A Double-Blind, Randomized, Placebo-Controlled Trial of Prilocaine and Felypressin (Citanest and Octapressin) for the Relief of Pain Associated with Cervical Biopsy and Treatment with the Semm Coagulator

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■ **Abstract**

Objective. To quantify the anticipated and actual pain experienced in association with preliminary cervical punch biopsies and subsequent ablative treatment with the Semm coagulator, and to test the hypothesis that the intracervical injection of prilocaine with felypressin reduces the intensity of the pain experienced.

Materials and Methods. One hundred consecutive women referred with abnormal cervical smears for colposcopic assessment and considered suitable for treatment with the Semm coagulator were recruited to a double-blind, randomized, prospective, placebo-controlled trial conducted in a colposcopy clinic in a university teaching hospital. Personal particulars were taken and anticipated pain scored. The patients were injected with randomized externally identical vials of prilocaine and felypressin (Citanest and Octapressin) or placebo. After biopsy and treatment, patients scored their actual pain experienced. Pain scores were compared as the main outcome measure. Relative risks with 95% CIs were calculated and compared using the CI Analysis computer programme (Professor Martin J Gardner and the British Medical Journal Version 1.1, copyright 1991).

Results. Anticipated pain was greater than the actual pain experienced in both groups. Women receiving the local anesthesia experienced a significantly greater reduction in pain ($p < .05$) with only 4.3% and 6.7% experiencing moderate pain during biopsy and treatment, respectively. The active drug abolished severe pain. In the placebo group, 44.7% felt mild pain at the most.

Conclusions. Intracervical injection of prilocaine and felypressin reduces the intensity of pain experienced in women undergoing cervical biopsy and treatment with the Semm coagulator. Its use is commendable but is not absolutely necessary in all cases. ■

Key Words: anesthesia conduction, cervical intraepithelial neoplasia, colposcopy, biopsy, pain, Semm coagulator

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The crude rate of cervical cancer for Scotland as a whole with a female population of 2,629,517 is 12.6 per 100,000 person-years of risk (95% CI, 12.0–13.2). Tayside, with a female population of

202,242 in the 2001 census [1], has a crude rate of 9.5 (95% CI, 7.8–11.6) [2], the second lowest incidence of cervical cancer of all 15 Health Board areas in Scotland. There are two colposcopy clinics in Tayside. These clinics undertake virtually all the colposcopy for the women of Tayside. In both clinics, the Semm coagulator (WISAP, Munich, Germany) is the standard treatment for cervical intraepithelial neoplasia (CIN) of all grades. Because of the distance from clinics and travel time, a "see and treat" approach is accepted by the National Health Service in Scotland [3]. The safety and cost–effectiveness of this approach using the Semm coagulator immediately after multiple colposcopically directed biopsies has been demonstrated [4, 5]. The latest publication on guidelines for the NHS Cervical Screening Programme, which applies to England only now that health care within the United Kingdom is devolved, concedes this but advises that "all patients must have a biopsy or biopsies taken before local destructive therapy" and "unless there are special circumstances, the result of the biopsy should be available (best practice)" [6].

Semm introduced the "cold coagulator" to treat benign cervical lesions [7] and described the process as completely painless in most cases and only occasionally causing slight discomfort. The term "cold" is misleading as the temperatures available are up to and in excess of 100°C. Comparing patient acceptability of laser and "cold" coagulation, Farquharson et al. [8] found that, of those not given analgesia at the start of treatment (95%), 21% treated by laser required local analgesia (paracervical block) for pain relief compared with 8% of those treated by "cold" coagulation. They concluded that a much higher proportion of patients feel pain during local therapy than is often realized. It has been our experience that many women feel nothing at all while exceptional individuals feel intense pain, and although local anesthesia is available it is not used routinely [9]. We assessed the effect of local anesthetic versus no anesthetic in a prospective, double-blind, randomized, placebo-controlled trial.

MATERIALS AND METHODS

The trial was performed in the colposcopy clinic of Ninewells Hospital, a university teaching hospital in Dundee, Tayside, Scotland. Ethical approval was obtained from the local medical ethics committee. Externally identical, numbered 5-mL vials of prilocaine 3% (30 mg/mL) with felypressin 0.03 IU/mL (Citanest; Astra Pharmaceuticals, Kings Langley, Hertfordshire, UK) or normal saline were prepared by the in-house pharmacy department along with randomized opaque sealed envelopes, each containing the number of a vial. The pharmacy retained the key to the vial contents until the end of the trial.

One hundred consecutive women attending the colposcopy clinic and expected to undergo colposcopically directed biopsy and treatment with the Semm coagulator were approached. Women with a history of allergy to local anesthetic, who were unsuitable for treatment at first colposcopic examination, who had undergone previous treatment to the cervix, or who were pregnant were excluded. All women attending the Ninewells Colposcopy Clinic are sent an information leaflet in advance of their appointment explaining colposcopy, biopsy, and treatment, and are given verbal information and the opportunity to ask questions and receive answers on attending before any procedure is performed.

