Thermal Ablation vs Cryotherapy or Loop Excision in Zambian Women Positive for Cervical Precancer

By Matthew Stenger and compiled by Liz Janetschek Pasini.

December 10, 2019

Partha Basu, MD

In the pilot phase of an ongoing randomized trial reported in *The Lancet Oncology*, **Partha Basu, MD**, and colleagues found that thermal ablation and cryotherapy produced similar treatment success rates in Zambian women positive for cervical precancer on visual inspection with acetic acid.

The investigators noted that cryotherapy is standard treatment for cervical precancer in see-and-treat programs in low-income and middle-income countries. However, cryotherapy presents logistical difficulties, including the need for, cost of, and supply chain problems with refrigerant gas, as well as equipment failure. The current pilot study included use of a recently developed, lightweight, portable battery-operated thermal ablator.

Study Details

The pilot study included 750 women aged 25 years or older seen at routine screen-and-treat clinics in Lusaka, Zambia, who were eligible for ablative therapy. Patients were randomly assigned between August 2017 and January 2019 to receive thermal ablation (n = 250), cryotherapy (n = 250), or large loop excision of the transformation zone (LLETZ; n = 250). The primary endpoint was treatment success, defined as either human papillomavirus (HPV) type-specific clearance among women positive for the same HPV type at baseline or negative visual inspection with acetic acid test at 6-month follow-up if baseline HPV test was negative. Outcomes were assessed in the per-protocol population. Enrollment for the full trial is ongoing.

Key Findings

Among all evaluable patients, treatment success at 6 months was reported in 120 (60%) of 200 patients in the cryotherapy group, 123 (64%) of 192 in the thermal ablation group, and 134 (67%) of 199 in the LLETZ group (overall P = .31).

Among patients who were HPV-positive at baseline, treatment success was reported in 48 (40%) of 121 patients in the cryotherapy group, 44 (42%) of 104 in the thermal ablation group, and 50 (47%) of 106 in the LLETZ group (overall P = .48).

Moderate to severe pain immediately after the procedure was reported by 2% of patients in the cryotherapy group, 2% in the thermal ablation group, and 2% in the LLETZ group. Moderate to severe pain at 2 weeks after the procedure was reported by < 1%, 0%, and < 1%, respectively.

No patients reported any complication requiring medical consultation or hospital admission.

The investigators concluded, “Results from this pilot study preliminarily suggest that thermal ablation has similar treatment success to cryotherapy, without the practical disadvantages of providing cryotherapy in an [low- and/or middle-income country]. However, the study was not powered to establish the similarity between the techniques, and results from the ongoing randomized controlled trial are need to confirm these results.”

Pinder LF et al: Lancet Oncol. November 13, 2019 (early release online). ■

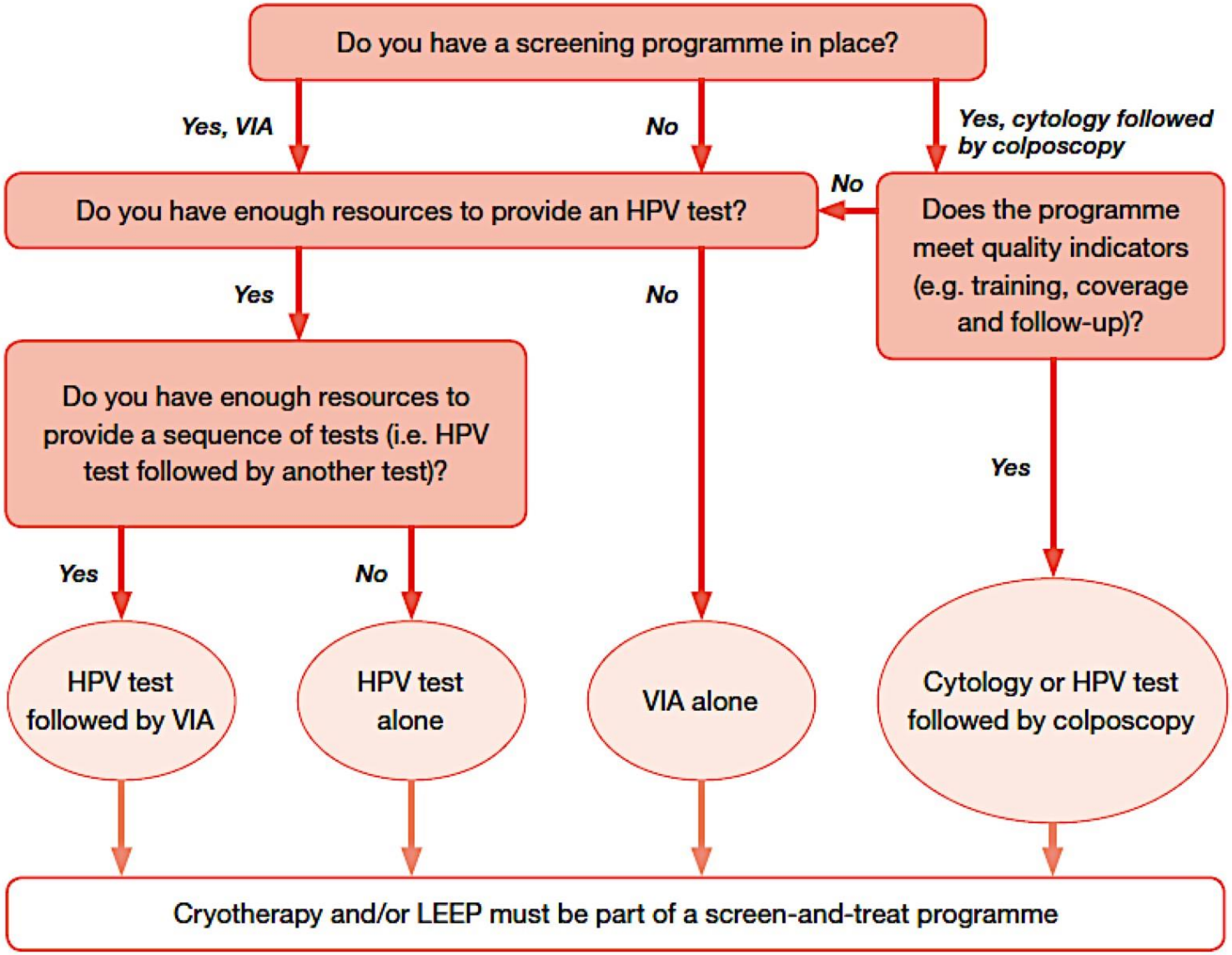
Development & Evaluation of a Hand-held, Portable & Affordable Thermo-coagulator

International Agency for Research on Cancer
Lyon, France

Principal Investigator: R. Sankaranarayanan, Screening Group, IARC
Grant No. 1UH2CA202721-01; Federal Award Date. 6 July 2016
Project Period. 07/07/2016 – 06/30/2018
ClinicalTrials.gov Identifier – NCT02956239

International Agency for Research on Cancer
World Health Organization

Cryotherapy to Treat Cervical Premalignant Lesions is Widely Recommended

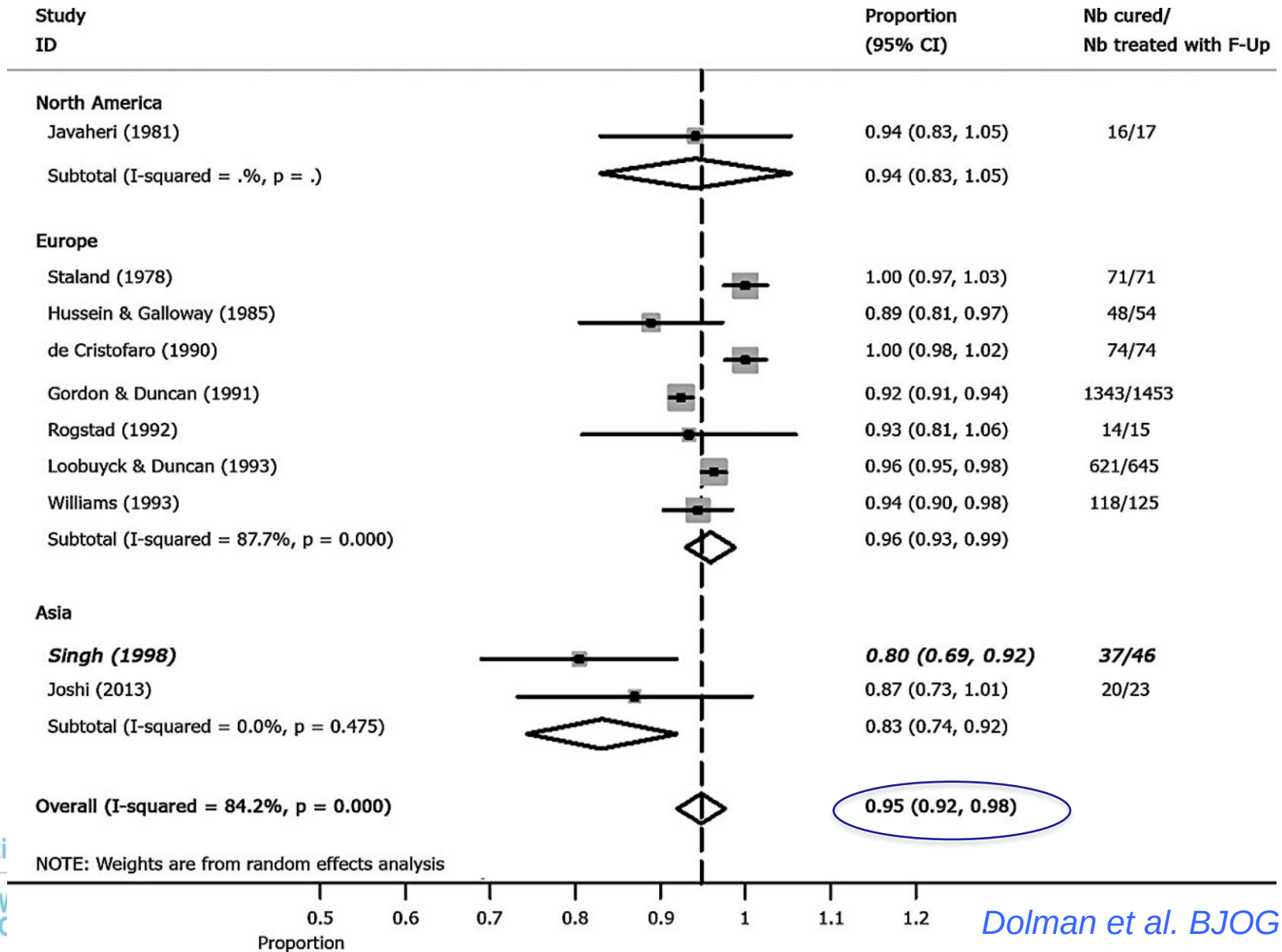


WHO guidelines for screening and treatment of precancerous lesions for cervical cancer prevention 2013

Cryotherapy - Practical Problems

- Difficult to ensure regular supply of refrigerant gas in many settings
- Carrying the large tanks is problematic
- Gas connectors are different in different countries and are difficult to modify
- Problems with the flow of refrigerant may occur, interfering with freeze adequacy
- Gas is expensive
- Profuse watery discharge can continue for 6 weeks

Cure Rate of Thermo Coagulation to Treat CIN2/3



Dolman et al. BJOG 2014

RANDOMIZED CONTROLLED TRIAL (RCT) OF THE LIGER THERMAL COAGULATOR VS CRYOCAUTERY AND VS LLETZ TO PREVENT CERVICAL NEOPLASIA IN VIA POSITIVE WOMEN

International Agency for Research on Cancer
World Health Organization

Objectives

- Develop & produce 20 novel lightweight hand-held cordless, portable battery driven & rechargeable Thermal Coagulators (LIGER Med.)
- Evaluate success rate of TC in an RCT comparing TC to cryotherapy & LLETZ as part of a screen and treat program in Zambia.
- Evaluate the user satisfaction scores of TC
- Determine the rate of over treatment in a VIA – screen & treat program

Study Scheme

Bench testing of the new TC — Complete

UH2 *in-vitro ablative efficacy* study — Complete

UH2 *in-vivo ablative efficacy* study

UH2 pilot RCT for efficacy

UH3 RCT for efficacy & cost-effectiveness (if extended)

Development of TC

- Ensured adequate battery capacity to achieve 20+ treatment cycles per battery charge
- Providing LED light illumination during treatment
- Can achieve automatic treatment cycle temp. & duration with clinician recognition of same
- Developed an effective non stick probe tip
- Incorporated a simple method to preset the temp. and duration of treatment variables
- FDA clearance (# 152843) has been achieved

Thermo Coagulator Final Version

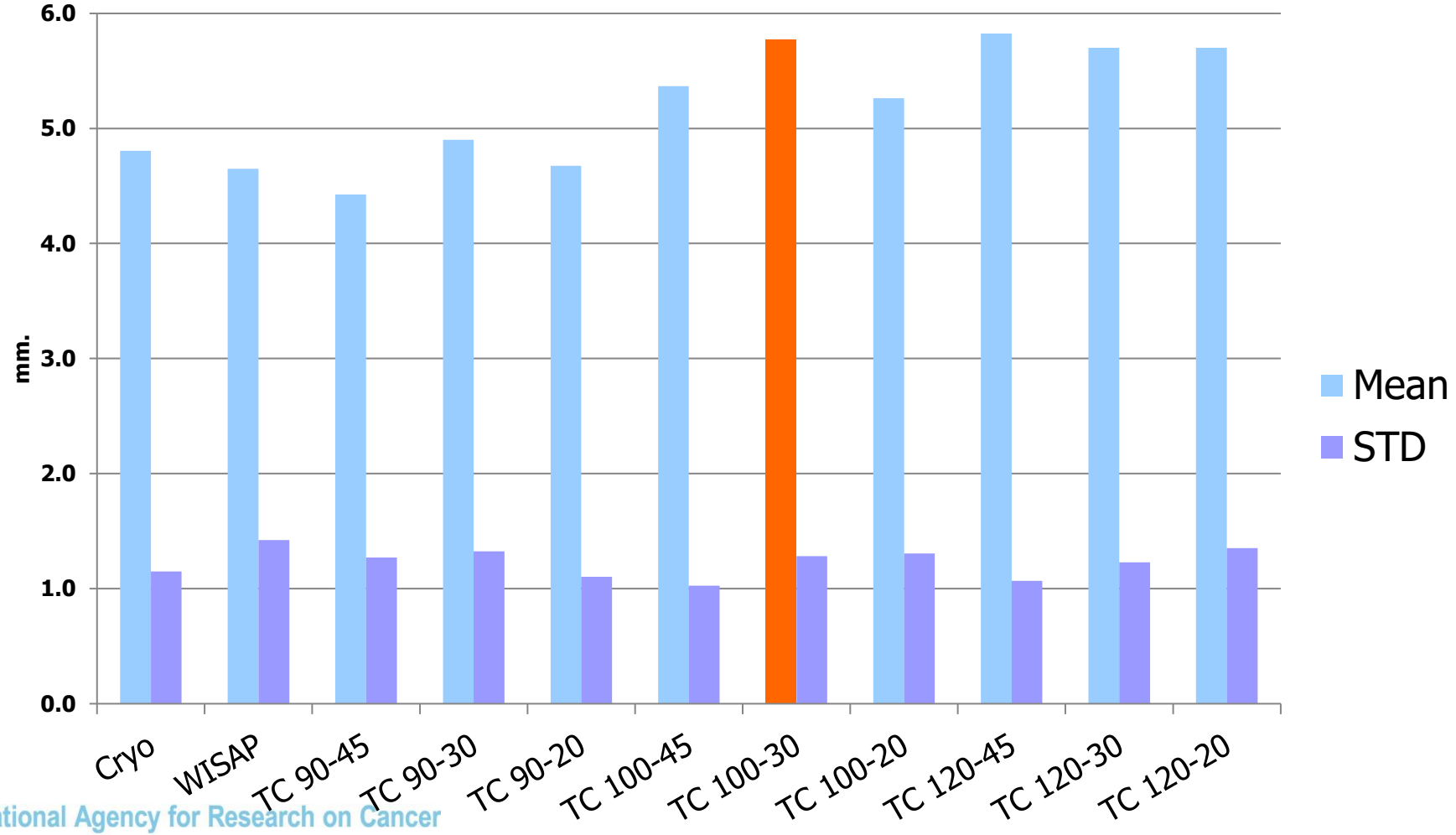
Field Testing of New TC

International
World
Orga

In-Vitro Ablative Efficacy Study

- Performed the following on skinless chicken tissue:
  - Double freeze Cryotherapy: 3 min-(5 min)-3 min x 20
  - WISAP TC at 100^{o}C for 45 sec x 20
  - LIGER TC at 90^{o}C for 20, 30 & 45 sec x 20 each
  - LIGER TC at 100^{o}C for 20, 30 & 45 sec x 20 each
  - LIGER TC at 120^{o}C for 20, 30 & 45 sec x 20 each
- Depth of destruction was measured blindly & compared
- Tissue damage was determined by detecting cytoplasmic coagulation (linear condensation of cytoplasm disrupting usual homogenous appearance) in striated muscle fibers

