Evaluation of efficacy and safety of cryotherapy in benign and premalignant cervical lesion

Kishankumar D. Patel1*, Ronak D. Karnavat2, Dimple G. Viramgama3, Roma K. Dalal4

INTRODUCTION

Cervical lesions irritate women physically, embarrass sexually, scare mentally. Glandular epithelium of cervix has lower cell mediated immunity that creates facilitatory environment for infections as well as carcinogenic implications.1 Changes in the cervical epithelium leads to many gynecological symptoms like vaginal discharge, painful coitus, pain in the lower abdomen and abnormal vaginal bleeding. Identifying premalignant and benign diseases of the cervix and selecting an appropriate treatment path can be challenging. Cervical cancer ranks 3rd leading cause of cancer in the world and the 2nd most common cancer among women between 15-44 years of age in world.5

Cervical erosion/ectropion (or cervical eversion) is a condition in which the central (endocervical) columnar epithelium protrudes out through the external OS of the cervix and onto the vaginal portion of the cervix, undergoes squamous metaplasia and transforms to stratified squamous epithelium.3 Prevalence of cervical erosion is 15-17% in women.4

Cervical erosion is mostly asymptomatic in women but when symptoms such as postcoital bleeding and
troublesome vaginal discharge occur in the presence of cervical erosion it becomes important to identify promptly whether the erosion is simply a benign lesion or a significant sign of associated infection, CIN or even cancer. Cervical erosion is indistinguishable from early cervical cancer; therefore, further diagnostic studies (e.g., Pap smear, biopsy) must be performed for a differential diagnosis. Pap smear cytology has remained an important tool in the screening of cervical cancer.

Chronic cervical infection can cause premalignant and malignant changes.17-20% association of low grade squamous intraepithelial lesion with cervical erosion. Treatment for benign and precancerous lesion can be provided by ablative or excisional methods.

Ablative methods include cryotherapy, cold coagulation, laser vaporization and excisional methods include loop electrosurgical excision procedure (LEEP) and laser conization.8,9

Cryotherapy was introduced to gynecology in the late 1960s to treat cervical lesions and it is proven to be a reliable treatment modality, with limited side effects and morbidity.10

Cryocauterisation machine includes cryoprobes of different sizes, cryogun, N2O or CO2 cylinder and connecting tube. The cryotherapy probe tip is applied to the cervix so that it covers the lesion and the cervical tissue is frozen for 3 minutes, thawed for 3 to 5 minutes and then frozen again for 3 minutes.11 Cryosurgery is appropriate for use in low resource settings because it is effective (>90% cure rate), has limited side-effects, does not require electricity, is inexpensive compared to other treatment options and is technically simple to implement.12

Aim

Aim of the study to evaluate the efficacy, safety and patients’ satisfaction of cryotherapy in treatment of cervical erosion.

METHODS

The type of the study was prospective observational and interventional study. The study conducted at the obstetrics and gynecology department, GMERS medical college and hospital, Sola, Ahmedabad. The study conducted from September 2019 to December 2020.

Sample size

The sample size was 100 (Convenient or purposive sampling method).

Ethical approval

The study was approved by the institutional ethics committee.

Inclusion criteria

Women willing to undergo cryotherapy ablation and give consent, age more than 18 years and less than 60 years old, negative for intraepithelial malignancy on pap smear, HIV and VDRL testing negative, women with benign and premalignant cervical erosion, clinically normal looking cervix, without malignant changes were included in the study.

Exclusion criteria

Patient who did not give consent, lesions extending into endo cervical canal, patient in menses, patient with active bleeding, patient with active infection, pregnant women, women infected with herpes virus were excluded from study.

Women among 18 to 60 years of age attending O.P.D. of the department of obstetrics and gynecology who has history of chronic discharge per vaginum, post-coital bleeding, dyspareunia, chronic pelvic pain during the study period were examined. On examination, pap smear was taken and divided in erosion with inflammatory changes and presence of low grade squamous intra epithelial lesion (LSIL).

