Original Article

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Co-Testing of Cervical Screening Tests in Detection of High Grade Cervical Intraepithelial Neoplasia

Oncology Section

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ABSTRACT

Introduction: Co-testing performance for detection of high grade Cervical Intraepithelial Neoplasia (CIN) has not been adequately addressed from Low Resource Countries (LRCs). Where isolated tests do not have adequate performance, further explorations are recommended.

Aim: To evaluate the co-testing of conventional cervical screening tests such as Papanicolaou (Pap) and Visual Inspection Cervix with Acetic Acid (VIA), with care HPV on Cervical Samples (CHPV) or on Vaginal Samples (VHPV) in the detection of high grade CIN.

Materials and Methods: The cross-sectional study was conducted on ever married women of age 30 to 59 years in a rural community of Dadri. Women were screened by CHPV, VHPV, and Pap and VIA methods. Confirmation of screen positives was done by histology. Sensitivity, Specificity and likelihood ratios of different combinations of test determined to evaluate the performance.

Results: Total eligible women, 66.2% (5032/7604) responded for screening. Analysis was performed on 4658, after excluding those who did not complete all screenings. Co-testing of CHPV (OR=246) or VHPV (OR=278) with Pap had highest association. Positive likelihood ratios of CHPV and VHPV with Pap in CIN II+ detection rates were 13.0 and 11.8 and in CIN III+ the detection rates were 18.0 and 16.0 respectively. Higher sensitivities and specificities were observed in co-testing for CIN III+ detection as against CIN II+ lesions.

Conclusion: Choice of co-testing in a pair of tests for detection of high grade CIN is likely to depend on whether screening is targeted for developed or low resource country. VIA in isolation might not yield optimal results for LRCs.

Keywords: Aided Visual Test, Care HPV screening, Cervical cancer, Cytology, Rural community

INTRODUCTION

Cervical cancer is the third most common cancer worldwide with 530000 new cases every year and the second most common cancer in resource limited countries [1]. Due to its long pre-invasive phase it is preventable and easily identifiable by clinical and pathological examinations. Identification and treatment of the precursors of cervical cancer can be done through screening by various screening methods. Screening methods for cervical cancer such as visual inspection of cervix with acetic acid (VIA), Papanicolaou (Pap) smear, and Human Papillomavirus (HPV) DNA testing on cervical and vaginal samples for the detection of CIN are reported in various study settings [2-6]. HPV-DNA testing has demonstrated a better yield over Pap and VIA conventional tests of cervical screening. Physician collected cervical sample for HPV (CHPV) is preferred over self-collected vaginal sample (VHPV) testing to detect high risk HPV as indicated through review based studies [7]. Single test approach by adopting any cervical screening test in isolation often lacks adequate performance in the detection of high grade CIN. Low sensitivities for cobas HPV testing and Pap testing were observed in ATHENA trial [8,9], which suggest routine cytology and HPV co-testing offering greatest protection against cervical cancer [10]. There was only a single large US study that adopted the Food and Drug Administration (FDA) approved co-testing strategy of cytology with Hybrid Capture (HCII) to assess the safety of routine clinical practice of three years screening intervals, using concurrent testing for HPV and cytology among women aged 30 years or older [11]. Investigating and exploring co-testing of the tests such as VIA, Pap and HPV would be of help to better understand different combination specific co-testing performance of tests for the detection of high grade CIN. Some studies have reported concurrent co-testing and triage comparative performances of various screening tests in different combinations [12-17]. These studies mainly tested combinations of Pap or VIA with HPV by HCII.

CareHPV has been recommended for LRCs in a multi-country setting demonstration project due to its low cost and minimum lab requirements [18]. The additional results of careHPV study conducted in a rural setting in North India as a part of multi-country project are separately reported [19]. Assessment of age-specific performance of careHPV in our rural setting was also evaluated and the study reported the findings of the option of CHPV testing for screening in all ages for detection of high grade CIN [20]. Qualitative assessment of careHPV through viral load was studied further and it was observed that with respect to viral load VHPV and CHPV demonstrated comparable performance using careHPV [21].

