Thermal ablation versus standard cryotherapy and loop excision for the treatment of women who screened positive for cervical precancer by visual inspection with acetic acid

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Abstract

Background: Cryotherapy is currently standard practice for treating cervical pre-cancer in see and treat programmes in low and middle income countries. Because of well documented logistic difficulties with cryotherapy (e.g. need for and costs and supply chain difficulties of refrigerant gas, equipment failure, treatment duration >10mins), a novel lightweight, portable, battery operated thermal coagulator (Liger T.A.) has been developed.

Methods: A prospective pilot randomised unblinded trial of cryotherapy vs Liger thermal ablation vs Large Loop Excision of the Transformation Zone (LLETZ) undertaken in routine 'Screen and treat' clinics in Lusaka, Zambia providing cervical screening using visual inspection with acetic acid (VIA). 750 women, eligible for ablative therapy were randomly allocated to TA, cryotherapy or LLETZ. Treatment success was defined as either HPV type-specific clearance among study participants positive for the same HPV type at baseline or negative VIA test at follow up, if the baseline HPV test was negative.

Findings: HIV prevalence was high in all study groups (TA - 49·2%; cryotherapy - 53·6%; LLETZ - 58·0%; p-value=0·71). Very few participants complained of moderate to severe pain in any group arms (TA- 1·6%; cryotherapy- 2·4%). Treatment success rates were 60·0%, 64·1% and 63·8% in the cryotherapy, TA and LLETZ arms respectively (p-value=0·31).

Interpretation: The results of this pilot would suggest that TA is a superior method of treatment for cervical pre-cancer in the context of a see and treat programme in LMIC, since it has treatment success rate equivalent to cryotherapy without the practical disadvantages of cryotherapy in an LMIC setting. TA was very much preferred by care providers and was quicker. There was no difference in complication or discomfort frequencies between the study arms. The LLETZ arm revealed that only 25% of participants deemed to be screen positive and eligible for ablation had high grade squamous intraepithelial lesions (HSIL).

Funding: The study is funded by the National Institute of Health, USA (Grant number 1UH2CA202721-01). The study is registered with the U.S. Clinical Trial Registry (https://clinicaltrials.gov/ct2/show/NCT02956239).

Keywords: Thermal ablation, cryotherapy, Large loop excision of transformation zone, efficacy, safety, randomized controlled trial

Research in context

It is well-known that the see-and-treat approach, in reducing the number of clinic visits, significantly improves the treatment compliance in a screening context. Screening cervical cancer by visual inspection with acetic acid followed by immediate procedure was the most common approach used in low- and middle-income countries (LMIC). Currently, the World Health Organization (WHO) recommends cryotherapy as the ablative method of choice for screen-and-treat programmes. Thermal ablation (TA) is an alternative ablative procedure. The WHO has endorsed cryotherapy as the standard method of treatment for cervical pre-cancer in LMICs for over 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 achieved penetration 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 list of the selected articles. A recent meta-analysis of the available published evidence revealed equivalence in effectiveness between cryotherapy and thermal ablation. There was only one small randomised-controlled trial in the studies included.

Added value of this study

The results of the pilot phase of our study reveals equivalence between thermal ablation and cryotherapy. TA was very much preferred by care providers and was quicker (45 seconds vs 11 minutes). There was no difference in complication or discomfort levels between the study arms. The excisional arm revealed that only 25% of participants deemed to be screen positive and eligible for ablation had high grade squamous lesions (HSIL).

Implications of all the available evidence

The study will continue until sufficient power has been achieved but the results of this pilot would suggest that TA is a superior method of treatment for cervical pre-cancer in the context of a see-and-treat programme in LMICs and that it has equivalent effectiveness to cryotherapy without the practical disadvantages of cryotherapy in a LMIC setting.

Introduction

Systematic high coverage and quality assured population screening with treatment of precursors to cervical cancer is highly effective. This 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, even in low and middle income countries (LMICs).[2] Large Loop Excision of the Transformation Zone or LLETZ,[3] also known as loop electrosurgical excision procedure (LEEP), has become the standard treatment in most developed countries. Ablative techniques are simpler, safer and less technically demanding than LLETZ. The currently available ablative methods are cryotherapy and thermal ablation. The techniques have been described in detail elsewhere.[4] Thermal ablation (TA) was previously known as cold coagulation in order to distinguish it from radical diathermy which reaches temperatures of approximately 300^{o}C.[5] TA functions by heating the Transformation Zone (TZ) epithelium, albeit to 100^{o}C. Cold coagulation was thus clearly a misnomer.

