Spray Versus Forced Coagulation in Large Loop Excision of the Transformation Zone: A Randomized Trial

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Objective: Large loop excision of the transformation zone (LLETZ) is the standard surgical treatment for cervical dysplasia. The optimal way to achieve local hemostasis in women undergoing LLETZ is unknown.

Materials and Methods: In a prospective, randomized trial, we compared spray coagulation and forced coagulation in women undergoing LLETZ in a 1:1 ratio. The primary endpoint was time to complete local hemostasis (TCLH). Secondary endpoints were blood loss (Δ hemoglobin before and after LLETZ), pain (numerical visual analog scale, 5-step graphical visual analog scale measured 2–3 hours after LLETZ), and perioperative/postoperative complications (intraoperative need for sutures, postoperative bleeding, infection, and unscheduled readmission). Analysis was by intention to treat.

Results: One hundred fifty-one women were enrolled and were eligible for analysis. Mean (SD) TCLH in 80 women with forced coagulation was 43.3(38.5) and 28.9(22.9) seconds in 71 women with spray coagulation ($p < 0.001$). The secondary endpoints blood loss (Δ hemoglobin, −0.8 [0.8] vs −0.7[1.1]; $p = 0.115$), pain (numerical visual analog scale, 4.1 [0.9] vs 4.2[0.9]; $p = 0.283$, graphical visual analog scale (1.9 [1.3] vs 1.8[1.3]; $p = 0.888$), and perioperative/postoperative complications (6/71 [8%] vs 7/80 [9%]; $p = 0.822$) were comparable between the 2 arms. In a multivariate analysis, coagulation method (odds ratio = 0.18; 95% CI = 0.09–0.38; $p < 0.001$) and size of the cervix (odds ratio = 2.43; 95% CI = 1.16–5.15; $p = 0.021$) were independent predictors of TCLH.

Conclusions: Spray coagulation is superior to forced coagulation in women undergoing LLETZ and should be used as the standard approach.

Key Words: cervical dysplasia, conization, LLETZ, coagulation, hemostasis

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Cervical dysplasia is the most common gynecological precancerous lesion affecting 1% to 3% of women in cervical cancer screening programs.[1] There is no established pharmacological treatment for high-grade dysplasia of the cervix.[2,3] Therefore, surgery is used to remove dysplastic cells from the cervix. Several local surgical treatment options are available to treat cervical dysplasia, among them are cryotherapy, loop electrosurgical excision procedure, large loop excision of the transformation zone (LLETZ), and cold-knife conization.[3] Based on the available evidence, conization is the mainstay of treatment for women with biopsy-proven high-grade squamous intraepithelial lesions (HSILs).[1,2] Three surgical methods are available for conization, eg, cold-knife conization, laser conization, and LLETZ using electrical current. In a systematic Cochrane review and meta-analysis of 29 randomized trials comparing different surgical conization techniques, no significant differences in treatment failures were demonstrated in terms of persistent disease after treatment.[3] However, LLETZ seemed to provide the most reliable specimens for histology with the least morbidity.[3] This is consistent with clinical practice, where LLETZ is the most commonly used surgical method to perform cervical conization because of its practical ease, steep learning curve, and cost considerations.[3–5]

Although conization is well standardized and the individual steps of this procedure have been studied in detail,[6–12] a number of aspects are still unclear. For example, the best way to achieve local hemostasis is unknown. In a systematic Cochrane review and meta-analysis of 12 randomized trials, vasopressin, tranexamic acid, and packing with Monsel's solution reduced primary and/or secondary hemorrhage. In addition, packing with Monsel's solution and local electrocoagulation were comparable regarding intraoperative blood loss in women undergoing cold-knife conization.[9] However, the optimal mode of electrocoagulation of the cervical wound during LLETZ is unknown.

With high-frequency current, local hemostasis is achieved by constricting vessels and denaturing tissue when a temperature greater than 70°C is reached. The coagulation effect is based on the transformation of electric current into thermic force. It mainly depends on the level and form of the output voltage, the form and size of the electrode, and the application time. There are 2 different coagulation modes available, namely, spray coagulation and forced coagulation. Spray coagulation is a no-touch technique with current flowing from the tip of the coagulation electrode onto the tissue surface. In contrast, forced coagulation is a contact technique with the tip of the coagulation electrode gently pressed on the tissue until coagulation is achieved. Based on a PUBMED literature search (search terms conization, LLETZ, coagulation, hemostasis, spray, forced, and randomized; search date May 22, 2015), there are no comparative published head-to-head trials available comparing both coagulation methods. Therefore, the optimal choice of intraoperative coagulation is unknown. Specifically, differences between spray and forced coagulation regarding procedural speed, pain assessment, and intraoperative or postoperative complications have not been clarified to date.