Studies on careHPV as an adjunct with conventional cervical screening tests are of interest as it has been reported with HCII and adjunct screening, considering this screening in parallel and series settings is reported [22]. CHPV using careHPV in parallel with VIA is recommended. However, under the present scenario co-testing performance for detection of high grade CIN has not been adequately addressed from LRCs, where isolated tests do not have adequate quality assurance for high sensitivity and specificity. Also, there are site specific variations in performance for detection of high grade CIN. Further explorations are recommended to understand the possible choice of combined testing [23]. Demonstration of combination of different methods of construction of parallel tests is probably an option of choice for using combined tests, as serial tests are not much beneficial. The present communication focuses only on parallel combination

of careHPV with tests but in different approach other than that adopted previously in order to determine best combination of tests using likelihood ratio test methodology.

MATERIALS AND METHODS

The study was conducted in a rural area Dadri Tehsil of Uttar Pradesh, from September 2011 to April 2012. All ever married women of 30-59 yrs of age were invited for screening at primary health centers/sub centers after obtaining informed consent. Women were excluded if they had a history of CIN, cervical cancer or hysterectomy. Women at clinic were first instructed by an Auxiliary Nurse Midwife (ANM) on how to obtain a self-collected vaginal sample for care HPV testing and were asked to provide a self-collected vaginal sample. Further tests were done by ANM in which women underwent per speculum examination during which additional cervical samples were taken for care HPV and papanicolau (Pap) test, and lastly, VIA were performed. The careHPV specimen for both vaginal and cervical samples was collected with careHPV sampler into Digene Collection Media (DCM). More details of methodology are reported elsewhere in the earlier papers published from the study on other aspects [18-21]. Ethical approval of institutions ethical committee was obtained.

The ratio of viral load, expressed in relative light units (RLU) was obtained by care HPV result divided with the RLU of positive control at 1 pg/ml cut-off (CO). The RLU/CO value more than or equal to 1.0 indicate test positivity [18]. Pap test results were reported according to the Bethesda 2001 classification system, and any smear with atypical cells of undetermined significance (ASC-US) or more severe changes was considered positive [24]. VIA was considered to be positive, if after applying 5% acetic acid with a cotton swab on cervix and allowing time of one minute, and the area became conspicuous with white colour against the pinkish background of normal epithelium [25]. All screen positives were referred for colposcopy and directed biopsy at Community Health Centre (CHC) of the area. Histologically proven CIN I and above were referred for appropriate treatment. The treatment of precancerous lesions was done as per IARC guidelines [24]. CIN I cases eligible for cryotherapy were treated at CHC by the physician or else referred to tertiary care hospital for appropriate management. A 10% random sample of negative biopsies and all CIN II+ histological specimens were independently reviewed by an external pathologist for quality control. Analysis on detection rates of CIN (for both CIN II+ and CIN III+) as outcome of interest was evaluated to assess of selected pair wise combinations of four screening tests. For example a pair of tests VHPV and Pap may have combinations of both Positive (+ve), both Negative (-ve) and either positive test.

Sensitivity, specificity, likelihood ratio (LR)+ve and (LR)-ve and post test probabilities were computed for Co-testing, performance of different pair of screening tests. In a particular combination of Co-testing positivity is defined as positivity on either or both of the tests. Strength of combinations of the tests was evaluated by likelihood ratios for positives and negatives. Both the likelihood ratios were used in assessing the strength of the test combination in the present study as against assessment based on only detection rates of the disease. Rankings of various combinations of Co-testing were decided based on some arbitrary criteria. For assessing the strength of the LR positives [26] the criteria used was: Excellent if LR+ is >=10, Very good if LR + is between <10 and >= 6, fair if LR+ is between <6 and >=2 and useless if LR+

