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CLINICAL ARTICLE

Gynecology

Efficacy of chitosan powder in reducing vaginal bleeding following a loop electrosurgical excision procedure: A randomized control trial

Kemal Güngördük[1] | Hikmet Can Ünver[2] | Berican Şahin Uyar[1] | Berke Nur Ergü[1] | Varol Gülseren[3] | İsa Aykut Özdemir[4]

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Muğla Sıtkı Koçman University, Muğla, Turkey

[2]Department of Obstetrics and Gynecology, Faculty of Medicine, Muğla Sıtkı Koçman University, Muğla, Turkey

[3]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Erciyes University, Kayseri, Turkey

[4]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Medipol University, İstanbul, Turkey

Correspondence
Varol Gülseren, Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, School of Medicine, Erciyes University, Kayseri, Turkey.
Email: drvarolgulseren@gmail.com

Abstract

Objective: To evaluate the efficacy of topical chitosan powder in reducing postoperative vaginal bleeding following a loop electrosurgical excision procedure (LEEP).

Methods: In this randomized controlled trial, patients who underwent LEEP were randomly assigned (1:1) to the chitosan group, in which the wound area was sprayed with chitosan powder using a spray pump, or the control group. The primary outcome was the median quantity of vaginal blood lost in the early postoperative period (defined as within 6 h of the procedure).

Results: The 124 women enrolled in the study were randomly divided into control ($n = 61$) and chitosan ($n = 63$) groups. The median amount of vaginal blood loss during the early postoperative period was significantly lower in the chitosan group than in the control group (198.85 [64.4–388.57] mL vs. 250.60 [67.7–552.87] mL; $P < 0.001$). The rate of late postoperative bleeding requiring hemostatic intervention was also lower in the chitosan group than in the control group (3.2% vs. 16.4%; $P = 0.013$). Superior cervical wound healing in the chitosan group compared to the control group was also observed.

Conclusion: The application of chitosan powder to the cervical wound bed can improve surgical outcomes by decreasing post-LEEP vaginal bleeding and facilitating the healing of cervical wounds.

KEYWORDS
chitosan, loop electrosurgical excision procedure, vaginal bleeding

1 | INTRODUCTION

Early intervention in cervical intraepithelial neoplasia (CIN) II–III helps prevent invasive cervical cancer. Although randomized studies have not agreed on the best management, the loop electrosurgical excision procedure (LEEP) is often preferred for its simplicity, cost-effectiveness, ease of learning, and low complication risk.[1,2] However, some patients encounter postoperative issues like vaginal bleeding, unusual discharge, abdominal pain, and infections, which can prolong recovery, increase anxiety, require further treatment, and disrupt daily life.[3,4]

Postoperative early and late vaginal bleeding (PVB) occurs in 2%–78% of cases.[4–7] Treatments like vasopressin, tranexamic acid,

Monsel's solution, and local hemostatics (such as TachoSil or Tisseel) aim to prevent or reduce PVB but lack clear advantages over standard methods.[8–10] Chitosan, a biodegradable and non-toxic polyaminosaccharide derived from chitin, exhibits antimicrobial and wound-healing properties and is also used to enhance hemostasis.[11–15] Only one trial has examined chitosan's effectiveness after LEEP so far.[15] That study demonstrated the potential of chitosan to reduce vaginal bleeding and improve wound healing after LEEP,[16] but it had several limitations. Therefore, we designed a randomized trial to assess the effects of locally administered chitosan on postoperative vaginal bleeding and wound healing in LEEP.

2 | MATERIALS AND METHODS

Our institution's Institutional Review Board approved this prospective single-blinded randomized trial, which was subsequently submitted to ClinicalTrials.gov (NCT05661708). The study was designed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and checklists. All procedures adhered to the Declaration of Helsinki. Patient enrollment was conducted between December 15, 2022 and May 17, 2024. This study was approved by the University Clinical Research Ethics Committee (date: December 24, 2021, no: E72855364-050.01.04–368 958).

