Review Article

Loop Electrosurgical Excision Procedure versus Cryotherapy in the Treatment of Cervical Intraepithelial Neoplasia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Pietro D'Alessandro[1], Bruno Arduino[1], Maria Borgo[1], Gabriele Saccone[1,*], Roberta Venturella[2], Annalisa Di Cello[1], Fulvio Zullo[1]

[1]Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, [2]Department of Obstetrics and Gynaecology, School of Medicine, Magna Graecia University of Catanzaro, Catanzaro, Italy

Abstract

Aim: Invasive cervical cancer is proceeded by a phase of preinvasive disease that is slow to progress and can be detected, treated, and collectively referred to as cervical intraepithelial neoplasia (CIN). Several excisional and ablative treatments for CIN have been studied, with loop electrosurgical excision procedure (LEEP) and cryotherapy being the two most commonly utilized. The objective of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to compare the compare harms and benefits of LEEP versus cryotherapy in women with CIN.
Methods: Electronic databases were searched from their inception until May 2018. We included all RCTs comparing cryotherapy versus LEEP in women with CIN. We included trials evaluating both HIV-seropositive and HIV-seronegative women. The primary outcome was the persistence of the disease at 6-month follow-up. Meta-analysis was performed using the random-effects model to produce summary treatment effects in terms of relative risk (RR) with 95% confidence interval (CI).
Results: Four trials, including 1035 women with CIN, were identified as relevant and included in the meta-analysis. Women who received LEEP for CIN had a significantly lower persistence at 6-month follow-up biopsy (RR: 0.87, 95% CI: 0.76–0.99) and significantly lower recurrence at 12-month follow-up biopsy (RR: 0.91, 95% CI: 0.84–0.99) compared to those who received cryotherapy. No between-group differences were found in the complications rate, but the analyses were not powered for these outcomes.
Conclusions: In women with CIN, treatment with LEEP was associated with a significantly lower risk of persistence disease at 6 months and recurrence disease at 12 months compared to treatment with cryotherapy.

Keywords: Cervical cancer, cervical intraepithelial neoplasia, colposcopy, gynecology, Pap test

Introduction

In the developing countries, cervical cancer is the most common cancer in women, with the highest rates in sub-Saharan Africa, Latin America, and South and South East Asia.[1] Invasive cervical cancer is proceeded by a phase of the preinvasive disease that is slow to progress and can be detected, treated, and collectively referred to as cervical intraepithelial neoplasia (CIN). CIN can be confirmed histologically from a biopsy sample and divided into three stages (CIN1, 2, and 3).[2]

Article History:
Received 2 June 2018
Received in revised form 19 July 2018
Accepted 13 August 2018
Available online 26 September 2018

Access this article online

Quick Response Code:

Website:
www.e-gmit.com

DOI:
10.4103/GMIT.GMIT_56_18

Address for correspondence: Dr. Gabriele Saccone, Department of Neuroscience, Reproductive Sciences and Dentistry, School of Medicine, University of Naples Federico II, Naples, Italy.
E-mail: gabriele.saccone. 1990@gmail.com

How to cite this article: D'Alessandro P, Arduino B, Borgo M, Saccone G, Venturella R, Di Cello A, *et al*. Loop electrosurgical excision procedure versus cryotherapy in the treatment of cervical intraepithelial neoplasia: A systematic review and meta-analysis of randomized controlled trials. Gynecol Minim Invasive Ther 2018;7:145-51.

It has been estimated that, in 70% of affected women, CIN2–3 can persist or progress to cervical cancer after 10–20 years.[2-4] For this reason, ablation or excisional of the transformation zone is typically offered to women with biopsy-proven CIN. Progression from CIN to cervical cancer is faster, and associated mortality is significantly higher, among HIV-seropositive compared to HIV-seronegative women.[5-7]

Several excisional and ablative treatments for CIN have been studied, including loop electrosurgical excision procedure (LEEP), cryotherapy, laser vaporization, cold knife conization, and hysterectomy. LEEP and cryotherapy are the two most commonly utilized.[3,8-10]

Thus, the aim of this systematic review and meta-analysis of randomized controlled trials (RCTs) was to compare the compare of LEEP versus cryotherapy in women with CIN.