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 significantly improve treatment compliance.[7] Cryotherapy was previously recommended by the World Health Organization (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 perform and being relatively effective. However, the costs and difficulties in ensuring uninterrupted supply of CO_2 or N_2O refrigerant gas, the long treatment duration (11 minutes) as well as difficulties with equipment failure have led to frustration with the method.[9,10] Thermal ablation is an alternative ablation therapy to cryotherapy. Equivalent effectiveness has been demonstrated in a recent pooled analysis of published observational studies.[11,12] It is a much faster treatment (20 to 40 secs) and requires no gas supply. Like cryotherapy it is simple to perform and almost any level of health care provider may perform it.

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 of USA collaborated with Liger Medical (Utah, USA) to evaluate the new device through a project funded by the National Institute of Health, USA (Grant number 1UH2CA202721-01). This study reports the pilot phase outcomes of a three-arm randomised controlled trial of TA using the new portable device compared to cryotherapy and to LLETZ in the context of a VIA-based *screen-and-treat* programme in Lusaka, Zambia. The primary objective of the study was to compare the success rate of the three treatment methods. The study also aimed to estimate the rate of over-treatment in a VIA- screen-and-treat programme based on the post-LLETZ histopathology results in the LLETZ arm. The study is registered with the U.S. Clinical Trial Registry (NCT02956239).

Method

The 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. In the trial, eligible VIA positive women were randomized to three arms to receive treatment using either the new TA device or the standard cryotherapy or LLETZ.

The new TA device

The portable battery-driven thermal ablator was developed by Liger Medical (Utah, USA) during 2016 and 2017 and bench tested in 2017. FDA clearance was obtained in 2017 as was the European CE mark. The device is powered by a small removable 12 volt battery incorporated into the handle, which may be recharged over two to three hours and holds enough charge to complete at least 20 treatment procedures.

Study setting

The study was conducted in a primary health clinic participating in the routine '*screen-and-treat'* programme in Lusaka, Zambia, where VIA is performed by trained nurses to screen women between 25 and 49 years of age.

Eligibility of study participants

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 as described by the IARC manual on VIA, and the VIA outcomes were categorized as negative, positive and suspected cancer.[13] The examining nurses assessed the eligibility of VIA positive women for ablative treatment. These are that the TZ 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 found to be 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. Women fulfilling any of the following criteria were excluded:

- 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
- Any genital tract cancer

As per routine practice in Zambia, all women undergoing VIA underwent HIV testing, unless a recent test result was available. Recently diagnosed HIV positivity required initiation of anti-retroviral therapy prior to cervical cancer screening.

Randomization and treatment allocation

Eligible participants were randomized at a 1:1:1 ratio to receive either TA or cryotherapy or LLETZ. All treatment was performed by one of four study nurses at the clinic. Request for allocation was obtained by the study nurse after checking the inclusion and exclusion

criteria. Concealed allocation to a study arm was through computer-generated sealed envelopes at IARC, which were accessed by the study coordinator in the clinic. Study arm allocation was conveyed to the nurse just before performing treatment of eligible participants. Once a treatment arm had been allocated the study participant received a unique identifier number.

Testing for high risk Human Papillomavirus (HPV)

The nurse collected a cervical sample prior to VIA using a Cervex-brush™ (Rovers Medical Devices, The Netherlands) in Preservcyt™ (Hologic INC, Marlborough, USA) medium for HPV DNA testing. If a woman was randomized to the study, her sample was sent to the University Teaching Hospital laboratory for the detection of DNA of any of the 14 high risk HPV types (along with type-specific information) by the Xpert™ HPV test (Cepheid, Sunnyvale, CA, USA). The HPV genotype information was obtained in separate channels for HPV 16, HPV 18 and/or 45, HPV 31, 33, 35, 52 and/or 58, HPV 51 and/or 59 and HPV 39, 56, 66 and/or 68. The test results were obtained later and did not alter treatment allocation and management of the eligible VIA positive women.