Women eligible for the study were over 21 years old, not pregnant, and undergoing LEEP. Those with pelvic infection, abnormal vaginal bleeding, coagulopathy, chronic pain syndromes, psychiatric disorders, prior hysterectomy with cervical removal, or a history of cervical cancer were excluded, as were patients unable to complete the follow-up examinations. Participants received an informative brochure detailing the study protocol, which they were required to read before providing consent.

The women were admitted to the hospital on the day of the procedure, during which time they provided personal and medical information. To alleviate anxiety, they were shown a descriptive video explaining the LEEP procedure. Pre-procedural anxiety levels were then assessed using the Hospital Anxiety and Depression Scale (HADS)-A. The seven items of the HADS-A are assessed on a four-point scale (0–3).[17] Chitosan powder was acquired from an Asian online marketplace.

Women who met the inclusion criteria and gave written consent were randomly assigned to the intervention group or the control group in a 1:1 ratio. Centralized permuted block randomization was conducted using an online module, with concealed block sizes generated by a computer-generated randomization sequence and varying between two, four, and six.

All LEEPs were carried out in an outpatient setting by the same resident physician (KG). A preoperative complete blood count was performed and the hematocrit was determined (first hematocrit). LEEP was performed based on colposcopy findings, considering the type of transformation zone and the location of the lesion. After patient positioning, 50 mg of lidocaine spray (5 pumps, 10 mg in each pump) was applied to the ectocervix, followed by the submucosal injection of 2 mL of bupivacaine hydrochloride at the 3, 6, 9, and 12 o'clock positions in the ectocervix using a 27-gauge needle tip. LEEP was conducted as detailed in a prior study.[18] Hemostasis was achieved with a ball electrode at a 40-W coagulation setting, after which the residual cervical tissue was rinsed with 20 cc of sterile saline, to confirm the absence of active bleeding from the cervical wound. A sanitary tampon was not used. For the intervention group, a nurse prepared a spray pump for the application of three or four sprays of chitosan powder into the wound bed. In the control group, an empty spray pump was used due to the unavailability of a comparable powder for the placebo. As a result, the patient's awareness of drug administration depended on her perception of air, making it difficult to determine whether the drug had been administered. While, for technical reasons, the surgeon could not be blinded to treatment allocation, throughout the study the patients and the evaluator (HCU) were kept unaware of the random allocation.

The amount of blood lost during LEEP was measured by weighing a gauze sponge throughout the procedure. To ensure precise blood collection, we employed a specially designed surgical gauze sponge and an electronic scale with a deviation range of 1 g. We carefully absorbed all blood lost during LEEP with gauze. The blood volume in milliliters was calculated using the formula: (weight of the used sponge[s]—weight of the sponge[s] before use)/1.05.[19,20] Details of the electrosurgical loop pass technique used during excision, endocervical curettage, the time needed for complete hemostasis, and the duration of the entire procedure, defined as the time from insertion to removal of the vaginal speculum, were recorded. Cone dimensions (length, anteroposterior dimension, and transverse dimension) were measured and recorded before fixation of the specimens, and cone volume was calculated according to consensus recommendations.[21]

Following LEEP, the patients underwent a 6-h observation period to monitor for any signs of complications before hospital discharge. A second complete blood count and a second hematocrit (second hematocrit) determination were performed immediately before the patient was allowed to go home. A research assistant (BSU) and requested the patient to assess her pain using a standard 10-cm visual analog scale (VAS) at 6-h post-procedure. No antibiotics or vaginal suppositories were given postoperatively. Patients were instructed to refrain from using vaginal tampons, engaging in sexual intercourse, intense physical workouts, and vaginal douching for 4 weeks. Additionally, they were informed that vaginal bleeding was possible for up to 4 weeks following the procedure and instructed to track their bleeding intensity daily using the Magnay menstrual pictogram chart (MMPC). Participants were advised to mark each towel used in case of multiple towels, excluding menstrual bleeding.

