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Is Loop Electrosurgical Excision Procedure (LEEP) More Effective Than Cryotherapy for Treating Cervical Intraepithelial Neoplasia?

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Abstract

Objective: Abnormal cervical cells, also called cervical intraepithelial neoplasia (CIN), are detected during a pap smear, and the grade of CIN determines the severity of the disease. Two treatments routinely used, loop electrosurgical excision procedure (LEEP), and cryotherapy are compared to determine efficacy in cure rates, disease persistence and related adverse effects.

Data Sources: MEDLINE, CINAHL and PUBMED were the selected databases for the literature search. The keywords used were CIN, LEEP, cryotherapy, abnormal cells and cervical cancer.

Study selection: The Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) guidelines were followed resulting in seven papers included in the review.

Data Extraction: A table was used to summarise the results of the data extraction process. The quality of the studies was assessed using the Holland & Rees [1] evaluation framework.

Data Synthesis: Comparisons of outcomes were made, and the results presented using a narrative synthesis following guidelines provided by Campbell, McKenzie, Sowden et al. [2].

Conclusion: Cryotherapy is less effective when endocervical lesions are involved, whereas LEEP can effectively excise cells extending into the cervical canal. LEEP was associated with significantly lower persistence rates, but cure rates were similar across both interventions.

Keywords: Cervical Cancer; Cryotherapy; LEEP; Pre-cancer cells; Treatment

Introduction

Globally, cervical cancer is the fourth most common cancer in women, with an estimated 604,000 new cases and 342,000 deaths reported in 2022. It primarily affects sexually active women aged 30-45 years. Incidence and deaths are heavily weighted in low- and middle-income countries [3]. It typically takes 15-20 years for abnormal cervical cells to advance to cancer, making the treatment of abnormal cervical pre-cancer cells crucial to prevent disease progression [4].

Pre-cancerous cells are a collective term to describe several abnormal characteristics of cervical changes, commonly described as cervical dysplasia or cervical intraepithelial neoplasia (CIN). CIN is classified on a scale of one to three, one being the least severe, with around 60% of cases of CIN 1 regressing to normal cells within a year, and CIN 2 and CIN 3 more likely to require treatment to prevent malignancy [5]. CIN is often caused by infection of the human papillomavirus (HPV) and approximately 90% of all women with CIN, and over 99% of cervical cancers presenting with HPV-positive results [6].

Pap smears are used to detect precancerous CIN and HPV in women between the age of 25 and 65 years. When abnormal cells are detected during a pap smear, women are referred for further investigation and biopsy. If CIN is present, the nurse or doctor will recommend treatment to remove the abnormal tissue.

Treatment options include cryotherapy when the entire pre-cancerous lesion is visible and does not cover more than 75% of the ectocervix; and LEEP is recommended in women with CIN2+ [7]. Cryotherapy involves a long cryoprobe that is pumped with liquid nitrogen or compressed argon gas, producing a very cold probe tip used to freeze and destroy the abnormal tissue [8]. LEEP involves the use of a small hot wire loop to remove a thin layer of area of abnormal tissue [9].

This review investigates WHO recommended treatments for CIN, considering barriers to screening and treatment, cure rates, and treatment outcomes. Specifically, it will consider: (1) whether treatment efficacy is variable to the CIN grade and location; (2) the differences in the recurrence rate of CIN following LEEP or cryotherapy; and (3) the adverse effects and risks associated with each intervention.

Methods

This review takes a global perspective. A review of this type would predominately focus on papers published in the past 10 years, however, a paucity of available research and several highly relevant articles outside of this date were included as they provided key contributions to this review.

An initial search was undertaken using multiple electronic databases, including CINAHL (EBSCO), PubMed and MEDLINE. The keywords used to identify relevant studies included LEEP, cervical intraepithelial neoplasia (CIN), cryotherapy, abnormal cells, and cervical cancer. Boolean operators were used to combine keywords using ‘AND’, ‘OR’ and ‘NOT’, ‘AND’ and ‘OR’. Inclusion criteria were women over 18 years, studies investigating LEEP or cryotherapy, undertaken anywhere in the world, published 2005- 2023 and focused on cervical CIN/ abnormal cells.