Treatment of VIA positive women eligible for ablative therapy

TA was performed using the Liger thermal ablator and as originally described by Duncan.[15] Cryotherapy was carried out using the double freeze technique (freeze for 3 minutes, thaw for 5 minutes and freeze again for 3 minutes) as per routine practice in the program.[4] LLETZ was performed under local anaesthesia as described by Prendiville et al[3] while no anaesthesia was used for eithe ablative technique. Any treatment side-effects during and immediately after treatment were recorded by the nurse performing the treatment.

Post-treatment procedures

The nurse performing treatment counselled each participant after the procedure about possible side-effects and complications of treatment and advised her to report to the clinic or call the study coordinator for advice. Abstinence from sexual intercourse for six 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 six months. Before leaving the clinic, she was interviewed by the project coordinator to document her perception of pain/discomfort during and immediately after treatment and also her level of 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 patient wanted the procedure to be stopped or was not at all satisfied).

Follow-up after treatment

The study coordinator called each participant 2 weeks after treatment to check if she had any complications or had visited a clinician or had been hospitalized during the intervening period. The level of pain/discomfort and the degree of satisfaction with the overall experience at that point of time was again recorded.

At the six month follow-up visit each participant was again asked about any complication,

medical consultation or hospitalization. She was examined by a study nurse who first collected a cervical sample for Xpert^{TM} HPV test and performed VIA. VIA positive participants were immediately referred for further assessment and appropriate management as per the local protocol. The participants negative on VIA but positive for HPV were advised to come for a repeat follow-up visit at 12 months. A data and safety monitoring board continues to oversee the project.

Statistical considerations

This pilot study, which is part of a larger randomized trial, recruited 250 participants in each arm and followed each participant for six months. The sample size used for the assessment of the preliminary safety and efficacy was empirically decided. Recruitment for the larger RCT is ongoing and is expected to complete recruitment and follow up over two years.

The primary outcome of interest was success of treatment at 6 months, which was defined as either a) HPV type-specific clearance at 6 months among participants positive for the same HPV type at baseline or b) negative VIA test at follow up, if the baseline HPV test was negative.

The following data were presented as proportions and compared between the three treatment modalities using a Pearson's chi-square test or Fisher's exact test for comparisons with very small cell sizes: baseline socio-demographic, reproductive and clinical characteristics; side-effects, pain scores and satisfaction after treatment; and 6-month cervical disease clearance rates. Statistical significance was set at the 5% level.

Results

Table 1 provides details of the baseline socio-demographic, reproductive and clinical characteristics between the three treatment groups. There was no significant difference in the distribution of any of these variables. There were slightly fewer HIV positive participants in the TA group than the cryotherapy and LLETZ groups at baseline assessment (49·2% vs 53·6% and 54·0%, respectively), though the difference was not statistically significant (p-value=0.71). The HPV positivity on Xpert^{TM} test was 60·0%, 54·6% and 58·0% in the cryotherapy, TA and LLETZ arms respectively (p-value=0.48).

Side-effects, adverse events and discomfort levels

The great majority of participants reported no, or the least level of discomfort with their treatment, either immediately after or within two weeks of treatment (table 2). Very few complained of moderate to severe pain (pain intensity score $\geq$4) during the procedure (cryotherapy – 6 [2·4%]; TA – 4 [1·6%]) and there was no statistically significant difference between the groups. 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, all three group scores approached 100%, both immediately and at two weeks after treatment. There were 5 deaths (intimate partner violence, suicide, metastatic breast cancer, renal failure of unknown cause and complications following a soft tissue tumour excision on thigh) in participants taking part in the study though none was related in any way to treatment. None of the participants reported any complication requiring medical consultation or hospitalization.

Follow-up examinations

Figure 1 presents details of the 6-month follow-up for this pilot study at the time of these analyses. Of 250 women in the cryotherapy arm, 246 were eligible (as they had completed 6 months post-treatment), of whom 206 (83·7%) had attended the 6-month follow-up examination. In the TA arm and LLETZ groups, these figures were 244 and 197 (80·7%) (TA) and 245 and 204 (83·3%) (LLETZ) respectively. The median interval between treatment and follow-up was 6·0 months (mean 6.6 months; range 4·8 – 19·6) with no difference between the treatment arms.