Mean and standard deviation measurements of tissue damage depth



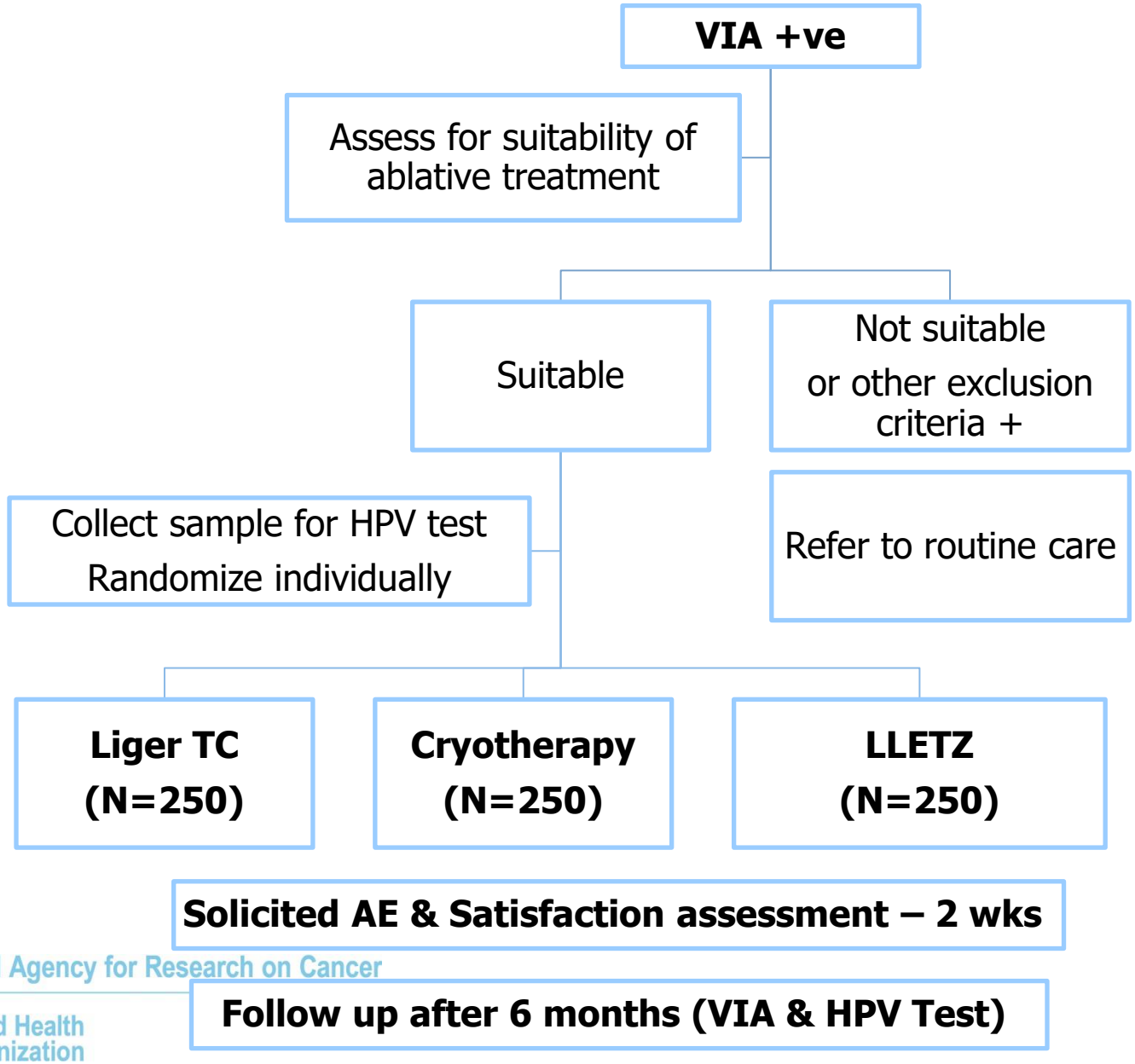
In Vivo Ablative Efficacy Study

- Perform the following on cervix just before the uterus is removed through hysterectomy (after RA/GA):
  - Double freeze Cryotherapy: 3 min-(5 min)-3 min x 20
  - Liger Thermo-coagulation at 100^{o}C for 20 sec x 20
  - Liger Thermo-coagulation at 100^{o}C for 30 sec x 20
  - Liger Thermo-coagulation at 100^{o}C for 45 sec x 20
  - Liger Thermo-coagulation at 120^{o}C for 20 sec x 20
  - Liger Thermo-coagulation at 120^{o}C for 30 sec x 20
  - Liger Thermo-coagulation at 120^{o}C for 45 sec x 20
- Make vertical sections of the cervix & stain
- Measure the depth of destruction blindly & compare

In Vivo Ablative Efficacy Study

- Inclusion criteria
  - Age 25-60 years
  - Hysterectomy for benign disease
  - Subject provides informed consent
- Exclusion criteria
  - No Precancer/cancer of cervix or treatment of cervix
  - Vaginal hysterectomy to be excluded
- To be conducted at UTH, Lusaka, Zambia
- Obtained approval from IRB of IARC & UNC and Zambian Medicines Regulatory Authority (ZAMRA)
- Pending approval from University of Zambia Biomedical Research Ethics Committee (UNZABREC)
- Site preparedness assessed & staff trained

UH2 Phase Pilot RCT - Protocol



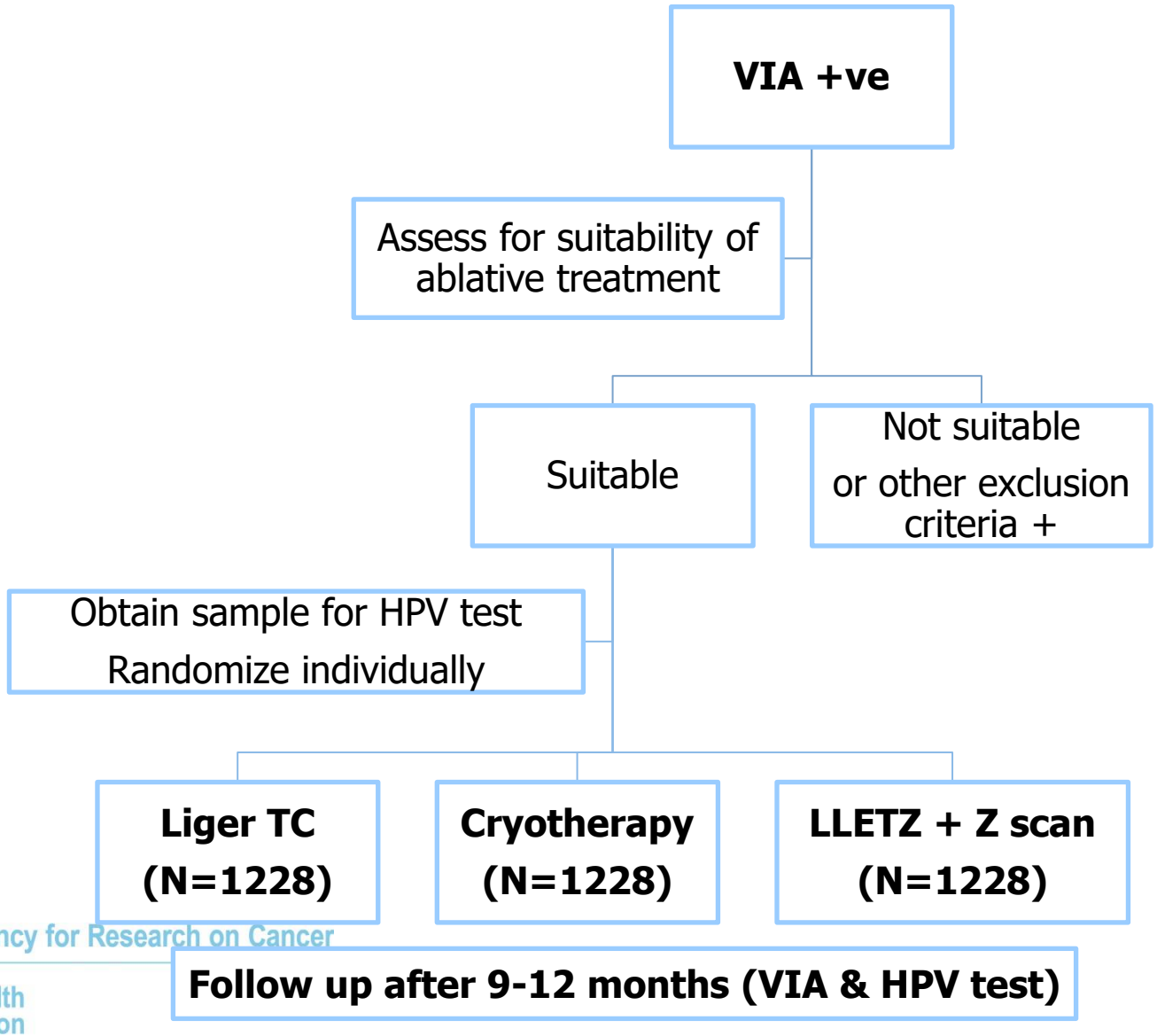
UH2 Phase Pilot RCT

- Inclusion criteria
  - Enrolled in screen & treat program
  - VIA positive
  - Eligible for treatment by ablation
  - Provides informed consent
- Exclusion criteria
  - Pregnancy
  - Previous treatment of cervix
  - Suspected or treated cancer
  - Type 2/3 TZ
- To be conducted at UTH, Lusaka, Zambia
- Obtained approval from IRB of IARC & UNC and Zambian Medicines Regulatory Authority (ZAMRA)
- Pending approval from University of Zambia Biomedical Research Ethics Committee (UNZABREC)
- Site preparedness assessed & staff recruited & trained

Performance Target (to be met to justify transition to UH3 phase)

Performance testing	Mandatory requirement	Preferred requirement
Bench-testing of functions	105 – 110 degree C achieved at probe tip & maintained for the entire duration of treatment (30 sec)	The indicator lights show accurately when to start treatment and when to stop
In-vitro testing of prototype (on chicken tissue)	--	Thickness of tissue damaged measured should not be less than 90% of the thickness achieved with cryotherapy & WISAP cold coagulator
In-vivo testing of prototype (on normal uterine cervix)	Thermal destruction should be at least upto 5mm from the surface	Thermal destruction should not be less than that achieved with WISAP cold coagulator
Acceptability, safety and early efficacy trial	Complication rate after TC not significantly higher than that after cryotherapy.	TC should be acceptable, as evidenced by >80% women showing satisfaction & <5% demanding interruption midway through treatment due to pain/ discomfort
	No major safety and technical concerns like under or over-heating, interruption of treatment, battery not retaining charge	In depth interview of the providers of treatment show high acceptability of new treatment
	Cure rates after treatment with TC should be at least 70% in the early efficacy trial.	

UH3 Phase Pilot RCT



The Delta Project Team

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Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial

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Summary

Background Cryotherapy is standard practice for treating patients with cervical precancer in see-and-treat programmes in low-income and middle-income countries (LMICs). Because of logistical difficulties with cryotherapy (eg, the necessity, costs, and supply chain difficulties of refrigerant gas; equipment failure; and treatment duration >10 min), a battery-operated thermal ablator that is lightweight and portable has been developed. We aimed to compare thermal ablation using the new device with cryotherapy.

Methods We report the pilot phase of a randomised controlled trial in routine screen-and-treat clinics providing cervical screening using visual inspection with acetic acid (VIA) in Lusaka, Zambia. We recruited non-pregnant women, aged 25 years or older, who were eligible for ablative therapy. We randomly assigned participants (1:1:1) to thermal ablation, cryotherapy, or large loop excision of the transformation zone (LLETZ), using computer-generated allocation. The randomisation was concealed but the nurses providing treatment and the participants were unmasked. Thermal ablation was achieved using the Liger thermal ablator (using 1–5 overlapping applications of the probe heated to 100°C, each application lasting for 40 s), cryotherapy was carried out using the double-freeze technique (freeze for 3 min, thaw for 5 min, and freeze again for 3 min), and LLETZ (using a large loop driven by an electrosurgical unit to excise the transformation zone) was done under local anaesthesia. The primary endpoint was treatment success, defined as either human papillomavirus (HPV) type-specific clearance among participants who were positive for the same HPV type at baseline, or a negative VIA test at 6-month follow-up, if the baseline HPV test was negative. Per protocol analyses were done. Enrolment for the full trial is ongoing. Here, we present findings from a prespecified pilot phase of the full trial. The final analysis of the full trial will assess non-inferiority of the groups for the primary efficacy endpoint. The study is registered with ClinicalTrials.gov, number NCT02956239.