Data Synthesis

The Holland and Rees quantitative framework [1] was used to critically review the relevance and quality of the included papers. Quantitative data is typically analysed using meta-analysis, however due to the small number of included papers, the data are presented as a narrative synthesis consistent with guidelines published by Campbell et al. [2].

Findings

The initial search identified 427 papers. After duplicates and studies that did not meet the inclusion criteria were removed or excluded, seven studies remained. This process is documented in the PRISMA diagram (Figure 1). The data extraction table is included as Appendix 1.

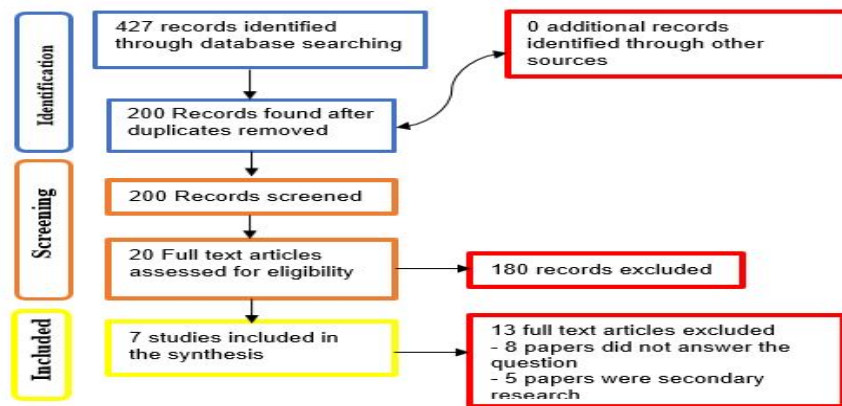


Figure 1: PRISMA.

The aim of this review was to compare the effectiveness of LEEP versus cryotherapy in treating cervical intraepithelial neoplasia (CIN), to prevent cervical cancer. The narrative synthesis is presented as comparisons: (1) cure rates; (2) cost-effectiveness and resource barriers; and (3) adverse effects.

Cure Rates

Sankaranarayanan et al. [10] investigated cure rates of LEEP and found 98.1% of women with CIN 1 were cured, 93.6% for CIN 2, and 85% for CIN 3, with a significantly lower cure rate of 89.2% for CIN 2-3 ($P < 0.001$). Similarly, cure rates one year post LEEP were 93% for CIN 1, 85.5% for CIN 2, and 72.7% for CIN 3 [11], area of the lesion was the only estimation of cure rates at one-year follow-up ($P < 0.05$). Duesing and colleagues [12] also demonstrated a very high efficacy of LEEP even 50 months following the procedure. CIN persistence was minimal and found in only 9 women (3.4%) and a disease recurrence in only 4 women (1.5%), with a further two women having persistent HPV infection after LEEP. In terms of recurrence, Lieb et al. [13] reported a 4.17% recurrence rate following LEEP but suggested that removing additional endocervical tissue appeared to minimise recurrence of CIN ($P < 0.003$).

Nene and colleagues [14] also suggested cryotherapy is less effective in the treatment of CIN 2 and CIN 3. They found 96.4% of women with CIN 1 were cured at follow-up, compared with 82.1% for CIN 2, and 82.1% for CIN 3 ($P < 0.001$) [14]. Similarly, Luciani et al. [15] reported that by the end of the follow-up period, 92.1% of women with CIN 1 were cured, 92% with CIN 2, and 70% with CIN 3. Cryotherapy effectively cured 418 women (88%), including 49 (70%) with a baseline diagnosis of CIN 3. However, 340 (18.6%) women who had an initial CIN 1 histology had persistent CIN 2-3 following cryotherapy. Further, out of 62 women with a baseline diagnosis of CIN 2, only 1 (1.6%) woman had CIN 2-3 detected at follow-up.

Wesley et al. [16] achieved 93% cure rates for CIN 1, and 86.7% for CIN 2, which correlate with other researchers. Wesley et al. [16] however, posited that cryotherapy should be avoided in lesions that extend to the endocervical canal. In women with CIN 1 involving endocervical lesions who received cryotherapy, only 60% were cured. This cure rate was 55% for CIN 2 and 25% for CIN 3 when endocervical lesions were present. They concluded that the low cure rates “clearly show the inappropriateness of cryotherapy when endocervical lesions are involved, especially for high-grade lesions” (page number?).

