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Original Article

J Clin Gynecol Obstet. 2017;6(3-4):58-64

Efficacy, Safety, and Acceptability of Thermal Coagulation to Treat Cervical Intraepithelial Neoplasia: Pooled Data From Bangladesh, Brazil and India

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Abstract

Background: Treatment of cervical intraepithelial neoplasia (CIN) using thermal coagulation has recently attracted interest among the medical community in view of the easily portable and light equipment, less treatment time, faster patient turnover, less discomfort, use of minimal amounts of electricity as consumable, less vaginal discharge following treatment and a similar efficacy in treatment of ectocervical CIN lesions as compared to cryotherapy. However, literature on its performance is scarce particularly from low- and middle-income settings. Here, we report the effectiveness, safety and acceptability of thermal coagulation in women treated for histologically proven ectocervical CIN.

Methods: We pooled data from five sites in Asia and South America for women treated for CIN with thermal coagulation from March 2010 to October 2015, and followed up within 6 - 12 months after treatment. Estimates of cure, adverse effects, or complications were presented as proportions. Bayesian models were used to assess factors affecting compliance to follow-up and cure rates.

Results: Of the 1,626 women treated for CIN at baseline, 775 (48%) had follow-up evaluation. Attendance for follow-up increased with increasing education and CIN grade, and was less likely to be among those aged ≥ 40 years. The estimates of the cure after thermal coagulation treatment were 88% (475/543) for CIN 1, 83% (113/137) for CIN 2 and 83% (79/95) for CIN 3 lesions. No serious adverse effects or complications were observed throughout the follow-up period for which hospitalization was required.

Conclusion: Thermal coagulation was effective, safe and accepted in treatment of women diagnosed with CIN. It should be used in the single-visit "screen-and-treat" approach, "see-and-treat" approach and in management of ectocervical CIN in cervical cancer control programs.

Keywords: Cervical intraepithelial neoplasia; Thermal coagulation; Efficacy; Acceptability; Pooled data

Introduction

Large loop excision of the transformation zone (LLETZ), also known as loop electrosurgical excision procedure (LEEP), is used more often than ablation in treatment of cervical intraepithelial neoplasia (CIN) in developed countries because excision allows for histological evaluation of the entire transformation zone and avoids missing occult invasive or glandular disease, though concerns about adverse obstetric outcomes are raised. In low- and middle-income countries (LMICs), however, widespread use of LEEP and other excisional techniques is not feasible mainly because of lack of required infrastructure, trained personnel and risk of hemorrhage. Thus, ablative treatment using cryotherapy is the most commonly used treatment method for CIN in LMICs as it can be performed by a wide range of healthcare workers including nurses [1]. It has been shown to have high efficacy in curing fully visible CIN lesions located on the ectocervix and occupy less than three quadrants of the transformation zone [1-5]. Furthermore, previous studies using the "single-visit approach" have demonstrated its feasibility and utility in screen-and-treat programs [6-9]. Nevertheless, difficulties and costs involved in ensuring constant supply of refrigerant gas as well as frequent equipment technical issues such as gas leaks are major challenges for sustaining

Manuscript submitted October 12, 2017, accepted October 19, 2017

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doi: https://doi.org/10.14740/jcgo464w

the use of cryotherapy in LMICs.

Thermal coagulation (also known as cold coagulation) is used as an alternative ablative method for treating CIN lesions since 1980s. This method has recently attracted interest among the medical community in view of easily portable and light equipment, less treatment time, faster patient turnover, less discomfort, use of minimal amounts of electricity as consumable, less vaginal discharge following treatment and a similar efficacy in treatment of ectocervical CIN lesions as compared to cryotherapy. We report in this manuscript the effectiveness, safety and acceptability of thermal coagulation in women treated for histologically proven CIN lesions in five sites in Asia and South America based on a pooled analysis and discuss its utility as an alternative option for cryotherapy in screen-and-treat programs, in programs using the see-and-treat approach and for the ablative treatment of CIN lesions in LMICs.

Materials and Methods

Data for women diagnosed with different grades of histologically proven CIN, and treated with thermal coagulation from March 2010 to October 2015 from the following study locations were pooled to assess cure rates and safety: Bangabhandu Sheikh Mujib Medical University (BSMMU) Hospital, Dhaka, Bangladesh (n = 1,294), Hospital de Clinicas de Porto Alegre, Federal University of Rio Grande do Sul, Porto Alegre, Brazil (n = 99), Christian Fellowship Community Health Center, Ambillikai, India (n = 87), Hirabai Cowasji Jehangir Medical Research Institute (HCJMRI) and Prayas, Pune, India (n = 83), and the Regional Cancer Center, Trivandrum, India (n = 51). All included women from Pune were HIV infected.