Test model combination*			Final diagnosis					
	Combined criteria	Screen positive (%) N=4658	Positive CIN II+ (N=32) (No.%)	Negative (No.%)	OR (95% CI)	Sensitivity (Specificity)	LR +ve (LR –ve)	Post test probability (Test strength using LR)
1	VHPV+ Pap +	17(.36)	8(25.0)	9(0.2)	278 (82.2,96.0)	59.3 (99.7)	11.8 (0.43)	9.0 (Excel and Very good)
	VHPV- Pap +	115(2.4)	6(18.7)	109(2.5)	17.3 (5.7,49.8)			
	VHPV+ Pap -	82(1.7)	5(15.6)	77(1.8)	20.4 (6.2,63.3)			
	VHPV- Pap -	-	13(40.6)	4078(95.4)	1.0			
2	CHPV+ Pap +	25(.53)	10(31.2)	15(0.3)	246 (81.9,747.9)	65.6 (95.0)	13.0 (0.37)	9.0 (Excel and Very good)
	CHPV- Pap +	107(2.3)	4(12.5)	103(2.4)	14(3.9,49.7)			
	CHPV+ Pap -	102(2.1)	7(21.8)	95(2.2)	27.2(9.3,777)			
	CHPV- Pap -	-	11(34.3)	4059(95.0)	1.0			
3	VHPV+ VIA +	12(.25)	1(3.1)	11(0.2)	30.0(#)	59.4 (92.7)	8.15 (0.44)	5.0 (Very good and very good)
	VHPV- VIA +	245(5.2)	6(18.7)	239(5.1)	8.3 (2.8,23.6)			
	VHPV+ VIA -	99(2.1)	12(37.5)	87(1.9)	45.5 (18.8,109.8)			
	VHPV- VIA -	-	13(40.6)	4289(1.9)	1.0			
4	CHPV+ VIA +	17((0.36)	1(3.1)	16(0.3)	29.7(#)	71.9 (92.3)	9.4 (0.32)	6.0 (Very good and Very good)
	CHPV- VIA +	240(5.1)	6(18.7)	234(5.0)	12.2 (3.8,37.7)			
	CHPV+ VIA -	120(2.5)	16(50.0)	104(2.2)	73.0 (29.6,183.5)			
	CHPV- VIA -	-	9(28.1)	4271(92.3)	1.0(-)			
5	VIA + Pap +	18(0.38)	2 (6.2)	16 (0.4)	37.9 (8.2,200)	59.4 (92.1)	7.55 (0.44)	5.0 (Very good and Very good)
	VIA + Pap -	223(4.7)	5(15.6)	218(5.1)	6.9(2.1,21.1)			
	VIA - Pap +	114(2.4)	12(37.5)	102(2.4)	35.6(14.8,85.5)			
	VIA - Pap -	-	13(40.6)	3937(92.1)	1.0			

[Table/Fig-1]: Co-testing of careHPV on cervical self or provider sampling along with Pap or VIA tests in the detection of CIN II+ .
VHPV: Vaginal careHPV self collected; CHPV: Cervical careHPV provider collected; VIA: visual inspection of cervix with acetic acid; Pap: Papanicolaou testing; CIN: Cervical intraepithelial neoplasia
OR (Odds ratio) and CI (confidence interval) not applicable or cannot be computed: marked with #
Excel: Excellent

Test combination*			Final diagnosis					
	Combined criteria	Screen positive (%) N=4658	Positive CIN III+ (N=13) (No.%)	Negative (No.%)	OR (95% CI)	Sensitivity (Specificity)	LR +ve (LR –ve)	Post test probability (Test strength using LR)
1	VHPV+ Pap +	17(.36)	5 (38.5)	12(0.3)	567 (101.9,3481)	76.9 (95.2)	16 (0.24)	5 (Excel and V. good)
	VHPV- Pap +	115(2.4)	3(23.1)	112(2.6)	36.5(5.8,228.7)			
	VHPV+ Pap -	82(1.7)	2(15.4)	80(1.9)	43.1(3.9,254)			
	VHPV- Pap -	-	3(23.1)	4088(95.2)	1.0			
2	CHPV+ Pap +	25(.53)	7(53.8)	18(0.4)	1582(179,36042)	92.3 (94.8)	18 (0.08)	5 (Excel and Excel)
	CHPV- Pap +	107(2.3)	1 (7.7)	106(2.5)	38.4(#)			
	CHPV+ Pap -	102(2.1)	4 (30.8)	98(2.3)	166.1(17.4,3937)			
	CHPV- Pap -	-	1 (7.7)	4069(94.8)	1.0			
3	VHPV+ VIA +	12(.25)	1(7.7)	11(0.2)	65.1(#)	53.8 (91.6)	7.0 (0.44)	1.7 (V.good and V.good)
	VHPV- VIA +	245(5.2)	0(0.0)	245(5.3)	#(#)			
	VHPV+ VIA -	99(2.1)	6(46.1)	93(2.0)	46.2(12.9,165.2)			
	VHPV- VIA -	-	6(46.1)	4296(91.5)	1.0			
4	CHPV+ VIA +	17((0.36)	1(7.7)	16(0.3)	133.7(#)	84.6 (94.1)	14 (0.16)	4.0(Excel and V.good)
	CHPV- VIA +	240(5.1)	0(0.0)	240(5.2)	#(#)			
	CHPV+ VIA -	120(2.5)	10(76.9)	110(2.4)	193.4(39.5,1300)			
	CHPV- VIA -	-	2(15.4)	4278(92.1)	1.0			
5	VIA + Pap +	18(0.38)	1(7.7)	17(0.4)	46.4(#)	61.5 (91.9)	7.61 (0.42)	2.0 (V.good and V.good)
	VIA + Pap -	223(4.7)	0	223(5.2)	#(#)			
	VIA - Pap +	114(2.4)	7(53.8)	107(2.5)	51.6(14.4,190.5)			
	VIA - Pap -	-	5(38.5)	3945(91.9)	1.0			