The prospective trial participants were given additional information about the trial and the pain scoring system. The latter consisted of an eleven point analogue linear scale from 0 to 10, where 0 indicates no pain at all and 10 indicates the worst pain imaginable. Each patient was asked to complete 4 such scales for expected and actual sensation associated with biopsies and expected and actual sensation associated with treatment with the Semm coagulator. Scores of 1 to 3 were classified as mild pain, 4 to 7 as moderate pain, and 8 to 10 as severe. Written consent was obtained. Patient details were noted including whether any analgesic medication had been taken in anticipation of the clinic visit. Colposcopic examination was performed by one of the authors.

In those patients where the transformation zone (TZ) was abnormal the number of affected cervical quadrants was noted. When the abnormality and the limits of the TZ were clearly visible and there was no suggestion of invasion, microinvasion, or a high-grade intraepithelial glandular lesion, the next envelope was opened to reveal the number of the vial. Some or all of the vial contents were then injected into the transformation zone circumferentially, and the volume injected was noted. Punch biopsies were taken from the colposcopically worst-looking areas and sent for histological examination and subsequent reporting. Treatment was performed with the Semm coagulator set at 100°C overlapping the treatment areas using a combination of flat and pointed thermoprobes to ensure destruction of the whole of TZ. Each area was treated for 20 seconds and a note was taken of the number of treatment areas and the probes used. The patients completed the pain scales.

Relative risks with 95% CIs were calculated and compared using the CI Analysis computer programme (Professor Martin J Gardner and the *British Medical Journal* Version 1.1, ©1991).

RESULTS

Of the 100 consecutive nonpregnant women with no history of allergy to local anesthetic or of previous cervical treatment who gave written informed consent, 7 did not meet the eligibility criteria for the "see and treat" approach and were excluded from the study. Forty-six women received the active anesthetic and 47 received the placebo. None of the women suffered any adverse reaction. Table 1 shows the patient characteristics of the groups; these were similar in both groups. A similar large majority in both groups had not taken any analgesic preparation in anticipation of their clinic visit. These patient similarities demonstrate the effectiveness of the randomization process.

The characteristics of the cervical lesions are shown in Table 2. The size, distribution, and degree of abnormality were similar in both those who received the active drug and those who received the placebo. More than 60% of the women in each group had CIN 2 or 3 and one patient in the placebo group had unsuspected microinvasion on colposcopically directed biopsy. The majority of patients had 2 or 3 punch biopsies taken, but women who received the placebo had significantly fewer biopsies taken (Table 2).

The majority of women anticipated that they would feel pain when cervical biopsies were being taken (Table 3). This was the same in both groups, with the minority anticipating that the pain would be severe. The pain actually experienced by both groups on biopsy was less than expected. One in three women in the placebo group still experienced moderate or severe pain, but this was virtually abolished in those receiving the active local anesthetic. One in eight women in the placebo group felt no pain at all on biopsy, and this increased to one in two in those receiving the active drug.

Similarly, it can be seen in Table 4 that most women expected treatment with the Semm coagulator to be painful. However, almost half the women in the placebo group experienced only mild pain or no pain at all during treatment. This proportion increased to more than 90% in those receiving the active agents, with 40% experiencing no pain at all.

Table 1. Patient Characteristics

	Active drug (n = 46)	Placebo (n = 47)	RR (95% CI) difference in means (95% CI)
White	44 (95.7%)	47 (100%)	0.96 (0.90–1.02)
Mean age (y)	31.3 [SD 8.4]	32.6 [SD 8.0]	–1.30 (–4.68–2.08)
Nulliparous	14 (30.4%)	10 (21.3%)	1.43 (0.71–2.89)
Single	18 (39.1%)	15 (31.9%)	1.0[a]
Married/cohabiting	20 (43.5%)	22 (46.8%)	0.86 (0.51,1.43)
Separated/divorced	8 (17.4%)	10 (21.3%)	0.87 (0.58–1.31)
No prior analgesia	42 (91.3%)	41 (87.2%)	1.05 (0.91–1.21)

RR, relative risk.
[a]Comparison of marital status with single status.