Counselling about the procedure and post cryocauterization care and follow up plans were explained in details before the procedure, consent for cryocauterization taken. After consent patient was taken on procedure table and for prevention of vasovagal attack and to relieve pain prophylactic intra muscular atropine and pentazocine were given to all patients before procedure. Procedure was carried out in lithotomy position under all aseptic precautions. Appropriate cryoprobe was taken according to site and size of lesion and gun was attached to nitrous oxide cylinder through gas conveying tube. Cryocauterisation was done using nitrous oxide refrigerant at temperature minus 55 to 58 degrees Celsius with the aim of creating an ice ball with a depth of freeze denoted by a peripheral margin of 2 mm of frost. The cryoprobe was placed on the lesion, not let it to touch the vaginal wall. The coolant gas was allowed to flow through the channels in the metal tip of the cryoprobe. Cryocauterisation was performed using a double-freeze single session procedure. The double freeze technique involves applying the coolant continuously for a 3-min freeze, followed immediately by a 3 to 5 min thaw, followed by another 3-min freeze till separation of probe by its own. The patients were asked to refrain from sexual intercourse and were advised not to use tampon for next 2-3 weeks after cryotherapy to avoid infection and bleeding and to allow re-epithelization of the cry lesion. Prophylactic antibiotics were given for 5 days to all women. Each patient was followed up at 2 weeks, 6 weeks and at 12 weeks. Findings, complications and patients’ satisfaction was recorded in study proforma. Data were compared with previous and next subsequent visit to
calculate cure rate of symptoms, healing of lesion and patients’ satisfaction (Figure 1).

Figure 1: Cryocautery equipment.

Statistical analysis

Normality of data was tested by non-parametric test, Chi-square and Fischer’s exact test were used. A p<0.05 was considered statistically significant. The data was entered in MS excel spreadsheet and analysis was done using Med Calc version 12.1.

RESULTS

In our study, out of the total patients, 93% had complaints of abnormal vaginal discharge followed by pelvic pain in 30%, dyspareunia in 24% and 7% patients had post coital bleeding. All patients’ PAP smears were satisfactory for evaluation. Inflammatory changes were present in 74% patients and mild dysplasia (low grade squamous intraepithelial lesions, CIN1) in 26%.

Majority of cases presented with abnormal vaginal discharge in inflammatory group (94.5%) and in LSIL (CIN 1) group (88.4%). The second most frequent complaint was pelvic pain among the inflammatory group (32.4%) and dyspareunia (34.6%) in LSIL (CIN 1) group. Post coital bleeding was present in 5.40% of the inflammatory group and 11.5% in LSIL (CIN 1) group. The prevalence of symptoms between two groups was not statistically significant. (p>0.05) The main indication for cryo was abnormal vaginal discharge (93%). Size of lesion and location of lesion distribution described in Table 1.

Table 1: Evaluation of chief complaints at 2-week, 6 week and 12 weeks.

| Chief complaints       | Cervical lesions | LSIL (CIN1) | P value |
|------------------------|------------------|-------------|---------|
|                        | Inflammation     |             |         |
|                        | Before cryo      | At 2 weeks  | At 6 weeks | At 12 weeks |
|                        |                  | N (%)       | N (%)    | N (%)      | N (%)    |
| Abnormal discharge     | 70 (94.5)        | 67 (95.7)   | 12 (18.1)| 5 (7.57)   | 23 (88.46)| 25 (96.15)| 4 (16.66)| 2 (8.33) |
| Abnormal bleeding      | 5 (6.75)         | 0 (0)       | 0 (0)    | 4 (15.38)  | 1 (3.84)  | 0 (0)     | 0 (0)    | 0.018    |
| Dyspareunia            | 15 (20.2)        | 2 (3.03)    | 0 (0)    | 9 (34.61)  | 0 (0)     | 1 (4.16)  | 0 (0)    | NA       |
| Post coital bleeding   | 4 (5.40)         | 0 (0)       | 0 (0)    | 3 (11.53)  | 0 (0)     | 0 (0)     | 0 (0)    | NA       |
| Pelvic pain            | 24 (32.4)        | 3 (4.28)    | 3 (4.54) | 1 (1.51)   | 6 (23.07) | 1 (3.84)  | 2 (8.33) | 0 (0)    |

| Variables               | Inflammation, n (%) | LSIL (CIN 1), n (%) |
|-------------------------|---------------------|---------------------|
| Complaints              |                     |                     |
| Abnormal vaginal discharge | 70 (94.59)         | 23 (88.46)          |
| Abnormal bleeding       | 5 (6.75)            | 4 (15.38)           |
| Dyspareunia             | 15 (20.27)          | 9 (34.61)           |
| Post coital bleeding    | 4 (5.40)            | 3 (11.53)           |
| Pelvic pain             | 24 (32.43)          | 6 (23.07)           |

Table 2: Chief complaints, size and location of cervical lesion.

| Variables | Inflammation, n (%) | LSIL (CIN 1), n (%) |
|-----------|---------------------|---------------------|
| Size (cm) |                     |                     |
| <2        | 66 (89.18)          | 19 (73.07)          |
| >2        | 08 (10.81)          | 07 (26.92)          |
| Mean size | 0.88±0.88           | 1.81±1.8            |

Continued.
Immediately after the procedure, majority had complaints of pain (21%), weakness (11%) and vomiting (2%) while the rest had no complaints. Lesions >2 cm size were all cured with cryotherapy (100%). 89.33% patients with cervical lesion <2 cm was cured with p=0.3431.