Findings Between Aug 2, 2017, and Jan 15, 2019, 750 participants were randomly assigned (250 per group). 206 (84%) participants in the cryotherapy group, 197 (81%) in the thermal ablation group, and 204 (84%) in the LLETZ group attended the 6-month follow-up examination. Treatment success was reported in 120 (60%) of 200 participants in the cryotherapy group, 123 (64%) of 192 in the thermal ablation group, and 134 (67%) of 199 in the LLETZ group (p=0·31). Few participants complained of moderate to severe pain in any group immediately after the procedure (six [2%] of 250 in the cryotherapy group, four [2%] of 250 in the thermal ablation group, and five [2%] of 250 in the LLETZ group) and 2 weeks after the procedure (one [<1%] of 241 in the cryotherapy group, none of 242 in the thermal ablation group, and two [<1%] of 237 in the LLETZ group). None of the participants reported any complication requiring medical consultation or admission to hospital.

Interpretation Results from this pilot study preliminarily suggest that thermal ablation has similar treatment success to cryotherapy, without the practical disadvantages of providing cryotherapy in an LMIC. However, the study was not powered to establish the similarity between the techniques, and results from the ongoing randomised controlled trial are need to confirm these results.

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Introduction

Systematic high coverage and quality-assured population screening, with treatment of precursors to cervical cancer, is highly effective in preventing the disease, which is not surprising given that the conditions for an ideal screening test[1] apply very precisely to cervical cancer. The disease has a long precancerous phase, effective easy screening tests are available, treatment of precursors is highly effective, and the disease is common enough to justify the expense of population screening,

Research in context

Evidence before this study

The see-and-treat approach, by reducing the number of clinic visits, improves treatment compliance in a cervical cancer screening programme in resource-limited settings. Screening cervical cancer by visual inspection with acetic acid (VIA) followed by immediate cryotherapy is the most commonly used approach in low-income and middle-income countries (LMICs).Thermal ablation is an alternative ablative procedure. WHO has endorsed cryotherapy as the standard method of treatment for patients with cervical pre-cancer in LMICs for more than a decade. Although cold coagulation (now known as thermal ablation) has been in use for many years in the UK and elsewhere, and despite evidence from large and long-term follow-up studies in Scotland, the method has not been accepted in LMICs, perhaps largely because of the WHO endorsement of cryotherapy. We searched PubMed with no language or date restrictions using the keywords "cervical intraepithelial neoplasia OR CIN OR cervical precancerous lesions" and "ablative treatment", and "LMICs" on Sept 7, 2018, for articles describing this ablative procedure in low-resource settings. We also checked the reference lists of the selected articles. A meta-analysis of the available published evidence revealed similar effectiveness of cryotherapy and thermal ablation. We found only one small randomised controlled trial in the studies included.

Added value of this study

The results of the pilot phase of our study revealed a similarity in efficacy between thermal ablation and cryotherapy, although the pilot study was not adequately powered because of the small sample size. We found no difference in complication or discomfort levels between the study groups. The excisional group revealed that only 25% of participants who were deemed to be screen positive and eligible for ablation had high-grade squamous lesions. The study adds valuable evidence for similar efficacy and safety of the two ablative techniques. The high rate of over-treatment in a screen-and-treat setting has been quantified.

Implications of all the available evidence

The study will continue until sufficient power has been achieved to establish equivalent efficacy between thermal ablation and cryotherapy. The results of this pilot study suggest that thermal ablation as a method of treating cervical precancers is as safe as cryotherapy and is highly acceptable to patients and providers. If the early results of the pilot study regarding the similarity of treatment efficacy between thermal ablation and cryotherapy are supported by our ongoing randomised controlled trial, thermal ablation without the practical disadvantages of cryotherapy will be the ablative treatment of choice in an LMIC setting.

even in low-income and middle-income countries (LMICs).[2] Large loop excision of the transformation zone (LLETZ),[3] also known as loop electrosurgical excision procedure (LEEP), has become the standard treatment in most high-income countries. Ablative techniques are simpler, safer, and less technically demanding than LLETZ. Available ablative methods are cryotherapy and thermal ablation. The techniques have been described in detail elsewhere.[4] Thermal ablation was previously known as cold coagulation to distinguish it from radical diathermy, which reaches temperatures of approximately 300°C.[5] Thermal ablation functions by heating the epithelium at the transformation zone, albeit to 100°C.

Screening by visual inspection with acetic acid (VIA),[6] followed by immediate treatment of VIA-positive women (screen-and-treat approach) can reduce the number of clinic visits by women and greatly improve treatment compliance.[7] Cryotherapy was previously recommended by WHO as the ablative method of choice for screen-and-treat programmes in LMICs.[8] The method has the advantage of not requiring electricity, being simple to use, and being effective. However, the costs and difficulties in ensuring uninterrupted supply of CO_2 or N_2O refrigerant gas, the long treatment duration (11 min), and difficulties with equipment failure have led to the frustration of treatment providers with the method.[9,10] Thermal ablation is an alternative ablation therapy to cryotherapy. Similar effectiveness between the two methods has been shown in a pooled analysis of published observational studies.[11,12] The method has a much faster treatment duration (20–40 s) and requires no gas supply. Like cryotherapy, thermal ablation is simple to use and could be given by almost any health-care provider.

Consequently, the search for a simpler, affordable, and mobile ablative treatment modality to incorporate into see-and-treat regimes in LMICs has led to the development of a cordless, lightweight, and battery-operated thermal ablator. The International Agency for Research on Cancer (IARC) and the University of North Carolina (NC, USA) collaborated with Liger Medical (UT, USA) to assess the new device. Here, we report the pilot phase outcomes of a three-group randomised controlled trial of thermal ablation using the new portable device compared with cryotherapy and LLETZ in the context of a VIA-based screen-and-treat programme in Lusaka, Zambia. We aimed to compare the success of the three treatment methods. We also aimed to estimate the proportion of over-treatment in a VIA screen-and-treat programme on the basis of the histopathology results after LLETZ in the LLETZ group.

Methods

Study design and participants

This prospective, unblinded, randomised trial was done in a primary health clinic participating in the routine

screen-and-treat programme in Lusaka, Zambia, where VIA is done by trained nurses to screen women aged between 25 and 49 years. Like many other LMICs, the access to quality assured cytology is poor in Lusaka and we, therefore, decided to adhere to the national protocol of VIA-based screening followed by treatment of screen-positive women.

Here, we present findings from a prespecified pilot phase of the full trial. This pilot phase was done on request of the funder, a condition set before further funding for the full trial could be awarded.

All women attending the study VIA screening clinic were counselled about the trial by a research nurse before going to the clinic room. VIA was performed done as described by the IARC manual on VIA, [13] and the VIA outcomes were categorised as negative, positive, and suspected cancer.[13] The examining nurses assessed the eligibility of VIA-positive women for ablative treatment. These eligibility criteria were that the transformation zone be a type 1 (completely ectocervical), not involving more than 75% of the ectocervix, not extending to the vagina, and with no suspicion of cancer.[4,14] Women who were eligible for ablative treatment by the clinic nurse were invited to participate in the trial. Eligible women who agreed to take part in the study then gave written, informed consent. Exclusion criteria were any reason whereby informed consent was not freely given, not eligible for ablative treatment, size of the lesion was such that it could not be covered by the largest cryotherapy probe, pregnancy, previous treatment to the cervix for any reason, and any genital tract cancer.

As per routine practice in Zambia, all women undergoing VIA underwent HIV testing, unless a test result from within the past 6 months was available. Recently diagnosed HIV positivity required initiation of antiretroviral therapy before cervical cancer screening.

This study was approved by the research ethics committee at IARC, the University of North Carolina, the University of Zambia, and the National Health Research Agency of Zambia. The full trial protocol can be provided on request.

Randomisation and masking

Eligible participants were randomly assigned (1:1:1) to receive either thermal ablation, cryotherapy, or LLETZ. All treatment was given by one of four study nurses at the clinic. A request for allocation was obtained by the study nurse after checking the inclusion and exclusion criteria. Concealed allocation to a study group was done using computer-generated sealed envelopes at IARC, which were accessed by the study coordinator in the clinic. Study group allocation was conveyed to the nurse immediately before treating eligible participants. Once a treatment group had been allocated, the participant received a unique identifier number. Neither the treating nurse, nor the participant, were masked to the treatment allocation.

Procedures

The nurse collected a cervical sample before VIA using a Cervex-brush (Rovers Medical Devices [Oss, the Netherlands]) in Preservcyt medium (Hologic [Marlborough, MA, USA]) for human papillomavirus (HPV) DNA testing. If a woman was randomly assigned, her sample was sent to the University Teaching Hospital, Lusaka, laboratory for the detection of DNA of any of the 14 high-risk HPV types (with type-specific information) using the Xpert HPV test (Cepheid [Sunnyvale, CA, USA]). The HPV genotype information was obtained in separate channels for HPV 16; HPV 18 and 45; HPV 31, 33, 35, 52, and 58; HPV 51 and 59; and HPV 39, 56, 66, and 68. The test results were obtained after randomisation and treatment and did not alter treatment allocation or the management of eligible VIA-positive women.

Thermal ablation was done using the Liger thermal ablator and as described in the IARC colposcopy manual.[15] The portable battery-driven thermal ablator was developed by Liger Medical (Lehi, UT, USA) during 2016 and 2017 and bench tested in 2017. US Food and Drug Administration clearance was obtained in 2017, as was the European CE mark. The device is powered by a small removable 12-volt battery that is incorporated into the handle, which can be recharged over 2–3 h and holds enough charge to complete at least 20 treatment procedures. The thermal ablator probe was heated to 100°C and applied over the transformation zone of the cervix for 40 s. Up to five overlapping applications, each lasting for 40 s were used to treat a large transformation zone.

Cryotherapy was carried out using the double-freeze technique (freeze for 3 min, thaw for 5 min, and freeze again for 3 min) as per routine practice in screen-and-treat programmes in Zambia.[4] LLETZ was done under local anaesthesia, as described by Prendiville and colleagues.[3] Briefly, a type 1 excision of the transformation zone was done using a large yet shallow metallic loop, following local infiltration with 1% lignocaine. No anaesthesia was used for either thermal ablation or cryotherapy. Any treatment side-effects during and immediately after treatment were recorded by the nurse providing the treatment. Safety was assessed as any major complications leading to hospitalisation, disability, or death.

The treating nurse counselled each participant after the procedure about possible side-effects and complications of treatment and advised participants to report to the clinic or call the study coordinator for advice. Abstinence from sexual intercourse for 6 weeks and avoidance from douching or any vaginal medications was advised. Neither analgesics nor antibiotics were prescribed. Every participant was invited to attend a follow-up clinic appointment at 6 months. Before leaving the clinic, participants were interviewed by the project coordinator to document

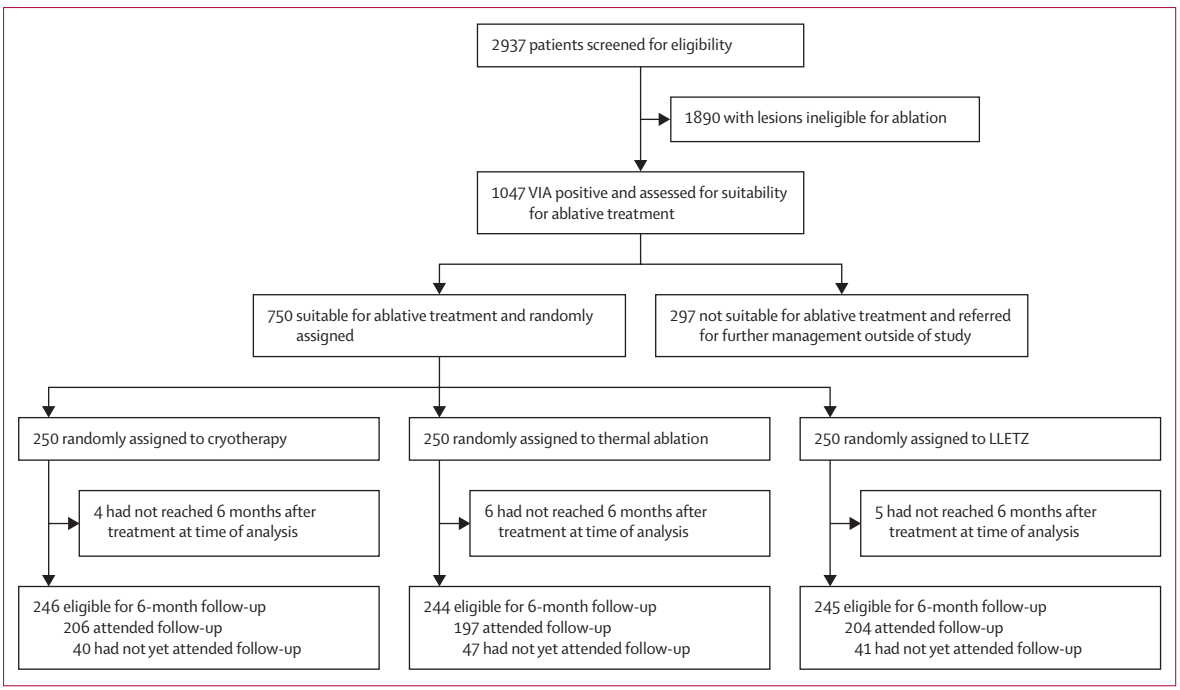

Figure: **Trial profile**
VIA=visual inspection with acetic acid. LLETZ=large loop excision of the transformation zone.

their perception of pain and discomfort during and immediately after treatment and also their satisfaction with the overall experience. Pain and satisfaction were assessed using a visual rating scale ranging from 1 (no pain at all or was highly satisfied) to 9 (pain was so severe that the participant wanted the procedure to be stopped or was not at all satisfied).

The study coordinator phoned each participant 2 weeks after treatment to check whether she had any complications, had visited a clinician, or had been admitted to hospital during the intervening period. The level of pain and discomfort and the degree of satisfaction with the overall experience at that timepoint was again recorded.

At the 6-month follow-up visit, each participant was asked about any complications, medical consultations, or hospitalisations. Participants were examined by a study nurse, who first collected a cervical sample for Xpert HPV testing and did VIA screening. VIA-positive participants were immediately referred for further assessment and appropriate management as per the local protocol. Participants who were negative on VIA, but positive for HPV, were advised to attend a repeat follow-up visit at 12 months.

Outcomes

The primary outcome was success of treatment at 6 months, which was defined as either HPV type-specific clearance at 6 months among participants positive for the same HPV type at baseline, or negative VIA test at follow-up, if the baseline HPV test was negative. The secondary outcomes were safety and acceptability of the three treatment methods. The proportion of participants undergoing LLETZ and having cervical intraepithelial neoplasias (CIN) on histopathology was also assessed as a secondary outcome, which helped us to assess the degree of over-treatment in screen-and-treat settings.

Statistical analysis

The sample size of 250 participants per group that was used for the assessment of the preliminary safety and efficacy was empirically decided. Recruitment for the full trial is ongoing and is expected to complete recruitment and follow-up within 2 years. A data and safety monitoring board continues to oversee the project.

The primary outcome was analysed per protocol. Treatment success, side-effects, complications, and acceptability presented as proportions and were compared between the three treatment modalities using a two-tailed Fisher's exact test. The interval between treatment and follow-up was compared using the Kruskal-Wallis equality-of-populations rank test. Statistical significance was set as $p<0·05$. Treated participants who had not yet reported for their 6-month follow-up (including those who were not yet eligible or those who were eligible, but did not attend a follow-up visit) were deemed not assessable in the analysis of the primary endpoint in the pilot phase. Statistical analyses were done using STATA (version 14.0) and R (version 3.6.0).