Table 2. Characteristics of Cervical Abnormalities

	Active drug (n = 46)	Placebo (n = 47)	RR (95% CI)
Quadrants of cervix affected			1/2 vs. 3/4
Missing data	2	0	1.06 (0.81–1.39)
1	13 (29.5%)	13 (27.7%)	
2	17 (38.6%)	21 (44.7%)	
3	8 (18.2%)	5 (10.6%)	
4	6 (13.6%)	8 (17.0%)	
Number of biopsies taken			1/2 vs. 3/4
1	5 (10.9%)	2 (4.3%)	
2	17 (37.0%)	32 (68.1%)	1.51 (1.07–2.15)[a]
3	22 (47.8%)	12 (25.5%)	
4	2 (4.3%)	1 (2.1%)	
Histopathology			
Viral/CIN 1	17 (37.0%)	17 (36.2%)	Viral/CIN 1 vs. CIN 2,3
CIN 2,3	29 (63.0%)	29 (61.7%)	
Microinvasion	0	1 (2.1%)	1.00 (0.73–1.37)

RR, relative risk.
[a]$p < .05$.

DISCUSSION

Colposcopic examination of women presenting with abnormal cervical cytology is commonplace in modern gynecologic practice. Taking directed biopsies before

Table 3. Pain Associated with Biopsy

	Active drug (n = 46)	Placebo (n = 47)	RR (95% CI)
Anticipated pain			None/mild vs. moderate/severe
None	2 (4.4%)	0	
Mild	10 (21.7%)	14 (29.8%)	
			1.14 (0.59–2.20)
Moderate	26 (56.5%)	26 (55.3%)	
Severe	8 (17.4%)	7 (14.9%)	
Experienced pain			
None	22 (47.8%)	6 (12.8%)	
Mild	22 (47.8%)	24 (51.1%)	
			0.67 (0.53–0.84)[a]
Moderate	2 (4.4%)	12 (25.5%)	
Severe	0	5 (10.6%)	

RR, relative risk; CI, confidence interval.
[a]$p < .05$.

Table 4. Pain Associated with Treatment with the Semm Coagulator

	Active drug (n = 46)[a]	Placebo (n = 47)	RR (95% CI)
Anticipated pain			None/mild vs. moderate/severe
None	2 (4.4%)	0	
Mild	10 (22.2%)	10 (21.3%)	0.80 (0.38–1.66)
Moderate	22 (48.9%)	32 (68.1%)	
Severe	11 (24.4%)	5 (10.6%)	
Experienced pain			
None	18 (40.0%)	2 (4.3%)	
Mild	24 (53.3%)	19 (40.4%)	0.48 (0.35–0.66)[b]
Moderate	3 (6.7%)	17 (36.2%)	
Severe	0	9 (19.1%)	

RR, relative risk; CI, confidence interval.
[a]Data were missing from 1 patient.
[b]$p < .05$.

treatment for histological diagnostic purposes is standard practice. This is commonly done without any previous local anesthesia being administered. Large loop excision of the TZ is a popular treatment for CIN. Intracervical and paracervical block using prilocaine with felypressin and lignocaine with adrenaline are commonly used to reduce the bleeding and pain associated with this procedure [10–13]. Bleeding is not an issue with the Semm coagulator, which does exactly as its name suggests, and several authors have reported using no anesthesia when using this device.

Hussein and Galloway used no anesthetic in their series of 65 patients [14]. A Medline search of journals from 1966 to November 2004 entering the words "Semm" and "coagulator" does not list their article but yields 5 articles, the first three of which were written by the current first author [4, 5, 9]. The fourth is by Staland [15], who routinely used paracervical local anesthesia and local anesthetic spray. The fifth article is from Germany and describes the therapeutic results of treatment of cervical ectropion [16]. We believe that this is the first reported placebo-controlled, prospective, randomized trial of a local anesthetic in the treatment of CIN with the Semm coagulator.

We have shown that the intracervical injection of prilocaine with felypressin significantly reduces the intensity of the pain experienced when treatment is being performed and preliminary biopsies taken compared with a placebo. Fewer biopsies were taken in the placebo group, and this may have been brought about in part by the individual patient's reaction to the initial biopsy. The active drugs completely abolished the pain during treatment in 40%, and a further 53.3% felt only mild pain. In the placebo group, 36.1% experienced moderate or severe pain associated with cervical biopsies and 55.3% with treatment with the Semm coagulator. Clearly, therefore, local anesthesia is highly commendable before biopsy and such treatment.

Fear of pain may be just as important if not more important than the pain itself in many women. Fear of needles also comes into play, as does the fact that the injection of local anesthetic is associated with a transient stinging sensation. In the placebo group without the physical benefit of the active drugs 12.8% felt no pain when the cervical biopsies were being taken and 51.1% scored the pain experienced as mild, while 44.7% experienced only mild pain or none at all during treatment. Moderate or severe pain was anticipated by 78.7% before treatment was performed. This demonstrates the importance of proper explanation and reassurance in advance of the procedure. The size of the lesion and the anticipated duration of treatment are important factors. Local anesthetic should be offered routinely; however, when an anesthetic is declined or if the woman is unsure, she can be reassured that biopsies and treatment with the Semm coagulator can be performed with an even chance of experiencing little or no pain. If necessary, the procedure can be interrupted and local anesthetic given.

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