Methods

Search strategy and selection criteria

This review was performed according to a protocol designed *a priori* and recommended for systematic review.[11] Electronic databases (i.e., MEDLINE, PROSPERO, Scopus, ClinicalTrials.gov, EMBASE, ScienceDirect, the Cochrane Library, Scielo) were searched from their inception until May 2018. Search terms used were the following text words: "LEEP," "cryotherapy," "cervical cancer," "CIN," "intraepithelial neoplasia," "electrosurgical excision," "Pap test," "meta-analysis," "meta-analysis," "review," "randomized," "clinical trial," "randomized," and "clinical trial." No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by two authors (MB and GS). Differences were discussed, and consensus reached.

We included all RCTs comparing cryotherapy versus LEEP in women with CIN. We included trials evaluating both HIV-seropositive and HIV-seronegative women. Any grade of CIN (CIN1, CIN2, or CIN3) was included. CIN was defined as biopsy-proven squamous intraepithelial lesions (SILs).

Quasi-randomized trials (i.e., trials in which allocation was done on the basis of a pseudorandom sequence, for example, odd/even hospital number or date of birth, alternation) were excluded. Trials evaluating other therapies other than cryotherapy and LEEP were also excluded.

Data extraction and risk of bias assessment

The risk of bias in each included study was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. Seven domains related to risk of bias were assessed in each included trial since there is evidence that these issues are associated with biased estimates of treatment effect: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) other bias. Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias.[11]

Two authors (MB and GS) independently assessed inclusion criteria, the risk of bias, and data extraction. Disagreements were resolved by discussion. Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. Differences were reviewed and further resolved by common review of the entire process. Data not presented in the original publications were requested from the principal investigators, if possible.

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. Primary and secondary outcomes were defined before data extraction. Outcomes were assessed at the time of biopsy follow-up at 6 months and at 12 months after the procedure. If women did not receive for any reason (e.g., lost to follow-up, pregnancy) biopsy at follow-up, they were excluded from the analysis. All authors were contacted for missing data.

The primary outcome was the persistence of the disease, defined as disease (any grade of CIN) present at 6-month follow-up after treatment. The secondary outcomes were recurrence, defined as disease (any grade of CIN) present at 12 months after treatment and treatment complications.

Statistical analysis

The data analysis was completed independently by two authors (MB and GS) using Review Manager version 5.3 (the Nordic Cochrane Centre, Cochrane Collaboration, 2014, Copenhagen, Denmark). The completed analyses were then compared, and any difference was resolved by discussion. Statistical heterogeneity across studies was assessed using the Higgins I^2 test. Meta-analysis was performed using the random-effects model of DerSimonian and Laird to produce summary treatment effects in terms of relative risk (RR) with 95% confidence interval (CI).

Potential publication biases were assessed statistically using Begg's and Egger's tests.

$P < 0.05$ was considered statistically significant.

We planned the following subgroup analyses for the primary endpoint: (1) HIV-seropositive versus HIV-seronegative women and (2) trials on CIN2 and CIN3 only.

The meta-analysis was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

Results

Study selection and population characteristics

Four trials, including 1035 women, were identified as relevant and included in the meta-analysis [Figure 1].[12-15] Data from one trial[13] were also obtained by a secondary analysis published only as abstract.[16] Publication bias, assessed statistically using Begg's and Egger's tests, showed no significant bias ($P = 0.47$ and $P = 0.51$, respectively). Statistically, heterogeneity within the trials was low with no inconsistency ($I^2 = 0\%$) for the primary outcome.

