collection, the test reading was standardized with 5% acetic acid (VIA or " *Visual Inspection Acetic acid* ") among professionals who routinely perform the Pap smear in selected UBS, and agreed to include the VIA test for their clientele. Also participating in these meetings were the four students of the Faculty of Medical Sciences and Health, who co-authored the study.

The film " *A Training Course Visual Inspection using 4% Acetic Acid (VIA) - theory and practice* "(Wesley RS, Head Community Oncology Division, Regional Cancer Center, Trivandrum, India)[13] Portuguese version. It was also provided to the professionals who joined the procedure, besides the necessary material, described below, the link of the course above (http://screening.iarc.fr/digital/cdVIApt/cdVIApt.html) plus a photo plastified with images of lesions typical of negative, positive results and cervical cancer itself "in situ". The following materials were provided to the professionals who agreed to collaborate:

a) acetic acid diluted at 5% by oiler, amount of approximately 50 ml, replaced every 15 to 21 days;
b) Speculums KOLPLUX [R] sizes P and M, in sufficient numbers for the demand foreseen in the UBS;
c) LED source, assigned to the UBS during the time of the research;
d) A summary sheet with Inclusion Criteria;
e) A material descriptive sheet necessary for the entire cervical cancer prevention procedure (Pap + VIA).

As depend on the good visualization procedure, have been invited and kindly provided by the company **KOLPLAST me LTDA** speculums with own lighting - KOLPLUX [R.] These speculums are coupled to an LED light source that plunges directly into the vagina, allowing excellent visualization of the cervix. Thusall speculums used in the study were supplied by the company as well as the LED sources (these in lending) for each participating UBS.

Thus, in two UBS, the procedures were performed mostly by the students under direct supervision of the counselor, while in the other three units the same procedures were performed by the professionals in charge of the routine Papanicoalou exams and who agreed to include the VIA procedure in practice. In all cases where the VIA test demonstrated white acetic zones, colposcopy was referred. A photo of possible situations found in the cervix and the proposed classification after the acetic acid bonding (suggested in the above-mentioned video-course), to be used as a comparison parameter, was provided to the examiners who participated in the study.

For all clients who agreed to add the VIA test to their Pap smear, a form with gynecological and obstetrical data from the client was completed, as well as the results of the VIA, Pap smear, colposcopy and biopsy tests.

2) Inclusion Criteria

We included women who sought the UBS for the preventive exam and

- Were in the age groupof 20 to 65 years, atthe time oftheexamination;
- Did not present demonstrable genital infectionatthe time ofcollection;
- Had never previouslybeendiagnosedwith HPV;
- Did not present previous results of neck lesions (ASCUS, AGUS, NICs, CIS)
- They were not pregnant;
- Who agreed to participate in the study, signing the TCLE.

The study was approved by the Research Ethics Committee of the Faculty of Medical Sciences and Health of PUCSP,

Sorocaba, under n. 16935413.9.0000.5373, opinion n. 371, 314 of 08/26/2013.

3. Results

The sample consisted of 248 women, distributed almost equitably in the age group (51.2% from 20 to 40 years old and 48.8% older than 40), with active sexual life (86.3%), with stable marital status (75.4%), with two children or less (60.5%), living in the territories assigned to the BHUs selected from the Regional Health East of Sorocaba. The majority (78.3%) reported a single partner in the last year and 65.7 % initiated sexual life with more than 15 years.

According to the inclusion criteria, the women participants had previously presented no pre-malignant lesions of the cervix and / or HPV-compatible outcome. Following the same criteria, those with some detectable genital infection at the time of the preventive examination were excluded.

Table 1 presents the results referring to the study objectives, showing that the percentage of VIA positive results (compatible with the presence of HPV) was significantly higher than the same results for the Papanicolaou. This occurred, probably because the HPV specificity of the VIA test is greater than in cervical cytology. As expected in the project, to validate the VIA positive results, all the women in this group were referred for Colposcopy and when positive, were submitted to a targeted biopsy.

Table 1:
https://documentcloud.adobe.com/link/track?uri=urn%3Aaaid%3Ascds%3AUS%3A703ae965-0daf-4d45-b08b-a517613862ea

Table 2 presents the results of the Colposcopies performed. These results refer only to the clients who presented the VIA positive test. The results of the Pap smears could not be included in this tabulation because the routine procedure for the results of "Intracellular Cervical Neoplasia - NIC I" and / or presence of HPV cytopathic effect is to repeat the examination in 6 months and only then to perform colposcopy [12]. However, the validation of the results of VIA positive tests was performed by colposcopic examination and biopsy, whenever any lesion was detected. These examinations were all carried out by the same professional, at Policlínica de Sorocaba, the reference site for the preventive exams coming from the UBSs of the municipality.