The healing efficacy of cryo therapy at 6th week was 87.8% and 91.1% at end of 12th week. Statistical analysis showed no difference in healing rate in both groups at 6th week and at 12th week. Cryo cautery is effective in both inflammation as well as LSIL (CIN 1). Statistical analysis showed that cure rate was not affected by location of lesion (p not significant 0.9188) and size of lesion (Table 2).

At 2nd week, satisfaction rate was only 11.34%. At 6th week, satisfaction rate was 91.1% and at 12th week, 92.22% patients were satisfied. Data analysis showed high satisfaction rate among all patients who underwent cryocauterisation for cervical lesion (p<0.001) (Figure 2).

In this study, immediate complications included pain in 21%, only 1% had lateral vaginal wall burn and 92% had no complaints. Similar findings were observed by Katakdhond et al where pain was found in 17% immediately after cryo and 80% had no complications.4 Matanyi et al observed that side effects were negligible in 1,248 cervical cryosurgeries.18

In a different study with sample size of 52 women, Naud et al (2016) reported pain/cramps (79%) as the most common adverse event followed by heat sensation (25%).19 Viviano et al found that 95.5% of 110 women studied experienced some degree of pain during therapy when no analgesia was used.20

All patients were given injection of pentazocine to relieve pain, similar study conducted by Duncan et al that compared two analgesics (Prilocaine and Felypressin) for pain relief during the procedure concluded that both drugs were efficient in reducing pain.21 Overall, the authors concluded that pain is well tolerated and that most patients do not require analgesia.

In this study, out of 100 patients 90 came for follow up after 12 weeks and 10 were lost to follow up. Abnormal vaginal discharge was the most common complaint in this study followed by pelvic pain. All complaints almost subsided after 12weeks of cryotherapy. Abnormal vaginal discharge was present only in 7.77% and pelvic pain in 1.11% after 12 weeks of cryocauterisation.

It must be considered that there is no difference in persistence of symptoms between inflammatory group and LSIL (CIN 1) group, as observed by Jahic et al.22 Similar findings were also found in a study done by Katakdhond et al and Jahic et al.4,22 Mohanty et al recorded that cryotherapy eliminates enhanced vaginal secretion and pain 12 weeks after the treatment.16

The efficacy of present study is 91.9% and is comparable with most studies. Peck et al, Alvarez et al, Cecmez et al, Jahic et al, Mohanty et al, were abnormal white discharge was found in 100%, 87%, 91.9%, 92.6% and 90% respectively.4,13-16 In another study conducted by Patil et al abnormal vaginal discharge was found in 55% of patients and this disparity might be because of different prevalence in the institute where the study was conducted.17 Hence, abnormal white discharge was the main indication of cryotherapy among all patients.

In this study, the average time of cryotherapy procedure was 15 minutes in most of the patients (85%). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention and Katakdhond et al show the same duration of the procedure.4,11

| Variables  | Inflammation, n (%) | LSIL (CIN 1), n (%) |
|------------|-------------------|---------------------|
| Location   |                   |                     |
| Anterior lip | 9 (12.16)        | 2 (7.69)            |
| Circumferential | 39 (52.17)    | 16 (61.53)          |
| Posterior lip | 26 (35.13)      | 08 (30.76)          |

**DISCUSSION**

In this study 93% of patients had abnormal white discharge per vagina followed by pelvic pain in 30% and dyspareunia in 24%. Similar findings were reported by Katakdhond et al, Jahic et al, Cecmez et al, Gay et al, Mohanty et al, where abnormal white discharge was found in 100%, 87%, 91.9%, 92.6% and 90% respectively.4,13-16 In another study conducted by Patil et al abnormal vaginal discharge was found in 55% of patients and this disparity might be because of different prevalence in the institute where the study was conducted.17 Hence, abnormal white discharge was the main indication of cryotherapy among all patients.

