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CITATION

Wyse, A; Seah, W A.; O'Neill, J; Byrne, Paul (2017): The use of cold coagulation for the treatment of cervical intraepithelial neoplasia. Royal College of Surgeons in Ireland. Journal contribution. https://hdl.handle.net/10779/rcsi.10787465.v2

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The use of cold coagulation for the treatment of cervical intraepithelial neoplasia

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Abstract

In 2015, Cold Coagulation was introduced as a treatment for cervical intraepithelial neoplasia (CIN) at our colposcopy clinic. We reviewed the 6-month follow up data of the first 200 women who underwent Cold Coagulation using cytology and HPV status as tests of cure (TOC). A random sample of 200 patients treated by Large Loop Excision of the Transformation Zone (LLETZ) during the same period was used to compare treatment outcome. Six months following treatment,173 (86.5%) of the women treated by CC and 167 (83.5%) treated by LLETZ had negative cytology. (x2= P>0.05). 148 (74%) treated by Cold Coagulation and 166 (83%) treated by LLETZ were HPV negative (x2= P<0.05). One hundred and thirty-nine (70%) women treated by Cold Coagulation and 152 (76%) treated with LLETZ had normal cytology and were HPV negative. This audit of our initial experience supports the observation that Cold Coagulation is as effective as LLETZ in the management of CIN when cervical cytology is used as a test of cure.

Introduction

Cervical Check, Ireland's National Cervical Screening Programme was set up in September 2008[1]. The programme provides free cervical smears to all women aged between 25 and 60 years to detect precancerous changes in the cervix. If abnormalities are detected on cytology or for clinical reasons, patients are referred for colposcopy. The colposcopy service identifies and treats patients with precancerous disease to prevent progression to cervical cancer[2]. To date, Large Loop Excision of the Transformation Zone (LLETZ) has been the main treatment provided[1]. Between 1.9.2013 to 31.8.2014 6,725 treatments were performed in Ireland[1]. Of these 5,674 (84.4%) were LLETZ procedures1. However, there is increasing evidence that LLETZ for treatment of cervical intraepithelial neoplasia (CIN) is associated with preterm delivery and may be associated with increased perinatal mortality[3,4,5].
Cold Coagulation is an ablative technique that was developed by Kurt Semm in the 1960's. Prior to treatment, a biopsy is taken to confirm the presence of CIN and exclude invasion. The Semm cold coagulator is heated to 100 °C, and applied to the transformation zone of the cervix for 30 seconds[6, 7]. Two, three, or four applications may be used depending on the size of the transformation zone. A recent meta- analysis looking at the efficacy of Cold Coagulation has found it to be as effective as LLETZ for treating CIN, with cure rates of up to 96%, and having the added benefit of no documented negative impact on fertility and subsequent pregnancies[6]. Until recently, eradication of CIN was assessed by cervical cytology, six and eighteen months following treatment[8]. In 2014, the National Cervical Screening Programme introduced an additional test of cure which assesses the presence of high risk Human Papilloma Virus (HPV) subtypes[8]. In the light of recent publications highlighting the adverse effects of LLETZ on pregnancy outcome, we introduced Cold Coagulation as a treatment option for some of our patients. This study assesses our initial experience with this treatment modality.

Methods

This study was undertaken on the first 200 women who underwent cold coagulation and for whom there was six months follow up data. Data was collected prospectively for patients treated between September 2014 and September 2015. As per the National Cancer Screening Service

Standard Guidelines all patients were required to have a colposcopically directed punch biopsy[8]. Patients with persistent low grade disease (CIN 1) or higher grade disease (CIN 2 or 3) were invited back to the clinic and were given the option of having a cold coagulation treatment if they fulfilled the criteria for treatment using this technique[8]. Patients were not considered suitable for cold coagulation if they were pregnant, if they had a previous ablative or excisional treatment, if the entire transformation zone was not visible, if there was suspicion of endocervical involvement, if there was evidence or suspicion of glandular or invasive disease or a discrepancy between the cytology and biopsy. At the clinic the procedure was explained to the patients and written consent was obtained. Patient data was recorded in the Mediscan colposcopy database and the APEC pathology database. A random sample of 200 patients who underwent a LLETZ procedure during the study period and who had follow up data available at 6 months was used to compare treatment success. All patients had a smear and HPV test done in the colposcopy clinic six months following treatment. Success was defined as negative cytology or a negative HPV test (for high risk sub-types HPV-16 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). The data was analysed in Excel. Ethical approval was obtained from the Clinical Audit department of the Rotunda Hospital.