The clearance rates of any high risk HPV in the high risk HPV positive participants at 6 months follow up were 40.0%, 42.0% and 47.0% in the cryotherapy, TA and LLETZ arms respectively. The clearance rates for HPV 16 (Cryotherapy- 43.8%, TA- 61.5% and LLETZ- 54.5%) was less compared to the clearance rates for HPV 18 and/or 45 (Cryotherapy- 100.0%, TA- 68.8% and LLETZ- 87.5%). There was no significant difference between the treatment arms.

Table 3 shows treatment success rates at 6 months following treatment based on a combination of HPV test and VIA. When based on HPV type-specific clearance and VIA negative findings among participants who were HPV negative at baseline, treatment success rates were 60·0% in the cryotherapy arm, 64·1% in the TA arm, and 63·8% in the LLETZ arm (p-value=0·31). The clearance rates of high-risk HPV at 6 months were similar between the cryotherapy (39·7% [48/121]), TA (42·3% [44/104]) and LLETZ (47·2% [50/106]) arms (p-value=0·52). HIV positive participants had lower success rates compared to the HIV negative women, irrespective of the treatment method and definition of cervical disease clearance. The rates of successful treatment as reflected by VIA examination alone (data not shown in the table) were similar across the groups, but overall slightly more participants treated by TA had a normal VIA examination compared to cryotherapy and LLETZ (83·9% vs 79·4% and 79·8%, respectively).

Histopathology reports of the cervical specimens removed at LLETZ

Table 4 shows the histopathology reports of participants whose transformation zones were excised in the LLETZ arm. Overall 30·7% (73/238) of participants underwent LLETZ had histological evidence of CIN 2-3. More than half of VIA positive participants (52·1% [124/238]) had some grade of CIN and none had invasive cancer. In HIV positive participants eligible for ablation, 43·0% (55/128) had CIN2-3 compared to 16·0% (17/106) in participants who were HIV negative. Of the HPV positive (and VIA positive) participants who had LLETZ 46·4% (64/138) had histologically proven CIN 2-3 compared to only 9·0% (9/105) who were HPV negative**.** Taking baseline combinations of high-risk HPV and HIV status, the CIN 2-3 detection rates were 4·5% (3/66) among participants negative for both HPV and HIV, 18·8% (6/32) for those HPV negative but HIV positive, 35·0% (14/40) among those HPV positive but HIV negative, and 51·0% (49/96) in those positive for both HPV and HIV.

Discussion

TA 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. Duncan[15] in

Scotland has produced the largest and longest series of patients treated with TA (1453 patients followed up for over 14 years) and the cure rates in his case series compare favourably with other treatment methods.[16] The effectiveness of TA has been evaluated in several meta-analytical reviews.[11,12] In the most recent review by Randall's group, the authors report an overall cure rate from 16 included studies for CIN2 or worse lesions to be 93·6% (95% CI 90·8% to 96·0%). The overall cure rates for CIN1+ were 92·9% (CI 90·4% to 95·1%) and for CIN 3 were 89% (84-95%).The only RCT included in the analysis came from Singapore.[17] In that study the authors reported no difference in success rates between cryotherapy and TA for any grades of CIN. The reported cure rates after TA in the Singapore study were 88·4%, 84·2% and 78·6% for CIN 1, CIN 2 and CIN 3 respectively. Duan and colleagues[18] have also presented the results of a randomised controlled trial of TA vs cryotherapy in a study of 149 women eligible for ablative therapy. In this study TA was as or more effective than cryotherapy at 8 months as judged by HPV and cytological assessment respectively.

We believe this study to be the only randomized study that included acceptability, safety as well as TA effectiveness, specifically using a modern battery-driven portable machine.The most important finding of the preliminary report of our study is that TA appears to be highly acceptable to women and is as effective as cryotherapy whilst being associated with minimal side effects. The shorter treatment time, less cumbersome equipment and non-dependance on refrigerant gas are distinct advantages of TA over cryotherapy. The cost of the battery driven TA is comparable to that of standard cryotherapy equipment and a huge cost-saving is expected due to low operational costs, if cryotherapy is replaced by TA. Also, current battery operated thermal ablators are small lightweight and highly portable. Avoiding cumbersome gas tanks is a genuine practical advantage to health care providers in LMIC. The outcomes of our study are particularly significant because of the high proportion of HIV positive women among the study participants. We have demonstrated equivalent efficacy for the two ablative techniques in HIV-positive women, albeit significantly lower than that in the HIV negative women.