In case of greater than normal menstrual blood loss, the patients were instructed to seek immediate medical attention. All women were scheduled for follow-up appointments at 1, 2, 3, and 4 weeks post-procedure, during which time they would be informed about their pathologic results and treatment plans and asked about any symptoms or complications, such as the extent of vaginal bleeding and discharge. During these clinical appointments, a blinded

clinical examiner (HCU) assessed the progression of wound healing as determined by colposcopy. A survey was conducted at the end of the first and second weeks to evaluate the level of patient satisfaction, using a scale in which four represented the highest satisfaction score and 16 the lowest satisfaction score (Table S1).

Vaginal bleeding was categorized as early postoperative bleeding (occurring from the time of LEEP to discharge home) and late postoperative bleeding (occurring within 4 weeks after discharge home and requiring hemostatic intervention such as electrocauterization, gauze packing, or cervical suturing, excluding menstrual bleeding). Blood loss in the early postoperative period was determined based on the disparity in hematocrit values, with estimated blood loss calculated as: estimated blood volume (first hematocrit–second hematocrit) / first hematocrit, with estimated blood volume in milliliters = bodyweight in kilograms × 85.[11] Blood loss in the late postoperative period was calculated based on the MMPC score for each week.[22]

The primary focus of this study was the median amount of blood loss during the early postoperative period. Additional assessment points were the VAS score for pain at 6 h following LEEP, the level of patient satisfaction at the end of the first and second weeks following LEEP, median late postoperative bleeding, late postoperative bleeding, the frequency of postoperative cervical infection (indicated by the requirement for antibiotic treatment due to purulent vaginal discharge or cervicitis), and the wound healing scores. Image J software (https://imagej.net/ij/) was used to analyze the wound area. The rate of wound healing was calculated as ([initial wound area—remaining wound area]/initial wound area) × 100 and expressed as a percent (Figure S1).

Before conducting the full trial, we carried out a non-blinded pilot study with 20 patients in each group and performed a power analysis. In the trial, the average early postoperative bleeding amounted to 316.03 ± 81.7 mL for the control group and 225.64 ± 32.5 mL for the chitosan group. Based on these results, we calculated a required sample size of 120 patients to attain 95% power with an alpha level of 0.01. To account for potential participant dropouts, we recruited an additional 10 participants.

Categorical variables are shown as counts and percentages, while quantitative variables are depicted with medians and ranges (min–max). Continuous data were assessed using the Student's *t*-test and Mann–Whitney *U* test. The paired *t*-test was used for normally distributed data, and the χ^2 test for categorical data. Med Calc (version 14.0 for Windows; Mariakerke, Belgium) executed the statistical analyses, with a significance threshold set at *P* values less than 0.05.

3 | RESULTS

According to the study flow diagram (Figure 1), 317 women were assessed for eligibility. Of these, 130 were randomly assigned to either a control ($n = 64$) or chitosan group ($n = 66$). After randomization, the study proceeded with 124 participants' data following the withdrawal of three from each group. The final analysis included 61 (49.2%) in the control group and 63 (50.8%) in the chitosan group. Table 1 reveals no significant differences in surgical characteristics such as operative time, surgical blood loss, cervical cone volume, transformation zone visibility, and positive margins between the groups.

Table 2 presents the study findings. Median early postoperative blood loss was significantly lower in the chitosan group than in the control group (198.85 [64.4–388.57] mL vs. 250.60 [67.7–552.87] mL; $P < 0.001$). Over 4 weeks, the chitosan group experienced significantly less bleeding (with figures at 1 week: 175 [145–200] vs. 222 [173–279]; 2 weeks: 118 [98–145] vs. 175 [145–200]; 3 weeks: 49 [40–74] vs. 80 [70–95]; and 4 weeks: 12 [4–15] vs. 29 [20–39], all $P < 0.001$). The chitosan group also had a lower incidence of late postoperative bleeding requiring intervention (2 [3.2%] vs. 10 [16.4%]; $P = 0.013$) and reported higher satisfaction in the first 2 weeks after surgery.