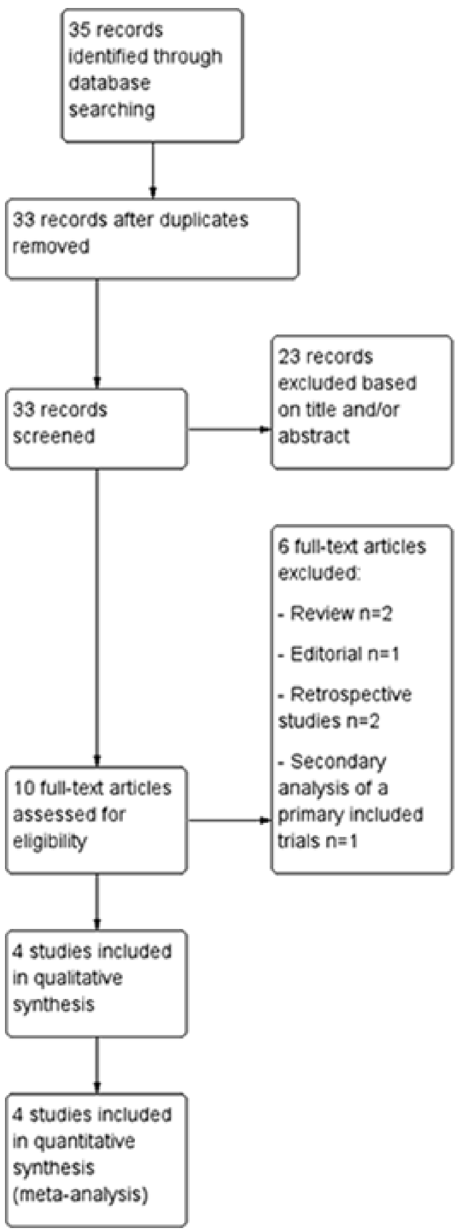

Figure 1: Flow diagram of studies identified in the systematic review (Preferred Reporting Items for Systematic Reviews and Meta-Analyses template)

The quality of the RCTs included in our meta-analysis was assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[11] Most trials were at low or moderate risk of bias. All the included studies had a low risk of bias in "random sequence generation." The appropriate method of sequence generation was used to assigned women to the treatment groups. Adequate methods for allocation of women were used in all the trials. None of the trials reported whether or not the outcome assessor was blinded, except for the trial of Chirenje *et al*. where the investigators collecting and analyzing the data were blinded to the treatment mode [Figure 2a and b].

Table 1 shows the characteristics of the included clinical trials. Of the 1035 enrolled women, 516 women were randomized in the LEEP group and 519 in the cryotherapy group.

LEEP was usually described as the following: staining the cervix with acetic acid solution; abnormal areas were identified and stained with Lugol's iodine; and local anesthetic was administered around the cervix. 20 mm × 8 mm loop was used to remove the lesion. Cryotherapy was usually described as the following: lesions were identified by colposcopy, freezing the lesions for two 3-min application of nitrous oxide separated by thaw [Table 2].

Mitchell *et al*. and Singh *et al*. included women with CIN1+, while Chirenje *et al*. and Smith *et al*. included only women with CIN2+ [Table 1]. Overall, a total of 200 women with CIN1 and a total of 835 women with CIN2–3 were included in the study [Table 3].

Synthesis of results

Table 4 shows the primary and secondary outcomes. Overall, 94.9% of the women (982/1035) had histological biopsy results at the 6-month follow-up visit, and data were available for the primary endpoint. Pregnancy was the most common cause of loss to follow-up. About 72.9% of the randomized women (755/1035) had histological biopsy results at the 12-month follow-up. Women who received LEEP for CIN had a significantly lower persistence at 6-month follow-up biopsy (RR: 0.87, 95% CI: 0.76–0.99) [Figure 3] and significantly lower recurrence at 12-month follow-up biopsy (RR: 0.91, 95% CI: 0.84–0.99) compared to those who received cryotherapy. No between-group differences were found in the complications rate, but the analyses were not powered for these outcomes. LEEP was also associated with significantly lower risk of high-grade SIL (HSIL) at 6-month Pap smear follow-up (RR: 0.45, 95% CI: 0.28–0.75) and at 12-month (RR: 0.41, 95% CI: 0.26–0.65) Pap smear follow-up compared to cryotherapy [Table 4].