[Table/Fig-2]: Co-testing of careHPV on cervical self or provider sampling along with Pap or VIA tests in the detection of CIN III+.
VHPV: Vaginal careHPV self collected; CHPV: Cervical careHPV provider collected; VIA: visual inspection of cervix with acetic acid; Pap: Papanicolaou testing; CIN: Cervical intraepithelial neoplasia
OR (Odds ratio) and CI (confidence interval) not applicable or cannot be computed: marked with #
Excel: Excellent
V good: very good

is between <2 and >=1. Similarly for LR negative (-ve), excellent if LR –ve is=< 0.1 and <0.2, Very good if LR-ve is between >0.2 and <=0.5, Fair if LR –ve is >=0.5 and <1.0, useless if LR-ve is >=1.0. Odds ratio along with 95% CI were presented for each co-test combination. Statistical analysis was done using IBM Statistical Package for the Social Sciences (SPSS) 21.0 statistical package.

RESULTS

A total of 5032 women reported for screening among all eligible women (7604). After excluding those who did not complete all screenings, and those who were lost to follow-up or had missing histology results, the analysis was performed on remaining 4658 women. Out of total analysed sample, 4537 (97.4%) were married, 82.7% with regular menstrual history and 17.3% with irregular menstrual history. The mean (SD) age of women screened was 37.9 (7.5) years.

The screening tests of careHPV by both cervical and self-collected vaginal samples, Pap and VIA detected 32 CIN II+ and 13 CIN III+ cases. Pairwise combinations of the four screening tests CHPV, VHPV, Pap and VIA had strong association for CIN III+ as compared to CIN II+ as depicted by odds ratios. A brief description of each model combination findings observed [Table/Fig-1,2] are as follows:

Model I: VHPV co-testing with Pap would pickup additional 15.5% of cases, each of CIN II+ and CIN III+. This Co-testing combination would yield 59.3% CIN II+ and 76.9% CIN III+ with post test probability of 9 and 6, respectively.

Model II: Co-testing of CHPV with Pap screening has advantage of picking up additional 21.8% CIN II+ and 30.8% of CIN III+ cases. Combined testing of CHPV and Pap yielded 65.6% of CIN II+ cases and 92.3% of CIN III+ cases.

Model III: Co-testing of VHPV and VIA would pick up an additional 37.5% of CIN II+ and 46.1% of CIN III+ that were missed by VIA. This combination would detect 59.3% of CIN II+ and 53.8% of CIN III+.

Model IV: The co testing of CHPV and VIA would detect 50% of CIN II+ and 76.9% of CIN III+. These cases missed by VIA, were picked up by CHPV. The detection of CIN was maximum (71.9% CIN II+ and 84.6% CIN III+ by this combination.

Model V: In the co testing of Pap with VIA, Pap is likely to pick-up 37.5% of CIN II+ cases and 53.8% of CIN III+ cases that are missed by VIA. The model of considering positive either in VIA or Pap detected 59.4% CIN II+ and 61.5% of CIN III+.