In this study, the average time of cryotherapy procedure was 15 minutes in most of the patients (85%). WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention and Katakdhond et al show the same duration of the procedure.4,11

**Figure 2: Results of cryotherapy.**
lesions (>3 cm, 61.5%).30 Mohanty et al concluded that cryocautery was well tolerated by patients, and had a cure rate of almost 100%.16

This difference in cure rate might be because of a larger probe used for larger lesion after the first freeze. WHO guidelines in 2012 concluded that the cure rate of cryotherapy is >90% even in low resource settings.12

In this study, satisfaction rate of cryocautery is 92.22% it is highly recommended to rate women by the patients. At the first follow up, satisfaction rates were low (11.34%) due to persistence of profuse white vaginal discharge for 2-3 weeks post cryotherapy. At 6th weeks, satisfaction rates significantly rose (p<0.001) up to 91.1% and at 12th weeks it was 92.22%.

Similarly, Katakdond et al. reported a high satisfaction rate in a sample size of 30 women.4 In 2019, Agah et al reported that cryotherapy showed no remarkable side effects and was associated with more satisfaction (p<0.001).31 Adefuye et al reported that 98.2% of 220 women believed that the procedure had been as they expected, and 95% said that they would recommend cryotherapy to other women.31 Lewis et al found 100% satisfaction with cryotherapy among 22 women surveyed at their 3-month follow-up visit.27 Phongsavan et al found that all 113 women treated with cryotherapy reported being satisfied or very satisfied with the treatment.32

Limitation

The study was unicentric study. Multicentric study will validate the findings of our study. Large sample size can remove observational bias.

CONCLUSION

Cryotherapy is effective method for treatment of cervical erosion. Cryotherapy effectively eliminates symptoms like abundant vaginal discharge and pelvic pain. Cryotherapy has minor morbidity till 6th week thereafter nil morbidity after 12th week. Majority (92.22%) of the patients were highly satisfied with this mode of therapy. Cryotherapy is a cheap, easy, and safe treatment. It is suitable for both hospital and office-based practice and it can be performed in ambulatory set up.