Several caveats apply to our study findings. The numbers reported here are small. The study continues to recruit eligible women and will do so until a sufficient sample size has been gained. According to our estimate, an additional 1,000 participants need to be recruited in each arm to give sufficient power to detect non-inferiority of TA as a treatment method for VIA-positive women compared to cryotherapy or LLETZ. A second caveat is that follow-up assessment at 6 months is probably too early to assess cure of disease, but we do not anticipate any difference arising between the study groups, well-balanced due to randomization. A major criticism of the study can be the lack 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' (i.e. VIA) to detect abnormalities pre- or post-treatment. To increase the validity of our study we have also used the most frequently used and powerful 'test of cure', which is a valid high-risk HPV test. The low rates of 'treatment success' as reflected in HPV status may reflect both the early follow-up appointment timing at 6 months but also the possibility of recurrent infection, particularly in the context of relatively high rate of HIV in recruited women. There is a possibility that the follow up VIA might have missed some of the lesions in the HPV negative women due to the low sensitivity of the test. However, similar success rates

observed between the ablative and excisional treatment arms using the stringent criteria of disease clearance gives us confidence in our study outcomes.

Duration of treatment is still an unresolved issue with TA. Randall's meta-analysis found that the cure rate did not vary significantly according to the duration of treatment. Patients treated for 20 seconds duration had a cure rate of 92·9%, those treated for 30 seconds 95·1% and those treated for 45 seconds 85%. The largest body of data with the longest duration of follow-up comes from Ian Duncan's case series where 20-second applications were used but with the important caveat that where the probe tip did not cover the entire TZ, overlapping applications were made. The variables of probe tip size and the number of applications are, as yet, open questions. So far in our study we used 45 seconds duration and multiple overlapping applications using a 20 mm probe. Our DSMB has recommended that we reduce the treatment time to 30 seconds.

It is reassuring that very low frequency 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 TA arm and this may be explained by the very much shorter treatment duration associated with TA when compared to cryotherapy (45 seconds vs 11 minutes). The relatively low reporting of pain or cramps during LLETZ may be explained by the fact that local infiltration was routinely used for LLETZ but not for ablative treatment of either kind. Also, similarly low discomfort levels were reported by women after they had left the procedure room and by telephone two weeks later.

One of the reasons that we included a third study arm (excision by LLETZ) was to discover the histological diagnosis in VIA positive women 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, specifically in the context of a *screen-and-treat* approach. Only 31% of women with a positive VIA and who were eligible for an ablative therapy had histologically proven high grade CIN 2 or worse. This percentage is higher for women in their 30s (43%) and for those who are HIV positive (43%). Much lower rates (~5%) have been reported from studies that were implemented in regions with low prevalence of cervical cancer.[19] It is reassuring to know that no invasive cancer was inadvertently treated at least in the LLETZ arm.

Conclusions

The World Health Organisation (WHO) has recently updated its clinical guidelines for the treatment of cervical precancer (to be published soon) and now endorses the use of TA for ablative treatment. The equally successful treatment of cervical lesions by TA when compared to cryotherapy and the low complication rates for either intervention reported by our study was a valuable evidence for the WHO to develop the new guidelines. If the early findings in this report are confirmed by our ongoing large RCT and other studies, then health care workers caring for screen positive women in '*screen-and-treat'* programmes in LMICs may choose modern cordless lightweight and battery operated TA devices over cryotherapy instruments because of the practical disadvantages of cryotherapy. In view of the relatively low rate of histologically proven CIN2+ in VIA screen positive women it is perhaps time to reconsider the optimal screening test for low and middle-income regions. Hopefully both

much less expensive and laboratory independent HPV tests will become available in the near future or alternative techniques, for example artificial intelligence image recognition systems, will emerge.