This study is registered with ClinicalTrials.gov, number NCT02956239.

	Cryotherapy group (n=250)	Thermal ablation group (n=250)	LLETZ group (n=250)
Age range, years			
25–29	92 (37%)	89 (356%)	84 (34%)
30–34	54 (22%)	65 (26%)	64 (26%)
35–39	44 (18%)	37 (15%)	47 (19%)
40–44	35 (14%)	31 (12%)	37 (15%)
45–49	15 (6%)	17 (7%)	11 (4%)
50–54	9 (4%)	8 (3%)	6 (2%)
55–60	1 (<1%)	3 (1%)	1 (<1%)
Education			
None	9 (4%)	7 (3%)	10 (4%)
Primary	88 (35%)	75 (30%)	74 (30%)
Secondary	101 (40%)	128 (51%)	123 (49%)
College or university	50 (20%)	40 (16%)	41 (16%)
Unknown	2 (<1%)	0	2 (<1%)
Occupation			
Housewife	62 (25%)	68 (27%)	57 (23%)
Manual	26 (10%)	23 (9%)	29 (12%)
Professional	43 (17%)	44 (18%)	37 (15%)
Business	92 (37%)	81 (32%)	86 (34%)
Other	16 (6%)	29 (12%)	31 (12%)
Unknown	11 (4%)	5 (2%)	10 (4%)
Marital status			
Unmarried	34 (14%)	32 (13%)	35 (14%)
Married or cohabiting	168 (67%)	171 (68%)	157 (63%)
Widowed	19 (8%)	17 (7%)	24 (10%)
Separated	28 (11%)	30 (12%)	34 (14%)
Unknown	1 (<1%)	0	0
Residence area			
Urban	146 (58%)	152 (61%)	149 (60%)
Semiurban	92 (37%)	90 (36%)	94 (38%)
Rural	11 (4%)	7 (3%)	7 (3%)
Unknown	1 (<1%)	1 (<1%)	0
Total pregnancies			
None	21 (8%)	14 (6%)	20 (8%)
1–2	74 (30%)	88 (35%)	102 (41%)
3–4	93 (37%)	90 (36%)	79 (32%)
≥5	62 (25%)	58 (23%)	49 (20%)
Total livebirths			
None	28 (11%)	22 (9%)	29 (12%)
1–2	97 (39%)	109 (44%)	120 (48%)
3–4	87 (35%)	85 (34%)	71 (28%)
≥5	38 (15%)	34 (14%)	30 (12%)
Last menstruation			
≤30 days	217 (87%)	213 (85%)	215 (86%)
>30 days to <12 months	18 (7%)	21 (8%)	22 (9%)
≥12 months	2 (<1%)	6 (2%)	3 (1%)
Unknown	13 (5%)	10 (4%)	10 (4%)
Size of the acetowhite area			
<50% of TZ	221 (88%)	223 (89%)	210 (84%)
>50% of TZ	29 (12%)	27 (11%)	40 (16%)
Baseline HIV status			
Negative	108 (43%)	119 (48%)	110 (44%)
Positive	134 (54%)	123 (49%)	135 (54%)
Unknown	8 (3%)	8 (3%)	5 (2%)
HIV positive on ART			
Yes	129/134 (96%)	117/123 (95%)	130/135 (96%)
No	4/134 (3%)	5/123 (4%)	1/135 (<1%)
Unknown	1/134 (<1%)	1/123 (<1%)	4/135 (3%)
HPV testing results			
Negative	100 (40%)	113 (45%)	105 (42%)
Positive	150 (60%)	136 (55%)	145 (58%)
Unknown	0	1 (<1%)	0
HPV type*			
HPV 16	38 (15%)	41 (17%)	51 (20%)
HPV 18 or 45	24 (10%)	21 (8%)	21 (8%)
HPV 31, 33, 35, 52, 58	99 (40%)	94 (38%)	101 (40%)
HPV 51 or 59	20 (8%)	11 (4%)	12 (5%)
HPV 39, 56, 66, or 68	60 (24%)	45 (18%)	54 (22%)

Data are n (%) or n/N (%). LLETZ=large loop excision of the transformation zone. ART=antiretroviral therapy. HPV=human papillomavirus. *Some patients had combinations of multiple HPV genotypes.

Table 1: **Baseline characteristics**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The raw data was accessed by RM (study statistician), PB, EL, and WP. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

Between Aug 2, 2017 and Jan 15, 2019, we assessed 2937 participants for eligibility (figure). We stopped recruitment for the pilot phase after 750 eligible participants were recruited. Participants were randomly assigned to thermal ablation (n=250), cryotherapy (n=250), or LLETZ (n=250). Table 1 provides details of the baseline sociodemographic, reproductive, and clinical characteristics between the three treatment groups.

In the cryotherapy group, 246 (98%) participants completed 6 months of treatment and were eligible for 6-month follow-up, of whom 206 (84%) attended the 6-month follow-up examination. In the thermal ablation group, 244 (98%) participants were eligible for 6-month follow-up and 197 (81%) attended the 6-month follow-up examination, and in the LLETZ group, 245 (98%) were eligible for 6-month follow-up and 204 (84%) attended the 6-month follow-up examination. The overall median

	Cryotherapy group	Thermal ablation group	LLETZ group	Fisher's exact p value
Overall				
Participants followed up*	200	192	199	..
Participants with no evidence of disease	120 (60%)	123 (64%)	134 (67%)	0·52
HPV positive at baseline				
High-risk participants followed up	121	104	106	..
Participants with no evidence of disease	48 (40%)	44 (42%)	50 (47%)	0·48
HIV negative at baseline				
Participants followed up	85	93	93	..
Participants with no evidence of disease	68 (80%)	77 (83%)	76 (82%)	0·72
HIV positive at baseline				
Participants followed up	109	95	101	..
Participants with no evidence of disease	50 (46%)	42 (44%)	55 (54·5)	0·36

Data are n, or n (%). LLETZ=large loop excision of the transformation zone. HPV=human papillomavirus. VIA=visual inspection with acetic acid. Treatment success was defined as either HPV type-specific clearance at 6 months among women positive for the same HPV type at baseline, or negative VIA test at follow-up, if the baseline HPV test was negative. *HPV reports were missing in six participants in the cryotherapy group, five participants in the thermal ablation group, and five participants in the LLETZ group, who had HPV-positive results at baseline; these participants were excluded from the analysis of treatment success proportion.

Table 2: **Treatment success proportions at 6-months follow-up after treatment**

interval between treatment and follow-up was 6·0 months (IQR 6·0–6·4 months) and the mean was 6·6 months (SD 1·8 months; range 4·8–19·6 months), with no difference between the treatment groups (p=0·83).

Table 2 shows treatment success proportions at 6 months after treatment based on a combination of HPV test and VIA. HPV reports were missing in six participants in the cryotherapy group, five participants in the thermal ablation group, and five participants in the LLETZ group, and these individuals were excluded from the analysis. When based on HPV type-specific clearance and VIA-negative findings among participants who were HPV negative at baseline, the proportions of participants treated successfully were 120 (60%) of 200 in the cryotherapy group, 123 (64%) of 192 in the thermal ablation group, and 134 (67%) of 199 in the LLETZ group (p=0·52). The proportions of participants with clearance of high-risk HPV at 6 months were similar between the cryotherapy (48 [40%] of 121), thermal ablation (44 [42%] of 104), and LLETZ (50 [47%] of 106) groups (p=0·48). The proportion of participants with clearance of HPV 16 (14 [43%] of 32 in the cryotherapy group, 18 [64%] of 28 in the thermal ablation group, and 18 [55%] of 33 in the LLETZ group) was lower than the proportion of participants clearing HPV 18, HPV 45, or both (16 [100%] of 16 in the cryotherapy group, 11 [69%] of 16 in the thermal ablation group, and 14 [88%] of 16 in the LLETZ group). Participants who were HIV-positive had lower treatment success than those who were HIV negative, irrespective of the treatment method (table 2). The proportions of successful treatment as reflected by VIA examination alone were similar across the groups (data not shown). The proportions of participants who had a normal VIA examination at follow-up were 162 (79%) of 204 in the cryotherapy group, 162 (84%) of 193 in the thermal ablation group, and 162 (80%) of 203 in the LLETZ group (p=0·47).

Almost all participants reported no or the least level of discomfort with their treatment, either immediately after or within 2 weeks of treatment, across all three groups (table 3). Few complained of moderate-to-severe pain immediately after the procedure and we found no statistically significant difference between the groups (table 3). When asked about the level of satisfaction with the service provided at the clinic and whether or not they would recommend the treatment to a friend, almost all women (99–100%) in each of the three groups reported that they would, both immediately and at 2 weeks after treatment. Five deaths occured (three in the cryotherapy group and one each in the thermal ablation and LLETZ groups, due to intimate partner violence, suicide, metastatic breast cancer, renal failure of unknown cause, and complications following a excision of a soft tissue tumour on the thigh); none of the deaths were related to treatment. None of the participants reported any complications requiring medical consultation or hospitalisation.

73 (31%) of 238 participants who underwent LLETZ and had histological evidence of CIN 2–3 (table 4). More than half of the VIA-positive participants (124 [52%] of 238) had some grade of CIN and none had invasive cancer. VIA-positive women aged 30–39 years had a higher proportion of CIN 2 or worse, compared with those aged 25–29 years and with those aged 40 years and older (table 4). In HIV-positive participants who were eligible for ablation, 55 (43%) of 128 had CIN 2–3, compared with 17 (16%) of 106 participants who were HIV negative. Of the HPV-positive (and VIA-positive) participants who had LLETZ, 64 (46%) of 138 had histologically proven CIN 2–3, compared with only nine (9%) of 100 who were HPV negative. Taking baseline combinations of high-risk HPV and HIV status, CIN 2–3 was detected in three (5%) of 66 participants who were negative for HPV and HIV, six (19%) of 32 participants who were HPV negative and HIV positive, 14 (35%) of 40 participants who were HPV positive and HIV negative, and 49 (51%) of 96 participants who were positive for HPV and HIV.

Discussion

To our knowledge, this study is the only report from a randomised study that assessed acceptability, safety, and performance of thermal ablation using a modern battery-driven portable machine. The most important finding of the preliminary report of our study is that thermal ablation appears to be acceptable to women and is associated with few side-effects. The early results of this

trial suggest similar performance between thermal ablation and cryotherapy in terms of treatment success; however, this pilot study was not powered for this outcome.

The shorter treatment time, less cumbersome equipment, and non-dependance on refrigerant gas are distinct advantages of thermal ablation over cryotherapy. The cost of the battery driven thermal ablation is similar to that of standard cryotherapy equipment and a huge cost saving is expected because of low operational costs, if cryotherapy is replaced by thermal ablation. Moreover, current battery-operated thermal ablators are small, lightweight, and highly portable. Avoiding cumbersome gas tanks is a practical advantage to health-care providers in LMICs.

Our results are particularly informative because of the high proportion of HIV-positive women in the study participants. The results suggest that thermal ablation using the Liger thermal ablator is safe in HIV-positive women. The preliminary results also suggest similar performance for the two ablative techniques in HIV-positive women, albeit substantially lower than that in HIV-negative women. Because the trial was implemented in routine health-care facilities in Zambia and treatment was provided by regular in-service nursing staff, the results could be generalisable to other LMIC settings.

Thermal ablation has been used extensively in Scotland since Semm first introduced the technique in Germany in the 1960s, and more recently in many other parts of the world. In Scotland, Duncan[16] has produced the largest and longest series of patients treated with thermal ablation (1453 patients followed up for >14 years) and the proportions of treatment success in his case series compare favourably with other treatment methods.[17] The effectiveness of thermal ablation has been assessed in several meta-analyses.[11,12] Randall and colleagues[12] report an overall treatment success from 16 included studies for CIN2 or worse lesions of 93·6% (95% CI 90·8–96·0). Treatment success was 92·9% (90·4–95·1) for CIN1 or worse and was 89·0% (84·0–95·0) for CIN 3. The only randomised controlled trial included in the analysis was done in Singapore.[18] In that study, the authors reported no difference in treatment success between cryotherapy and thermal ablation for any grades of CIN. The reported proportions of treatment success after thermal ablation in the Singapore study were 88·4% for CIN1, 84·2% for CIN2, and 78·6% for CIN3. Duan and colleagues[19] have also presented the results of a randomised controlled trial of thermal ablation versus cryotherapy in a study of 149 women eligible for ablative therapy. In this study, thermal ablation was equallyor more effective than cryotherapy was at 8 months, as judged by HPV and cytological assessment.

There are several limitations in our study. The numbers of participants reported are small and the efficacy estimates should be interpreted with caution. The study continues to recruit eligible women and will do so until a sufficient sample size has been reached for the full trial. According to our sample size calculation, an additional 1000 participants need to be recruited in each group to give sufficient power to detect non-inferiority of thermal ablation as a treatment method for VIA-positive women compared with cryotherapy or LLETZ. A second caveat is that follow-up assessment at 6 months is probably too early to assess treatment success, but we do not anticipate any difference arising between the study groups, which are well balanced because of randomisation. Another limitation of the study is the absence of histopathology verification either at baseline or at follow-up. Ablative techniques are likely to be used widely in screen-and-treat settings and we have followed the standard of care (ie, VIA) to detect abnormalities before or after treatment. VIA is not a perfect screening test, with low-to-moderate sensitivity and low specificity.[6]

	Cryotherapy group	Thermal ablation group	LLETZ group	Fisher's exact p value
Immediately after treatment				
Participants assessed	250	250	250	..
Intensity of pain or discomfort felt				
1 (no pain)	120 (48%)	115 (46%)	134 (54%)	0·40
2–3 (least pain)	123 (49%)	129 (52%)	111 (44%)	..
4–6	6 (2%)	3 (1%)	5 (2%)	..
7–9 (worst pain)	0	1 (<1%)	0	..
Unknown	1 (<1%)	2 (1%)	0	..
Level of satisfaction with the services				
1–3 (least satisfied)	0	0	0	0·27
4–6	3 (1%)	1 (<1%)	0	..
7–9 (highly satisfied)	246 (98%)	248 (99%)	250 (100%)	..
Unknown	1 (<1%)	1 (<1%)	0	..
Will recommend the screening procedure to others				
Yes	248 (99%)	250 (100%)	249 (100%)	0·34
No	0	0	1 (<1%)	..
Cannot say	2 (<1%)	0	0	..
2 weeks after treatment				
Participants assessed	241	242	237	..
Intensity of pain or discomfort felt				
1 (no pain)	214 (89%)	227 (94%)	208 (88%)	0·21
2–3 (least pain)	25 (10%)	15 (6%)	27 (11%)	..
4–6	1 (<1%)	0	2 (<1%)	..
7–9 (worst pain)	0	0	0	..
Level of satisfaction with the services				
1–3 (least satisfied)	0	0	0	0·55
4–6	1 (<1%)	0	0	..
7–9 (highly satisfied)	239 (99%)	242 (100%)	237 (100%)	..
Unknown	1 (<1%)	0	0	..
Will recommend the screening procedure to others				
Yes	239 (99%)	242 (100%)	237 (100%)	0·34
No	0	0	0	..
Cannot say	2 (<1%)	0	0	..