ACKNOWLEDGMENTS

Authors would like to thank department of obstetrics and gynecology, GMERS medical college and hospital, Sola, Ahmadabad, Gujarat, for all the kind support and thanks to all the participants for their cooperation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Louv WC, Austin H, Perlman J, Alexander WJ. Oral contraceptive use and the risk of chlamydial and gonococcal infections. Am J Obstet Gynecol. 1989;160(2):396-402.
2. World Human papilloma virus and related disease report, summary report 2019. Available at https://hpvcentre.net/statistics/reports/XWX.pdf. Accessed on 19 june 2021.
3. Katz: Comprehensive Gynecology, 5th Edition Mosby’s Guide to Physical Examination, 7th Edition. 2012:558.
4. Katakdond S, Samant P. Cryotherapy for cervical lesions: efficacy and patient satisfaction. Int J Reprod Obstet Gynecol. 2017;6:2331-6.
5. Ugboma HAA, Aburoma HLS. Pap smear: an important screening technique for preventing and detecting cervical cancer. Cont J Med Res. 2010;4:13-7.
6. Shafi ML. Premalignant and malignant lesions of the cervix. In: Edmonds DK, editor. Dewhurst’s Textbook of Obstetrics and Gynaecology, Oxford, UK: Blackwell Publishing. 2007:7.
7. Sarkar PK, Steele PRM. Routine colposcopy prior to treatment of cervical ectopy: Is it worthwhile? J Obstetr Gynaecol. 1996;16:2:96-7.
8. Wright TC, Richart RM, Ferencyz A. Electrosurgery for HPV related diseases of the lower genital tract: a practical handbook for diagnosis and treatment by loop electrosurgical excision and fulguration procedures. Quebec7 Arthur Vision Incorporated. 1992.
9. Sankaranarayanan R. Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. Brit j cancer. 2007;96(5):738-43.
10. Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. Cryobiology. 1998;37(3):171-86.
11. WHO Guidelines: Use of Cryotherapy for Cervical Intraepithelial Neoplasia. Geneva: World Health Organization; 2011. Available at: https://www.who.int/reproductivehealth/publications/cancers/9789241502856/en/. Accessed on 20 June 2021.
12. WHO: Cryosurgical Equipment for the Treatment of Precancerous Cervical Lesions and Prevention of Cervical Cancer: WHO Technical Specifications. Geneva, Switzerland, WHO, 2012. Available at: https://www.who.int/reproductivehealth/publications/cancers/9789241504560/en/ accessed on 20 June 2021.
13. Jahic M. Cryotherapy of Erosion of Cervix and Low Grade Squamous Intraepithelial Lesion. Mater Sociomed. 2018;30(4):294-6.
14. Çekmez Y, Şanlıkan F, Göçmen A, Vural A, Türkmen SB. Is Cryotherapy Friend or Foe for Symptomatic Cervical Ectopy? Med Princ Pract. 2016;25:8-11.
15. Gay C, Riehl C, Ramanah R, Desmoulin G, Violaine B. Cryotherapy in the management of symptomatic
cervical ectopy, Gynecol Obstet Fertil. 2006;34(3):214-23.
16. Mohanty KC, Rand RJ, Berry B. Cryotherapy in the management of cervical ectopy. Genitourin Med. 1985;61(5):335-7.
17. Patil P, Sharma P. Colposcopic evaluation of cervical erosion in symptomatic women. Int J Reprod Contracept Obstet Gynecol. 2017;6:2207-11.
18. Matányi S. Side effects and complications of cervical cryotherapy. Acta Chir Hung. 1992-1993;33(1-2):157-62.
19. Naud PS et al: Efficacy, safety, and acceptability of thermo-coagulation for treatment of cervical intraepithelial neoplasia in a hospital setting in Brazil. Int J Gynaecol Obstet. 2016;133:351-4.
20. Viviano M, Kenfack B, Catarino R. Feasibility of thermocoagulation in a screen-and-treat approach for the treatment of cervical precancerous lesions in sub-Saharan Africa. BMC Womens Health. 2017;17:2.
21. Duncan ID, McKinley CA, Pinion SB, Wilson SM. A double-blind, randomized, placebo-controlled trial of prilocaine and felypressin (Citanest and Octapressin) for the relief of pain associated with cervical biopsy and treatment with the Semm coagulator. J Low Genit Tract Dis. 2005;9(3):171-5.
22. Jahic M. Cryotherapy of Erosion of Cervix and Low Grade Squamous Intraepithelial Lesion. Mater Sociomed. 2018;30(4):294-296.
23. Peck JE. Cryosurgery for benign cervical lesions. Br Med J. 1974;2(5912):198-9.
24. Alvarez Bravo A. Cryosurgery of the uterine cervix. Our experience in 3,184 cases. Ginecol Obstet Mex. 1991;59:105-11.
25. Wojtyś A, Zdebski Z. Effects of low-temperature treatment of pathologic changes of the cervix uteri. Ginekol Pol. 1989;60(5):276-9.
26. Guijon F, Paraskevas M, McNicol P. Human papillomavirus infection and the size and grade of cervical intraepithelial neoplastic lesions associated with failure of therapy. Int J Gynaecol Obstet. 1993;42(2):137-42.
27. Lewis KD, Sellors JW, Dawa A, Tsu VD, Kidula NA. Report on a cryotherapy service for women with cervical intraepithelial neoplasia in a district hospital in western Kenya. Afr Health Sci. 2011;11(3):370-6.
28. Adefuye PO, Dada OA, Adefuye BO, Shorunmu TO, Akinyemi BO, Idowu-Ajiboye BO. Feasibility, acceptability, and effectiveness of visual inspection of the cervix with acetic acid and cryotherapy for dysplasia in Nigeria. Int J Gynaecol Obstet. 2015;129(1):62-6.
29. Kwikkel HJ, Helmerhorst TJ, Bezemere PD, Quaak MJ, Stolk JG. Laser or cryotherapy for cervical intraepithelial neoplasia: a randomized study to compare efficacy and side effects. Gynecol Oncol. 1985;22(1):23-31.
30. Ferenczy A. Comparison of cryo- and carbon dioxide laser therapy for cervical intraepithelial neoplasia. Obstet Gynecol. 1985;66(6):793-8.
31. Agah J, Sharifzadeh M, Hosseinizadeh A. Cryotherapy as a Method for Relieving Symptoms of Cervical Ectopy: A Randomized Clinical Trial. Oman Med J. 2019;34(4):322-326.
32. Phongsavan K, Phengsavanh A, Wahlström R, Marions L. Safety, feasibility, and acceptability of visual inspection with acetic acid and immediate treatment with cryotherapy in rural Laos. Int J Gynaecol Obstet. 2011;114(3):268-72.

Cite this article as: Patel KD, Karnavat RD, Viramgama DG, Dalal RK. Evaluation of efficacy and safety of cryotherapy in benign and premalignant cervical lesion. Int J Reprod Contracept Obstet Gynecol 2021;10:3066-71.