Results

Data on the first 200 patients who were treated with cold coagulation are presented. The mean age was 31 years (SD = 6.37 years). One hundred and fifteen (57.5%) were nulliparous. Pre-treatment biopsy histology was as follows: CIN 1: 7 (3.5%), CIN 2: 146 (73%), CIN 3: 47 (23.5%).

Table 1. Outcome for women treated with Cold Coagulation compared to those treated with LLETZ.

Follow up results at 6 months	Cold Coagulation	LLETZ	Chi Square
Negative cytology	173 (86.5%)	167 (83.5%)	Chi Sq. = 0.400814 ($p > 0.05$)
HPV negative	148 (74%)	166 (83%)	Chi Sq. = 0.028471 ($p<0.05$)
Negative cytology and HPV negative	139 (70%)	152 (76%)	Chi Sq. = 0.144326 ($p > 0.05$)

Table 2. Cytology results six months following treatment.

Cytology results at 6 months	**CC**	**LLETZ**
NAD	173 (86.5%)	167 (83.5%)
LSIL	20 (10%)	14 (7%)
HSIL	2 (1%)	6 (3%)
ASC-H	1 (.5%)	1 (.5%)
ASC-US	4 (2%)	12 (6%)
Total	**200 (100%)**	**200 (100%)**

Similar outcome data was analyzed for a random sample of 200 patients who had been treated with LLETZ during the same period. The mean age of this group was 36 years (SD = 8.29), 51 (25%) were nulliparous. Pre–treatment referral smear cytology for the LLETZ group was as follows : AGUS : 11 (5.5%), ASC-H :19 (9.5%), GIN :1 (0.5%), LSIL :43 (21.5%), HSIL :113 (56.5%). Thirteen (6.5%) were referred for clinical reasons.

Table 3. Histology results of LLETZ procedures (n-=200)

Normal	4 (2%)
Inadequate sample	1 (.5%)
HPV/ Cervicitis	4 (2%)
CIN 1	43 (21.5%)
CIN 2	45 (22.5%)
CIN 3	100 (50%)
CGIN	2 (1%)
Microinvasive Cancer	1 (.5%)

Patients were followed up at 6 months with a cervical smear and HPV test. The results are shown in Table 1. The cytology results at 6 months for women treated with Cold Coagulation and for those treated with LLETZ are shown in Table 2. The histology results for the 200 women treated with LLETZ are shown in Table 3. None of the women treated with cold coagulation developed any serious complications. One woman was reviewed in the clinic 7 days following treatment complaining of a heavy vaginal discharge. Microbiological culture failed to grow any pathogens in this case.

Discussion

This is an audit of our initial experience with cold coagulation, which was introduced in 2015 as a treatment option for patients with cervical intra-epithelial neoplasia. Subject to strict criteria, it is offered as a choice for nulliparous women or for those whose families are incomplete. We decided to introduce Cold Coagulation as a treatment for our patients because the current gold standard treatment, LLETZ, has been linked with long term obstetrical complications such a preterm labour and miscarriage[3,4]. Published studies to date have used cytology alone as a test of cure to measure treatment success. HPV testing was introduced in 2014 by the National Cancer Screening Service as a test of cure following treatment of CIN. IN view of this, we reviewed both cytology and HPV status as tests of cure[8]. Despite our relative inexperience with this treatment modality, our results have been reassuring. Using cytology as a test of cure, cold coagulation was successful in 173 (86.5%) women (Table1). This compares favourably with other national studies. A recent study in University Hospital Limerick by McCarthy et al, included 93 patient who were treated by cold coagulation and reported treatment success of 79.9% for patients with CIN1 and 81.1% for patients with CIN2/3[9]. A study in Northern Ireland reviewed 725 patients who underwent cold coagulation and reported negative cytology in 632 (87.1%) cases[10]. However when compared with international data, our cure rate is lower. A study in the UK by Parry-Smith et al which looked at 557 patients who were treated by cold coagulation over a ten-year period recorded treatment success rates of 95.7%[11]. Similarly, a study done by Duncan in the early 1990's looked at 1,628 women with CIN3 treated by cold coagulation, and found that disease was eradicated in 95% of cases when reviewed at one year[7].