Data are n, or n (%). LLETZ=large loop excision of the transformation zone.

Table 3: **Intensity of pain and level of satisfaction reported immediately and 2 weeks after treatment**

	Participants with histology report	Histological diagnosis at baseline				
		Normal	CIN1	CIN2	CIN3	CIN2–3
Overall	238/250 (95%)	114/238 (48%)	51/238 (21%)	32/238 (13%)	41/238 (17%)	73/238 (31%)
Age, years						
25–29	81/84 (96%)	46/81 (57%)	20/81 (25%)	7/81 (9%)	8/81 (10%)	15/81 (19%)
30–39	105/111 (95%)	42/105 (40%)	18/105 (17%)	21/105 (20%)	24/105 (23%)	45/105 (43%)
≥40	52/55 (95%)	26/52 (50%)	13/52 (25%)	4/52 (8%)	9/52 (17%)	13/52 (25%)
HPV test results						
Negative	100/105 (95%)	66/100 (66%)	25/100 (25%)	5/100 (5%)	4/100 (4%)	9/100 (9%)
Positive	138/145 (95%)	48/138 (35%)	26/138 (19%)	27/138 (20%)	37/138 (27%)	64/138 (46%)
Baseline HIV status						
Negative	106/110 (96%)	60/106 (57%)	29/106 (27%)	7/106 (7%)	10/106 (9%)	17/106 (16%)
Positive	128/135 (95%)	51/128 (40%)	22/128 (17%)	25/128 (20%)	30/128 (23%)	55/128 (43%)
Baseline HPV and HIV status combinations						
HPV negative, HIV negative	66/70 (94%)	44/66 (67%)	19/66 (29%)	2/66 (3%)	1/66 (2%)	3/66 (5%)
HPV negative, HIV positive	32/33 (97%)	20/32 (63%)	6/32 (19%)	3/32 (9%)	3/32 (9%)	6/32 (19%)
HPV positive, HIV negative	40/40 (100%)	16/40 (40%)	10/40 (25%)	5/40 (13%)	9/40 (23%)	14/40 (35%)
HPV positive, HIV positive	96/102 (94%)	31/96 (32%)	16/96 (17%)	22/96 (23%)	27/96 (28%)	49/96 (51%)

Data are n/N (%). LLETZ=large loop excision of the transformation zone. CIN=cervical intraepithelial neoplasia. HPV=human papillomavirus.

Table 4: **Histology findings at baseline in the LLETZ group**

However, WHO recommend VIA for LMICs that cannot afford an HPV detection test for population screening. The National Cancer Control Strategic Plan (2016–21) by the Zambian Ministry of Health also stipulates the use of VIA as the screening test of choice, followed by immediate cryotherapy or thermal ablation in all VIA-positive women eligible for ablation.[20] We implemented a pragmatic study and followed the existing protocol for VIA screen and treat. In the VIA screen-and-treat programme, a negative VIA result alone is considered as the test of cure. To increase the validity of our study, in addition to VIA, we used the most frequently used and powerful test of cure, which is a validated high-risk HPV test. This approach allowed us to investigate the association between HPV and VIA status and also to have a more valid endpoint than VIA alone. The results of HPV testing were masked because of management decisions. The low proportions of treatment success, as defined by HPV status, might reflect the early follow-up at 6 months and the possibility of recurrent infection, especially considering the high prevalence of HIV in participants. The follow-up VIA might have missed some of the lesions in HPV-negative participants because of the low sensitivity of the test. However, similar success proportions observed between the ablative and excisional treatment groups using the stringent criteria of disease clearance gives us confidence in the findings.

The duration of treatment with thermal ablation is still an unresolved issue. Randall and colleagues'[12] meta-analysis found that the proportion of patients achieving a cure did not vary significantly according to the duration of treatment. The proportions who were successfully treated were 92·9% in patients who were treated for 20 s, 95·1% in those treated for 30 s, and 84·8% in those treated for 45 s. In Duncan's[16] case series, 20 s applications were used but with the important caveat that where the probe tip did not cover the entire transformation zone, overlapping applications were made.[16] The variables of probe tip size and the number of applications are, as yet, open questions. So far, in our study we used a duration of 45 s and multiple overlapping applications using a 20 mm probe. Our data and safety monitoring board has recommended that we reduce the treatment time to 30 s in the larger randomised controlled trial because the board members could not find evidence in the published literature for an advantage of a treatment duration of longer than 30 s.

Reassuringly, very low frequencies of discomfort during and after treatment were reported in all three study groups. The frequencies reported in the procedure room during and immediately after treatment were slightly lower in the thermal ablation group, which might be explained by the shorter treatment duration associated with thermal ablation when compared with cryotherapy (45 s *vs* 11 min). The low reporting of pain or cramps during LLETZ might be because local infiltration was routinely used for LLETZ but not for ablative treatment of either kind. Furthermore, similarly low discomfort was reported by participants after they had left the procedure room and by telephone 2 weeks after treatment.

All participants were advised to avoid penetrative sex for 6 weeks to reduce the risk of post-treatment bleeding and infection. Although an important concern for HIV-infected women, viral shedding does not increase after ablative treatment if women are already on antiretroviral

therapy.[21,22] All of our HIV-positive participants were on antiretroviral therapy at the time of VIA screening. Earlier studies have shown that 5–31% of women treated with cryotherapy did not comply with the advice for abstinence and the proportion of compliance increases with improved counseling.[23] Although we ensured appropriate counseling of each participant, some participants might have been non-compliant and therefore had bleeding or infection. However, we found that documenting the compliance proportion was difficult because of the cultural sensitivities around questions related to sexual practices.

One of the reasons that we included a third study group (excision by LLETZ) was to investgiate the histological diagnosis in VIA-positive women who were eligible for cryotherapy and thereby to better assess the test characteristics of visual inspection in its ability to discriminate between high-grade and low-grade or normal transformation zones. Thus, this approach allowed the analysis of the proportion of over-treatment specifically in the context of a screen-and-treat approach. Participants required a type 1 LLETZ, which has been shown to be safe in our study. Only 31% of women with a positive VIA and who were eligible for an ablative therapy had histologically proven high-grade CIN2 or worse. This positive predictive value (PPV) is higher for women in aged 30–39 years (43%) and for those who are HIV positive (43%). Much lower proportions (around 5%) have been reported from studies that were done in regions with a low prevalence of cervical cancer.[24] A meta-analysis of 26 cross-sectional studies by Sauvaget and colleagues observed that the average PPV of VIA to detect CIN2 or worse disease was 10%.[6] The PPV in our study population was higher because of the high prevalence of HIV infection. Most of the earlier studies used punch biopsy as the gold standard to define disease status. Our study provides a more valid estimate of PPV by including the entire transformation zone in histopathological assessment. Nevertheless, the low PPV and resulting over-treatment (nearly half of the women treated had no CIN) in a VIA screen-and-treat programme is concerning. This finding also underscores the need for a safe treatment method that causes minimal discomfort to patients. We were reassured to know that no invasive cancer was inadvertently treated at least in the LLETZ group.

WHO has recently updated its clinical guidelines for the treatment of cervical precancer[25] and now endorses the use of thermal ablation for ablative treatment. The low incidence of complications for either intervention reported by our study, especially in many HIV-positive women, formed part of the evidence for WHO to develop the new guidelines. A randomised controlled trial to compare thermal ablation with cryotherapy (using standard cryotherapy or cryopen) to treat histopathologically proved CIN2 or CIN3 is ongoing in Colombia, El Salvadore, and Peru (NCT03084081). If our early findings on the similar performance of the two ablative techniques are supported by our ongoing large trial and other studies, then health-care workers caring for screen-positive women in screen-and-treat programmes in LMICs could choose modern thermal ablation devices that are cordless, lightweight, and battery operated over cryotherapy instruments because of the practical disadvantages of cryotherapy. In view of the low incidence of histologically proven CIN2 or worse in VIA-screen positive women, the optimal screening test for LMICs should perhaps be reconsidered. We hope that less expensive HPV tests that do not require elaborate laboratory facilities will become available soon or alternative techniques—eg, artificial intelligence image recognition systems—will emerge.

Contributors

LFP implemented the study, oversaw data collection, analysed the data, drafted and revised the paper. GPP and PB designed the study protocols, oversaw the implementation of the study, analysed the data, and revised the draft manuscript. RM analysed and interpreted the data and revised the draft paper. EL, NN, CS, and MHM implemented the study and supported data collection, interpreted the data, and revised the draft paper. RS designed the protocol, interpreted the data, and revised the draft paper. WP designed the study, trained the study staff, interpreted the data, and prepared the draft paper.

Declaration of interests

WP has worked closely with Liger Medical to provide technical inputs in the design and development of the battery-operated thermal ablator during the past several years; he has not received any financial reward from the company. All other authors declare no competing interests.

Data sharing

External researchers can make written requests for sharing of data before publication or presentation. Requests will be assessed on a case-by-case basis in consultation with lead and co-investigators. A brief analysis plan and data request will be required and reviewed by the investigators for approval of data sharing. When requests are approved, data will be sent electronically in password protected files. All data sharing will abide by rules and policies defined by the sponsor; relevant institutional review boards; local, state, and federal laws and regulations. Data sharing mechanisms will ensure that the rights and privacy of individuals participating in research sponsored by the US National Institutes of Health will be protected at all times.

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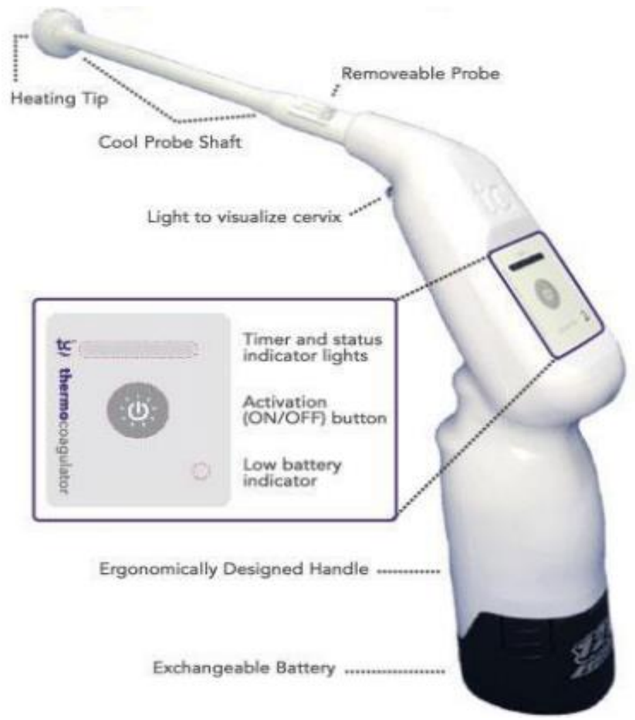
Comparison of key product attributes for thermal ablation devices

December, 2018

	WiSAP c3 cold coagulator	Cure Medical Thermocoagulator
Temperature	Fixed temperature setting (100 degrees C)	Fixed temperature setting (100 degrees C, default)[1]
Heating	Heating can be turned on and off	Heating can be turned on and off
Timer	Timer (visual and acoustic feedback) with manual on/off	Timer (visual and acoustic feedback) with automated on/off
Treatment process	Heat up and cool down of device happens before/after inserting into patient	Heat up (8 seconds) and cool down (10 seconds) happens while device is inside the patient
Set treatment time at 100C[3]	40 seconds	40 seconds (default but can be adjusted by manufacturer upon request)[2]
Power	Standard power grid or external rechargeable portable battery pack	Two internal rechargeable batteries (12VDC)
Battery ability	Battery lasts for 140 treatments on one charge[4]	Battery lasts for 50 (30-60) treatments on one charge (2 batteries provided)
Portability	Designed to be lightweight and portable (compared to gas cryotherapy with gas cylinder)[5]	Designed to be lightweight and portable (compared to gas cryotherapy with gas cylinder)
Cord	Has a cord (to wall socket or external battery pack)	Cordless
Safety	Probe shaft does not conduct heat; heat protection slider over tip to protect vagina	Probe shaft does not deliver heat but contact should be avoided
Light	One LED light on top of probe	Two LED lights under probe
Disinfection	Probe and sheath cleaned then disinfected with high-level disinfectant (HLD, no autoclave)	Probe cleaned then disinfected with HLD or sterilized in autoclave
Probes	Two sizes (17mm flat, 20mm flat)	Three sizes (16mm flat, 19mm nipple, 19mm flat)
Base cost[6]	~$1,600 (includes 1 handle, 2 probes, 2 sliders, connection to power grid, table stand, case)	$1,500 (includes 1 handle, 3 probes, 2 batteries, charging base, case)
Spare parts and accessories cost	~$150 for battery pack and cable	$100 per additional probe; $30 for additional charging base
Regulatory	CE Mark	U.S. FDA 510(k); CE Mark
Warranty[6]	One year	Two years
Photo		

[1]Can be set by user or adjusted by manufacturer per user's request (80, 90, 100 or 120 degrees C).
[2]Can be set by user or adjusted by manufacturer per user's request (20, 30, 40 or 60 seconds).
[3]Treatment time may eventually depend on WHO normative/clinical guidelines.
[4]Battery has been tested for 180-200 treatments per charge.
[5]Portability requires purchase of a battery (see spare parts and accessories cost).
[6]Cost is for a single device and included accessories/parts at retail. Excludes shipping, taxes, and other fees.

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Treating Precancerous Lesions with Thermocoagulation

Thermal ablation received endorsement by the **World Health Organization** for treatment of CIN 2/3

An immediate point-of-care treatment for precancerous lesions

ThermoGlide offers the physician an immediate precancer treatment option within a single sitting.

This lightweight, portable, and battery-run device does not require complex training. It could be used by non-OB/GYN physicians and providers that are not trained to perform LEEP, increasing the availability of cervical precancer treatment.

ThermoGlide allows the clinician to treat lesions that appear during a cervical examination, safely and effectively, with minimal side effects. The procedure does not require general anesthetic and the majority of women report mild or moderate discomfort.

How does it work?

The ThermoGlide uses heat to decimate tissue. The probe is heated quickly within 8 seconds and remains at 100°C allowing for rapid cervical ablation. The superficial epithelium withers and dissipates after the treatment, while the stroma and glandular crypts are destroyed.

Minimal pain and downtime

Does not require general anesthetic. The majority of women report mild or moderate discomfort.

Safe and effective

Safe, quick, and acceptable as an outpatient procedure(1).

Short treatment time

Thermo-coagualation offers shorter treatment time as compared to cryotherapy(2)

Easy to use

Quick learning curve, simple handling and assembly . Could be used by non-OB/GYN physicians and providers.