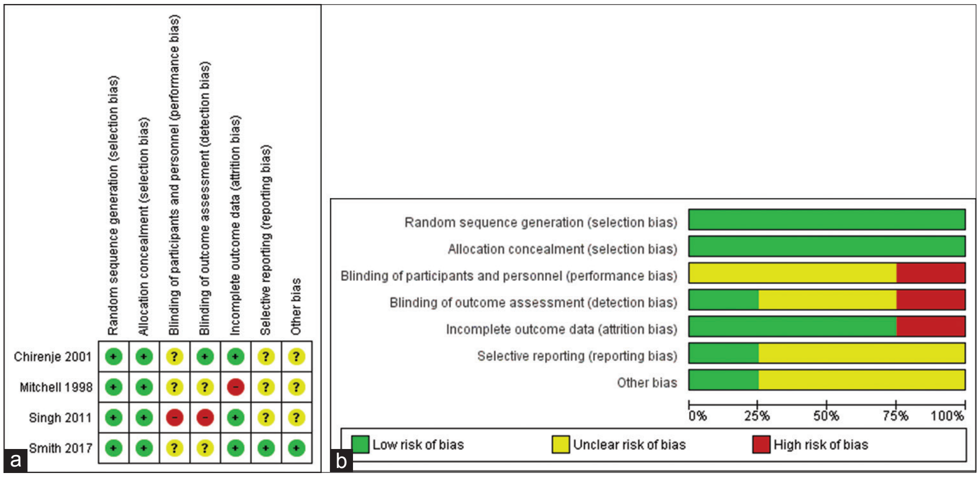

Figure 2: Assessment of risk of bias. (a) Summary of risk of bias for each trial; plus sign: low risk of bias; minus sign: high risk of bias; question mark: unclear risk of bias. (b) Risk of bias graph about each risk of bias item presented as percentages across all included studies

Table 1: Characteristics of the included studies

	Study location	Number of participants*	Inclusion criteria	HIV status	Exclusion criteria
Mitchell *et al.*, 1998[12]	USA	269 (130 vs. 139)	CIN1+	HIV-seropositive and HIV-seronegative	Prior treatment for high-grade cytology; invasive cervical cancer
Chirenje *et al.*, 2001[13]	Zimbabwe	400 (200 vs. 200)	CIN2+	HIV-seropositive and HIV-seronegative	Prior treatment for high-grade cytology; invasive cervical cancer
Singh *et al.*, 2011[14]	India	200 (100 vs. 100)	CIN1+	HIV-seropositive and HIV-seronegative	Prior treatment for high-grade cytology; invasive cervical cancer
Smith *et al.*, 2017[15]	South Africa	166 (86 vs. 80)	CIN2+	HIV-seropositive only	Prior treatment for high-grade cytology; invasive cervical cancer; cervical lesions not appropriate for cryotherapy (>75% of the cervix or lesion within the cervical canal with borders not visible)

*Data are presented as total number (number in the LEEP group vs. number in the cryotherapy group). HIV: Human immunodeficiency virus, CIN: Cervical intraepithelial neoplasia, LEEP: Loop electrosurgical excision procedure

Table 2: Details of procedures

	LEEP	Cryotherapy
Mitchell *et al.*, 1998[12]	Staining the cervix with acetic acid solution. Abnormal areas were identified and stained with Lugol's iodine. Local anesthetic was administered around the cervix. 20 mm × 8 mm loop was used to remove the lesion and the transformation zone in one pice if the cervix was 4 cm or smaller. If the cervix was larger than 4 cm, the tissue was removed in two section	Lesions identified by colposcopy. Freezing the lesions for two 3 min application of nitrous oxide separated by thaw
Mitchell *et al.*, 1998[12]	Staining the cervix with 4% acetic acid solution Local anesthetic was administered around the cervix. 2 cm × 2 cm electrode was used for large lesions and 1 cm × 1 1 cm for smaller lesions. A few of the large lesions were removed in two sections	Lesions identified by colposcopy. Freezing the lesions for two 2 min application of nitrous oxide separated by thaw
Singh *et al*, 2011[14]	leep was done under short general anesthesia	Freezing the lesions for two 3 min application of nitrous oxide separated by 5 min of thawing
Smith *et al.*, 2017[15]	Electrosurgical unit with smoke evacuation system. Staining the cervix with 5% acetic acid solution. Abnormal areas were identified and stained with Lugol's iodine. Local anesthetic was administered around the cervix. The selection of a loop electrode was made depending on the size of lesion. A few of the large lesions were removed in two sections	VIA conducted by applying 5% acetic acid solution. Freezing the lesions for two 3 min application of nitrous oxide separated by 5 min of thawing

LEEP: Loop electrosurgical excision procedure, VIA: Visual inspection with acetic acid

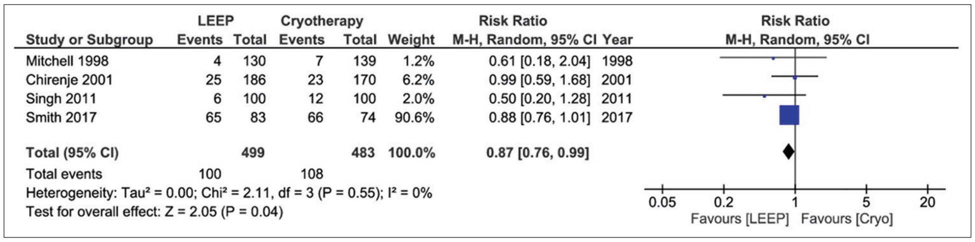

Figure 3: Forest plot for the risk of persistence of the disease, defined as any grade of cervical intraepithelial neoplasia at the biopsy 6 months after the procedure