Participating women diagnosed with histologically confirmed CIN were explained about the thermal coagulation treatment procedure. Women diagnosed with CIN received thermal coagulation if the lesion was located in the ectocervix without the involvement of vagina or the endocervix, occupying less than three-quarters of a fully visible type 1 transformation zone, had no evidence of invasive cancer, and could be adequately covered by single or multiple applications of thermal coagulation treatment probe. Before treatment, women received an explanation about the diagnostic findings, treatment procedure and the potential adverse effects/complications and informed consent was obtained. After application of 5% acetic acid followed by Lugol's iodine to visualize the lesion and the entire transformation zone, the thermal coagulation probe, heated to 100 °C, was applied to the cervix for 45 s. If necessary, two or more overlapping applications of same duration were used to cover the entire transformation zone of the cervix needing treatment. No local anesthesia was used. Immediately after treatment, women were observed for any side-effects such as bleeding, lower abdominal pain or cramps or for any accidental vaginal burns. They were advised to report back if they experienced high fever for more than 2 days, severe bleeding, pain, cramps and excessive foul smelling discharge. They were advised to avoid vaginal douche, sexual contact (or at least use of condoms) or taking bath in rivers or use of tampons for 1 month after treatment. No antibiotics were routinely prescribed after treatment. All treated women were requested to come back 6 - 12 months after treatment for follow-up on treatment outcome. At follow-up, they were examined using visual inspection with acetic acid (VIA) or cytology, colposcopy, directed biopsies if any abnormalities were observed on colposcopy and subsequent treatment for any residual/recurrent CIN lesion or progressive disease such as invasive cervical cancer was arranged.

The characteristics of patients treated with thermal coagulation at baseline are presented as proportions. Assessment of patient characteristics that determine adherence to follow-up after treatment was done using Bayesian logit models. Our main outcome was cure at least 6 months to 1 year after thermal coagulation treatment; cure was defined as no evidence of disease, i.e. no histologically confirmed CIN or no abnormalities detected on colposcopy. Cure rate was estimated as proportion of women with no evidence of disease among those followed up after treatment. Bayesian Cox proportional hazard regression models were used to assess the association between baseline patient characteristics and CIN cure rates. Survival time to cure was calculated from the date of treatment to date of the first follow-up at which no evidence of disease was observed or to the last date of follow-up for those with no CIN clearance. The adjusted regression models included all patients' characteristics being assessed.

Complications during or after treatment including severe bleeding requiring hospital admission or blood transfusion, unintended major surgery, cervicitis and pelvic inflammatory disease, local cervical infections and severe pain requiring hospitalization were considered as an indicator of safety [10]. Acceptability was determined using the side-effects arising during or after treatment including mild pain or cramps, fainting and flushing, mild bleeding or spotting or malodorous excessive discharge [10]. Both safety and acceptability measures were presented as proportions among all women treated. Data were analyzed using Stata version 14.2 (StataCorp LP, TX, USA) and Just Another Gibbs Sampler (JAGS) software run using the R software interface.

The study was funded by the Ministries of Health of the different sites and funding support provided by the Union for International Cancer Control (UICC), Geneva under the UICC Cervical Cancer Initiative for the Pune, India study site. The funding did not include support for external peer review for scientific quality or priority assessment, for example by a patient and public involvement panel. The funders did not play any role in conducting research and writing the paper.

Results

Of the 1,626 women treated with thermal coagulation included in this pooled analysis, 1,284 had CIN 1, 221 had CIN 2 and 121 had CIN 3 at baseline. About 80% of the women were aged below 40 years; over 80% had some formal education; about 78% had had at least two pregnancies (Table 1). Attendance for follow-up evaluation after CIN treatment increased with increasing education and CIN grade, and was significantly less likely to be among those aged 40 years or more (Table 2).