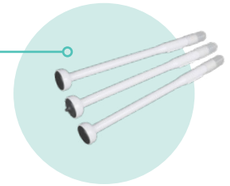
(1) https://pubmed.ncbi.nlm.nih.gov/24597779/#:~:text=Main%20results%3A%20Among%204569%20CIN,and%20fertility%20was%20not%20impaired.
(2) Thermal ablation versus cryotherapy or loop excision to treat women positive for cervical precancer on visual inspection with acetic acid test: pilot phase of a randomised controlled trial Leeya F Pinder, Groesbeck P Parham, Partha Basu, Richard Muwonge, Eric Lucas, Namakau Nyambe,Catherine Sauvaget, Mulindi H Mwanahamuntu, Rengaswamy Sankaranarayanan, Walter Prendiville. Lancet Oncol 2020 Jan;21(1):175-184.

ThermoGlide

A complete thermo coagulation solution for the treatment of precancerous cervical lesions

Heated Probe Tip

Specifically designed for the treatment of cervical anomalies



Safety timer

The unit checks the functionality of each probe during heat-up mode. Embedded timer for patient safety

Rechargeable battery

Rechargeable battery, with no need for electricity

Ergonomically designed handle

Light weight and portable. Ergonomically designed handle for accurate and optimal use.

The ThermoGlide has been validated in multiple clinical studies where physicians found it to be reliable and clinically effective

> I just used the ThermoGlide for CIN2-3, I only had to do one cycle, it was great, so smooth. My patient asked me to thank you for making the device so much better than cryo

Dr. Heather Jackson, Family Practice, Salt Lake City, Utah, USA.

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mobileODT offers a full turnkey diagnostic and treatment program utilizing the EVAPro digital colposcope and the ThermoGlide for thermo coagulation treatment of precancerous lesions. The single sitting screen and treat program allows us overcome the major challenge of loss to follow-up.

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Systematic review

Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review

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Background Cold coagulation is an ablative method for treatment of cervical intraepithelial neoplasia (CIN). Despite reports of efficacy against all grades of CIN (CIN1-3), cold coagulation has been infrequently used since the 1980s, and was absent from the recent Cochrane review on CIN treatment.

Objectives To provide a systematic review of cold coagulation efficacy and acceptability for CIN treatment through meta-analysis of clinical reports and a randomised control trial.

Search strategy A literature search in PubMed, Web of Science, EMBASE, and regional databases yielded 388 papers. Title, abstract and/or reference list review identified 22 papers describing cold coagulation treatment of CIN, with 13 providing adequate data for inclusion in the meta-analysis.

Selection criteria Publications or conference abstracts describing original data (number of women treated, followed up and cured, provider type, cure definition) were retained. No language or publication date limitations were imposed.

Data collection and analysis Data extracted from 13 studies were pooled, and statistical analyses of proportion cured were conducted with data stratified by lesion grade and study region.

Main results Among 4569 CIN patients treated with cold coagulation, summary proportion cured of 96% [95% confidence interval (CI) 92–99%] and 95% (92–98%) were obtained for CIN1 and CIN2-3 disease, respectively. Side-effects and adverse effects were infrequent, and fertility was not impaired.

Conclusions Cold coagulation CIN cure rates were comparable to those of other excisional and ablative methods. Cold coagulation is indicated for all grades of CIN, is safe, quick and acceptable, and may be of particular relevance for use in resource-limited settings.

Keywords Acceptability, cervical intraepithelial neoplasia, cold coagulation, efficacy, pooled analysis.

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Introduction

Several excisional and ablative methods exist for treatment of cervical intraepithelial neoplasia (CIN). Cold knife conisation, large-loop excision of the transformation zone (LLETZ), and laser conisation are effective excisional options indicated for CIN3 disease, but require highly trained personnel and expensive infrastructure, and may impair fertility.[1] As such, more conservative ablative methods may be preferable in resource-limited settings, or in younger patients of child-bearing age. Ablative methods, including cold coagulation, cryotherapy, laser ablation, and electrocoagulation diathermy,[1–6] are generally indicated for CIN1-2 treatment, and can be performed on an out-patient basis.

Our group recently published a meta-analysis on the efficacy of cryotherapy as an ablative procedure of relevance in resource-limited settings. Cryotherapy ablates cervical tissues by freezing with compressed refrigerant gas. This method demonstrates high cure rates across world regions (94% for CIN1, 92% for CIN2, and 85% for CIN3), and can be effectively performed by mid-level providers.[7] However, cryotherapy poses challenges in certain regions, given the limited availability of refrigerant gas.[8] In these contexts, cold coagulation may constitute a more feasible treatment option for CIN.

The Semm cold coagulator – developed by Kurt Semm in 1966[9] – has been used worldwide, but most notably in the UK in the 1980s.[4,10] This method utilises electricity to heat a thermosound to temperatures of 100–120°C, allowing for ablation of cervical lesions by 'boiling'.[1,3,11] Cold coagulation is indicated for non-pregnant women of any age with CIN1-3 when the entire transformation zone is visible, when there is no suspicion of endocervical involvement or of micro-invasive, invasive, or glandular disease, and when the transformation zone has not previously been treated.[1,3–5,11–13] The procedure is fast (20–45 seconds per application) and achieves a treatment depth of 4–7 mm.[14] Anaesthesia can be avoided in most patients, and complications and adverse effects are minimal.[3,4,15–19] Of particular relevance for resource-limited or field settings, the instrument is small, self-sterilises by heating, has minimal infrastructural requirements, and can be used by mid-level providers.[3,18]

Cold coagulation is infrequently used at present,[12,20] and is often substituted by excisional methods, which have the added advantage of allowing for a histology exam. This method was also absent from the recent Cochrane review on CIN surgical techniques.[5] The aim of the current systematic review was to provide a comprehensive literature search and meta-analysis of randomised control trials and clinical reports, in order to report on the summary efficacy and acceptability of cold coagulation for CIN treatment.

Methods

Literature search strategy and inclusion criteria

With assistance from a medical librarian, an electronic literature search was performed through PubMed, Web of Science, EMBASE, and regional databases. Given the diversity in terminology used to describe cold coagulation in the literature, our search employed a broad range of keywords. A preliminary search in PubMed using the keywords 'Cervical Intraepithelial Neoplasia' [MeSH] OR 'Cervical Intraepithelial Neoplasia' (tiab) OR CIN (tiab) AND 'cold coagulation' (tiab) OR 'thermosurgery' (tiab) yielded only 18 papers, so a more comprehensive search was attempted by adding 'electrocautery' (tiab), 'Semm' (tiab), 'electrocoagulation' (tiab), 'electrocoagulation' (MeSH), and 'ablative' (tiab) to the search terms. This second attempt yielded 245 papers in PubMed. In Web of Science, keywords were 'Cervical Intraepithelial Neoplasia' OR CIN AND 'cold coagulation' OR 'thermosurgery', yielding 17 papers. In EMBASE, keywords were: 'Cervical Intraepithelial Neoplasia' or CIN AND 'cold coagulation' or 'thermosurgery', yielding 125 papers. To include research from resource-limited regions, regional databases were also queried for 'Cervical Intraepithelial Neoplasia' and 'cold coagulation', including the African Index Medicus (AIM), Caribbean Health Sciences Literature (MedCarib), Index Medicus for South-East Asia Region (IMSEAR), Index Medicus for Eastern Mediterranean Region (IMEMR), Indian Medlars National Informatics Centre (IndMed), and Latin American and Caribbean Center on Health Sciences Information (LILACS) databases. Only one paper was retrieved from a regional database (IMSEAR) with these search terms. This search strategy retrieved 388 papers in total (Figure 1).

The title and/or abstract of each article was reviewed, and peer-reviewed publications or conference abstracts with original qualitative or quantitative data were retained. Reviews of previously published data, and studies in which cold coagulation treatment was provided in combination with another method, were excluded from the analysis. No language or publication date limitations were imposed. Finally, reference lists of eligible publications were reviewed to ascertain additional relevant papers. The breakdown of papers retrieved and included through our search strategy

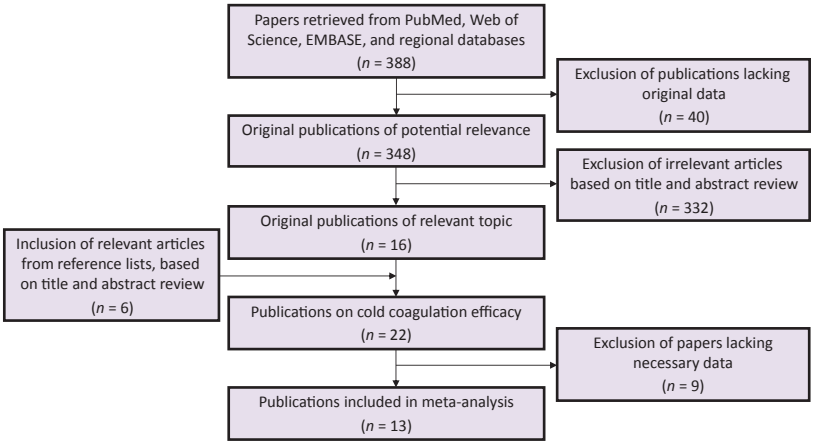

Figure 1. Flowchart summarising inclusion and exclusion criteria used in literature search strategy.

is shown in Figure 1. Overall, 22 studies on cold coagulation treatment of CIN were identified, with 13 being eligible for inclusion in the meta-analysis. Studies were excluded when the follow-up information was missing and consequently the cure could not be verified; studies with a treatment outcome other than CIN or cold coagulation used in combination with another treatment were also excluded.

Data extraction

Data from each study were extracted into a Microsoft EXCEL spread sheet, corresponding to the following categories: year of publication; world region; study period; study setting; study design; patient age (range and/or mean); case definition; biopsy confirmation; endocervical involvement of lesion; performer; treatment procedure (e.g. temperature, duration, and number of applications); duration of follow up; type of examination at follow up; number of patients treated; patients lost to follow up; patients with persistent or recurrent disease at follow up; definitions of cure and treatment failure (successful treatment was defined as a negative cytology at the follow-up visit, from at least 4–6 months following treatment); and information on complications (safety) or adverse effects (acceptability). Some authors were also contacted when relevant information was missing in studies published within the last 2 years. All extracted data were independently verified by two researchers (LD; CS).

Assessment of study quality

The 13 studies eligible for inclusion in the meta-analysis were assessed for quality of study design and data reporting, using a modified 27-item quality assessment checklist created by Downs and Black (Table S1).[21] Each article was assigned points in the areas of quality of reporting, external validity, internal validity (bias and confounding), and study power (based on sample size), to a maximum score of 28. Study power was estimated according to the sample size of patients followed up; according to quintiles, studies were scored as follows: 0 (≤40 women followed up); 1 (41–62 women followed up); 2 (63–71 women followed up); 3 (72–116 women followed up); 4 (117–924 women followed up); and 5 (>925 women followed up). Based on tertiles, studies receiving a score of <9 were classified as 'poor', 9–19 as 'moderate', and >19 as 'high' quality. A moderate or high quality score was required for inclusion in the meta-analysis.

Statistical analysis

A random effects model using the method of DerSimonian and Laird was used for all the meta-analyses carried out, with the estimate of heterogeneity being taken from the Mantel–Haenszel model. Meta-analyses were conducted on coded data stratified by lesion grade (CIN1-3) and by region of study (North America, Europe or Asia). As few papers provided data on CIN3 disease specifically, we analysed the efficacy of cold coagulation in the treatment of CIN1 and CIN2-3 lesions. CIN2-3 disease cure rates were also assessed by duration of follow up and by treatment provider. Data were graphically displayed in Forest plots, which display point estimates of cure rate within squares of variable size (representative of the weights given to the studies based on the precision of the effect size), with 95% confidence intervals (CI). I^2 statistic values were calculated to quantify degree of heterogeneity among studies, where values of 25–50% represented moderate heterogeneity and values of >50% large heterogeneity among studies.[22] The influence of each study on the overall estimate of the CIN2 or worse disease outcome was assessed. Publication bias was assessed using the Egger's test at the 1% level of significance. All analyses were conducted using STATA version 12.1 (StataCorp, College Station, TX, USA), with the 'metan', 'metareg' and 'metainf' software commands.

Results

Of 388 papers reviewed, 22 papers on treatment of CIN by cold coagulation were identified, with 13 being eligible for inclusion in the meta-analysis (Table 1). These 13 studies represented work conducted primarily in Europe, as well as a single study from North America and two from Asia. No studies from South America or Africa were identified. In total, the 13 papers described the efficacy of cold coagulation as observed among 4569 women with CIN1-3.[4,15–19,23–29] The remaining nine studies were not included in the meta-analyses for the following reasons: cold coagulation was provided in combination with another treatment method ($n = 2$); treatment was for non-CIN cervical anomalies ($n = 1$); data corresponded to safety/acceptability rather than efficacy ($n = 2$); and insufficient data were provided for calculation of cure rates ($n = 4$).[13,20,30–36]

All 13 included studies were scored as having 'moderate' ($n = 9$) or 'high' ($n = 4$) methodological quality (Appendix Table 1). Quality scores ranged from 9 to 21, with lowest scores arising in the categories of sample size (women followed up ranged from 30 to 1453), and internal validity. Poor internal validity scores were most often due to a lack of adequate description of patients lost to follow up. Studies additionally often lacked patient characteristics (such as age), and identification of cold coagulation provider. However, details of patient inclusion criteria and treatment methodology (e.g. temperature, application duration, and number of applications) were consistently reported.

Details of the 13 included studies are given in Table 1. Ten studies (77%) reflected work conducted in Europe, with seven (54%) coming from the UK specifically.

Table 1. Summary of studies on cold coagulation treatment of cervical intraepithelial neoplasia.

