Dindigul District Cervical Screening Study, India: Acceptability, Effectiveness and Safety of Treatment of Cervical Precancerous Lesions by Nurses using Cryotherapy

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BACKGROUND:

The effectiveness of a single round of screening using visual inspection with acetic acid (VIA) on cervical cancer incidence and mortality is investigated in a randomised controlled trial in Dindigul district, India[1]. Women aged 30-59 years were randomised to VIA screening (57 clusters, 48,225 women) by nurses and to a control group (56 clusters, 30,167 women) to receive usual care and health education on cervix cancer prevention. VIA-positive women had colposcopy by a trained nurse, under the supervision of a medical officer. A colposcopic diagnosis was made in terms of normal, inflammation, probable low-grade lesion (CIN 1), probable high-grade lesion (CIN 2-3), probable invasive cancer, and frank invasive cancer. Punch biopsies were taken from any abnormal areas on the cervix. Biopsy specimens were processed and reported on locally.

Notional Map Showing Dindigul District, Tamil Nadu State, India

METHODS:

Indications for cryotherapy:

Women with colposcopically diagnosed low- and high-grade lesions, meeting all the following criteria, were advised to be treated immediately, by cryotherapy, after a directed biopsy:

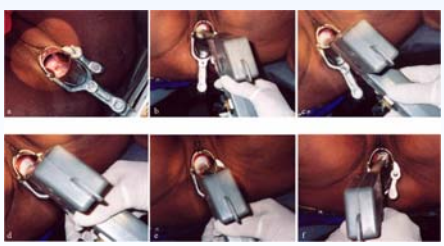
- The lesion involved less than 3 quadrants of the cervix;
- There was no extension of the lesion into the endocervical canal and/or vagina;
- The whole lesion could be covered by the cryoprobe.

Before treatment, the nurse explained the colposcopy results and the treatment procedure, potential benefits and side effects of cryotherapy and encouraged the woman to accept immediate treatment. Women with lesions more extensive than those eligible for cryotherapy were advised loop electrosurgical excision procedure (LEEP) or cold knife conization.

Cryotherapy equipment

Cryotherapy procedure:

Cryotherapy was done using nitrous oxide refrigerant, using a 20-24 mm ectocervical cryo probe tip, with a shallow nipple; by standard double-freeze technique (3-min freeze; 5-min thaw; 3-min freeze; thaw). No local anaesthetic or analgesics were used prior to the procedure. All treated women received prophylactic antibiotic treatment with oral metronidazole and doxycycline for 5 days after treatment. Women were given home-care instructions and were asked to avoid sexual intercourse for 4 weeks.



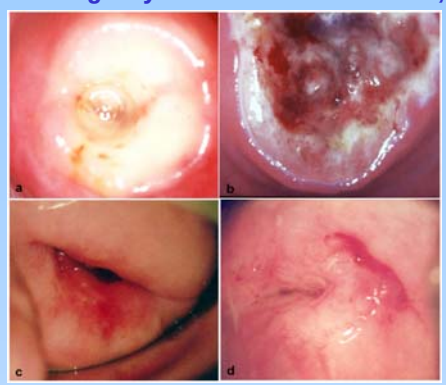
Cryofreezing in progress. Note the cryoprobe covers the lesion well (a, b). Note the iceball formation in c, d and e. Note the appearance after thawing in f.

Problem visits:

Women were instructed to return to the clinic immediately if they had fever for more than 2 days, had bleeding severe enough to involve passing blood clots, or severe lower abdominal pain following cryotherapy.

Follow-up assessment:

Women were advised a follow-up visit 1-year after treatment to assess the cervix and to rule out cervical neoplasia. At follow-up, VIA and colposcopy were done, and biopsies were obtained from abnormal areas. Absence of CIN or cancer at follow-up was defined as cure.



(a) Note the iceball on the cervix immediately after cryotherapy; (b) Appearance 2 weeks after cryotherapy; (c) 3 months after cryotherapy; (d) 1 year after cryotherapy.

RESULTS:

VIA screening, colposcopy and biopsy:

30,577 women were screened during 2000-2003 in village screening clinics. 2,939 (9.6%) VIA positive women had colposcopy. Of these, 2458 were treated with cryotherapy after directing a biopsy. The colposcopic and histological diagnoses of these women are given in Table 1: 2130 had a colposcopic diagnosis of probable CIN and were treated with cryotherapy; in addition, 328 women with features of inflammation or ectropion were treated with cryotherapy. 1862 (75.8%) had treatment in the same session as VIA and colposcopy and 146 (5.9%) within 7 days from testing.

Table 1: Colposcopy and histology findings of women treated with cryotherapy

Colposcopy findings	Histology					
	Normal	CIN 1	CIN 2	CIN 3	Cancer	Total
Ectropion/ inflammation	243	79	3	2	0	328
Probable low-grade disease (CIN 1)	758	1045	88	34	8	1933
Probable high-grade disease (CIN 2-3)	50	109	24	11	3	197
Total	**1051**	**1233**	**115**	**48**	**11**	**2458**

Problem visits within one month from cryotherapy:

91 (3.7%) of treated women reported for a problem visit, the reasons for which are given in Table 2. The most common reason for the visit was lower abdominal pain and cramps The clinical findings among them are given in Table 3. There was no instances of severe bleeding or pelvic inflammatory disease requiring hospitalization.

Histology findings:

Of the 2458 women who had cryotherapy, 1233 (50.2%) had histologically confirmed CIN 1; 115 (4.7%) had CIN 2; 48 (2.0%) had CIN 3, and 11 (0.4%) had early invasive cancer.