Table 2:
https://documentcloud.adobe.com/link/track?uri=urn%3Aaaid%3Ascds%3AUS%3Aef2b993c-fe76-4b0b-8d8e-4897fc039aca

One bias that hampered this assessment was the large number of women who did not attend colposcopy. Some were called and reoriented, but nevertheless refused to take this exam (see Table 2).

It was verified that in 5 women with positive VIA was diagnosed, in the biopsy, "Cervical Intraepithelial Neoplasia – NIC I"; of these, 4 had had the result of Papanicolaou Normal and in one was detected "Scaly Lesion of Undetermined Significance" (ASCUS). This result is generally consistent with the cytopathic effect of HPV [11]. The observed occurrence alerts to the low specificity of the Pap test for HPV-induced lesions that is known to be the precursor of cervical cancer. For this reason, the FOSP Manual [12] as well as the Brazilian Guidelines for the Screening of Cervical Cancer [14] they recommend performing two consecutive negative tests - guaranteed the presence of squamous-columnar junction cells - to indicate the preventive examination every three years.

We have observed in practice that this last orientation has been fulfilled, but the representativeness of at least two epithelia in the smear (the squamous and glandular and / or metaplastic) has not been seriously considered. A recent study in Sorocaba [15] showed that the number of Papanicolaou results is still high, and the lamina contains only squamous cells, especially in women over 40 years of age, a fact that compromises the validity of the Papanicoalaou result.

The number of VIA positive tests in each of the five Health Units included in the study can be evaluated in Table 3.

Table 3:
https://documentcloud.adobe.com/link/track?uri=urn%3Aaaid%3Ascds%3AUS%3A9f2efa8f-c058-465b-abd5-f4f4b61e9b6b

The higher number of exams at the UBS of Eden is due to the large number of exams performed by the students, co-authors of the study, accompanied by the counselor, in unusual hours for this service (from 18 to 22h), in addition to the considerable adherence of professionals of this Unit (see Table 3).

This study aimed to obtain a broader casuistry, but the adherence to the procedure by the professionals who carry out the preventive examination in the public network was very low and, even with the goodwill of the students involved, the low availability of rooms in the UBS during normal hours made the job difficult. It was then necessary for the researchers to go in unusual times, when there were idle rooms. This was what happened at UBS do Éden, whose examinations were scheduled for the night, contributing, in a way, to equalize the demand of women for preventive examinations in this Unit.

In all 248 cases of this study, only one slide was rejected because it was unsatisfactory to read. The patient, in this case, was called for a new collection.

4. Comments and Discussion

Exfoliative cytology has been the leader in cervical cancer screening, showing efficacy in early detection and has favorably influenced morbidity and mortality statistics from this disease in previous decades. In Brazil, data from SISCOLO[16] report that 80% of the women interviewed reported having at least one cytology Previous but the offer apparently sufficient examination, now need to focus attention to the quality of it, because the number of

unsatisfactory samples is still above 5% in some regions. The tracking quality and its practical opportune í stica has not caused satisfactory impact on the statistics of morbidity and mortality in the last decade.[17]

Recent studies have evaluated the use of the HPV test associated with ci oncology, or Pap smears [18], demonstrating that this procedure increases sensitivity by 35% for the detection of cervical cancer when compared to screening by isolated cytology. Another study, carried out with 2 281 women in CAISM-UNICAMP[7], reached a similar conclusion, showing that the cytology performance associated with visual inspection of the cervix after application of 5% acetic acid was more efficient than the Cytology associated with Hybrid Capture or than isolated cytology.

Publishing recent BMJ-British Medical Journal [19], involving 58, 000 women aged 30-60 years in southern Finland, in two years of observation, they have concluded that screening for HPV showed more sensitivity than cytology to detect severe precancerous lesions in the cervix (CIN III). But the study's authors agree that a single test does not guarantee good protection; periodic repetition every 3 years is advised. The authors also point out that the majority of women with cervical cancer belong to the group not covered by any type of screening.

Recently, the United States test was launched in **cobas** ® PCR *Cell Collection Media*, Roche Molecular Systems, Inc.[20] which makes it possible to identify types 16 and 18 DNA and 12 other HPV cancer types. However, the high cost of this test makes it utopian for mass use, especially in countries with low health investments, such as Brazil.

While the HPV-vaccinated generation does not reach age 25, the onset of vulnerability to genital cancer, and that virus DNA testing is still unrealistic for most Brazilian women, it is understood that simple, low-cost procedures can be added to the cytology in order to obtain more efficient results and that will result in a favorable impact on cervical cancer mortality.