Large loop excision of the transformation zone is one of the most common surgical procedures in gynecology. Thus, establishing the superiority of 1 coagulation method over another would be of clinical relevance and would have an impact on clinical practice. Because there are no data available guiding clinical practice regarding local hemostasis during LLETZ, we designed a prospective, randomized trial comparing spray and forced coagulation in women undergoing LLETZ for cervical dysplasia. We hypothesized that spray coagulation will achieve local hemostasis faster than forced coagulation without compromising safety and local postoperative pain. Therefore, we chose time to complete local hemostasis (TCLH) as the primary endpoint and blood

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The study was approved by the Ethics Committee of the Ruhr University Bochum, Germany.

The trial was registered with ClinicalTrials.gov (NCT02330471).

loss, pain, and perioperative/postoperative complications as the secondary endpoints.

METHODS

A prospective, randomized, open clinical trial (study ID CONE-1) was designed at the Department of Obstetrics and Gynecology of the Ruhr University Bochum. An institutional review board approval was obtained (Ethics Committee of the Ruhr University Bochum, Bochum, Germany; registry number 4844-13; issue date January 7, 2014). The trial was registered with ClinicalTrials.gov (NCT02330471). Women were eligible if they had biopsy-proven HSIL or a Pap smear suggestive of HSIL and an inconclusive colposcopy or persistent, biopsy-proven low-grade squamous intraepithelial lesions (LSILs). Inclusion criteria included an age between 18 and 80 years, blood counts, electrolyte counts, and liver and renal function parameters within 10% of the normal range established in the laboratory of the study institution. Women must have provided written informed consent. Women were ineligible if they had a history of conization or if they had previously been enrolled in the present study. Exclusion criteria included a known coagulation disorder, severe renal or hepatic impairment with organ-specific functional parameters more than twice the upper norm, an immunocompromised status such as immunosuppressive therapy, or a known disease of the immune system.

The LLETZ procedure was performed as follows: acetic acid 5% was applied to the cervix before surgical removal of the lesion. Then, the electrosurgical unit was set at 120 W on blend 3, and the high-cut mode was set (effect 4, 180 W). We used the device Vio 300 D (Erbe, Tübingen, Germany). An isolated handpiece with loops of 3 different sizes (small [15 mm], medium [20 mm], and large [25 mm]) was chosen according to the size of the cervix for electrosurgical excision. The loop was carefully passed around the transformation zone from top (12 o'clock position) to bottom (6 o'clock position). After the transformation zone was removed, a Hegar dilator was used to explore the length of the cervical canal. Additional tissue was excised from the cervix using a rectangular loop with a small diameter (5 mm). This was an optional step performed when an endocervical lesion was suspected on the basis of colposcopy. Endocervical curettage was not performed. After completion of the excision, hemostasis was obtained with a ball electrode using either the spray coagulation mode (effect 2, 80 W) or the forced coagulation mode (effect 2, 80 W). The whole wound surface was coagulated with exception of the cervical canal. A packing with Monsel's solution was not allowed. Also, no vasoactive agents or local anesthetics were used for the procedure.

The primary endpoint of the study was TCLH measured using a stop watch following the surgeon's commands "start" and "stop," which marked the beginning of the coagulation, defined as pressing the coagulation button on the handheld device attached to the coagulation electrode, and the moment when the surgeon stopped all coagulation efforts. Secondary endpoints were blood loss (measured as Δ hemoglobin on the day before LLETZ and 2–3 hours after LLETZ), pain (measured by a numerical visual analog scale [nVAS] using consecutive numbers from 0 [no pain] to 10 [strongest imaginable pain] and a 5-step graphical visual analog scale [gVAS] using graphic pictorials ranging from "smiling" to "crying" measured 2–3 hours after LLETZ), and perioperative/postoperative complications (defined as intraoperative need for sutures, postoperative bleeding after completion of the procedure, local cervical or uterine or urinary infection within a week after completion of the procedure, and unscheduled readmission). Histologic assessment was conducted by the Department of Pathology, Ruhr University Bochum, Klinikum Bergmannsheil, Bochum, Germany.