Contributors

LP implemented the study, oversaw data collection, analysed the data, drafted and revised the paper. GP and PB designed the study protocols, oversaw implementation of study, conducted data analysis and revised the draft manuscript. RM conducted data analysis and revised the draft paper. EL, NN, CS and MM 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

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Table 1: Baseline socio demographic, reproductive health and clinical characteristics

	Randomization arm								
	Cryotherapy		Thermal ablation		LLETZ		Total		
	n (%)		n (%)		n (%)		n (%)		p-value
Participants recruited	250		250		250		750		
Age (years)									
25-29	92	(36·8)	89	(35·6)	84	(33·6)	265	(35·3)	0·871
30-34	54	(21·6)	65	(26·0)	64	(25·6)	183	(24·4)	
35-39	44	(17·6)	37	(14·8)	47	(18·8)	128	(17·1)	
40-44	35	(14·0)	31	(12·4)	37	(14·8)	103	(13·7)	
45-49	15	(6·0)	17	(6·8)	11	(4·4)	43	(5·7)	
50-54	9	(3·6)	8	(3·2)	6	(2·4)	23	(3·1)	
55-60	1	(0·4)	3	(1·2)	1	(0·4)	5	(0·7)	
Participant education									
None	9	(3·6)	7	(2·8)	10	(4·0)	26	(3·5)	0·303
Primary	88	(35·2)	75	(30·0)	74	(29·6)	237	(31·6)	
Secondary	101	(40·4)	128	(51·2)	123	(49·2)	352	(46·9)	
College/university	50	(20·0)	40	(16·0)	41	(16·4)	131	(17·5)	
Unknown	2	(0·8)	0	(0·0)	2	(0·8)	4	(0·5)	
Occupation									
Housewife	62	(24·8)	68	(27·2)	57	(22·8)	187	(24·9)	0·369
Manual	26	(10·4)	23	(9·2)	29	(11·6)	78	(10·4)	
Professional	43	(17·2)	44	(17·6)	37	(14·8)	124	(16·5)	
Business	92	(36·8)	81	(32·4)	86	(34·4)	259	(34·5)	
Other	16	(6·4)	29	(11·6)	31	(12·4)	76	(10·1)	
Unknown	11	(4·4)	5	(2·0)	10	(4·0)	26	(3·5)	
Marital status									

Unmarried	34	(13·6)	32	(12·8)	35	(14·0)	101	(13·5)	0·789
Married/cohabiting	168	(67·2)	171	(68·4)	157	(62·8)	496	(66·1)	
Widowed	19	(7·6)	17	(6·8)	24	(9·6)	60	(8·0)	
Separated	28	(11·2)	30	(12·0)	34	(13·6)	92	(12·3)	
Residence area									
Urban	146	(58·4)	152	(60·8)	149	(59·6)	447	(59·6)	0·903
Semi-urban	92	(36·8)	90	(36·0)	94	(37·6)	276	(36·8)	
Rural	11	(4·4)	7	(2·8)	7	(2·8)	25	(3·3)	
Unknown	1	(0·4)	1	(0·4)	0	(0·0)	2	(0·3)	
Total pregnancies									
None	21	(8·4)	14	(5·6)	20	(8·0)	55	(7·3)	0·183
1-2	74	(29·6)	88	(35·2)	102	(40·8)	264	(35·2)	
3-4	93	(37·2)	90	(36·0)	79	(31·6)	262	(34·9)	
5+	62	(24·8)	58	(23·2)	49	(19·6)	169	(22·5)	
Total number of live births									
None	28	(11·2)	22	(8·8)	29	(11·6)	79	(10·5)	0·386
1-2	97	(38·8)	109	(43·6)	120	(48·0)	326	(43·5)	
3-4	87	(34·8)	85	(34·0)	71	(28·4)	243	(32·4)	
5+	38	(15·2)	34	(13·6)	30	(12·0)	102	(13·6)	
Last menstruation									
<=30 days	217	(86·8)	213	(85·2)	215	(86·0)	645	(86·0)	0·788
> 30 days - < 12 months	18	(7·2)	21	(8·4)	22	(8·8)	61	(8·1)	
12 months+	2	(0·8)	6	(2·4)	3	(1·2)	11	(1·5)	
Unknown	13	(5·2)	10	(4·0)	10	(4·0)	33	(4·4)	
Size of the acetowhite area									
<50%	221	(88·4)	223	(89·2)	210	(84·0)	654	(87·2)	0·173
>50%	29	(11·6)	27	(10·8)	40	(16·0)	96	(12·8)	
Baseline HIV status									
Negative	108	(43·2)	119	(47·6)	110	(44·0)	337	(44·9)	0·722