It is worth remembering that early detection must be accompanied by a good referral and referral system as well as adequate care at the secondary and tertiary levels for effective resolution and modification in the course of the diseases found. The social aspect of female genital cancer, especially of the cervix, should not be neglected since it affects women in the age group where they generally play a nuclear role in the family.

Regarding the results of this study, even considering the small sample and the difficulties in complying with the established rules for positive VIA results, it can be inferred that the findings corroborate the study by Cordeiro et al.[21] showing greater sensitivity of VIA to cytology for cases of CIN I and induced HPV lesions. This author proposes to join the acetic acid test to the cytology, making it possible to detect one-third more cervical lesions, with the advantage of allowing immediate reading of the result and therapeutic initiative, allowing minimizing the failures in the follow-up of the client. As stated by Laganá et al.[22], "*non-follow-up screening is unethical and cannot be effective without appropriate treatment [...]* " In this study we cannot consistently compare the specificity found in similar studies for the poor adherence obtained from the colposcopic examination (from 25 results VIA + only 13 underwent colposcopy).

Some other factors considered influential for the prevalence of cervical cancer, in addition to HPV, such as smoking, use of hormonal contraceptives, multiple partners, and early onset of sexual intercourse [23] were not confirmed in this study: most women with VIA + reported only one partner, stable marital life, onset of sexual intercourse after 15 years; the five women who tested positive on the biopsy reported being non-smokers and only two reported using hormonal contraceptive methods at the time of the test.

5. Conclusions

The prevalence of positivity for the VIA procedure (*visual inspection acetic acid*) occurred in 25 cases (10%) versus 4 cases (1.6%) of changes compatible with the presence of HPV and / or CIN I in the Papanicolaou results. This difference in the results of both procedures was considered significant ($x^2 = 17.86$ - P = 0.0001).

Of the 25 VIA positive cases, 13 colposcopies were performed, 6 of which were negative for cervical lesion and 5 were positive, with immediate biopsy.

The result of the five biopsies was CIN I, ie, low grade cervical intraepithelial lesion and / or HPV cytopathic effect. Of these women, 4 had had normal results in the Papanicolaou, alerting to the low specificity of the latter for HPV. In the fifth case the result of the cytology was the presence of "Atypical Squamous Cells of Undetermined Significance". For this woman, the conduct would not be different if she had only performed the Pap smear but for the other four, the VIA + result altered the conduct, making her more cautious because the return that, for the cytological result would only be annual examinations or tri-annual routine, required to return in 6 months for repeat cytology and new decision, depending on the new result.

The confirmation of VIA positive cases by colposcopy and biopsy was impaired since 12 women (48% of those referred) did not attend the examination, even after the convocation and reorientation. In 6 women (46% of those referred) no lesions were detected in the cervix, so biopsy was not necessary. This is actually a consequence of the low sensitivity of the VIA test, leading some women to unnecessary procedures.

6. Final Considerations

Considering:

- The greater specificity of the VIA test for detection of pre-clinical HPV lesionsthanthe Papsmear ;
- Proven knowledge that cancerous types of persistent HPV in the cervix induce cervical cancer;
- The ease in carrying out andsafetyofthe VIA procedure;

- The possibilityof training professionalstoperformthe VIA test in a short time;
- The very low cost of the necessary material;
- The time of the procedure (only 1 minute more in the Papanicolaou exam);
- Cost-effective in increasing the number of colposcopies and orbiopsies.

The findings of this study suggest the need to evaluate the cost-benefit of adding, in all routine Pap smears, the VIA test, with posterior colposcopy for all those who are positive.

Thanks

The authors thank the National Council for Scientific and Technological Development (CNPq) for the Scientific Initiation Grant awarded to the student Giovanna Rela Matricardi, co-author of the study.

The KOLPLAST me Ltda for the assignment of all self - illuminated vaginal speculums and Led sources that enabled the required quality of the images during the VIA (*visual inspection acetic acid*) used in this study.

Also thank the nurses Helena Ferreira Solla and Silvana Sanavio; to the doctors Dra. Sara Toassa Gomes Solha and Dra Elisabete Mass Mimura, for having included the VIA procedure in the preventive examination carried out in their respective Basic Health Units during the period of data collection. Our thanks also to the nursing technician Valdete Sueli de Oliveira Pereira, who worked on the search for women in arrears with the Papanicolaou, and diligently took care of the annotation of suspicious results for the proper referral.

They are most grateful to Dr. Eduardo Martins Marques, who performed all the colposcopies and biopsies, making the notes available for this study.