Table 1. Characteristics of Women Treated for CIN at Baseline

Characteristics	Women treated at baseline, n (%)
Women assessed	1,626
Site (period)	
Dhaka, Bangladesh (January 2010 - December 2015)	1,294 (79.6%)
Porto Alegre, Brazil (November 2010 - November 2015)	99 (6.1%)
Ambillikai, India (March 2009 - October 2015)	96 (5.9%)
Pune, India (October 2010 - November 2011)	83 (5.1%)
Trivandrum, India (November 2008 - February 2012)	54 (3.3%)
Age (years)	
< 40	1,272 (78.3%)
40+	352 (21.7%)
Education	
Illiterate	310 (19.2%)
Primary	639 (39.7%)
Middle	317 (19.7%)
High school and above	345 (21.4%)
Number of pregnancies*	
0 - 1	321 (21.8%)
2 - 3	914 (62.0%)
4+	240 (16.3%)
Baseline histological diagnosis	
CIN 1	1,284 (79.0%)
CIN 2	221 (13.6%)
CIN 3	121 (7.4%)

*Percentages obtained from the total of 1,475 participants for the three sites that provided the information. CIN: cervical intraepithelial neoplasia.

The median follow-up time for treatment outcome was 12 months (interquartile range: 9 - 18 months). Table 3 shows the outcome during follow-up of women treated with thermal coagulation for CIN lesions. The estimates of the cure rates after thermal coagulation treatment were 88% (475/543) for CIN 1, 83% (113/137) for CIN 2 and 83% (79/95) for CIN 3 lesions. Of the women treated for CIN 1, CIN 2 and CIN 3, the frequency of high-grade CIN at follow-up was 8, 8 and 6, respectively. No invasive cancers were diagnosed during follow-up.

Information on side-effects and complications during or after treatment was available from four study sites (Brazil and India) in 318 women while such information was not available from Bangladesh. The side-effects reported included mild pain/cramps in 52% (n = 164), mild bleeding in 1% (n = 4), and foul smelling discharge in 0.3% (n = 1). The complications involved heat sensation in the vagina in 4% (n = 12), severe lower abdominal pain in 0.3% (n = 1), and vasovagal reaction in the form of fainting in 0.3% (n = 1).

Discussion

Use of thermal coagulation is the simplest of all ablative treatment methods for CIN. It can readily be performed by a variety of trained health care providers such as primary care doctors, nurses, midwives and health workers. To our knowledge, this pooled analysis presents the largest experience so far assessing the outcomes after thermal coagulation of histologically proven CIN from low- and middle-income settings. We observed that thermal coagulation was effective in the treatment of women diagnosed with CIN lesions suitable for ablative treatment. It was highly accepted and safe given the minimal side-effects and complications observed in four study sites.

The observed cure rates of 88% and 83% for CIN 1 and CIN 2-3 lesions respectively in this study were similar to the summary cure rates (89% and 83%, respectively) reported from the two studies from Asia included in a previous meta-analysis [11]. Cure rates following cryotherapy ranged 90-100% for CIN 1, 75-96% for CIN 2 and 71-92% for CIN 3 [3, 4, 12]; in an earlier meta-analysis, the reported cure rates of cryotherapy were 94%, 92% and 85% [1]. Previously reported cure rates following thermal coagulation treatment of women with high-grade disease ranged 80-100% [11, 13-15]. The reported cure rates ranged 70-93% for laser ablation, 83-97% for laser conization, 85-97% for cold knife conization, and 71-98% for LLETZ in the treatment of all grades of CIN [12].

Table 2. Determinants of Treatment Follow-Up

Characteristics	Women treated for CIN at baseline	Women with follow-up, n (%)	Adjusted odds ratio (95% CI)*
Women assessed	1,626	775 (47.7%)	
Age (years)			
< 40	1,272	625 (49.1%)	1.0
40+	352	149 (42.3%)	0.7 (0.5 - 0.9)
Education			
Illiterate	310	102 (32.9%)	1.0
Primary	639	256 (40.1%)	1.4 (1.0 -1.8)
Middle	317	187 (59.0%)	2.7 (1.9 -3.7)
High school and above	345	215 (62.3%)	3.2 (2.2 -4.4)
Number of pregnancies**			
0 - 1	321	167 (52.0%)	1.0
2 - 3	914	434 (47.5%)	1.1 (0.8 -1.5)
4+	240	98 (40.8%)	1.0 (0.6 -1.4)
Baseline histological diagnosis			
CIN 1	1,284	543 (42.3%)	1.0
CIN 2	221	137 (62.0%)	2.3 (1.7 -3.1)
CIN 3	121	95 (78.5%)	4.8 (2.8 -7.4)

*All variables included in the adjusted regression model. **Percentages obtained from the total of 1,475 participants for the three sites that provided the information. CI: confidence interval; CIN: cervical intraepithelial neoplasia.

