

Efficacy of Cold Karman Cannulae in Reducing Pain During Office-Based Endometrial Biopsy: A Prospective Randomized Controlled Trial

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ABSTRACT

OBJECTIVE: The study aimed to evaluate the efficacy of cold Karman cannulae, stored at -17°C, in reducing pain levels during office-based endometrial biopsy procedures.

STUDY DESIGN: This prospective, randomized controlled trial was conducted between 2021 and 2022, involving 300 female patients aged 30-60, with abnormal uterine bleeding or increased endometrial thickness. Participants were randomly assigned to two groups: the experimental group, which used cold Karman cannulae (n=150), and the control group, which used room temperature cannulae (n=150). Pain levels were assessed using the Numeric Rating Scale (NRS) immediately after the procedure and ten minutes later.

RESULTS: The mean NRS pain score was significantly lower in the cold cannula group (4.70 ± 1.278) compared to the room temperature cannula group (6.27 ± 1.089) ($p < 0.05$). No significant complications, such as cervical damage or infection, were observed in either group. The use of cold cannulae also facilitated the easier technical performance of the biopsy due to reduced cervical resistance.

CONCLUSION: The application of cold Karman cannulae significantly reduces pain perception during office-based endometrial biopsy, making it a viable option for improving patient comfort and procedural efficiency. These findings support the integration of cold application techniques in gynecological procedures to enhance pain management.

Keywords: Cold karman cannulae; Endometrial biopsy; Patient comfort

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Introduction

Endometrial sampling is an important part of gynecological practice and is widely used to diagnose endometrial cancer, hyperplasia, polyps, and other endometrial pathologies.

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Early diagnosis of endometrial pathologies helps create appropriate treatment plans and prevents disease progression (1). Traditionally, endometrial biopsy procedures were performed in a hospital setting, often using dilatation and curettage (D&C) methods under anesthesia. While these methods provide comprehensive sampling, they are more invasive and carry additional risks for patients due to the need for general anesthesia, potentially prolonging recovery (2).

In recent years, interest in minimally invasive techniques has increased. Particularly, office-based endometrial biopsy techniques have been accepted as a less invasive, faster, and more comfortable alternative for patients. These techniques eliminate the need for general anesthesia, shorten patients' recovery time after the procedure, and provide cost-effectiveness (3). One of the commonly used tools in office settings is the Karman cannula. These cannulas allow the sampling of endometrial tissue through aspiration and can often be used without the need for cervical dilatation (4).

However, when analgesia use is limited in office-based procedures, pain becomes a significant issue during the procedure. Studies show that approximately 30-40% of patients report moderate to severe pain during endometrial biopsy (5).



The prevalence of pain not only reduces patient comfort but can also lead to the procedure being incomplete in some cases. Therefore, developing effective pain management strategies for office-based endometrial biopsies is critical for the success of the procedures and patient satisfaction (5,6).

The primary aim of this study is to investigate the potential benefits of cold application in improving pain management. Cold application has been a method used in pain management for many years due to its anti-inflammatory and analgesic effects. Cold can reduce pain perception by slowing nerve conduction and inhibiting the release of neurotransmitters (7). These positive effects of cold application on pain may also be beneficial during gynecological procedures. For example, cold compresses are known to reduce pain after an episiotomy (8).

In this context, we aimed to evaluate the levels of pain experienced by patients during the endometrial biopsy procedure using Karman cannulas that had been stored in a deep freezer at -17°C . The results of this study may reveal the effectiveness of cold application in pain management during office-based endometrial biopsies and offer an innovative approach to clinical practice.

Material and Method

This prospective, randomized controlled trial was conducted between January 2021 and December 2022 at Basaksehir Cam and Sakura City Hospital, a tertiary referral center in Istanbul, Türkiye. The study was performed in the Department of Gynecology and Obstetrics, where office-based endometrial biopsy procedures are routinely conducted. The research setting was standardized to ensure consistency, with all procedures performed in an outpatient clinic under uniform room conditions, including a controlled temperature of $22-24^{\circ}\text{C}$, appropriate lighting, and standardized equipment. The study was approved by the Basaksehir Cam and Sakura City Hospital Ethics Committee (Approval No: KAEK/2021.03.18, Date: March 18, 2021), and permission was obtained from the provincial health director. All participants were informed about the study details, and written informed consent was obtained before enrollment. The study adhered strictly to the principles of the Declaration of Helsinki and international ethical standards.