Author, Year	Country	Study year	Setting	Study design	Age of recipient	Case definition	Case confirmed by biopsy	Endocervix involvement	HIV	Performer	Treatment at 1st visit (screen-and-treat)	Duration of follow up	Number of women treated	Number (%) of women followed up	Cure definition
Studies included in the meta-analysis															
Cassidy (1987)	UK (Scotland)	1979–86	IIIry H	Clinical report	–	CIN1-2-3	–	–	–	Gynaecologist	–	–	924	924 (100%)	Response to treatment
de Cristofaro (1990)	Italy	1985–?	IIIry H	Clinical report	–	CIN1-2-3	Yes	No	–	Gynaecologist	–	6–12 months	212	116 (55%)	Absence of CIN at follow-up cytology
Goodman (1991	UK (England)	1987–88	IIIry H	Clinical report	Mean 27	HPV+ or CIN1-2-3	Yes	Yes and no	–	Gynaecologist	–	4 months (83%)	78	62 (79%)	Absence of dyskaryosis at follow-up cytology
Gordon (1991)	UK (Scotland)	1975–89	IIIry H	Clinical report	15 to >50	CIN3	Yes	No	–	Colposcopist	Yes	4 months (98%) to 10 years (87%)	1628	1453 (89%)	Normal cytology at follow up
Grubišić (2010)	Croatia	1999–2000	IIIry H	Clinical report	Mean 30	CIN1-2	Yes	No	–	Gynaecologist	–	–	30	30 (100%)	Normal cytology at follow up
Hussein (1985)	UK (Scotland)	1982–83	IIIry H	Clinical report	–	CIN1-2-3	Yes	No	–	Colposcopist	–	4 months to 2 years	65	65 (100%)	Normal cytology and colposcopy at follow up 4 months after treatment
Javaheri (1981)	USA	1974–79	IIIry H	Clinical report	15 to >50	CIN1-2	Yes	No	–	Physician	–	1–5 years (>50% followed up for 3 years)	43	40 (93%)	Absence of CIN within 1st year follow up (persistence) and after 1st year follow up (recurrence)
Joshi (2013)	India	2010–2011	Iry H	Clinical report	21–60	CIN1-2-3	Yes	No	Yes	Physician	Yes	6–12 months	83	45 (54%)	No evidence of CIN2 or worse at follow up
Loobuyck (1993)	UK (Scotland)	1978–90	IIIry H	Clinical report	–	CIN1-2	Yes	No	–	Colposcopist	Yes	6 months to 11 years (>80% followed up for 3 years)	1165	1104 (95%)	Normal cytology at follow up
Rogstad (1992)	UK (England)	1988–89	IIIry H	Clinical report	–	CIN1-2	Yes	No	–	Physician	–	12–18 months	59	35 (59%)	No persistence or progression of CIN at follow up

Table 1. (Continued)

Author, Year	Country	Study year	Setting	Study design	Age of recipient	Case definition	Case confirmed by biopsy	Endocervix involvement	HIV	Performer	Treatment at 1st visit (screen-and-treat)	Duration of follow up	Number of women treated	Number (%) of women followed up	Cure definition
Singh (1988)	Singapore	1983–88	IIIry H	RCT	Mean 35 (20–53)	CIN1-2-3	Yes	No	–	Colposcopist	–	3 months to 4 years (88% followed up for >1 year)	89	89 (100%)	No evidence of CIN at follow up
Staland (1978)	Sweden	1971–?	IIIry H	Clinical report	–	CIN2-3	No	–	–	Gynaecologist	–	3–4 years (80% followed up for >2 years	71	71 (100%)	Normal colposcopic view
Williams (1993)	UK (England)	1988–89	IIIry H	Clinical report	Mean 25 (16–46)	CIN2-3	Yes	No	–	Physician	–	18 months (78%)	125	125 (100%)	Absence of abnormality at follow-up cytology and colposcopy
Studies excluded due to lack of necessary data															
Allam (2005)	UK (Scotland)	1992–2000	IIIry H	CC combined with another procedure	Mean 33	CIN1-2-3	Yes	No	–	Colposcopist	Yes (in some)	12 months	666	541 (81%)	No persistent CIN in cytology & colposcopy
Duncan (2005)	UK (Scotland)	–	IIIry H	Safety and acceptability RCT	Mean 32	CIN1-2-3	Yes	No	–	Colposcopist	Yes	–	93	–	–
Farquharson (1987)	UK (Scotland)	–	IIIry H	Safety and acceptability clinical report	–	CIN2-3	–	–	–	Colposcopist	No	6 months	714 (laser or CC)	–	–
Fergusson (1974)	UK (England)	–	IIIry H	Cryosurgery or CC clinical report	–	Benign cervical erosion	No	–	–	–	–	2–4 months	24	23 (96%)	No residual erosion
Hughes (1992)	UK (Scotland)	–	IIIry H	CC or laser (combined data given)	–	CIN2-3	Yes	No	–	Colposcopist	–	9 months to 2.5 years	856 (laser or CC)	856 (laser or CC) (100%)	Absence of CIN based on cytology, colposcopy, and biopsy

Table 1. (Continued)

Author, Year	Country	Study year	Setting	Study design	Age of recipient	Case definition	Case confirmed by biopsy	Endocervix involvement	HIV	Performer	Treatment at 1st visit (screen-and-treat)	Duration of follow up	Number of women treated	Number (%) of women followed up	Cure definition
Lee (2009)	Korea	1994–2005	IIIry H	CC combined with another procedure	Median 39 (27–67)	CIN1-2-3	Yes	No	–	–	–	Median 81 months (13–127 months)	70	70 (100%)	Absence of recurrent disease above CIN1
Semple (1999)	UK (England)	1996–97	19 IIIry Hs	Assessing screening and treatment across multiple centers	–	Dyskaryosis or CIN1-2-3	Yes	–	–	Colposcopist or Gynaecologist	Yes (in 41%)	1 year	268	–	Normal cytology and/or colposcopy at follow up
Smart (1987)	UK (Scotland)	1983–?	IIIry H	Comparing laser with CC	–	CIN2-3	Yes	No	–	Colposcopist	–	2 years	1169 (laser or CC)	–	Normal cytology, colposcopy, or biopsy
Zawislak (2003)	N. Ireland	1980–94	IIIry H	Clinical report	Mean 28 (17–52)	CIN 1-2-3	Yes	No	–	Colposcopist	Yes	3 months to 12 years	725	619 (85%)	Absence of persistent or recurrent abnormalities

RCT, randomised control trial; HPV, human papillomavirus; CIN, cervical intra-epithelial neoplasia; IIIry H, tertiary hospital; Iry H, primary hospital; CC, cold coagulation; –, missing data (information not reported or available). ?, unknown.

Reflecting its era of greatest popularity, 11 (85%) studies assessed patients treated with cold coagulation in the 1970s and 1980s. Only one (8%) was a randomised control trial; the remaining studies were prospective or retrospective clinical reports. Eleven (85%) studies reported that CIN disease was confirmed with biopsy, and 10 (77%) reported that cases with endocervical involvement were excluded. Three studies provided immediate cold coagulation treatment as part of a screen-and-treat programme. Duration of follow up ranged from a minimum of 4 months to a maximum of 11 years, and follow up was most often by cytology with colposcopic assessment. Cure was defined as absence of dyskaryosis or CIN at follow up, based on cytology, colposcopy and/or biopsy. Treatment failure was indicated by persistent or recurrent dyskaryosis or CIN at follow up. Treatment recipients were similar across studies, most commonly comprising patients referred for abnormal smears and treated at a tertiary referral hospital, with the exception of the study by Joshi and colleagues,[16] which assessed treatment among HIV-positive women seen at a primary care centre in India.

Summary estimates of cold coagulation cure rates obtained from the 13 studies are shown for CIN1 (Figure 2), and CIN2-3 (Figure 3), stratified by world region. Proportion cured of 96.0% (95%CI 92–99%; 593 women cured/620 women treated with a follow-up visit) and 95.0% (95%CI 92–98%; 1019/1070) were achieved for CIN1 and CIN2-3 disease, respectively. The overall efficacy of cold coagulation against all grades of CIN (CIN1-3) was 94.0% (95%CI 91–96%; 3912/4159) (data not shown). I^2 statistics ranged from 41.3% (CIN1) to 84.2% (CIN2-3), suggesting a high degree of heterogeneity among studies on high-grade disease in particular. None of the studies included in the final analysis had a significant influence on the overall estimate of the CIN2 or worse disease outcome. Egger's test showed that there was no publication bias (P-value = 0.715). Proportion-cured estimates for CIN2-3 disease were additionally stratified by duration of patient follow up and by treatment provider (Table 2); estimates were similar for follow-up periods of ≤2 years and of >2 years, and when treatment was provided by colposcopists, physicians or gynaecologists.

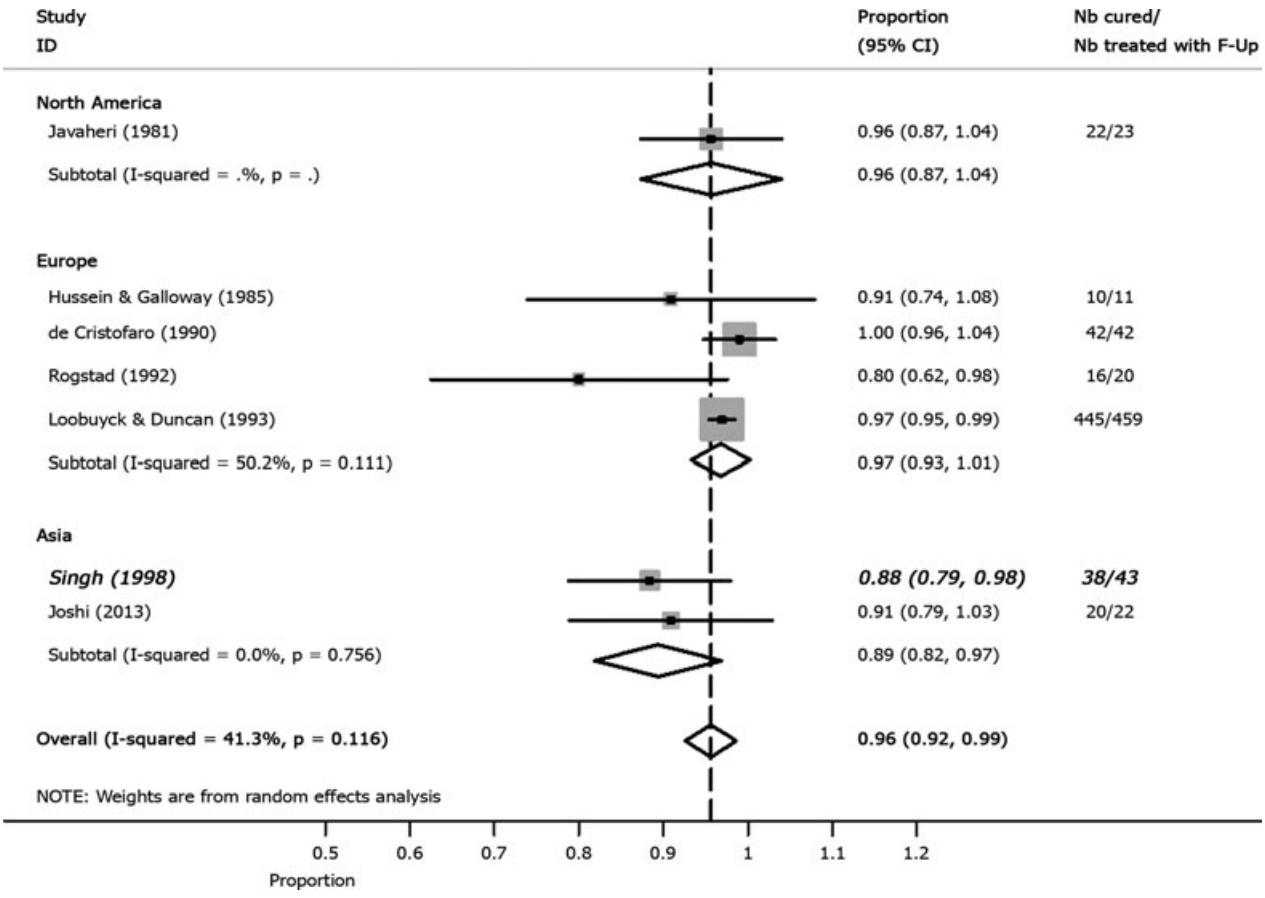

Figure 2. Proportion-cured estimates associated with cold coagulation treatment for CIN1 disease, by world region.

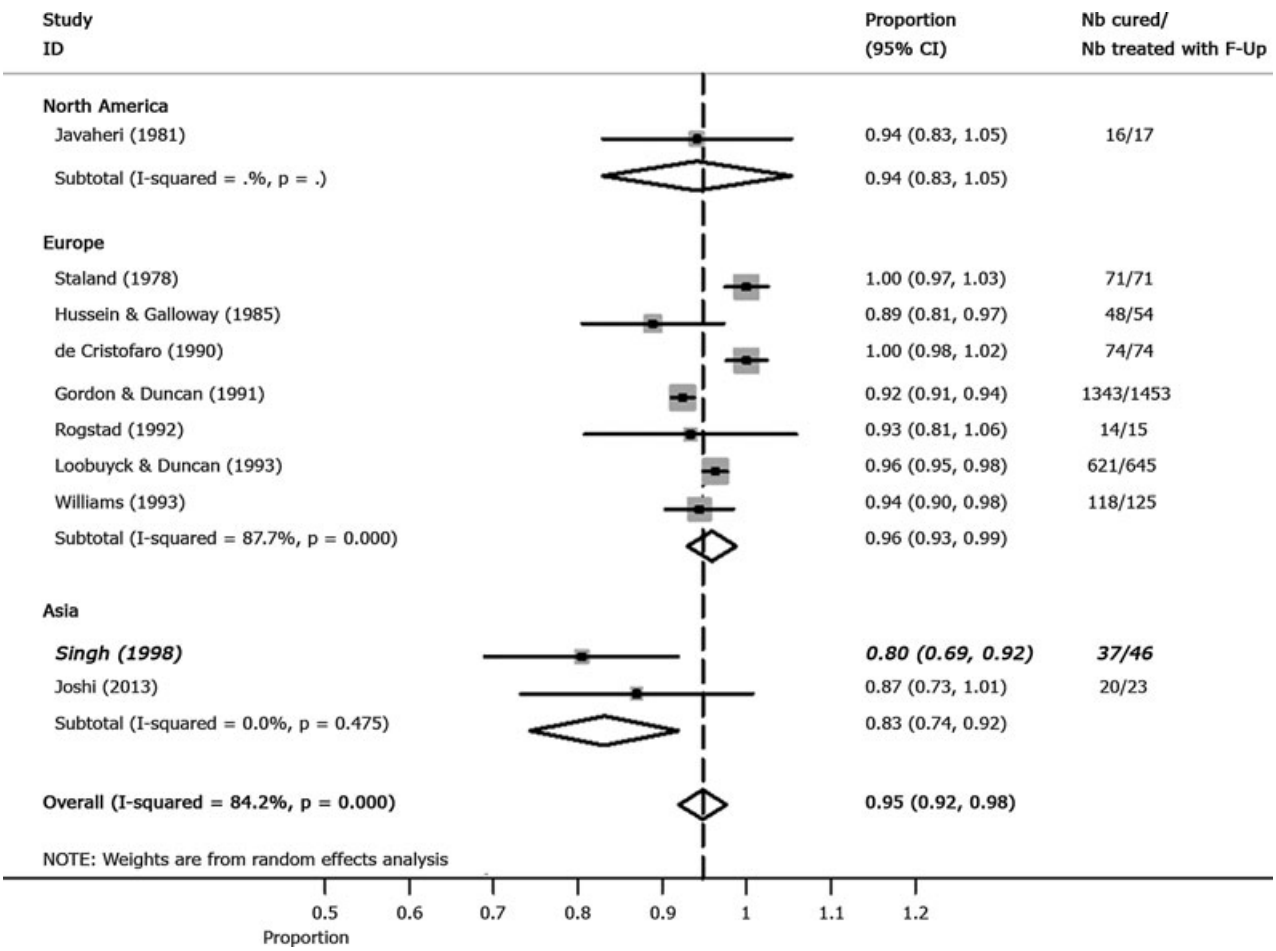

Figure 3. Proportion-cured estimates associated with cold coagulation treatment for CIN2-3 disease, by world region.