Follow-up and women evaluated for effectiveness of cryotherapy:

The follow-up details of the 1396 women with CIN are given in Table 4. The analysis of the effectiveness of cryotherapy in curing CIN was restricted to 1014 women after excluding those with no follow-up (N=334), follow-up period less than 6 months after cryotherapy (N=29) and women for whom histology results were not yet available (N=19). The range of follow-up for these evaluable women are given in Table 5.

Table 2:Reasons for problem visits with in a month from cryotherapy (N= patients)

Reason	Number (%)
Longer than usual menstrual bleeding	14
Vaginal bleeding	8
Lower abdominal pain/cramps	25
Excessive vaginal discharge	23
Fever/chills	3
Backache	18
Total	**91**

Table 3: Clinical findings in problem visits

Clinical findings	Number (%)
Fever	3
Vaginal bleeding	3
Blood clots in vagina	1
Bleeding from biopsy site in the cervix	3
Vaginal burn	1
Cervicitis	14
Pelvic tenderness	1

Table 4: Follow-up details of 1396 women treated with cryotheray who had CIN

Follow-up	Histology at baseline			
	CIN 1	CIN 2	CIN3	Total
No follow-up	280	33	21	334
Follow-up at <6 months from cryotherapy	27	2	0	29
Follow-up at ≥ 6months from cryotherapy	910	77	27	1014
Follow-up at ≥ 6 months but histology awaited	16	3	0	19
TOTAL	**1233**	**115**	**48**	**1396**

Cure rates:

The findings at follow-up and cure rates for the 1014 evaluable women are given in Tables 6 and 7, respectively. Overall, 87% of the women had no evidence of disease at follow-up period raging from 6-48 months. The cure rate for CIN 1 lesions was 87.4% and CIN 2-3 lesions 83.7% and the difference in cure rates by CIN grade did not reach statistical significance.

The cure rates according to patient characteristics such as age, visibility of squamocolumnar junction (SCJ), extent of ectocervical surface involvement by lesion and follow-up period are given in Table 8. Women aged 40-59 years, with no visible SCJ and lesions involving 50-75% of the cervix had lower survival, the differences did not reach statistical significance.

Table 5: Distribution of follow-up time after cryotherapy for 1014 evaluable women

Follow-up in months	Cases (%)
6-12	30 (3)
13-24	374 (37)
25-36	385 (38)
37-48	225 (22)
TOTAL	**1014 (100)**

Mean follow-up time: 22 months (663 days)
Range of follow-up time: 6-48 months (180-1440 days)

Table 6: Distribution of histology at baseline (at the time of treatment) vs. disease status at follow-up

Disease status at follow-up	Histology at baseline			
	CIN 1	CIN 2	CIN 3	Total
Clinically normal	343	38	14	395
Histologically normal	452	24	11	487
CIN 1 histology	104	9	0	113
CIN 2 histology	8	5	1	14
CIN 3 histology	1	1	1	3
Invasive cancer histology	2	0	0	2
TOTAL	**910**	**77**	**27**	**1014**

Table 7: Cure rates for CIN

CIN grade at baseline	Cure rate
CIN 1	87.4% (795/910)
CIN 2-3 lesions	83.7% (87/104)
CIN 2	*80.5% (62/77)*
CIN 3	*92.6% (25/27)*
All grades	**87.0% (882/1014)**

Cure defined as clinical or histological absence of disease at last follow-up

Table 8: Cure rates at follow-up according to patient characteristics

Characteristic	Cure rate	Test for homogeneity P value	Score test for trend P value
Age		0.07	0.07
30-39 years	87.9% (738/840)		
40-59 years	82.8% (144/174)		
Visibility of SCJ		0.12	0.12
Yes	87.5% (800/914)		
No	82.0% (82/100)		
Ectocervical surface area involvement		0.20	0.44
Lesion covers <25%	87.1% (737/846)		
25-50%	88.3% (113/128)		
50-75%	73.7% (14/19)		
Cure rates among women followed up at different follow-up times from Rx		0.23	0.58
6-12 months	80.0% (24/30)		
13-24 months	88.2% (330/374)		
25-36 months	84.9% (327/385)		
>36 months	89.3% (201/225)		

Long term sequelae:

The SCJ was fully visible in 941 (93%) of the women at follow-up. Cervical stenosis was observed in 11 (1%) women.

Accuracy of VIA in detecting treatment failures at follow-up:

The VIA findings for different follow-up outcomes are given in Table 9. The sensitivity and specificity of VIA to detect CIN 2-3 lesions were 47.4% and 86.6%, respectively.

Table 9: Performance of VIA in detecting post treatment recurrences

Follow-up Diagnosis	VIA negative	VIA positive
Normal	781	101
CIN 1	81	32
CIN 2-3	10	9
Total	872	142

CONCLUSIONS:

- **Cryotherapy by trained nurses in field clinics is a safe, acceptable and effective treatment for ectocervical CIN lesions involving less than three-fourths of the cervix.**
- **The results of cryotherapy by nurses in this Indian field study are similar to those reported for cryotherapy in western health care settings.**
- **Cryotherapy is a safe method of treatment with no serious side-effects and long-term sequelae.**

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[1] Sankaranarayanan R. Rajkumar R, Theresa R, Esmy PO, Mahé C, Bagyalakshmi KR, Thara S, Frappart L, Lucas E, Muwonge R, Shanthakumari S, Jeevan D, Subbarao TM, Parkin DM, Cherian J. Initial results from a randomized trial of cervical visual screening in rural south India. Int J Cancer. 2004 Apr 10;109(3):461-7.