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Original Research Article

## Effect of curcumin in prevention of pre-invasive lesions of the cervix

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### ABSTRACT

**Background:** Cervical cancer is the leading cause of deaths of women due to malignancies in developing countries world-wide. Having a latency period of upto 10 years, pre-invasive lesions of cervix give us a wide margin for detection and treatment before it becomes cancerous. It has been estimated that even after putting in all the resources it's not possible to screen one fourth of the population of women in India. This is the aim of this study to establish a pattern of prevalence of these pre-invasive lesions and find out correlation with various epidemiological factors and establish best screening modality in low resource settings like ours. Curcuminoids are the extract of curcuma longa, and it has been found to have myriad effects like anti-inflammatory, antibiotic, and anti-cancerous as well. In this study we have tried to determine its effect on precancerous lesions of the cervix.

**Methods:** In this study, patients coming to the OPD of the Gynaecology Department with various complaints like vaginal discharge and post coital bleeding etc were subjected to en VIA examination (visual inspection with acetic acid), and cytology. Selected cases were subjected to colposcopy and biopsy, which is taken as gold standard in the study. The cases were studied in terms of their epidemiologic characteristics. The diagnostic accuracy of VIA and cytology was assessed using colposcopy and biopsy as the gold standard, chi square test applied and power of the screening test calculated.

**Results:** 226 cases were subjected to VIA examination, using freshly prepared 5% acetic acid. 105(46.5%) cases were VIA positive. Same no of cases were also subjected to cytological evaluation. Upon cytological evaluation, 21(9.3%) had a normal cytology, 158(69.9%) were inflammatory, 3(1.3%) had ASCUS, 1(0.4%) had AGUS, 26(11.6%) had LSIL and koilocytic changes, 11(4.9%) had HSIL, and 6 cases (2.6%) had squamous cell carcinoma. Abnormal cytology (47/226) was mostly found in age group 30-40 29/47 (61.7%), were para 2 to 4 34/47 (72.3%), belonged to class IV-V socioeconomic class 28(59.6%), belonged to rural areas 32/47(68%) were illiterate 29/47(61.7%) were married at a young age 15-17 23/47(49%) and were not using any contraception 22/47(46.8%).

**Conclusions:** Cervical cancer being one of the most easily preventable cancer owing to the easy accessibility of the cervix to the clinician, and easy screening methods available, is amenable to eradication of the disease one day.

**Keywords:** Cervical intraepithelial neoplasia, Chemoprevention, Curcumin, Epidemiology, Risk factors, Screening

### INTRODUCTION

Cervical cancer is the leading cause of deaths of women due to malignancies in developing countries world-wide.<sup>1</sup> Having a latency period of upto 10 years, preinvasive lesions of cervix give us a wide margin for detection and

treatment before it becomes cancerous.<sup>2</sup> It has been estimated that even after putting in all the resources it's not possible to screen one fourth of the population of women in India.<sup>3</sup> This is the aim of this study to establish a pattern of prevalence of these preinvasive lesions and find out correlation with various epidemiological factors and

establish best screening modality in low resource settings like ours.

Curcuminoids are extracts of turmeric a traditional medicine and also a food ingredient. Its history goes back to 5000 years to the heyday of ayurveda. It has been proven by research that it has myriad properties like effects on stability of p53, release of cytochrome c, and the generation of reactive oxygen species.<sup>4</sup> Inhibition of cell signalling pathways involving Akt, NF- $\kappa$ B, AP-1 or JNK, as with upregulation of growth arrest and DNA damage (GADD) gene and downregulation of the expression of survival genes *egr-1*, *c-myc*, *bcl-X(L)*, and *IAP* or abnormal tumor suppressor gene such as *p53*.<sup>5</sup>

It inhibits COX activity.<sup>6</sup> Curcumin averts the HPV infected cell from constructing the E6 and E7 proteins, the p53 and Rb gene can function successfully and DNA damage can be controlled.<sup>7</sup>

Curcumin, commonly called diferuloyl methane, is a hydrophobic polyphenol derived from rhizome (turmeric) of the herb *Curcuma longa*. Extensive research over the last half century has revealed important functions of curcumin. In vitro and in vivo research has shown various activities, such as anti-inflammatory, cytokines release, antioxidant, immune modulatory, enhancing of the apoptotic process, and anti-angiogenic properties. Curcumin has also been shown to be a mediator of chemoresistance and radio-resistance. The anti-cancer effect has been seen in a few clinical trials, mainly as a native chemoprevention agent in colon and pancreatic cancer, cervical neoplasia and Barrett's metaplasia.<sup>8</sup>

Apart from all these it has antioxidant, anti-inflammatory, anti-fungal, anti protozoal, antiviral, anti-bacterial, anti-diabetic, effects.