In the multivariate analysis, chitosan was shown to reduce the late postoperative bleeding rate (Table 3). Compared with the chitosan group, the control group had a lower wound healing rate during the 4-week period (43 [39–48] vs. 51 [45–59] at 1 week, 54 [42–69] vs. 65 [52–74] at 2 weeks, 71 [63–82] vs. 79 [71–88] at 3 weeks, 89 [80–98] vs. 93 [86–98] at 4 weeks; all *P* values <0.001). No adverse effects of the use of chitosan were observed following the procedure.

4 | DISCUSSION

Three key insights were obtained from this randomized trial examining the effects of chitosan powder application following LEEP: (a) treatment resulted in decreased early and late postoperative bleeding, (b) it reduced the occurrence of bleeding requiring hospital intervention, and (c) it hastened cervical wound healing.

While LEEP is widely performed due to its diagnostic and potentially therapeutic utility, postprocedural hemorrhage remains a significant concern. The occurrence of PVB can greatly impact patients' everyday activities, leading to unplanned visits to the clinic or emergency room and increased medical expenses. Consequently, reducing the incidence of PVB following LEEP is of high priority.

Chitosan plays a crucial role in hemostasis by promoting blood clotting and the constriction of blood vessels at the site of injury. It has also been shown to boost the activity of polymorphonuclear leukocytes, macrophages, and fibroblasts.[15] Based on these properties, chitosan been used to control bleeding in various settings.[23–25] In obstetrics, multiple studies have shown that chitosan-coated tamponades are effective in managing persistent and challenging postpartum hemorrhage.[26] However, the use of chitosan for gynecologic surgery has thus far been extremely limited, with only one published trial examining chitosan application after LEEP.[16] That study had several limitations. First, it lacked information regarding the power analysis, and the sample size was small. Second, although chitosan is often employed in critical scenarios, such as severe bleeding following combat injuries, the authors failed to address early postoperative bleeding. Rather, they reported that chitosan application can reduce