Positive	134	(53·6)	123	(49·2)	135	(54·0)	392	(52·3)	
Unknown	8	(3·2)	8	(3·2)	5	(2·0)	21	(2·8)	
If HIV positive, patient on ART									
Yes	129	(96·3)	117	(95·1)	130	(96·3)	376	(95·9)	0·346
No	4	(3·0)	5	(4·1)	1	(0·7)	10	(2·6)	
Unknown	1	(0·7)	1	(0·8)	4	(3·0)	6	(1·5)	
HPV testing results									
Negative	100	(40·0)	113	(45·4)	105	(42·0)	318	(42·5)	0·476
Positive	150	(60·0)	136	(54·6)	145	(58·0)	431	(57·5)	
HPV type									
HPV 16	38	(15·2)	41	(16·5)	51	(20·4)	130	(17·4)	0·335
HPV 18 and/or 45	24	(9·6)	21	(8·4)	21	(8·4)	66	(8·8)	0·682
HPV 31, 33, 35, 52 and/or 58	99	(39·6)	94	(37·8)	101	(40·4)	294	(39·3)	0·665
HPV 51 and/or 59	20	(8·0)	11	(4·4)	12	(4·8)	43	(5·7)	0·233
HPV 39, 56, 66 and/or 68	60	(24·0)	45	(18·1)	54	(21·6)	159	(21·2)	0·325

LLETZ: Large loop excision of the transformation zone; HIV: human immunodeficiency virus; ART: antiretroviral therapy; HPV: human papilloma virus

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

	Randomization arm								
	Cryotherapy		Thermal ablation		LLETZ		Total		
	n (%)		n (%)		n (%)		n (%)		p-value
Immediately after treatment									
Participants assessed	250		250		250		750		
Intensity of pain or discomfort felt (score ranging from 1 to 9)									
1 (no pain)	120	(48·0)	115	(46·0)	134	(53·6)	369	(49·2)	0·406
2-3 (least pain)	123	(49·2)	129	(51·6)	111	(44·4)	363	(48·4)	
4-6	6	(2·4)	3	(1·2)	5	(2·0)	14	(1·9)	
7-9 (worst pain)	0	(0·0)	1	(0·4)	0	(0·0)	1	(0·1)	
Level of satisfaction with the services (score ranging from 1 to 9)									
1-3 (least satisfied)	0	(0·0)	0	(0·0)	0	(0·0)	0	(0·0)	0·280
4-6	3	(1·2)	1	(0·4)	0	(0·0)	4	(0·5)	
7-9 (highly satisfied)	246	(98·4)	248	(99·2)	250	(100·0)	744	(99·2)	
Will recommend the screening procedure to others									
Yes	248	(99·2)	250	(100·0)	249	(99·6)	747	(99·6)	0·321
No	0	(0·0)	0	(0·0)	1	(0·4)	1	(0·1)	
Cannot say	2	(0·8)	0	(0·0)	0	(0·0)	2	(0·3)	

Two weeks after treatment									
Participants assessed	241		242		237		720		
Intensity of pain or discomfort felt (score ranging from 1 to 9)									
1 (no pain)	214	(88·8)	227	(93·8)	208	(87·8)	649	(90·1)	0·203
2-3 (least pain)	25	(10·4)	15	(6·2)	27	(11·4)	67	(9·3)	
4-6	1	(0·4)	0	(0·0)	2	(0·8)	3	(0·4)	
7-9 (worst pain)	0	(0·0)	0	(0·0)	0	(0·0)	0	(0·0)	
Level of satisfaction with the services (score ranging from 1 to 9)									
1-3 (least satisfied)	0	(0·0)	0	(0·0)	0	(0·0)	0	(0·0)	0·540
4-6	1	(0·4)	0	(0·0)	0	(0·0)	1	(0·1)	
7-9 (highly satisfied)	239	(99·2)	242	(100·0)	237	(100·0)	718	(99·7)	
Will recommend the screening procedure to others									
Yes	239	(99·2)	242	(100·0)	237	(100·0)	718	(99·7)	0·335
No	0	(0·0)	0	(0·0)	0	(0·0)	0	(0·0)	
Cannot say	2	(0·8)	0	(0·0)	0	(0·0)	2	(0·3)	