## METHODS

In this study, patients coming to the OPD of the Gynaecology Department with various complaints like vaginal discharge and post coital bleeding etc were subjected to an VIA examination (visual inspection with acetic acid), and cytology.

Selected cases were subjected to colposcopy and biopsy, which is taken as gold standard in the study. The cases were studied in terms of their epidemiologic characteristics. The diagnostic accuracy of VIA and cytology was assessed using colposcopy and biopsy as the gold standard, chi square test applied and power of the screening test calculated.

Patients coming to gynaecology OPD were divided into two groups.

Group 1: (curcumin group) was given oral curcumin capsules containing 400 mg of curcuminoids, two capsules

twice a day which makes a total daily dose of 1.6 gm daily for 3 months.

Group 2: (conventional group) was treated conventionally medically (e.g. antibiotics). Ablative treatment like cryotherapy or excisional procedure such as LEEP/LLETZ was done when the cases did not respond to medical therapy or cytology showed HSIL or persistent low grade lesion.

## RESULTS

226 cases were subjected to VIA examination, using freshly prepared 5% acetic acid. 105 (46.5%) cases were VIA positive. Same no. of cases was also subjected to cytological evaluation. Upon cytological evaluation, 21 (9.3%) had a normal cytology, 158 (69.9%) were inflammatory, 3 (1.3%) had ASCUS, 1 (0.4%) had AGUS, 26 (11.6%) had LSIL and koilocytic changes, 11 (4.9%) had HSIL, and 6 cases (2.6%) had squamous cell carcinoma.

Abnormal cytology (47/226) was mostly found in age group 30-40 29/47 (61.7%), were para 2 to 4 34/47 (72.3%), belonged to class IV-V socioeconomic class 28 (59.6%), belonged to rural areas 32/47 (68%) were illiterate 29/47 (61.7%) were married at a young age 15-17 23/47 (49%) and were not using any contraception 22/47 (46.8%). The diagnostic accuracy of the screening tests i.e. VIA and cytology was tested against the gold standard test which was taken as colposcopy and biopsy in our study

The sensitivity of VIA examination, taking colposcopy and biopsy as the gold standard was found out to be 83.01% and specificity 64.73%. The positive predictive value was 67.64% and negative predictive value was 68.75%. Upon application of chi square test the value was found out to be 37.2 and the p value was <0.001, which was statistically significant.

The sensitivity of cytological examination, using colposcopy and biopsy as the gold standard, was 62.5% and specificity was 62.5%.

When the cases in group 1 were followed in terms of symptoms 76% of the cases were relieved of discharge per vaginam. 46.8% reported relief in pelvic pain. Hundred percent of the cases reported relief in post coital bleeding. 70% of cases reported relief in menstrual complaints and a total of 55% of the cases reported relief from other complaints.

In group 2, 55% of the cases were relieved of their complaints of discharge per vaginam, and 44% of the cases were relieved of pelvic pain. 50% of the cases were relieved of menstrual complaints and same no. for other complaints.

**Table 1: Association of abnormal cytology and abnormal VIA with high risk factors (n=226).**

Risk factors	Normal cytology (n-179)	Abnormal cytology n-47	VIA + N-105	VIA – N-121
<b>Age in years</b>				
20-30	61(34.1)	11(23.4)	34(32.4)	38(31.4)
30-40	74(41.3)	29(61.7)	44(42)	59(48.8)
>40	4(24.6)	7(14.9)	27(25.7)	24(19.8)
<b>Parity</b>				
P0	3(1.7)	-	2(1.9)	1(0.8)
P1	17(9.5)	1(19.1)	8(7.6)	10(8.2)
P2-4	73(40.7)	34(72.3)	60(57.1)	47(38.8)
P>or= 5	86(48)	12(25.5)	22(21)	76(62.8)
<b>Socioeconomic class</b>				
Class I-III	102(57)	19(40.4)	43(41)	78(64.4)
Class IV-V	77(43)	28(59.6)	62(59)	43(35.5)
<b>Residence</b>				
Rural	110(61.5)	32(68)	66(62.9)	76(64.4)
Urban	69(38.5)	15(32)	39(37.1)	45(37.2)
<b>Literacy status</b>				
literate	74(41.3)	18(32.3)	54(51.4)	38(31.4)
illiterate	105(58.7)	29(61.7)	51(48.5)	83(68.6)
<b>Religion</b>				
Hindu	68(38)	29(61.7)	47(44.7)	50(41.3)
muslim	111(62)	18(38.3)	58(55.2)	71(58.7)
<b>Age at marraige</b>				
15-17	83(46.4)	23(49)	41(39)	65(53.7)
18-20	77(43)	17(34.7)	50(47.6)	44(36.3)
21-30	19(10.6)	7(14.3)	14(13.3)	12(10)
<b>Contraception</b>				
No contraception	35(19.5)	22(46.8)	24(22.9)	33(27.3)
Barrier	87(48.6)	16(34)	56(53.3)	47(38.8)
IUD	14(7.8)	4(8.5)	7(6.6)	11(9)
Ligation	18(10)	3(6.4)	8(7.6)	13(10.7)
OCP	25(14)	2(4.3)	10(10)	17(14)