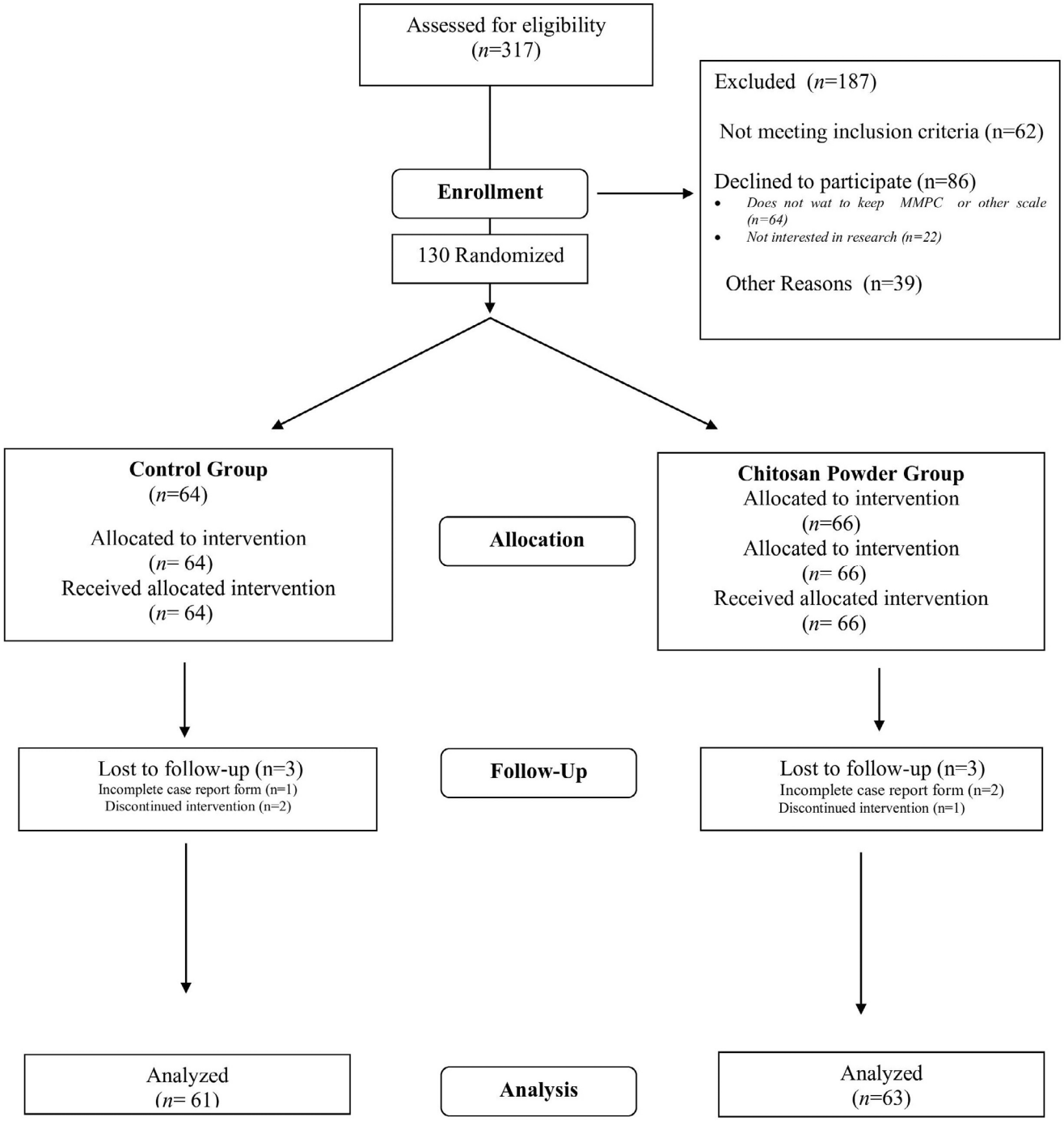

FIGURE 1 Flow diagram of patient recruitment and follow-up.

postoperative bleeding after 2 weeks. Late bleeding presents a significant medical challenge that frequently necessitates medical treatment, leading to prolonged recovery and increased patient anxiety. However, early postoperative hemorrhage is an equally significant a concern as that of bleeding occurring later. Third, the assessment of cervical wound healing was based on subjective measures.[16]

Wound healing is an intricate, highly dynamic process involving coagulation, inflammation, cell proliferation, the formation of new blood vessels, and alterations in the extracellular matrix. Chitosan may expedite wound healing by boosting the activities of inflammatory cells, including polymorphonuclear leukocytes, macrophages, fibroblasts, and osteoblasts, in addition to fostering the generation of hyaluronic acid at the site of injury. These activities are likely to contribute to the ability of chitosan to reduce the risk and frequency of late vaginal bleeding. Delayed wound healing following cervical procedures could result in scar formation and impaired cervical function, leading to negative obstetric consequences. Our study demonstrated that chitosan application has a beneficial effect on cervical wound healing, with no risk of adverse effects.

TABLE 1 Clinical, pathologic and operative characteristics.