This study was designed and conducted as a prospective, randomized controlled trial in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines. The study methodology, including participant enrollment, randomization, intervention allocation, and outcome assessment, followed the principles outlined in the CONSORT checklist to ensure methodological rigor and transparency. The CONSORT flow diagram was utilized to depict the patient recruitment, allocation, follow-up, and analysis process. The CONSORT 2010 checklist and flow diagram are provided as supplementary material to enhance the reproducibility and clarity of reporting.

The study included female patients aged 30 to 60 years who were scheduled for office-based endometrial biopsy. Eligible participants presented with a history of abnormal uterine bleeding, including postmenopausal bleeding, or had endometrial thickening or intracavitary fluid collection detected via ultrasonography. Patients with a body mass index (BMI) between 18.5 and 30, who were either premenopausal or postmenopausal, were recruited. Exclusion criteria included cervical stenosis requiring cervical dilation, a history of pregnancy or current pregnancy, chronic analgesic use that could interfere with pain perception, known severe allergies or contraindications to the procedure, and active cervical or uterine infections.

A total of 300 patients were enrolled in the study and were assigned to two groups to ensure homogeneity in demographic characteristics such as age, BMI, and menopausal status. Randomization was performed using a computer-generated sequence, and a closed-envelope method was used to maintain allocation concealment. Each envelope was labeled only as "experimental" or "control," and envelopes were randomly assigned to patients to determine their group allocation. The experimental group consisted of 150 patients who underwent endometrial biopsy using a Karman cannula that had been stored in a deep freezer at -17°C for at least two hours before the procedure. The control group, also consisting of 150 patients, underwent the biopsy with a Karman cannula at room temperature ($20-24^{\circ}\text{C}$).

All procedures were performed with patients in the lithotomy position on a standard gynecological examination table. Before the biopsy, patients were instructed to empty their bladder to reduce discomfort. The cervix was gently grasped with a tenaculum, and visualization was achieved with a speculum. No cervical dilation was performed, and the biopsy was conducted exclusively with a Karman cannula. The choice of cannula size (4 mm or 5 mm) was determined based on the patient's cervical condition and the clinician's discretion. To standardize the methodology, the procedure duration was strictly limited to five minutes for all participants.

Pain assessment was conducted immediately after the procedure using the Numeric Rating Scale (NRS), on which patients rated their pain on a scale from 0 (no pain) to 10 (worst pain imaginable). Pain scores were recorded twice: immediately after the procedure and ten minutes later, allowing for the evaluation of both acute procedural pain and short-term post-procedural pain. Additionally, potential complications, such as cervical injury, bleeding, or infection, were systematically recorded.

Collected data included demographic variables such as age, BMI, and menopausal status, in addition to pain scores and procedural duration. Statistical analyses were conducted to assess the significance of differences between the two groups. The Student's t-test was used for parametric variables, while the Mann-Whitney U test was applied for non-parametric data.

A p-value of <0.05 was considered statistically significant. Regression analysis was also performed to identify significant independent risk factors associated with pain perception.

All statistical analyses were carried out using SPSS Version 21 for Windows (SPSS, Chicago, IL). The detailed methodology of this study enhances its reproducibility and ensures methodological rigor. By providing precise descriptions of sample characteristics, randomization procedures, and pain assessment methods, this study strengthens the reliability of its findings. Furthermore, these methodological refinements contribute to a clearer interpretation of the study results and support their applicability in clinical practice.

Results

A total of 380 patients were assessed for eligibility, of whom 50 were excluded due to not meeting the inclusion criteria (n=30), declining to participate (n=15), or other reasons (n=5). Consequently, 330 patients were randomized into two groups: the experimental group (cooled Karman cannula) and the control group (room temperature Karman cannula), each initially comprising 165 patients. Following allocation, five patients in each group did not receive the assigned intervention, resulting in 160 patients per group receiving the allocated treatment. During follow-up, no patients were lost, but four patients in the cooled cannula group and six in the room tem-

perature cannula group discontinued the intervention. In the final analysis, 150 patients per group were included, with six patients from the experimental group and four from the control group excluded due to protocol deviations (e.g., incomplete data, crossover cases) (Figure 1).