References

[1] Herbert J, Coffin J. ReducingPatient Risk for Human Papilloma virus Infection and Cervical Cancer. JAOA 2008; 108 (2): 65-70.
[2] HPV Institute. National Institute of Science and Technology of Human Papilloma virus Diseases. HPV Guide. 2012 Jul; Available at www.incthpv.org.br
[3] Bragagnolo AL, Eli D, Haas P P. Human Papilloma Virus (HPV). RBAC 2010; 42 (2): 91-96.
[4] Neves NA, Andrade L, Neves RA, Abade B. Natural history of human papilloma virus infection. Rev Bras Pat Trato Gen Inf 2011; 1 (1): 9-12
[5] Ministry of Health (Brazil). Vigitel 2009. [quoted in Jan 23, 2011]. Availableat: http://portal.saude.gov.br/ portal / archives / pdf / prevencao_cancer_16_8_10.pdf
[6] American Cancer Society (ACS). Screening Guidelines for the prevention and early detection of cervical cancer. CA Cancer J Clin 2012 May- Jun ; 62 (3): 147-72. Available in http://cacancerjournal.com
[7] Gontijo RC, Derchain SFM, Roteli- Martins C, Sarian LOZ, Bragança JF, Zeferino LC, Silva SM. Evaluation of alternative Methods to Cytology in Cervical Lesion Tracking: DNA-HPV Detection and Visual Inspection. RBGO 2004; 26 (4): 269-275.
[8] Wright TC Jr. Cervical cancer screening using visualization techniques. J Natl Cancer Inst Monogr. Chapter 10 2003 ; (31): 66-71.
[9] Cruz FJ, Melo VH. Factors associated with the persistence of HPV infection in the cervix. Femina 2010 Aug ; 38 (8): 423-27.
[10] O'Meara AT. Present standards for cervical cancer screening. Curr Opin Oncol. 2002; 14: 505-11.
[11] Shastri SS, Mittra I, Mishra G, Gupta S, Dikshit R, Badwe RA. Effectof visual inspection with acetic acid (VIA) screening by primary health workers on cervical cancermortality: A cluster randomizedcontrolledtrial in Mumbai, India. J Clin Oncol 31, 2013 (suppl ; abstr 2).
[12] Fundação Oncocentro de São Paulo-FOSP. Clinical conduct versus theresultsofthe Papsmear. 4 ed. Stateof São Paulo Official Press: 2011. 52p.
[13] Wesley RS. A Training Course Visual Inspectionusing 4% AceticAcid (VIA) – theory and practice. Head Communitty Oncology Division, Regional Cancer Center, Trivandrum, India. Available in http://screening.iarc.fr/digital/cdVIApt/cdVIApt.html. Accessin August 2013.
[14] Brazil. National Cancer Institute. Brazilian guidelines for the screening of cervical cancer. Rio de Janeiro: Ministry of Health; 2011.
[15] Souza ES, Palmezani MNS, Campos TAF, Pereira VM. Without the addition of representative results of prevalences quamous columnar Pap tests performed in Basic Health Units in thecityof Sorocaba / SP. Proceedingsofthe 10th Global Network of WHO Collaborating Centers for NursingandObstetrics Conference, Coimbra / Portugal.
[16] NationalCancerInstitute (Brazil). Planofactiontoreducetheincidenceandmortality of cervical cancer: executivesummary / NationalCancerInstitute. - Rio de Janeiro: INCA, 2010.
[17] Thuler LCS. Mortalityduetocancerofthecervix in Brazil. Editorial. Rev Bras Ginecol Obstet. 2008; 30 (5): 216-8
[18] Perkins RB. Should US womenbescreened for cervical cancer with Paptests, HPV tests, or both? Annals of Internal Medicine: Ideas and Opinions. American College of Physicians. Available online at annals.org on 10 June 2014.
[19] Anttila A, Kotaniemi-Talonen L, Leinonen M, Hakama M, Laurila P, Tarkkanen J et al. Rate of cervical cancer, severe intraepithelial neoplasia and adenocarcinoma in situ primary HPV DNA screening with cytologytriage: randomized study With in organized screening program. BMJ, 2010; 340 (apr 271): c1804.
[20] cobas © HPV Test, FDA approved for first-line primary screening. 2014 Hoffmann-La Roche Ltd - Canada
[21] Nelson R. Cervical Cancer Screening with Vinegar Reduces Mortality. June 03, 2013
[22] World Health Organization Human papilloma virus and HPV vaccines:. Technicalinformation for policy–makers and health professionals [monographonthe Internet]. Geneva (Switzerland): WHO; 2007. [cited 2009 set 15]. Available in http://whqlibdoc.who.int/hq/2007/WHO_IVB_07.05_eng.pdf