Cost-Effectiveness and Barriers to Treatment

Various barriers have been identified in the implementation of cryotherapy and LEEP in low and middle-resource settings. The main findings were lack of well-trained medical staff, poor infrastructure, unclear communication of results and women not fully understanding the importance of immediate treatment following an abnormal cervical result. Nene et al. [14] stated that additional training of health professionals to perform cryotherapy would improve cervical screening programs in settings lacking resources, while also emphasising common difficulties in tracing women for follow-up appointments. Similarly, Luciani et al. [15], suggested that performing cryotherapy treatment in primary settings immediately following cervical inspections ensures that the pre-cancerous lesions are treated early, and would reduce the number of women lost to follow-up. Luciani et al [15] also stated that many follow-up failures were due to the loss of referrals to secondary care with statistics showing only 10% of women did not receive scheduled treatment in primary care, compared to 40% of women that did not receive scheduled treatment when referred to secondary care in a hospital. In terms of cost, cryotherapy is less expensive than other treatments due to the low cost of carbon dioxide (US \$8.18), compared with LEEP which costs US \$27.28. However, insufficiency of persistent gas supply, supply logistics, and cost of gas refrigerants may make cryotherapy unattainable in low resource settings [16]. Despite this, several studies suggested that training mid-level healthcare staff to perform cryotherapy increased the accessibility and availability of treatment in primary settings, as well reduce follow-up losses [14-16].

LEEP has similar barriers to access and treatment availability. Sankaranarayanan et al. [10] asserted that to improve CIN treatment coverage, loop electrodes need to be more affordable, and more health professionals require training so that see-and-treat same-day screening and treatment can be implemented. Follow-up was also noted as an issue in this study, with 25% of the women lost to follow-up. Despite this, the findings showed that LEEP can be effectively performed in low-resource settings, with a low prevalence of complications, and a high rate of disease management. In low- and middle-income countries a lack of trained medical professionals in the use of LEEP place women in these settings at a disadvantage [11]. However, from a practical perspective, LEEP is a superior treatment due to its low equipment costs and shorter duration of training.

Adverse Effects

All seven studies discussed adverse effects experienced by women following either cryotherapy or LEEP treatments. Luciani et al. [15], conducted a study on 1398 women following cryotherapy treatment and reported no serious complications; however, 5.8% reported abnormal discharge, 2% reported bleeding and 1% reported fever within two weeks post-treatment. Nene et al. [14] used a large sample of women ($n=1068$) following cryotherapy. The minor adverse effects reported were consistent with Luciani and colleagues [15] and included pain or cramps 1% women, mild bleeding in 1.9%, excessive discharge in 1%, and fever in 0.4%. Further support was added by Wesley et al. [16] with women experiencing discharge 17.3%, mild pain and cramping 5.8%, light bleeding 1.2%, fainting and flushing 0.6%, a mild allergy 0.6%, and an inflamed cervix 0.6%. Combining the findings of these three papers, the most significant reported adverse effect of cryotherapy was vaginal discharge.

The adverse effects reported post LEEP were consistent with those reported for cryotherapy. 2.5% of women reported mild pain or cramps. 3.2% vaginal discharge, 2.8% mild bleeding, 2.5% menorrhagia, and 1.1% fever [11]. Rema and colleagues findings were consistent with Sankaranarayanan et al. [10], who found mild pain or cramps were experienced in 3.5% of women, while others experienced mild bleeding 1.6%, vaginal discharge 0.5%, menorrhagia 0.3%, and fever 0.4%. However, Duesing et al. [12] found that 251 women (or 94.65%) of women from a sample size of 266 reported no complications at all. Finally, Lieb et al. [13] found evidence of an increased risk of vaginal infections during pregnancy in women who had previously undergone LEEP. 4.4% ($n=91$) of women suffered a vaginal infection, and this was thought to be caused by the alteration of the micro-environment of the uterine cervix by the intervention.