All p values are 2-tailed and a p value of less than 0.05 was considered statistically significant. The sample size was calculated on the basis of the study hypothesis that spray coagulation would achieve TCLH quicker with at least 20% difference compared with forced coagulation. The assumption of a 20% reduction of TCLH in women undergoing spray coagulation as compared with forced coagulation was based on previous personal experience. We assumed a risk of α value of 0.05 (type 1 error) and β value of 0.10 (type 2 error), and a drop-out rate of less than 5%. With 75 participants in each arm of the study using a 1:1 randomization, this study has a power of more than 80% to detect a difference of 20% of TCLH. Randomization was achieved using a computer-generated randomization list using a block size of five. We used opaque, sealed envelopes with each patient's allocation (group 1 vs group 2) opened at the start of surgery by the study nurse. Patients were blinded to their

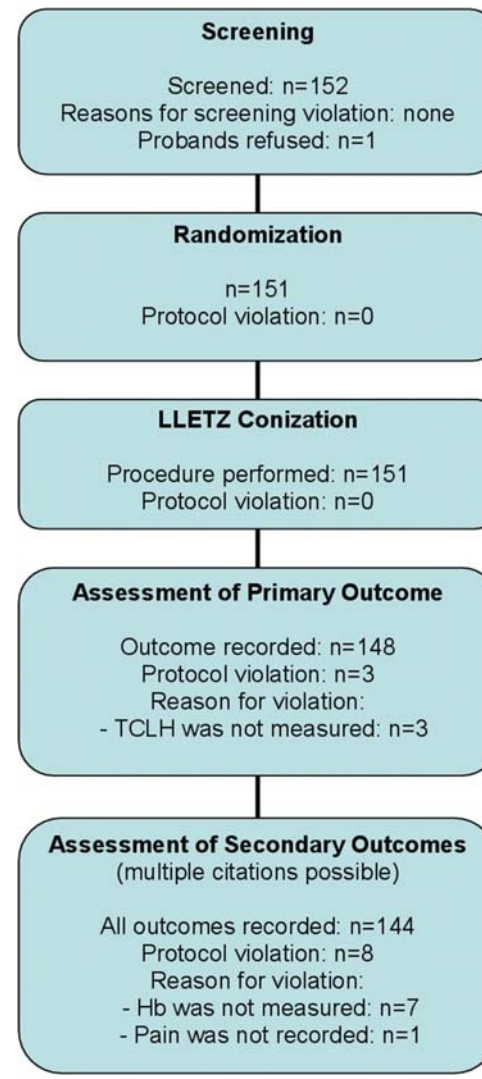

FIGURE 1. Consort diagram of the study probands' flow through the study.

TABLE 1. Patient Characteristics of 151 Women Undergoing LLETZ

Patient characteristic	Group 1 Forced coagulation	Group 2 Spray coagulation	*p*
No. patients	80	71	
Age, mean (SD), y	34.6 (8.8)	34.5(9.1)	0.9
Indication for LLETZ			
HSIL	64 (80)	54 (76)	0.6
LSIL	5 (6)	5 (7)	1.0
Abnormal Pap smear, inconclusive colposcopy	11 (14)	12 (17)	0.6
Body mass index, mean (SD)	24.7(5.3)	24.4 (4.0)	0.7
Smoking (yes/no)	39 (49)/41 (51)	27 (38)/44 (62)	0.1
Regular alcohol use (yes/no)	1 (1)/79 (99)	4 (6)/67 (94)	0.1
Drug abuse (yes/no)	2 (3)/78 (97)	0 (0)/71 (100)	0.4
Prescription drug use (yes/no)	25 (31)/55 (69)	24 (34)/47 (66)	0.8
Concomitant disease (yes/no)	35 (44)/45 (56)	26 (37)/45 (63)	0.4
Cervix size (small/large)	41 (52)/38 (48)	39 (55)/32 (45)	0.7

Data are presented as n (%), unless otherwise indicated. *p* values: Fisher exact test (2-tailed) for categorical variables, Mann-Whitney *U* test otherwise.

LLETZ indicates large loop excision of the transformation zone, HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion.

group assignment. Analysis was performed using parametric or nonparametric tests when data were normally distributed or skewed, respectively. Values are given as means (SD). We performed a multivariate logistic regression analysis with TCLH (< median [28.0] vs ≥ median) as the dependent variable and age (<30 vs ≥30 years), size of the cervix (small vs large), body mass index (BMI, 25 vs ≥25), and coagulation mode (spray coagulation vs forced coagulation) as the independent variables We used the statistical software SigmaPlot 12.5 (Systat Software Inc., San Jose, Calif) for statistical analysis.