A total of 300 patients participated in the study, with 150 patients assigned to the experimental group, where endometrial biopsy was performed using cooled Karman cannulas, and 150 patients assigned to the control group, where room-temperature Karman cannulas were used. The mean Numeric Rating Scale (NRS) pain score in the cooled cannula group was 4.70 ± 1.278 , whereas, in the room temperature cannula group, the mean score was 6.27 ± 1.089 . The comparison of mean pain scores between the two groups was conducted using the Student's t-test, and the difference was found to be statistically significant ($p < 0.05$), indicating that the application of cooled Karman cannulas led to a significant reduction in pain perception during the procedure (Table I). Beyond the primary pain assessment, additional observations revealed that patients treated with cooled cannulas experienced significantly lower pain levels ($p < 0.05$), and cervical resistance was reduced in these patients, facilitating the technical performance of the biopsy. The pain scores of patients in both groups were further evaluated using the median pain score and interquartile range (IQR) to provide a comprehensive understanding of pain distribution. The median Numeric Rating

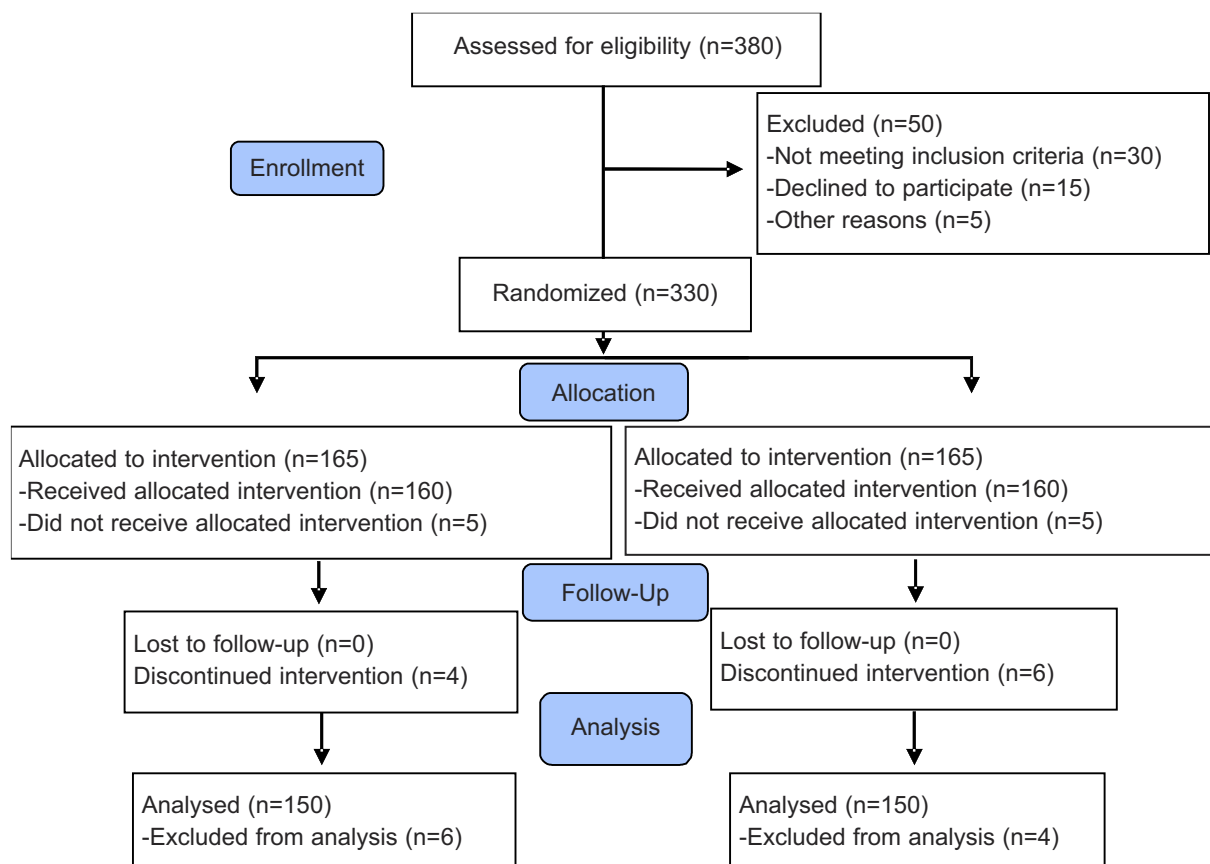


Figure 1: CONSORT Flow Diagram

Scale (NRS) pain score in the cooled cannula group was 4.5, with an interquartile range (IQR) of 3.8 to 5.6. In contrast, the room temperature cannula group had a higher median pain score of 6.2, with an IQR of 5.5 to 7.1. Statistical analysis revealed that this difference was statistically significant ($p < 0.05$), indicating that the application of cooled Karman cannulas led to a considerable reduction in pain perception. The narrower interquartile range in the cooled cannula group suggests less variability in pain scores, reinforcing the consistency of the analgesic effect of cold application (Table II).