Discussion

CIN cure rates are variable based on the severity, size, and areas involved. CIN 3 cure rates are significantly lower, and this is inconsistent for LEEP and cryotherapy treatments. Not treating CIN 3 would inevitably lead to cervical cancer, so despite lower cure rates it is essential that interventions are utilised. LEEP was found to have lower disease persistence rates [12], compared with cryotherapy 18.6%, [15]. LEEP removes the abnormal lesion as well as surrounding healthy tissue at a depth of 6 to 7 mm, whereas cryotherapy only removes 5 to 7 mm, which may explain why disease persistence and recurrence are higher in cryotherapy [17]. In CIN 1 and CIN 2 lesions, there is no clear indication that LEEP or cryotherapy is more effective. Both treatments have high cure rates, with the only independent factor that can be identified to choose a treatment option is the location and severity of the lesion. LEEP can be used when lesions are further into the cervical canal, and cryotherapy should only be used in visible localised lesions as it will not be as effective.

Barriers to CIN treatment were common across the studies carried out in low- and middle-income countries due to a lack of trained medical staff, and low health literacy. Findings of Wesley et al. [16] state that low performance of CIN screening and treatment programmes in low- and middle-income countries is attributed by poor infrastructure, no or untimely communication of screening results, and travel-related factors that all lead to loss of follow-up. This study found multiple limitations to CIN treatment, one being the poor messages conveyed by the doctors and counsellors about the importance of receiving cryotherapy immediately after cervical cancer screening. This meant that women were not fully aware of the severity of their results, and many preferred to consult with their family members prior to returning for treatment. Nene et al. [14] also stated that the dearth of individuals trained to perform colposcopy and CIN treatment is a major constraint in low-income countries.

Nene et al [14] showed that cryotherapy is more cost-effective than LEEP, however, there is not enough research and evidence to choose the “right” treatment, regardless of cost-effectiveness, but the most important aspect is that patients have access to treatment and monitoring, regardless of which intervention is used. In summary, cryotherapy is more cost-effective than LEEP, but both treatments are equally efficient. LEEP instruments are expensive and require electricity, but cryotherapy requires a constant gas supply and refrigerant storage. In low-income countries cryotherapy seems to be the more cost-effective treatment due to lower costs and availability for local purchase [15], however, linking back to cure rates, LEEP can be used on larger lesions, so this is also important when considering which treatment to invest in.

All seven studies highlighted associated mild adverse effects in their participants after LEEP or cryotherapy. Abnormal discharge had the highest incidence among women following cryotherapy, and postoperative bleeding was the most common after LEEP. Adverse effects were the same or similar across the two treatments and were all mild and easily managed. It is difficult to say whether one treatment has fewer adverse effects than the other, as there are similar trends across both, and every procedure comes with side effects, but not all patients will experience them.

Recommendations for Practice

LEEP and cryotherapy are both effective procedures with high cure rates and mild, highly tolerable adverse effects. It is recommended, to reduce the risk of recurrence, LEEP should be performed on larger, high-grade lesions, that extend further into the endocervix or cervical canal, as this method can excise the lesion and remove extra tissue. Cryotherapy should be used in smaller and more visible lesions, as the evidence suggests less efficacy when endocervical lesions are involved [16]. However, given the effectiveness of both LEEP and cryotherapy on CIN 1 and CIN 2 lesions, early treatment is vital to ensure removal of effected cells and reduce the risk of disease progression.

A further recommendation is implementing cryotherapy and LEEP treatment into primary care settings. This would reduce known barriers to attending outpatient appointments [16,18], and enable treatment to be provided in a local, familiar environment by a trusted GP or nurse. This could mitigate the risk of losing women to follow-up when referred to secondary care and increase the number of women screened and treated.

Conclusion

Both LEEP and cryotherapy were highly effective treatments in CIN 1 lesions, with a slightly reduced efficacy in CIN 2. All studies indicated significantly lower cure rates when CIN 3 lesions were involved. Cryotherapy is less effective when CIN lesions are large and are present in the endocervix or endocervical canal. LEEP is more effective at treating larger, high-grade lesions as it can excise more tissue and remove cells in the endocervix, lowering disease persistence. Minor adverse effects were reported in all studies, the most troubling being increased vaginal discharge. It is unclear which treatment is more cost-effective, and further financial analysis needs to be undertaken to determine this.

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