**Table 2: Post treatment analysis of cases in terms of symptom relief on cases receiving curcumin therapy, n=100.**

Curcumin group (n-70)	Curcumin group (n-70)			Conventional group (n-30)		
	No of cases	Relieved	Not relieved	No of cases	Relieved	Not relieved
Abnormal vaginal discharge	64	46 (71.9%)	28 (23.5%)	20	11 (55%)	9 (45%)
Pelvic pain	47	22 (46.8%)	25 (53.2%)	25	14 (56%)	11 (44%)
Contact bleeding	2	2 (100%)	-	6	5 (83.3%)	1 (16.7%)
Menstrual complaints	10	7 (70%)	3 (30%)	4	2 (50%)	2 (50%)
Others	9	4 (44.4%)	5 (55.6%)	2	1 (50%)	1 (50%)

When both the groups were followed up by VIA examination, 33 (51.6%) of the cases became VIA negative on follow up, and in group 2, 8 (30.8%) of the cases turned VIA negative at the end of the treatment. In the group 1, fifty two cases who had inflammatory smear pre-treatment, 6/52 (11.5%) became normal after treatment. 32/52 (67.3%) remained inflammatory and one

case progressed to LSIL. Three cases were lost to follow up, and 7 cases are yet to report. Out of the nine cases of LSIL, 2 regressed, and 2 persisted, one case was lost to follow up, and four cases are yet to report.

Out of the eight cases of HSIL, 1 regressed and 6 persisted. One case is yet to report. We found that 6/52 (11.5%) of

the inflammatory smears turned normal, and 2/8 (25%) of the high grade lesions along with 2/9 (22.2%) of the low grade lesions have benefitted from the therapy.

**Table 3: Post treatment analysis of cases by VIA.**

Pre treatment VIA +	Post treatment VIA	
	VIA -	VIA +
Treatment given		
Curcumin n-67	33(51.6%)	31(46.3%)
Conservative n-27	8(30.8%)	18(69.2%)

After curcumin therapy, out of 52 cases with inflammatory smear, 35/52 (67.3%) cases persisted. Among these 7/52

(14%) had to be given cryotherapy for additional complaints, and one case underwent LEEP.

Two persistent cases of LSIL, both received cryotherapy and one had to undergo LEEP. 6/8(75%) of the persistent cases of HSIL underwent LEEP. One of the cases is yet to report. In group 2, among 19 cases of inflammatory smear, 2/19 (10.5%) had a normal cytology post treatment, and 16/19 (84.2%) remained inflammatory. 6/19(31.6%) were given cryotherapy, and 3/19 (15.8%) underwent LEEP. Among nine cases of LSIL, 3 (33.3%) underwent cryotherapy, and 1 (11.1%) underwent LEEP. Among two cases of HSIL both underwent LEEP.

**Table 4: Post treatment cytology in the curcumin group.**

Pre treatment cytology	Normal	Inflammatory	LSIL	HSIL
Normal – n-1	1			
Inflammatory n-52	6 (11.5%)	35 (67.3%)	1 (1.9%)	-
LSIL n-9	-	2 (22.2%)	2 (22.2%)	-
HSIL n-8	-	1 (12.5%)	-	6 (75%)

**Table 5: Post treatments follow up in conventional group.**

Pre-treatment cytology	Normal	Inflammatory	LSIL	HSIL
Inflammatory n-19	2 (10.5%)	16 (84.2%)	-	-
LSIL n-9	1 (11.1%)	7 (77.8%)	-	-
HSIL n-2	-	2 (100%)	-	-