RESULTS

One hundred fifty-one patients with biopsy-proven HSIL (n = 118), with a Pap smear suggestive of HSIL and an inconclusive colposcopy (n = 23), and with biopsy-proven persistent LSIL (n = 10) were screened and enrolled between January 2014 and January 2015. Eighty patients were randomized in arm 1 (forced coagulation) and 71 patients were randomized in arm 2 (spray coagulation). One patient was screened for this study but declined to participate before randomization. All other

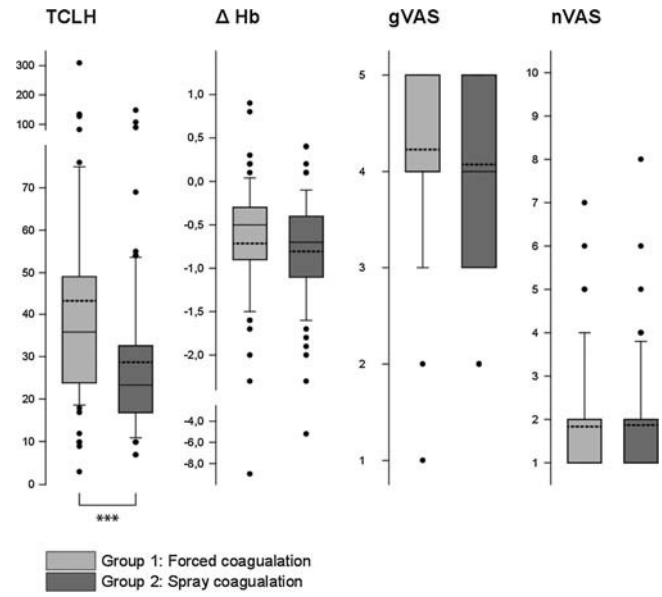

FIGURE 2. Box and whisker plot of primary and secondary outcome measures. Boundaries indicate the 25th/75th percentiles, horizontal lines within the boxes mark the medians, interrupted lines the means. Whiskers indicate the 10th/90th percentiles, dots represent outliers. Light gray boxes represent group 1 (forced coagulation), dark gray boxes represent group 2 (spray coagulation). Statistically significant differences are indicated (***p<0.001). TCLH indicates time to complete local hemostasis (seconds); Δ Hb, Δ hemoglobin (g/dL); gVAS, graphical visual analog scale; nVAS, numerical visual analog scale.

TABLE 2. Results for Primary and Secondary Endpoints

Endpoint	Group 1 Forced coagulation	Group 2 Spray coagulation	*p*
TCLH, mean (SD), sec	43.3(38.5)	28.9(22.9)	<0.001
Blood loss (ΔHb), mean (SD), g/dL	−0.7(1.1)	−0.8(0.8)	0.1
Pain, mean (SD)			
gVAS	4.2 (0.9)	4.1(0.9)	0.2
nVAS	1.8(1.3)	1.9(1.3)	0.8
Complications, n (%)	7 (9)	6 (8)	0.8

TCLH indicates time to complete local hemostatis; gVAS, graphical visual analog scale; nVAS, numerical visual analog scale.

patients screened for this study also participated in the study and all randomized patients also underwent LLETZ. Eleven protocol violations occurred. Time to complete local hemostasis was not measured in 3 patients, hemoglobin was not measured in 7 patients, and pain was not assessed in 1 patient. A flow diagram depicting the patents' flow through the study is shown in Figure 1. Patient characteristics according to study allocation are shown in Table 1 and were comparable between the 2 treatment groups.

The histopathologic results were as follows: 15 patients had cervical intraepithelial neoplasia 1 (CIN 1), 121 patients had CIN 2/3, 10 patients had no CIN in the specimen, and 5 patients had a microinvasive squamous cell cancer (pT 1a1).