Table 3: Characteristics of the included women

	CIN1, *n* (%)	CIN2, *n* (%)	CIN3, *n* (%)	HPV DNA positive, *n* (%)	Pap smear negative, *n* (%)	LSIL, *n* (%)	HSIL, *n* (%)
Mitchell *et al*., 1998[12]	40/130 (30.8) versus 42/139 (30.2)	43/130 (33.0) versus 50/139 (36.0)	47/130 (36.2) versus 47/139 (33.8)	70/130 (53.8) versus 76/139 (54.7)	Not reported	Not reported	Not reported
Mitchell *et al*., 1998[12]	Not reported	Not reported	Not reported	Not reported	0/200 (0) versus 0/200 (0)	0/200 (0) versus 0/200 (0)	200/200 (100) versus 200/200 (100)
Singh *et al*., 2011[14]	55/100 (55.0) versus 63/100 (63.0)	37/100 (37.0) versus 32/100 (32.0)	8/100 (8.0) versus 5/100 (5.0)	Not reported	Not reported	Not reported	Not reported
Smith *et al*, 2017[15]	Not reported	60/86 (69.9) versus 56/80 (70.0)	26/86 (69.2) versus 24/80 (30.0)	74/86 (86.0) versus 70/80 (87.5)	2/86 (2.3) versus 2/80 (2.5)	20/86 (23.3) Versus 18/80 (22.5)	64/86 (74.4) versus 60/80 (75.0)
Total	95/230 (41.3) versus 105/239 (43.9)	140/316 (44.3) versus 138/315 (43.8)	81/316 (25.6) versus 76/319 (24.1)	144/216 (66.7) versus 146/219 (66.7)	2/286 (0.7) versus 2/280 (0.7)	20/286 (7.0) versus 18/280 (6.4)	264/286 (92.3) versus 260/280 (92.9)

Data are presented as *n* (%) in the LEEP group versus *n* (%) in the cryotherapy group. CIN: Cervical intraepithelial neoplasia, LEEP: Loop electrosurgical excision procedure, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, HPV: Human papillomavirus

Subgroup analysis in trials including only women with CIN2+ and subgroup analysis in trials including HIV-positive only women concurred with the overall analysis in showing significant benefit of LEEP for the primary endpoint (RR: 0.89, 95% CI: 0.77–0.98 and RR: 0.88, 95% CI: 0.76–0.99, respectively).

Discussion

Main findings

This meta-analysis of four RCTs, including 1035 women with CIN, showed that treatment with LEEP was associated with a significantly lower risk of persistence disease at 6 months and recurrence disease at 12 months compared to treatment with cryotherapy. The meta-analysis also showed a significant reduction of HSIL at 6-month and at 12-month Pap smear follow-up and nonsignificant benefits in the other secondary outcomes, including CIN3 at 6 and 12-month follow-up biopsy. No between-group differences were found in the complications rate comparing the two treatments with a nonsignificant increase in pain, infection, and bleeding in women receiving LEEP. However, the meta-analysis was not powered for these outcomes.

Strengths and limitations

This may be the first meta-analysis of RCTs comparing LEEP with cryotherapy in women with CIN. No prior meta-analyses are up to date and comprehensive in terms of included studies, and the number of women included in our analysis is the highest among all review available. Potential publication bias was assessed by statistical tests, and statistics suggested no publication bias. The statistical heterogeneity within the trial was low for the primary endpoint. Overall, >90% of the women had histological biopsy results at the 6-month follow-up visit for the primary endpoint.

The major shortcoming of this review was the inclusion of only four trials. Given the intervention, none of the included trials were double blind. The meta-analysis was underpowered to detect significant differences in the complications rate.