	Control group ($n=61$)	Chitosan group ($n=63$)	*P* value
Age (years)			
≤40[a]	47 (77.0%)	45 (71.4%)	0.305
>40[a]	14 (23.0%)	18 (28.6%)	
Body mass index (kg/m^2)[b]	26 (19–37)	26 (19–42)	0.574
Usual duration of menstruation (days)[b]	5 (3–9)	5 (3–9)	0.524
Parity[a]			
Nulliparous	12 (19.7%)	12 (19.0%)	0.903
Primiparous	30 (49.2%)	29 (46.0%)	
Multiparous	19 (31.1%)	22 (34.9%)	
Mode of delivery[a]			
Vaginal	30 (61.2%)	34 (66.7%)	0.360
Cesarean section	19 (38.8%)	17 (33.3%)	
Vaginal delivery[a]			
1	11 (36.7%)	15 (44.1%)	0.363
≥2	19 (63.3%)	19 (55.9%)	
Alcohol use[a]	12 (19.7%)	12 (19.0%)	0.555
Smoking[a]	29 (47.5%)	25 (39.7%)	0.242
Intrauterine device use[a]	5 (8.2%)	7 (11.1%)	0.404
Previous uterine cervical surgery[a]	3 (4.9%)	2 (3.2%)	0.622
HADS-Av[b]	3 (2–5)	5 (2–7)	<0.001
Indication for LEEP[a]			
Persistent LGSIL on punch biopsy	4 (6.6%)	4 (6.3%)	0.902
HGSIL on punch biopsy	47 (77.0%)	52 (82.5%)	
Unsatisfactory colposcopy	5 (8.2%)	3 (4.8%)	
Discrepancies between cytologic reports and colposcopic impressions	3 (4.9%)	3 (4.8%)	
Microinvasion or adenocarcinoma in situ on punch biopsy	2 (3.3%)	1 (1.6%)	
Number of passes with LEEP[a]			
Single pass	53 (86.9%)	54 (85.7%)	0.978
Double pass	7 (11.5%)	8 (12.7%)	
Triple pass	1 (1.6%)	1 (1.6%)	
Endocervical curettage[a]	8 (13.1%)	6 (9.5%)	0.364
Tz-zone type[a]			
1	51 (83.6%)	48 (76.2%)	0.580
2	7 (11.5%)	11 (17.5%)	
3	3 (4.9%)	4 (6.3%)	
Cone dimensions[b,c]			
Transvers dimension (mm)	11 (7–18)	11 (7–18)	0.684
Anteroposterior dimension (mm)	24 (14–40)	24 (14–40)	0.609
Length (mm)	19 (10–25)	19 (10–25)	0.888
Volume (cm^3)[d]	1.6 (0.4–4.7)	1.6 (0.5–4.8)	0.759
Top Hat[a]	11 (18.0%)	13 (20.6%)	0.445
Procedure time[b]	165 (147–298)	170 (145–284)	0.960
TCH[b]	49 (32–139)	50 (32–119)	0.968
Intraoperative blood loss (mL)[b]	33 (20–102)	33 (22–98)	0.781
LEEP histopathology[a]			
No epithelial lesion	2 (3.3%)	–	0.385
LGSIL	15 (24.6%)	13 (20.6%)	
HGSIL	41 (67.2%)	49 (77.8%)	
Microinvasive cancer	1 (1.6%)	–	
Invasive cancer	2 (3.3%)	1 (1.6%)	
Involved margins[a]	1 (1.6%)	2 (3.2%)	0.578

Note: BMI, calculated as weight in kilograms divided by the square of height in meters.

Abbreviations: HADS, Hospital Anxiety and Depression Scale; HGSIL, high grade squamous intraepithelial lesion; LEEP, loop electrosurgical excision procedure; LGSIL, low-grade squamous intraepithelial lesion; TCH, time to complete hemostasis; Tz, transformation zone.

[a]Values are the frequency (percentage).

[b]Values are the medians (range; min–max).

[c]Cone dimensions were defined according to Kyrgiou et al.

[d]Cone volume was calculated as length × transverse × anteroposterior/3.

TABLE 2 Primary and secondary outcome measures.

	Control group ($n=61$)	Chitosan group ($n=63$)	*P* value
Early postoperative blood loss (mL)[a]	250 (67–552)	198 (67–388)	<0.001
VAS score 6 h[a]	2 (1–5)	2 (1–5)	0.957
Late postoperative blood loss (mL)[a]			
at 1 week	222 (173–279)	175 (145–200)	<0.001
at 2 weeks	175 (145–200)	118 (98–145)	<0.001
at 3 weeks	80 (70–95)	49 (40–74)	<0.001
at 4 weeks	29 (20–39)	12 (4–15)	<0.001
Wound healing score[a]			
at 1 week	43 (39–48)	51 (45–59)	<0.001
at 2 weeks	54 (42–69)	65 (52–74)	<0.001
at 3 weeks	71 (63–82)	79 (71–88)	<0.001
at 4 weeks	89 (80–98)	93 (86–98)	<0.001
Patient satisfaction at 1 week[a]	9 (5–13)	7 (4–9)	<0.001
Patient satisfaction at 2 weeks[a]	6 (4–8)	5 (4–6)	<0.001
Late postoperative bleeding[b]	10 (16.4%)	2 (3.2%)	0.013
Cervical infection[b]	3 (4.9%)	1 (1.6%)	0.294

Abbreviation: VAS, visual analog scale.