The demographic characteristics of the study participants were analyzed to ensure comparability between the experimental and control groups. The mean age of patients in the cooled cannula group was 45.6 ± 7.2 years, while in the room temperature cannula group, the mean age was 46.2 ± 6.9 years ($p = 0.56$), indicating no statistically significant difference. Similarly, there was no significant difference in body mass index (BMI) between the two groups, with mean values of 24.5 ± 3.1 in the cooled cannula group and 24.8 ± 3.0 in the room temperature cannula group ($p = 0.44$). Regarding menopausal status, 80 patients (53%) in the cooled cannula group and 82 patients (55%) in the room temperature cannula group were premenopausal, while 70 patients (47%) in the cooled cannula group and 68 patients (45%) in the room temperature cannula group were postmenopausal ($p = 0.78$). These findings confirm that there were no significant baseline differ-

ences between the two groups in terms of age, BMI, or menopausal status, ensuring the validity of comparisons made in subsequent analyses (Table III).

The incidence of procedural complications was assessed to evaluate the safety profile of the intervention. In both the cooled cannula group and the room temperature cannula group, no cases of cervical injury or infection were reported. Minor complications such as bleeding or other adverse effects were observed in one patient (0.7%) in the cooled cannula group and two patients (1.3%) in the room temperature cannula group. The difference between the two groups in terms of complication rates was not statistically significant ($p = 0.56$), suggesting that the use of cooled Karman cannulas does not increase the risk of procedural complications. These findings confirm that cooling the cannulas before the biopsy procedure does not compromise patient safety and maintains a similar complication rate to conventional methods (Table IV).

These findings further support the notion that cold application plays a critical role in pain management, as evidenced by the significant difference observed between the two groups. The lower pain scores in the cooled cannula group suggest that this method may be a more effective strategy for minimizing procedural discomfort in office-based gynecological interventions. Additionally, the absence of cervical damage, infections, or other complications in either group further supports

Table I: Average pain scores for cold and room temperature cannulas and the results of distribution analysis

Cannula Type	Number of Patients (n)	Mean Pain Score (Mean \pm SD)	p
Cold Cannula	150	4.70 \pm 1.278	<0.05
Room Temperature Cannula	150	6.27 \pm 1.089	

Table II: Comparison of Patient Characteristics between Cold Cannula and Room Temperature Cannula Groups

Characteristic	Cold Cannula Group (n=150)	Room Temperature Cannula Group (n=150)	p
Age (Mean \pm SD)	45.6 \pm 7.2	46.2 \pm 6.9	0.56
BMI (Mean \pm SD)	24.5 \pm 3.1	24.8 \pm 3.0	0.44
Premenopausal, n (%)	80 (53%)	82 (55%)	0.78
Postmenopausal, n (%)	70 (47%)	68 (45%)	0.78

Table III: Median pain scores and interquartile ranges for groups treated with cold cannulas and room temperature cannulas.

Cannula Type	Median Pain Score	1st Quartile	3rd Quartile	p
Cold Cannula	4.5	3.8	5.6	< 0.05
Room Temperature Cannula	6.2	5.5	7.1	

Table IV: Observed complications in the groups treated with cold and room temperature cannulas.

Type of Complication	Cold Cannula Group (n=150)	Room Temperature Cannula (n=150)	p
Cervical Injury	0	0	N/A
Infection	0	0	N/A
Other (Bleeding, etc.)	1	2	0.56

the safety and feasibility of the technique. These findings suggest that the use of cooled Karman cannulas not only improves patient comfort but also enhances procedural efficiency without increasing the risk of complications.

Discussion

The analgesic effects of cold application are widely utilized in pain management across various medical procedures. Previous studies have demonstrated that cold therapy significantly reduces pain and swelling, particularly in postoperative settings. For instance, a study by Kunkle et al. (2021) found that cold application effectively decreased pain intensity and edema in patients following orthopedic surgery (9). Similarly, in gynecological practice, Francisco et al. (2018) reported that cold compresses reduced perineal pain and improved patient comfort after episiotomy procedures (10).

Our study yielded similar findings, showing that the use of a cooled Karman cannula significantly reduced pain perception during office-based endometrial biopsy. The mean pain scores were statistically significantly lower in the cold cannula group compared to the room temperature cannula group ($p < 0.05$). These results suggest that cold application could serve as an effective, non-pharmacological pain management strategy in outpatient gynecological procedures and might be considered for broader implementation.

Several mechanisms may explain the observed reduction in pain with cold application. Studies have shown that cold exposure can inhibit inflammation, slow nerve conduction velocity, and induce localized analgesia through vasoconstriction. Additionally, cold application reduces neurotransmitter release, further contributing to decreased pain perception (11). These physiological effects align with the observed outcomes in our study, where patients treated with cold Karman cannulas reported significantly lower pain scores.