Implications

The American College of Obstetricians and Gynecologists and the American Society for Colposcopy and Cervical Pathology in the 2012 ASCCP Consensus Guidelines Conference recommended colposcopy for women with HSIL cytology.[17] In the case of colposcopy and biopsy, women with CIN should be managed with either excision or ablation. Therefore, both LEEP and cryotherapy are reasonable and recommended treatment for women with CIN.[17] No specific recommendations are made in HIV-positive women. HIV-positive women have an increased risk of cervical cancer, as well as an increased risk of procedure-related complications.[18]

Table 4: Primary and secondary outcomes

	Mitchell *et al.*, 1998[12]	Mitchell *et al.*, 1998[12]	Singh *et al.*, 2011[14]	Smith *et al.*, 2017[15]	Total, *n* (%)	I^2 (%)	RR (95% CI)
Persistence at 6 months*	4/130 versus 7/139	25/186 versus 23/170	6/100 versus 12/100	65/83 versus 66/74	100/499 (20.0) versus 108/483 (22.4)	0	0.87 (0.76-0.99)
Recurrence at 12 months**	17/130 versus 26/139	18/168 versus 18/161	Not reported	74/83 versus 72/74	109/381 (26.6) versus 116/374 (31.0)	0	0.91 (0.84-0.99)
Biopsy CIN3 at 6 months	Not reported	3/186 versus 4/170	2/100 versus 2/100	1/83 versus 4/74	6/369 (1.6) versus 10/344 (2.9)	0	0.59 (0.21-1.66)
Biopsy CIN3 at 12 months	Not reported	4/168 versus 12/161	Not reported	4/83 versus 5/74	8/251 (3.2) versus 17/235 (7.2)	0	0.45 (0.20-1.04)
Pap-smear LSIL at 6 months	Not reported	4/186 versus 8/170	Not reported	67/83 versus 67/74	71/269 (26.4) versus 75/244 (30.7)	41	0.77 (0.41 to-1.46)
Pap-smear LSIL at 12 months	Not reported	2/168 versus 6/161	Not reported	78/83 versus 73/74	80/251 (31.9) versus 79/235 (33.6)	77	0.63 (0.13-3.09)
Pap-smear HSIL at 6 months	Not reported	3/186 versus 4/170	Not reported	15/83 versus 31/74	18/269 (6.7) versus 35/244 (14.3)	0	0.45 (0.28-0.75)
Pap-smear HSIL at 12 months	Not reported	4/168 versus 12/161	Not reported	16/83 versus 33/74	20/251 (8.0) versus 45/235 (19.1)	0	0.41 (0.26-0.65)
Pain	1/130 versus 0/139	86/186 versus 74/170	43/100 versus 14/100	Not reported	130/416 (31.3) versus 88/409 (21.5)	85	1.84 (0.69-4.93)
Infection	1/130 versus 0/139	0/200 versus 0/200	0/100 versus 0/100	Not reported	1/430 (0.2) versus 0/439	Not applicable	3.21 (0.13-78.01)
Bleeding	7/130 versus 0/139	4/200 versus 1/200	4/100 versus 3/100	Not reported	15/430 (3.5) versus 4/439 (0.9)	28	3.03 (0.75-12.20)
Stenosis	1/130 versus 2/139	0/200 versus 0/200	0/100 versus 0/100	0/83 versus 0/74	1/513 (0.2) versus 2/513 (0.4)	Not applicable	0.53 (0.05-5.83)

*Any grade of CIN at 6 months follow-up, **Any grade of CIN at 12-month follow-up. Boldface data, statistically significant. Data are presented as *n* (%) in the LEEP group versus *n* (%) in the cryotherapy group. RR: Relative risk, CI: Confidence interval, LSIL: Low-grade squamous intraepithelial lesion, HSIL: High-grade squamous intraepithelial lesion, CIN: Cervical intraepithelial neoplasia

In LEEP, a wire electrical loop removes the abnormal cervical lesion within a clinical setting. Cryotherapy treatment is the local destruction of cervical tissue by application of subfreezing temperatures causing crystallization and rupture of cell membranes. Cryotherapy has the limitation that approximately 25% of CIN2+ lesions cannot be treated adequately (those that cover >75% of the cervix or extend into the cervical canal).[9,10,19]

Our review provided evidence that LEEP treatment is superior in terms of less persistence and less recurrence rate at 6 and 12-month follow-up visit compared to cryotherapy. Our study concurred with prior findings of Santesso *et al*.[20]