These findings further confirm that thermal coagulation is as successful as other treatment modalities in curing ectocervical CIN lesions located in type 1 transformation zone.

Like in other studies [11, 13, 16], we observed minimal side-effects and complications which were not life-threatening, reflecting that thermal coagulation is well accepted and safe. Being highly safe, acceptable and efficacious makes thermal coagulation a suitable alternative to cryotherapy in the treatment of ectocervical CIN lesions, especially in low-resource settings. Similar to cryotherapy, it could be used in the programs in low resource settings using the single visit "VIA screen and treat" approach, in which treatment is provided to all VIA-positive women with small lesions involving less than three-quadrants of the cervix and with no clinical evidence of invasive cancer, avoiding triage by colposcopy or histology in view of the non-availability or inadequate capacity for these

Table 3. Effect of Women Characteristics on CIN Cure Rates After Treatment With Thermal Coagulation

Characteristics	Women with follow-up	Women with no evidence of disease during follow-up, n (%)	Crude hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)*
Women assessed	775	667 (86.1%)		
Age (years)				
< 40	625	538 (86.1%)	1.0	1.0
40+	149	128 (85.9%)	1.1 (0.9 - 1.4)	1.1 (0.9 - 1.4)
Number of pregnancies**				
0 - 1	167	135 (80.8%)	1.0	1.0
2 - 3	434	386 (88.9%)	1.3 (1.1 - 1.6)	1.3 (1.1 - 1.6)
4+	98	84 (85.7%)	1.1 (0.8 - 1.5)	1.1 (0.8 - 1.4)
Baseline histological diagnosis				
CIN 1	543	475 (87.5%)	1.0	1.0
CIN 2	137	113 (82.5%)	1.1 (0.9 - 1.4)	1.2 (0.9 - 1.4)
CIN 3	95	79 (83.2%)	1.1 (0.9 - 1.4)	1.2 (0.9 - 1.5)

*All variables included in the adjusted regression model. **Percentages obtained from the total of 699 participants for the three sites that provided the information. CI: confidence interval; CIN: cervical intraepithelial neoplasia.

services, particularly in many sub-Saharan African countries. This approach has been shown to be acceptable, safe, efficacious and feasible in demonstration projects and large-scale national or regional programs are on-going in countries such as Thailand and Zambia [4, 6, 7, 17-20]. Recently a screen-and-treat approach using thermal coagulation has been evaluated in a large screen-and-treat field program in Malawi, in which thermal coagulation for treatment of VIA-positive lesions was introduced as an alternative to cryotherapy [21]. Of the 7,088 women screened with VIA, 429 women (6.1%) were VIA-positive; of these 361 (84.1%) were treated on the same day with thermal coagulation and 20 women were treated within 1 month from screening thermal coagulation. No women complained of pain or cramps or any other side-effect while receiving treatment. The treatment providers expressed satisfaction with the ease with which thermal coagulation could be administered. At 3 months from treatment, 234 women returned for first follow-up assessment and 220 (94%) had their lesions healed as assessed by repeat VIA. Thus in the screen-and-treat setting, thermal coagulation was associated with 94% cure rate and was feasible as well as acceptable. In a VIA screen-and-treat study involving 5,190 women in Nigeria, 262 VIA screen positive women were treated with thermal coagulation and a recurrence rate of 16.4% (n = 29) was reported among 177 treated women reporting for follow-up at 6 months from treatment; the recurrence rate was 18.3% (22/120) in HIV-positive women compared to 12.3% (7/57) in HIV-negative women [22].

In settings where colposcopy and histopathology services are available, the "see-and-treat" approach could be used offering thermal coagulation (in place of cryotherapy) based on colposcopy diagnosis and after taking punch biopsies to maximize compliance to treatment and additional treatment offered *a posteriori* when histology report is available to those with lesions previously inadequately treated. Again, the feasibility, safety, efficacy and acceptability of this approach using cryotherapy have been demonstrated previously in India and Peru [3, 4, 23].