Although cold application appears to be a promising technique, its clinical integration presents certain challenges. While the increased stiffness of cold Karman cannulas may provide technical ease for the physician, some patients may experience temporary discomfort due to the initial cold sensation. Future studies should assess how long this discomfort persists and whether specific patient populations are more sensitive to cold application. Furthermore, it is crucial to provide adequate patient education and informed consent before using cold cannulas in clinical practice to ensure patient compliance and satisfaction.

Moreover, long-term pain relief and patient satisfaction were not assessed in this study. Previous research suggests that cold application can enhance postoperative recovery and patient comfort (12). Future studies should evaluate whether the analgesic effects of cold application persist beyond the immediate post-procedure period and explore its impact on patient satisfaction and overall clinical experience.

This study has several strengths. It is one of the few prospective, randomized controlled trials investigating the impact of cold application on pain management in office-based endometrial biopsy. The standardized methodology, including strict inclusion and exclusion criteria, strengthens the internal validity of our findings. Additionally, using a validated pain assessment tool (Numeric Rating Scale, NRS) ensures the reliability of pain reporting. The relatively large sample size ($n=300$) further enhances the statistical power and generalizability of the results.

However, some limitations must also be acknowledged. One notable limitation is that this study was conducted at a single center, which may limit the external validity of the findings. Future multi-center studies involving diverse patient populations are needed to confirm the reproducibility of these results. Additionally, patients' pain tolerance and psychological factors were not assessed, despite their potential influence on pain perception. Another limitation is that although the procedure duration was standardized, operator-dependent variations may have introduced subtle differences in technique, potentially affecting pain outcomes. Furthermore, while short-term pain perception was evaluated, long-term patient satisfaction and potential delayed pain responses were not analyzed. Future research should include follow-up assessments to determine whether the cold application has prolonged analgesic benefits beyond the immediate post-procedure period.

Given the promising results observed in this study, future research should focus on expanding the study to multi-center trials to improve external validity and generalizability. Exploring alternative cooling techniques, such as cold gels, ice packs, or cold air devices, and comparing their effectiveness in pain management could provide further insights. Additionally, investigating the role of cold application in other outpatient gynecological procedures, such as IUD insertion or cervical biopsies, would be valuable. Another important area for future research is assessing long-term patient satisfaction and recovery outcomes to determine whether cold application has lasting analgesic benefits. Moreover, it is essential to explore the effects of cold application in specific patient subgroups, such as those with higher pain sensitivity or anxiety disorders, to identify populations that may benefit most from this approach.

Despite some limitations, this study provides strong evidence that cold Karman cannulas significantly reduce pain perception during office-based endometrial biopsy. These findings suggest that cold application could serve as an effective, non-pharmacological pain management strategy in gynecological procedures. Further multi-center studies with larger and more diverse patient populations are warranted to validate these findings and explore new applications of cold therapy in clinical practice.

Conclusion

The findings of this study demonstrate that the use of a

cooled Karman cannula significantly reduces pain perception during endometrial biopsy, providing a viable non-pharmacological option for enhancing patient comfort in gynecological procedures. The analgesic effects of cold application are not only effective but also offer a safe method for pain management, reducing the need for additional pharmacological interventions. These results support the potential integration of cold cannulas into routine clinical practice, potentially improving patient compliance and procedural efficiency.

However, while our findings are promising, they also highlight the need for larger, multi-center studies to validate these results across diverse patient populations and clinical settings. Future research should explore the long-term effects of cold application on patient satisfaction and recovery, as well as its applicability to other outpatient gynecological procedures. Additionally, assessing the cost-effectiveness and practicality of implementing cold therapy in various healthcare environments could further support its adoption.

In summary, the incorporation of cooled Karman cannulas in endometrial biopsy procedures presents a promising advancement in pain management. Continued research and refinement of this technique will be essential to maximize its benefits and ensure its effective implementation in clinical practice.

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Ethics Approval and Consent to Participate: This study was conducted following approval from the Basaksehir Cam and Sakura City Hospital Ethics Committee (Approval No: KAEK/2021.03.18, Date: March 18, 2021) and in compliance with the Declaration of Helsinki. Written informed consent was obtained from all participants before their enrollment in the study.

Availability of Data and Materials: The data supporting this study are available from the corresponding author upon reasonable request.

Competing Interests: The authors declare that they have no competing interests.

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Authors' Contributions: According to the CRediT Taxonomy, the author's contributions to this study are as follows: EB Conceptualization, Methodology, Investigation, Data Collection, Formal Analysis, Writing-Original Draft. GBUB: Methodology, Data Curation, Supervision, Writing-Review & Editing. Both authors read and approved the final manuscript.

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