Conclusions

In summary, in women with CIN, treatment with LEEP was associated with a significantly lower risk of persistence disease at 6 months and recurrence disease at 12 months compared to treatment with cryotherapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Parkin DM. Cancer in developing countries. Cancer Surv 1994;19-20:519-61.
2. Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. Obstet Gynecol 2009;113:18-25.
3. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, *et al.* Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: A retrospective cohort study. Lancet Oncol 2008;9:425-34.
4. Jones HH. Treatment of cervical intraepithelial neoplasia. Clin Obstet Gynecol 1990;33:826-36.
5. De Vuyst H, Lillo F, Broutet N, Smith JS. HIV, human papillomavirus, and cervical neoplasia and cancer in the era of highly active antiretroviral therapy. Eur J Cancer Prev 2008;17:545-54.
6. Massad LS, Riester KA, Anastos KM, Fruchter RG, Palefsky JM, Burk RD, *et al*. Prevalence and predictors of squamous cell abnormalities in Papanicolaou smears from women infected with human immunodeficiency virus-1. J Acquir Immune Defic Syndr 1999;21:33-41.
7. Abraham AG, D'Souza G, Jing Y, Gange SJ, Sterling TR, Silverberg MJ, *et al*. Invasive cervical cancer risk among HIV-infected women: A North American multi-cohort collaboration prospective study. J Acquir Immune Defic Syndr 2013;62:405-13.
8. Chamot E, Kristensen S, Stringer JS, Mwanahamuntu MH. Are treatments for cervical precancerous lesions in less-developed countries safe enough to promote scaling-up of cervical screening programs? A systematic review. BMC Womens Health 2010;10:11.
9. Pfaendler KS, Mwanahamuntu MH, Sahasrabuddhe VV, Mudenda V, Stringer JS, Parham GP, *et al.* Management of cryotherapy-ineligible women in a "screen-and-treat" cervical cancer prevention program targeting HIV-infected women in Zambia: Lessons from the field.

Gynecol Oncol 2008;110:402-7.
10. Mwanahamuntu MH, Sahasrabuddhe VV, Pfaendler KS, Mudenda V, Hicks ML, Vermund SH, *et al.* Implementation of 'see-and-treat' cervical cancer prevention services linked to HIV care in Zambia. AIDS 2009;23:N1-5.
11. Higgins JP, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. The Cochrane Collaboration; 2011. Available from: http://www.training.cochrane.org/handbook. [Last update on 2011 Mar 15; Last accessed on 2017 Nov 05].
12. Mitchell MF, Tortolero-Luna G, Cook E, Whittaker L, Rhodes-Morris H, Silva E, *et al.* A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. Obstet Gynecol 1998;92:737-44.
13. Chirenje ZM, Rusakaniko S, Akino V, Mlingo M. A randomised clinical trial of loop electrosurgical excision procedure (LEEP) versus cryotherapy in the treatment of cervical intraepithelial neoplasia. J Obstet Gynaecol 2001;21:617-21.
14. Singh A, Arthur B, Agarwal V. LEEP verses cryotherapy in CIN. J Obstet Gynaecol India 2011;61:431-5.
15. Smith JS, Sanusi B, Swarts A, Faesen M, Levin S, Goeieman B, *et al.* A randomized clinical trial comparing cervical dysplasia treatment with cryotherapy vs. loop electrosurgical excision procedure in HIV-seropositive women from Johannesburg, South Africa. Am J Obstet Gynecol 2017;217:183.e1.
16. Chirenje ZM, Rusakaniko S, Akino V, Munjoma M, Mlingo M. Effect of HIV disease in treatment outcome of cervical squamous intraepithelial lesions among Zimbabwean women. J Low Genit Tract Dis 2003;7:16-21.
17. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, *et al.* 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis 2013;17:S1-27.
18. Sansone M, Saccone G, Migliucci A, Saviano R, Capone A, Maruotti GM, *et al.* Screening for cervical carcinoma in HIV-infected women: Analysis of main risk factors for cervical cytologic abnormalities. J Obstet Gynaecol Res 2017;43:352-7.
19. Sansone M, Sarno L, Saccone G, Berghella V, Maruotti GM, Migliucci A, *et al.* Risk of preeclampsia in human immunodeficiency virus-infected pregnant women. Obstet Gynecol 2016;127:1027-32.
20. Santesso N, Mustafa RA, Wiercioch W, Kehar R, Gandhi S, Chen Y, *et al.* Systematic reviews and meta-analyses of benefits and harms of cryotherapy, LEEP, and cold knife conization to treat cervical intraepithelial neoplasia. Int J Gynaecol Obstet 2016;132:266-71.