DISCUSSION

Co-testing of different pair combinations using CHPV, VHPV, Pap and VIA has demonstrated higher sensitivities and better strengths of the tests as compared to isolated tests in the present study setting that are reported earlier [19]. Study demonstrated that co-testing of CHPV or VHPV with Pap yields best results in the detection of CINII+ or CINIII+. This was followed by a decreasing performance of co-testing of CHPV with VIA, VHPV with VIA and Pap with VIA. Co-testing of Pap with VIA was better or performed equally as compared to VHPV with VIA. A Small number of CINIII+ (n=13) cases were observed in this rural community based study that analysed data on 4658 women. This low case detection could be due to possible low magnitude of precancerous lesions existing in the community.

The detection rates of CIN II+ by various tests CHPV, Pap, VHPV and VIA in isolation were 53.1%, 43.8%, 40.6% and 21.9%, respectively [19]. Among the four tests for cervical screening in isolation, CHPV performed best and its co-testing strength as detected by likelihood ratios was higher with Pap as compared to VIA. Co-testing of HPV and Pap has definitely improved performance as reported by other studies [10,15,16]. Various studies, have shown combined testing to be beneficial for cervical

cancer screening [11-14,17,27-31]. Co-testing of VHPV (Self-sample HPV) in combination with Pap performed better than VIA for detection of CIN II+. In co-testing of VIA, VHPV proved no better than Pap in the detection of CIN III+.

Though, there is enough literature in favour of self sampling in various studies a recent review of studies showed that self sampling to be less sensitive and specific and recommended physician collected sample for HPV [7]. This was observed in our study also [19]. Though, collection of samples for VHPV obviates the need for a clinical setting and allows direct lab assessment, VHPVs performance being not better than to Pap restricts its use and its recommendation in co-testing in LRCs.

Pap or HPV testing have been found to be accurate triaging method for women suspected of having high grade lesions on visual inspection [14]. VIA primary screening and combination with other tests for triaging was not a suitable option, as case detection using VIA as a primary screening tool was very low. The VIA screen positives in the present study were by and large, not observed to be positive by other screen tests and were not confirmed to be CINII+, thereby, leaving no opportunity for further triaging with any other test. But screening with VIA has advantage in co-testing model with HPV and Pap tests.

Likelihood test approach is used by combining sensitivity and specificity for evaluation of suitable tests for co-testing. As evaluated by likelihood tests, co-testing of CHPV or VHPV with Pap was found best to be recommended and CHPV with VIA would be a second option for CIN II+ or CIN III+ detection. It is known that Pap option is not feasible, VIA is a less efficient tool and careHPV test has advantages but cost consideration are still prohibitive for implementation in LRCs. Likelihood ratios are considered for evaluation of suitable combined screening tests in co-testing. Pap with VIA is also a difficult option for LRCs. Choice of tests for co-testing should be different for LRCs and high income countries. VIA in isolation is not likely to yield much in LRCs. However, Tamil Nadu state of India initiated district level VIA and VILI combined screening [32]. In this programme, VIA/ Visual Inspection with Lugol's Iodine (VILI) positivity was lower then that reported in literature. Follow up rates were also relatively low and very few precancerous lesions were detected. A number of implementation challenges were encountered which influenced the programme outcome. In the mean time, Ministry Health and Family welfare, Government of India initiated and planned a 100 district coverage policy implementation of cervical screening with VIA along with screening of other preventable cancers viz., oral and breast cancer, and non-communicable diseases such as diabetes and hypertention. Thus, the choice of co-testing combination becomes region dependent, whether screening is targeted for a developed country or a LRC.

LIMITATION

Lower number of high grade (CIN III+) lesion positivity on biopsy was a major limitation. Other important limitation was that the colposcopist was not blinded for screening test results which could be a possible source of bias.

CONCLUSION

Co-testing options of CHPV with Pap or VHPV with Pap are encouraging and Pap with VIA should perhaps be the last option for LRCs, if they can gear up for cytology. Pair of tests for detection of high-grade CIN is likely to depend on whether screening is targeted for developed or low resource country. Though, VIA in isolation is not expected to yield much in the absence of any screening for LRCs, this may be a preferable one.

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