In the intention-to-treat analysis, women with spray coagulation had a significantly shorter TCLH compared with women with forced coagulation (see Figure 2 and Table 2). Specifically, the mean (SD) TCLH was 28.9(22.9)seconds in women with spray coagulation and 43.3(38.5)seconds in women with forced coagulation ($p < 0.001$). The secondary endpoints blood loss (Δ hemoglobin, −0.8[0.8]g/dL vs −0.7[1.1]g/dL; $p = 0.12$) and pain (gVAS, 4.1[0.9] vs 4.2[0.9]; $p = 0.28$ and nVAS 1.9[1.3] vs 1.8[1.3]; $p = 0.89$) were not significantly different between the 2 treatment groups. There were 13 treatment-associated perioperative/postoperative complications. Specifically, 3 patients had an intraoperative need for sutures because bleeding could not be stopped by electrocauterization. Furthermore, 8 patients had a postoperative bleeding in a period 2 to 7 days after discharge. None of these 8 patients needed sutures, they were all treated conservatively. One patient had a local infection and 1 patient had an injury of the small labium during coagulation but did not require further treatment. These complications were equally distributed between the 2 treatment arms (7/80 [9%] in arm 1 vs 6/71 [8%] in arm 2; $p = 0.82$). Two patients had involved margins, one in each treatment arm (p = not significant).

In addition, we compared the performance of residents and senior gynecologists regarding TCLH, blood loss, pain, and perioperative/postoperative complications and there were no statistically significant differences (p = not significant for all comparisons; data not shown).

In a multivariate linear regression analysis, coagulation method ($p = 0.007$) and cervix size ($p < 0.001$), but not BMI and age were identified as predictors of TCLH. In a multivariate logistic model using categorized variables with TCLH as the dependent variable and coagulation method, size of the cervix, age, and BMI as the independent variables, coagulation method (odds ratio [OR] = 0.18; 95% CI = 0.09–0.38; $p < 0.001$) and size of the cervix (OR = 2.44; 95% CI = 1.16–5.15; $p = 0.019$), but not age (OR = 1.74; 95% CI = 0.81–3.73; $p = 0.157$) and BMI (OR = 1.32; 95% CI = 0.61–2.86; $p = 0.474$) were independent predictors of TCLH.

DISCUSSION

Our study shows that spray coagulation is superior to forced coagulation in women undergoing LLETZ. Spray coagulation achieved TCLH quicker than forced coagulation. Blood loss, safety, and pain were not different in both treatment arms. Specifically, blood loss measured as Δ Hb, perioperative and postoperative complications, and pain, measured by graphical and numerical VAS, were comparable. Together, these data suggest that spray coagulation is superior to forced coagulation for achieving local hemostasis and should therefore be used as the standard approach in women undergoing LLETZ for cervical dysplasia.

Although LLETZ is one of the most common procedures in operative gynecology, a recent systematic review underscored the need of more randomized trials to objectively identify the best interventions to achieve local hemostasis and reduce blood loss associated with LLETZ.[9] Based on a PubMed literature search (search terms conization, LLETZ, coagulation, hemostasis, spray, forced, and randomized; search date May 13, 2015), this is the first head-to-head, randomized, comparative trial assessing intraoperative coagulation methods. Only 2 studies compared the effect of electrical coagulation with other interventions on hemostasis after conization. A retrospective analysis showed that electrocoagulation is superior to cervical sutures and a randomized trial found packing with Monsel's paste to be equivalent to electrocoagulation.[9] Both studies, however, used cold-knife conization and are therefore not comparable with our study.

Importantly, spray coagulation had the same rates of intraoperative and postoperative complications and resulted in comparable pain assessments by the patients compared with forced coagulation in our study. Based on these results, spray coagulation should be the method of choice for achieving local hemostasis during LLETZ and can be recommended as such.

In our study, we observed a treatment-associated complication rate of 8% and 9% in both treatment arms. This is comparable with what has been reported by others regarding the incidence of intraoperative and postoperative hemorrhage, resection margin status, and other complication rates.[8,10–12] Our randomized, open trial comparing spray and forced coagulation has limitations. First, patients in this trial were selected. For example, women with a history of conization and those with known or suspected coagulation disorders were excluded. Thus,

the external validity of this study is limited to women comparable with the study population. Second, 151 subjects and the length of follow-up may be insufficient for a rare adverse event. Third, the clinical significance of the absolute benefit of 14 seconds, while statistically significant, could be debated, in the context of the total procedure time. Also, we have no long-term follow-up data and cannot rule out differences between the 2 study arms regarding late adverse events such as cervical stenosis or preterm birth. All of these limitations have to be acknowledged when interpreting the results of our study.

CONCLUSIONS

Our study shows that spray coagulation is superior to forced coagulation in women undergoing LLETZ regarding TCLH without compromising safety or procedure-related pain.

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