Use of thermal coagulation has several advantages over cryotherapy treatment: shorter treatment time; lower morbidity (such as reduction in discharge after treatment) [24]; less bulky equipment lending itself to easy portability in field conditions; use of electricity which is easily available in low-resource settings than gas refills required by cryotherapy; no noise, smoke and smell which contribute to its higher acceptability among patients and providers [25]; and thermal coagulation applicator ("thermo-probe") does not stick to the tissue during treatment which is another time-saving feature, whereas cryotherapy needs defrosting of the cryoprobe before it can be removed from the cervix. Like cryotherapy, thermal coagulation does not require general anesthesia and can be performed without local anesthesia, though it is advised for a large transformation zone that would require more overlapping applications [26].

A major limitation of our study is that about 20% of the women with CIN 3 lesions and more than half of the women with any grade of CIN did not report back for treatment follow-up. Women not turning up for follow-up were more likely to be older women with no formal education. In addition, women treated for low-grade lesions were less likely to attend follow-up for treatment outcome, might have known their treated disease was not so severe and hence believed cured with the primary treatment received. Convincing older women and less educated women, especially if diagnosed with high-grade disease, to comply for follow-up assessment after treatment needs to be stepped up, since treatment could be higher in these women. Furthermore, some of the characteristics of participants (such as economic status and distance between their residence and the location of the service) that could affect attendance for treatment follow-up and cure (such as time of delay for treatment and number of applications used) could not be assessed. A major strength of the current study is a large number, than previously presented for low- and middle-income regions, of treated women for all grades of CIN lesions, particularly high-grade lesions that allowed us to estimate the cure rates after treatment with thermal coagulation with more accuracy. Also the study pooled data for low-resourced settings from the different parts of the world that makes our estimates generalizable.

In view of the present findings and considering its many practical advantages and lower operating costs, it is evident that thermal coagulation, offered by well-trained providers, should be the preferred modality for use in the single-visit "VIA screen-and-treat" aproach and "see-and-treat" approach in the management of ectocervical CIN in cervical cancer control programs.

Acknowledgments

We thank the Ministries of Health of the different sites for their valuable financial and technical support. We gratefully acknowledge the funding support provided by the Union for International Cancer Control (UICC), Geneva under the UICC Cervical Cancer Initiative for the Pune, India study site. We thank the local health authorities at the study sites for their cooperation. We especially thank the women and their families for their participation, the public health and other administrative authorities, and staff members of each site of different projects who facilitated the conduct of the projects. We thank Mrs Krittika Guinot, IARC, for her help in the preparation of the manuscript.

Author Contributions

AN, PN, POE, SJ and RW were involved in the conception, planning and carrying out of the study; PR, MK were involved in the planning and carrying out of the study; CS was involved in the writing up of the manuscript; RM was involved the analysis and writing up the first draft of the manuscript; RS was involved in the conception, planning, carrying out of the study and writing up of the manuscript. All authors revised and approved the final version of the manuscript.

Conflict of Interest

Authors declare they do not have any conflict of interest.

Ethics Approval

For the Bangladesh site, the government through the Ministry of Health and Family Welfare, in 2004 authorized the Bangabandhu Sheikh Mujib Medical University (BSMMU) and the United Nations Population Fund (UNFPA), Bangladesh to conceive, coordinate and support the initial pilot screening project using existing government health care infrastructure in 16 of 64 administrative districts. Based on the experience in the pilot study, the Government of Bangladesh decided to expand the programme to all the 64 districts of Bangladesh with support from UNFPA, Bangladesh. The data used were of the screen-positive women from the project that reported at the colposcopy clinic of BSMMU. Ethical approval to treat women with CIN using thermocoagulation and to use the data for future studies was obtained from the ethical review committee of the Hospital de Clinicas for the site of Porto Alegre, Brazil. For the Ambilikkai site, the data were from the cervical, breast and oral cancer screening project which was approved by the institutional scientific and ethics review committees of the Christian Fellowship Community Health Center, Ambilikkai, Dindigul District, India in 2007. For the Pune site, the data used were obtained from the cervical cancer screening project among HIV-infected women in Pune, India which was approved by the scientific and ethical review committees of the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO), Lyon, France, and the ethics committees of Hirabai Cowasji Jehangir Medical Research Institute (HCJMRI), and Prayas Health Group, Pune, India. For the Trivandrum site, we used screening data collected by Regional Cancer Centre (RCC) in the routine health care cervical cancer screening project. The screening project received approval from the ethics committee of the RCC, Trivandrum, India. All participating women provided a signed informed consent.

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