Table 2. CIN2-3 proportion cured according to potential determinants

Predictor	No. of studies that included the predictor	Proportion cured (%)	95% confidence interval	I^2 statistic	*P*-value
Duration of follow-up					
≤2 years	5	94	89–99	69.3	0.011
>2 years	5	95	91–98	89.4	<0.001
Overall	10	95	92–98	84.2	<0.001
Provider					
Colposcopist	4	92	89–96	85.9	<0.001
Gynaecologist	2	100	98–102	0.0	1.000
Physician	4	94	90–97	0.0	0.791
Overall	10	95	92–98	84.2	<0.001

Side-effects (representative of life-threatening events) and adverse effects (representative of acceptability) were infrequently reported across the 13 studies, being mentioned in only eight papers (61.5%). Among these eight studies, five reported an absence of side-effects during treatment, and two reported an absence of post-treatment adverse effects. In the remaining papers, side-effects during treatment included mild cramping in up to 25.0%,[15,16] moderate pain

in 10.5%,[24] severe pain in 3.5%,[24] mild bleeding in <1.0%,[16] and fainting attacks in <1.0%.[16] After treatment, adverse effects included watery or foul-smelling vaginal discharge in <2.5%,[16,17,25] pain after treatment in <1.0–5.0%,[16,25] cervical stenosis requiring dilation in <1.0%,[17,23] vaginal bleeding in 1.5%,[17] and local cervical infection in 1.1%.[18] Pain during treatment did not appear to limit practice, as only two studies routinely provided local anaesthesia to all treated patients, either by injection[25] or by spray.[27] In six studies, no analgesia was provided for all or the majority of patients undergoing cold coagulation.[4,15–19]

There were no demonstrable adverse effects on fertility and delivery in pregnancies conceived after cold coagulation, according to long-term follow-up studies. For instance, among 226 pregnancies conceived after CIN3 treatment in one cohort, no increases in miscarriage rates or preterm deliveries were observed: nine had a first trimester miscarriage, three had ectopic pregnancies, and three had preterm deliveries, with the remainder proceeding to term.[4] Among six patients analysed by Williams and colleagues after CIN2-3 treatment, all had normal pregnancies with vaginal deliveries at term.[19] Cassidy and colleagues analysed nine pregnancies conceived after CIN1-3 treatment, and reported that all proceeded to term (beyond 35 weeks) with normal fetal outcomes.[23] Treatment during pregnancy is not advised,[3,13,31] but the procedure can be performed on women with an intrauterine device (IUD) in place, as the operating temperature does not damage the threads.[17]

Discussion

Main findings

Of 22 studies on cold coagulation treatment, 13 studies described its efficacy in 4569 women with CIN1-3. These studies primarily described European patients, most of whom received treatment at tertiary hospitals from colposcopists, physicians or gynaecologists. Summary proportion-cured estimates of 96.0 and 95.0% were reported for CIN1 and CIN2-3, respectively, and no influence of treatment provider or duration of follow up on estimates was observed. The 13 studies displayed heterogeneity in terms of study quality, sample size, duration of follow up, and definition of cure.

Strengths and weaknesses

Cure rate estimates from this meta-analysis are, to our knowledge, derived from all applicable existing studies on cold coagulation efficacy. However, estimates are subject to limitations. Research on cold coagulation efficacy is scarce, and the literature search is hindered by the diversity of terminologies used to refer to cold coagulation, including moderate heat thermosurgery,[29] low heat electrocautery,[27,33] and electrocoagulation.[26] Only a single study was available on treatment in a primary care centre of a low-income country,[16] and as this cohort comprised HIV-positive women, resulting cure rates may underestimate what is achievable in non-immunocompromised women in similar settings. Additionally, several factors were difficult to account for in analysis. Loss of patients to follow up was frequent across studies, and this could have variable impacts on reported cure rates: failure to return due to remission of symptoms could contribute to underestimation of cure rate, and failure to return due to low socio-economic status could contribute to overestimation of cure, as such patients are at higher risk of treatment failure.[7]

Interpretation

The current meta-analysis suggests that cold coagulation cure rates are comparable with those of other excisional and ablative methods.[5] Among excisional methods, cure rates of CINs confirmed by biopsy range from 90–94% with knife cone biopsy, 91–98% with LLETZ, and 93–96% with laser conisation.[5] Among ablative techniques on CIN1 and worse lesions confirmed by biopsy, cryotherapy cure rates reached 85–94%,[7] and laser ablation achieved cure rates of 95–96%.[5] As mentioned in the Cochrane review, this evidence suggests that there is no one superior method of CIN treatment,[5] and our meta-analysis shows that cold coagulation is on a par with these techniques.

Of interest for resource-limited settings, seven of the 22 retrieved studies provided cold coagulation treatment through a 'screen-and-treat' strategy. Screen-and-treat programmes provide visual assessment of cervical anomalies or rapid HPV-DNA testing, followed by immediate treatment at the same visit. In cryotherapy studies, this strategy has been shown to increase treatment adherence rates, particularly in settings where patients are less likely to return for a second appointment.[37] Among three studies, cure rates were 92–97% for CIN1-3 in Europe,[4,17] and exceeded 85% for CIN1-3 cases among HIV-positive women treated in India.[16] As such, cold coagulation may be an effective therapeutic option in screen-and-treat programmes, particularly in low socio-economic settings where patients are less likely to return for treatment. Cold coagulation may also be preferable to cryotherapy in these settings, as the most economical cryotherapy gas tanks are large and heavy (10–15 kg), difficult to move, and require refilling.[8]

Nine studies on cold coagulation treatment of CIN were excluded from meta-analyses (Table 1). Two of these studies assessed cold coagulation when used in combination with another procedure. Among 666 CIN1-3 cases treated with LLETZ in combination with cold coagulation, 0.6% of high-grade and no low-grade patients had abnormal cytology at 1 year post-treatment. The authors suggested that such a combined approach might be of benefit in

environments in which follow-up compliance is low.[30] In the second study, 85 patients with CIN1-3 or microinvasive cancer (stage IA1) were treated with electrosurgical conisation and cold coagulation.[35] Cold coagulation was used to achieve haemostasis and to destroy residual lesions at resection margins. Over a median follow-up period of 81 months, 1.2% displayed recurrent disease. Hughes and colleagues assessed persistence in 856 CIN2-3 patients treated by either CO_2 laser, or cold coagulation.[34] A total of 130 patients (15%) presented with persistent CIN over 9–30 months' follow up. Although data were not segregated by treatment method, the authors commented that 'no demonstrable difference' was observed in detection of persistent CIN between laser and cold coagulation patients. Finally, Smart and colleagues randomised 1169 CIN2-3 patients to laser or cold coagulation treatment.[13] In their preliminary data on 589 patients followed for at least 12 months, the treatment failure rates for cold coagulation and laser were not significantly different (10 and 11.5%, respectively).

Cold coagulation also constitutes a safe and acceptable procedure, as side-effects among analysed studies were infrequent and of low or moderate severity. Farquharson and colleagues randomised 714 CIN2-3 patients to treatment with either cold coagulation or CO_2 laser, and observed statistically significant differences between procedures: patients treated with cold coagulation reported lower pain scores, and only 8% requested local analgesia during treatment, relative to 21% in the laser treatment group.[32] After treatment, a significantly lower proportion of cold coagulation patients experienced bleeding, and significantly fewer required hospital attention for bleeding events. Patients in both arms of the study had pain after treatment (in 30%), and vaginal discharge lasting longer than 1 week (in 35%). Smart and colleagues also randomised 1169 CIN2-3 patients to cold coagulation or CO_2 laser treatment, and observed significantly shorter treatment times among cold coagulation patients (median time of 3 minutes) compared with laser patients (median time of 12 minutes).[13] Fergusson and Craft contrasted 24 cold coagulation patients with 27 cryosurgery patients and found that whereas pain during treatment occurred exclusively in cold coagulation patients (affecting 21%), watery discharge after treatment was much more common among cryosurgery patients (93%) than cold coagulation patients (17%).[33] Finally, in the majority of studies, local analgesia was not required during cold coagulation treatment. This is consistent with the results of a recent randomised placebo-controlled trial in which 44.7% of patients receiving cold coagulation treatment experienced only mild or no pain in the absence of local anaesthesia. However, local anaesthesia may be advisable as it significantly reduced the incidence of severe pain, which affected 19.1% of cold coagulation patients not receiving anaesthesia in that study.[31]

Finally, the analysed studies reported an absence of adverse events on fertility, consistent with previous reports of a 94% conception rate among CIN1-3 patients within 2 years of cold coagulation treatment. Investigators reported that women had normal post-treatment pregnancies, likely due to the minimal scarring with this procedure.[3]

Conclusions

Our comprehensive meta-analysis has demonstrated that cold coagulation generates cure rates comparable to other excisional and ablative methods in use worldwide. Despite its efficacy and acceptability, cold coagulation has progressively been replaced by excisional methods, such as LLETZ, since the 1980s.[12,20] Low rates of use may stem from availability, as only a single manufacturer exists at present. As relatively few studies (and almost no randomised control trials) have analysed cold coagulation efficacy, cure rates should be further assessed in large cohorts with consistent, long-term follow up of patients. In particular, research is needed on the cure rates achievable in resource-limited settings with mid-level treatment providers, where patients have never been or are not often screened. Overall, this systematic review has demonstrated that cold coagulation may be indicated for all grades of CIN, and is safe, quick, and acceptable as an outpatient procedure. Cold coagulation may be of particular relevance for use in resource-limited settings, when access to cryotherapy gas is limited.

Disclosure of interests

The authors have no conflicts of interest.

Contribution to authorship

L.D.: literature search and review; data extraction; data interpretation; drafting the manuscript. C.S.: study initiation and design; data extraction; data interpretation; drafting the manuscript. R.M.: statistical analysis; data interpretation. R.S.: data interpretation; participation in final manuscript. All authors reviewed and approved the final version of the paper.

Details of ethics approval

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Scoring of methodological quality of studies on cold coagulation efficacy. ■

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There is still some heat in the cold coagulator

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Mini commentary on 'Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review'

In the 1970s and 1980s a variety of techniques were available to ablate cervical intraepithelial neoplasia (CIN), including radical electrodiathermy, laser, cryosurgery, and the quirkily named 'cold coagulator' (CC), which comprised a hot thermaprobe applied at 100–120°C.

Following the report of 'large loop' excision of the transformation zone (LLETZ) (Prendiville et al. BJOG 1989;96:1054–60), ablative methods yielded significantly to a technology that helped to avoid inadvertent and, potentially inadequate, treatment of occult invasive cancer and glandular disease (representative reference: Alvarez et al. Gynecol Oncol 1994;52:175–9). However, for all the benefits of LLETZ (or LEEP: loop electrosurgical excision procedure as it became known in the USA) it is relatively expensive and involves multiple additional resources that are not readily available in the parts of the world where the burden of cervical cancer is greatest: developing nations.

This systematic review by Dolman and colleagues from the International Agency for Research on Cancer was stimulated by interest in implementing treatment methods most applicable to such resource-limited settings. Meta-analysis of data on the use of CC to treat over 4500 women with CIN, mostly from two to three decades ago, revealed estimated cure rates for CIN1 of 96% and CIN2-3 of 95%. It is no surprise that CC would be effective, as both Semm[1] and later Haddad demonstrated that the necessary depth of tissue destruction could be achieved. As with cryosurgery, CC is well tolerated, often without local anaesthetic and with minimal short-term complications.[2,3] Although data on pregnancy outcomes is incomplete, morbidity would be expected to be low based on a meta-analysis of perinatal and obstetric outcomes that included other forms of ablation. (Arbyn et al. BMJ 2008;337:a1284).

Reported experience with CC in resource-limited settings has lagged behind that for cryotherapy, which has been evaluated in programmes utilising mid-level providers in the community.[4] There would seem no reason that CC might not be delivered in such situations but with the added advantages of easier use and without reliance on refrigerant gas. Although a few cases of early invasive carcinoma of the cervix would inevitably be missed with ablation of CIN, this would likely be trumped by the overwhelming need for cervix cancer prevention in populations in developing nations.

This report is valuable in reminding us of the efficacy and side-effect profile of a technology that has gone largely out of fashion. The authors are to be commended for having the vision to see its potential to help treat women with CIN in developing nations. Kurt Semm as a pioneer and those who promoted the use of CC, principally in the UK, should be recognised. This systematic review should stimulate further research on CC. In areas of the world where resources are limited but need is great, this might take the form of a comprehensive 'modern era' RCT of CC versus cryotherapy for all grades of CIN. Closer to home, it might even generate more interest in CC, possibly including a trial of CC versus LLETZ for those with CIN involving type 1 transformation zones (Prendiville. BJOG. 2013; 120:510–1).

Disclosure of interests

I have no conflicts of interest. ■

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Pregnancy outcomes following cold coagulation for CIN have not yet been reported

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Mini commentary on 'Meta-analysis of the efficacy of cold coagulation as a treatment method for cervical intraepithelial neoplasia: a systematic review'

The meta-analysis of 13 studies published by Dolman et al. (BJOG) in this month's *BJOG* concludes that cure rates for high-grade CIN treated by cold coagulation are high (95%) and comparable to those reported for other excisional or ablative techniques (Martin-Hirsch et al. Cochrane Database Syst Rev 2010;6:CD001318). Although most of the included studies were conducted nearly two decades ago, the reported outcomes are likely to be applicable to contemporary settings.

The systematic review included only non-controlled observational studies and therefore the level of derived evidence must be considered to be low. Moreover, none of the included studies was conducted in developing countries, where cold coagulation might have the most utility, given its ease of application. The systematic review considered absence of cytological lesions as evidence for treatment success, but as cytology is only moderately sensitive for predicting recurrent or residual high-grade CIN (Arbyn et al. Vaccine 2012;30 S 5:F88–99), it is likely that treatment failure is underestimated in this study.

Excisional techniques, particularly LLETZ, have largely replaced ablative techniques for the treatment of CIN in developed countries. This is because LLETZ is cheap, quick, easy to perform and readily available. The resulting cone specimen provides information about the grade of disease, the presence or absence of microinvasive disease and the completeness of excision. These data provide important prognostic information.

The obstetric consequences of excisional treatment are now widely recognised (Kyrgiou et al. Lancet;367:489–98). It appears that the amount of cervical tissue removed is important and studies suggest a dose–response effect (Arbyn et al. 2008;18;337:a1284): the deeper the cone (>10 mm) or greater amount of tissue removed, the higher the risk of premature delivery in subsequent pregnancies.

By contrast, there is no evidence for adverse pregnancy outcomes after laser ablation (Kyrgiou et al. Lancet;367:489–98). This may be because the laser beam can be directed with some accuracy at the abnormal areas on the cervix, thereby avoiding unnecessary destruction of healthy tissue (Martin-Hirsch et al. Cochrane Database Syst Rev 2010;6:CD001318).

The obstetric effects of cold coagulation have not yet been studied. Different ablative techniques (laser ablation, radical diathermy and cold coagulation) may result in different risks of prematurity because the precision of destruction caused by each technique varies. Large and extensive ablations may still result in higher risk of preterm labour than smaller treatments, although the destruction

caused by ablation is difficult to quantify. A return to ablation by colposcopists would prevent accurate assessment of the amount of cervical tissue removed, which in turn would limit our ability to provide individualised risk stratification following treatment for CIN for women who desire future pregnancies.

The effects of cold coagulation on future pregnancies have never been investigated. More research is needed on both the obstetric and oncological consequences of cold coagulation, especially in developing countries.

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