Our study reports cure rates at 6 months following treatment. Most of the published reports have longer periods of follow up. This is one factor that may be responsible for our lower cure rates. We were anxious to determine if cold coagulation was as effective as LLETZ, so we audited our cure rates at six months rather than waiting for 18 months.When cytology was assessed six months following treatment, there was no significant difference in cure rates for women treated with cold coagulation compared to those treated with LLETZ. Using cytology alone as a test of cure six months following treatment, 167 (83.5%) women treated with LLETZ had a normal cervical smear compared to 173 (86.5%) treated with cold coagulation. We are mindful that the two groups are different in many aspects including age, parity and disease distribution and indeed many patients considered for LLETZ would be deemed unsuitable for ablative treatment. However, prior to the introduction of cold coagulation, this group of women would have been offered a LLETZ treatment. Cold coagulation is primarily offered to a specific group of women who are younger and

nulliparous or with incomplete families. However. the comparison is presented to allow us to assess the relative success of cold coagulation in our unit.

To date, very little data has been published using HPV status as a test of cure following cold coagulation. Reviewing HPV status at 6 months following treatment 148 (74%) of those treated by cold coagulation were HPV negative. This compares less favourably to the group of patients treated by LLETZ with 166 (83%) cases HPV negative at 6 months following treatment. The difference is statistically significant. While studies have shown that HPV testing is helpful as an adjunct to cytology for its high negative predictive value,[12,13,14] its validity as a test of cure indicator is less reliable due to the lack of available data on the natural history of the HPV infection. Kim et al tracked the clearance of HPV infection after conization and noted that persistent HPV infections were detected in 45.6%, 14.3%, 6.3%, 2.2%, 1.5% and 1.1% of patients at 3, 6, 9, 12, 18 and 24 months after loop excision[15]. This leads us to question if using HPV as a test of cure at 6 months following treatment is too early to accurately evaluate the effectiveness of our treatment. Indeed, we now see many women in our unit who are cytology negative at 6 months following treatment, but who are still HPV positive. Prior to the introduction of HPV testing, such women would have been asked to return 12 months later for a second cervical smear. It is now recommended practice that women who are cytology negative but HPV positive six months following treatment should be reassessed at the colposcopy clinic. This practice has led to an increased the number of women who need a repeat colposcopy following treatment.

Previous studies have shown that cold coagulation is well tolerated by women and has minimal side effects and no documented long term impact on fertility[6,9]. We found cold coagulation to be a very safe procedure with no significant complications. One of the main reasons for a renewed interest in cold coagulation relates to the potential pregnancy morbidity that may be associated with LLETZ. The volume of cervical tissue removed is important. Studies have shown that the deeper the excision (>10 mm) or greater amount of tissue removed, the higher the risk of premature delivery in subsequent pregnancies[5]. During cold coagulation, on average 4-7mm of the cervix is ablated[6]. It is presumed that cold coagulation is likely to be associated fewer pregnancy related complications than excisions techniques such as LLETZ although this data has not been published. However, morbidity would be expected to be low based on a meta-analysis of perinatal and obstetric outcomes that included other forms of ablation[5]. There is an urgent need for a randomised controlled trial comparing the safety of LLETZ and Cold Coagulation, particularly in relation to pregnancy morbidity.

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Conflict of Interest

The authors have no conflicts of interest.

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