[a]Values are medians (range; min–max).

[b]Values are frequencies (percentage proportions), *n*.

TABLE 3 Univariate and multivariate analyses of the risk factors for late postoperative bleeding.

	Univariate			Multivariate		
	95% CI	OR	*P* value	95% CI	OR	*P* value
Use of chitosan	0.03–0.79	0.16	0.025	0.03–0.83	0.17	0.029
Age	0.82–1.07	0.99	0.521	0.91–1.09	1.00	0.983
Cone volume	0.13–1.23	0.45	0.140	0.23–1.47	0.59	0.262
Nulliparity	0.46–2.67	1.06	0.827	0.49–3.07	1.22	0.659
Type of Tz zone	0.12–2.79	0.77	0.634	0.32–3.55	1.06	0.917
Body mass index (BMI)	0.72–1.09	0.85	0.136	0.82–1.14	0.97	0.731
Indication for LEEP	0.86–3.12	1.54	0.179	0.50–2.34	1.09	0.820

Note: BMI, calculated as weight in kilograms divided by the square of height in meters.

Abbreviations: CI, confidence interval; LEEP, loop electrosurgical excision procedure; OR, odds ratio; Tz, transformation zone.

Assessing patient satisfaction with respect to treatment outcome is a crucial component in evaluating the quality and efficiency of healthcare. In our study, patient satisfaction following LEEP was evaluated in a survey of self-reported symptoms that could potentially hinder daily functioning. Greater satisfaction was reported by the chitosan group than by the control group.

The limitations of our study should also be noted. The study design prevented double-blinding and the small sample size hindered the examination of factors such as late vaginal bleeding and cervical infection occurrence. Assessment of the late vaginal bleeding rate should be based on an analysis of aggregated data from multiple trials to derive stronger conclusions. Another drawback of the research is figuring out how much chitosan should be dispersed using a spray pump. To overcome this issue, we administered three to four sprays of chitosan powder to ensure complete coverage of the entire wound area. Nevertheless, our study also had a number of strengths, specifically, its prospective randomized design and its inclusion of patients with comparable demographic and clinical characteristics that could potentially impact post-procedure vaginal bleeding. In addition, all LEEPs were carried out by one highly experienced senior gynecologist with extensive expertise in the procedure, thus eliminating a potential source of bias. Finally, the procedure and patient management protocols can be replicated in subsequent clinical studies.

In conclusion, our study demonstrated that the application of chitosan powder to cervical wounds is a proactive strategy to reduce PVB following LEEP. Furthermore, chitosan shows promise in stimulating tissue repair and improving the healing of cervical wounds. Further studies with a larger group of patients and longer follow-up periods are necessary to confirm our results.

AUTHOR CONTRIBUTIONS

Kemal Güngördük wrote the manuscript. İsa Aykut Özdemir edited the manuscript. Varol Gülseren and Berke Nur Ergü, literature research. Varol Gülseren performed the statistical analysis. Berican Şahin Uyar and Hikmet Can Ünver, collection of data. İsa Aykut Özdemir and Kemal Güngördük, evaluation.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

Data may be given if an acceptable justification is provided to us.

CLINICAL TRIAL REGISTRATION

ClinicalTrials code=NCT05661708. ClinicalTrials.gov. URL link that leads directly to the trial registration: https://clinicaltrials.gov/study/NCT05661708?cond=NCT05661708&rank=1.

ORCID

Kemal Güngördük https://orcid.org/0000-0002-2325-1756
Hikmet Can Ünver https://orcid.org/0000-0002-3007-4356
Berican Şahin Uyar https://orcid.org/0000-0003-1463-7021
Berke Nur Ergü https://orcid.org/0009-0003-9845-7622
Varol Gülseren https://orcid.org/0000-0002-0779-8305
İsa Aykut Özdemir https://orcid.org/0000-0001-5457-3312

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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