## DISCUSSION

Abnormal cytology (47/226) was mostly found in age group 30-40 29/47 (61.7%), were para 2 to 4 34/47 (72.3%), belonged to class IV-V socioeconomic class 28 (59.6%), belonged to rural areas 32/47 (68%) were illiterate 29/47 (61.7%) were married at a young age 15-17 23/47 (49%) and were not using any contraception 22/47 (46.8%). The diagnostic accuracy of the screening tests i.e. In our study most common presenting complaint was abnormal discharge, similar to a study conducted by Aggarwal et al VIA and cytology was tested against the gold standard test which was taken as colposcopy and biopsy in our study.<sup>9</sup>

Appleby et al showed that ocp use was associated with increased risk of cervical cancer, but in our study maximum cases were not using any contraception at all. Poor socioeconomic condition has been found to be associated with cancer as in poor living conditions.<sup>10,11</sup> Poor literacy rate as by Lindau et al.<sup>12</sup> A study of Stone et al showed early age of sexual debut and a large number of sexual partners were associated with increased cervical cancer.<sup>13</sup> The sensitivity of cytological examination, using colposcopy and biopsy as the gold standard, was 62.5 %

and specificity was 62.5%.<sup>14</sup> Nanda et al showed a sensitivity of 68% and specificity of 75% of cytological examination.

The sensitivity of VIA examination, taking colposcopy and biopsy as the gold standard was found out to be 83.01% and specificity 64.73%. The positive predictive value was 67.64% and negative predictive value was 68.75%. Upon application of chi square test the value was found out to be 37.2 and the p value was <0.001, which was statistically significant. A study conducted by Ardhan et al showed sensitivity of 82.14%, and specificity of 50%.<sup>15</sup> The sensitivity was almost comparable our study.

A study by Cheng et al, in which oral curcumin was given for three months to patients with CIN, histological improvement was seen in 1 out of 4 patients and progression to cancer seen in 1 out of 4 patients.<sup>16</sup>

Curcumin modulates the in vitro expression and function of p-gp in multidrug resistant human KB – V1 cells and sensitizes cisplatin – resistant SiHa cells to cisplatin induced apoptosis, indicating its ability to reverse MDR in cervical cancer cells.<sup>17</sup>

A study by Melinkow et al states that 68.2% of the ASCUS, 47.2% of the LSIL, and 35% of the HSIL regress to normal after 24 months. 7.1% of the LSIL, 20.8% of the LSIL, and 23.4% of the HSIL regress to or persist as high grade lesion. 0.3% of the ASCUS, 0.2% of the LSIL, and 1.4% of the HSIL progress to invasive cancer at 24 months follow up.<sup>18</sup>

In our study, we have found that in the cases receiving curcumin there was significant relief from the discharge per vaginum, and fewer no of cases needed to be intervened surgically in the curcumin group for inflammatory cytology. No of cryotherapy was 7/52 (14.3%) and 1/52 (2%) cases underwent LEEP. Whereas no. of cryotherapy for inflammatory cytology in conventional group was 6/19 (31.6%) and 3/19 (15.8%) cases underwent LEEP.

100% of the cases were relieved of contact bleeding and 70% were relieved of menstrual disorders in the curcumin group, whereas 80% of the cases were relieved of contact bleeding and 50% relieved of menstrual disorders in the conventional group.

All the cases of LSIL regressed to normal / inflammatory cytology in group 2 (conventional group). But in curcumin group, two cases 2/9 (22.2%) regressed to normal after treatment. Both the cases of HSIL in the conventional group underwent LEEP, but in curcumin group, 6/8 (75%) of the cases underwent LEEP. One case regressed and one is relieved.

The percentage of VIA negativity was higher in the curcumin group. 33/67 (51.6%), whereas in conventional group, it was 8/27(30.8%). Curcumin is remarkably well tolerated, but its bioavailability is poor. It does not appear to be toxic to animals or humans even at high doses.<sup>19,20</sup> Turmeric is generally recognized as safe by the FDA, and curcumin has been granted an acceptable daily intake level of 0.1-3 mg/kg-BW by the Joint FAO/WHO Expert Committee on Food Additives, 1996.<sup>21</sup>

High risk individuals and cancer survivors alike may benefit from chemoprevention, not only because primary cancer chemoprevention is beneficial for high risk groups but also because of the devastating nature of the disease course when patients experience SPT or recurrence. As curcumin is a non-prescription dietary derivative that has multiple targets at different levels in multiple pathways, it has great potential in the prevention of cancer and SPT. When its systemic bioavailability is increased through the development of different analogs and formulations, the promise of curcumin in chemoprevention may be feasible in many cancer types.<sup>22</sup>

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