LLETZ: Large loop excision of the transformation zone

Table 3: Treatment success rates at 6 months follow-up after treatment (treatment success based on follow-up HPV and VIA results) [a]

	Randomization arm								
	Cryotherapy		Thermal ablation		LLETZ		Total		p-value
	n (%)		n (%)		n (%)		n (%)		
Treatment success based on HPV and VIA results at 6 months follow-up [a]									
Overall									
Participants followed up [b]	200		192		199		591		
Participants with no evidence of disease [a]	120	(60·0)	123	(64·1)	134	(67·3)	377	(63·8)	0·311
HPV positive at baseline									
Participants followed up	121		104		106		331		
Participants with no evidence of disease [a]	48	(39·7)	44	(42·3)	50	(47·2)	142	(42·9)	0·517
HIV negative at baseline									
Participants followed up	85		93		93		271		
Participants with no evidence of disease [a]	68	(80·0)	77	(82·8)	76	(81·7)	221	(81·5)	0·890
HIV positive at baseline									
Participants followed up	109		95		101		305		
Participants with no evidence of disease [a]	50	(45·9)	42	(44·2)	55	(54·5)	147	(48·2)	0·297

LLETZ: Large loop excision of the transformation zone; HIV: human immunodeficiency virus; HPV: human papilloma virus;

[a] Treatment success was defined as either a) HPV type-specific clearance at 6 months among women positive for the same HPV type at baseline or b) negative VIA test at follow up, if the baseline HPV test was negative

[b] HPV reports were missing in 6 participants in cryotherapy arm, 5 participants in TA arm and 5 participants in LLETZ arm. They were excluded from the analysis of treatment success rate.

Table 4: Histology findings at baseline in the LLETZ arm

	Women treated n	Women with histology report n (%)	Histological diagnosis at baseline				
			Normal n (%)	CIN 1 n (%)	CIN 2 n (%)	CIN 3 n (%)	CIN 2/3 n (%)
Overall	250	238 (95·2)	114 (47·9)	51 (21·4)	32 (13·4)	41 (17·2)	73 (30·7)
Age (years)							
25-29	84	81 (96·4)	46 (56·8)	20 (24·7)	7 (8·6)	8 (9·9)	15 (18·5)
30-39	111	105 (94·6)	42 (40·0)	18 (17·1)	21 (20·0)	24 (22·9)	45 (42·9)
40+	55	52 (94·5)	26 (50·0)	13 (25·0)	4 (7·7)	9 (17·3)	13 (25·0)
HPV testing results							
Negative	105	100 (95·2)	66 (66·0)	25 (25·0)	5 (5·0)	4 (4·0)	9 (9·0)
Positive	145	138 (95·2)	48 (34·8)	26 (18·8)	27 (19·6)	37 (26·8)	64 (46·4)
Baseline HIV status							
Negative	110	106 (96·4)	60 (56·6)	29 (27·4)	7 (6·6)	10 (9·4)	17 (16·0)
Positive	135	128 (94·8)	51 (39·8)	22 (17·2)	25 (19·5)	30 (23·4)	55 (43·0)
Baseline HPV and HIV status combinations							
HPV negative, HIV negative	70	66 (94·3)	44 (66·7)	19 (28·8)	2 (3·0)	1 (1·5)	3 (4·5)
HPV negative, HIV positive	33	32 (97·0)	20 (62·5)	6 (18·8)	3 (9·4)	3 (9·4)	6 (18·8)
HPV positive, HIV negative	40	40 (100·0)	16 (40·0)	10 (25·0)	5 (12·5)	9 (22·5)	14 (35·0)
HPV positive, HIV positive	102	96 (94·1)	31 (32·3)	16 (16·7)	22 (22·9)	27 (28·1)	49 (51·0)

LLETZ: Large loop excision of the transformation zone; CIN: cervical intraepithelial neoplasia; HIV: human immunodeficiency virus; HPV: human papilloma virus

Figure 1: Flow chart for the pilot RCT study in the evaluation of the new Liger Thermal Coagulator