Doctor of Biomedical Engineering

Safety and clinical outcomes of two-session catheter-directed sclerotherapy using 99% ethanol for endometrioma

자궁내막종에 대한 99% 에탄올을 사용한 2세션 카테터 유도 경화요법의 안전성과 임상적 결과

The Graduate School

of the University of Ulsan

Department of Medical Sciences

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Safety and clinical outcomes of the application of two-session catheter-directed sclerotherapy using 99% ethanol for endometrioma

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ABSTRACT

Background: Endometrioma is a cystic lesion formed in the ovaries consisting of old menstrual blood and tissue. It often is seen in women of reproductive ages, making fertility challenging for those with an immediate or future desire for pregnancy. Current treatment options include medical treatment, laparoscopic cystectomy, drainage, and ablative techniques, but each option has its limitations. Transvaginal sclerotherapy using highly concentrated ethanol under ultrasound guidance aims to destroy endometrial tissue inside the cyst while sparing the cyst wall, protecting surrounding oocytes from damage. However, the optimal retention duration remains controversial. To increase the retention duration without leaving ethanol inside for a long term, a two-session catheter-directed sclerotherapy (CDS) 1 day apart was proposed. Therefore, the purpose of the study was to evaluate the safety and clinical outcomes of two-session CDS with 99% ethanol in patients with endometrioma.

Materials and Methods: This prospective study was approved by the institutional review board with written informed consent obtained from all participants and was registered on clinicaltrial.gov. Consecutive patients with ovarian endometrioma between June 2020 and March 2023 were prospectively evaluated for two-session CDS. After successful transvaginal ultrasound-guided puncture of the endometrioma, the biopsy needle was exchanged for a 7- or 8.5-F catheter for aspiration and ethanol injection. The catheter was retained *in situ* for a second session the next day. Endometrioma volume was measured on ultrasound before and 1, 3, and 6 months after CDS, and volume reduction ratio (VRR) was calculated. Serum anti-Müllerian hormone (AMH) was measured before and 6 months after CDS to assess ovarian reserve.

Results: Thirty-one endometriomas in 22 patients (mean age, 31.0 years; range, 19–44 years) were treated; 28 endometriomas were successfully treated with two-session CDS, while one session was incomplete in three endometriomas (3/31, 9.7%; the first session was incomplete in one patient and the second session in two patients) in three patients due to contrast medium

leakage or pain. Therefore, a technical success rate of 90.3% (28/31 endometriomas) was achieved. Minor procedure-related complications developed in four patients and resolved spontaneously before discharge on the same day of the second session. No recurrence was identified during follow-up. At the 6-month follow-up, the mean endometrioma diameter decreased from 5.5 ± 1.7 cm to 1.4 ± 0.9 cm ($P < 0.001$), and the serum AMH level was lowered without statistical significance (1.37 ± 0.96 ng/mL vs. 1.18 ± 0.92 ng/mL; $P = 0.170$). VRRs at 1, 3, and 6 months after CDS were 84.3 ± 13.7%, 94.3 ± 5.8%, and 96.4 ± 4.7%, respectively. **Conclusion:** Two-session CDS with 99% ethanol is safe, feasible, and effective for treating endometrioma with the ovarian function well preserved.

Keywords: Endometrioma; Sclerotherapy; Ultrasound; Ovarian reserve

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INTRODUCTION

Endometriosis is an estrogen-dependent gynecological disorder caused by the migration of endometrial tissue outside the uterus and is most commonly located in the ovaries [1, 2]. Of the three typical types of endometriosis, namely superficial peritoneal lesions, deep infiltrating endometriosis, and ovarian endometrioma, ovarian endometrioma is a cystic lesion formed in the ovaries consisting of old menstrual blood and tissue [3]. It occurs in up to 44% of women with endometriosis and often is seen in women of reproductive ages, making fertility challenging for those with an immediate or future desire for pregnancy [4-6]. In addition, patients with endometrioma usually suffer from dysmenorrhea, lower abdominal or pelvic pain, and dysfunctional uterine bleeding. Current treatment options include medical treatment, laparoscopic cystectomy, drainage, and ablative techniques [4]. Common medical treatments, such as combined oral contraceptives, progestins, and gonadotropin-releasing hormone agonists, can effectively control endometriosis-related pain and reduce 40–70% of endometrioma volume. However, the size reduction and level of pain relieved in individual patients vary, and not all patients respond to medical treatment [7-9]. Although laparoscopic cystectomy is associated with a lower rate of recurrence and therefore remains the standard treatment, it may diminish ovarian reserve by removing healthy tissue surrounding the cyst wall and inducing excessive electrosurgery-related ovarian coagulation, increasing the risk of infertility and early menopause [10-15]. Therefore, alternative treatment options that can effectively treat endometrioma while minimizing iatrogenic damage are warranted.

Sclerotherapy using highly concentrated ethanol aims to destroy endometrial tissue inside the cyst while sparing the cyst wall, protecting surrounding oocytes from damage [4]. It can be performed either laparoscopically or transvaginally under ultrasound guidance, with the latter choice being less painful for patients due to fewer anesthetic and/or surgical complications, sequentially shorter hospital stays, and potentially a lower cost [16, 17]. The

technique was introduced in 1988 [18] with expectations of clear advantages over the laparoscopic approach, such as avoiding abdominal scars and simultaneously treating multiple endometriomas of various sizes [19], and modified to needle-directed sclerotherapy (NDS) in 2009. Although ethanol sclerotherapy was reported as an effective alternative to surgery particularly for recurrent endometriomas and those planning for *in vitro* fertilization [20], difficult aspiration of the viscous cyst content through a thin needle imposed an obstacle of NDS, which can be resolved laparoscopically using a cannula of 5 mm in diameter. In 2020, to overcome this major disadvantage and other inherent limitations of NDS (e.g., risk of needle displacement and subsequent spillage of content or sclerosant into the peritoneal cavity), catheter-directed sclerotherapy (CDS) was tested and concluded to be a promising modification for managing endometrioma [21].

Endometrioma is associated with a high recurrence rate up to 62.5% [22]. A lower recurrence rate can be achieved by increasing the duration of ethanol washing due to increased contact between the sclerosing agent and cyst wall [23]. However, in a previous study where ethanol was retained inside the aspirated endometrioma for the long term, the total pregnancies were lower than that in the ethanol irrigation group [24]. Since the optimal retention duration remains controversial, and to increase the retention duration without leaving ethanol inside for a long term, a two-session CDS 1 day apart was proposed. Therefore, the purpose of the study was to evaluate the safety and clinical outcomes of two-session CDS with 99% ethanol in patients with endometrioma.

MATERIALS AND METHODS

Study design

This prospective study was approved by the institutional review board (No. S2022-2027-0001) with written informed consent obtained from all participants and was registered on clinicaltrial.gov (Identifier: NCT06274086). The inclusion criteria were: 1) aged ≥ 18 years; 2) symptom manifestation as endometriosis (i.e., dysmenorrhea, dyspareunia, and lower abdominal or pelvic pain); 3) endometrioma (appearing as an avascular unilocular cyst containing low-level, homogeneous 'ground glass' echogenicity) ≥ 3 cm confirmed on ultrasound; 4) no evidence of solid mass on ultrasound; and 5) no suspected extraovarian endometriosis. Patients with a history of gynecologic malignancy, active inflammation or infection, abnormal coagulation profile, or lost to follow-up were excluded (**Figure 1**).

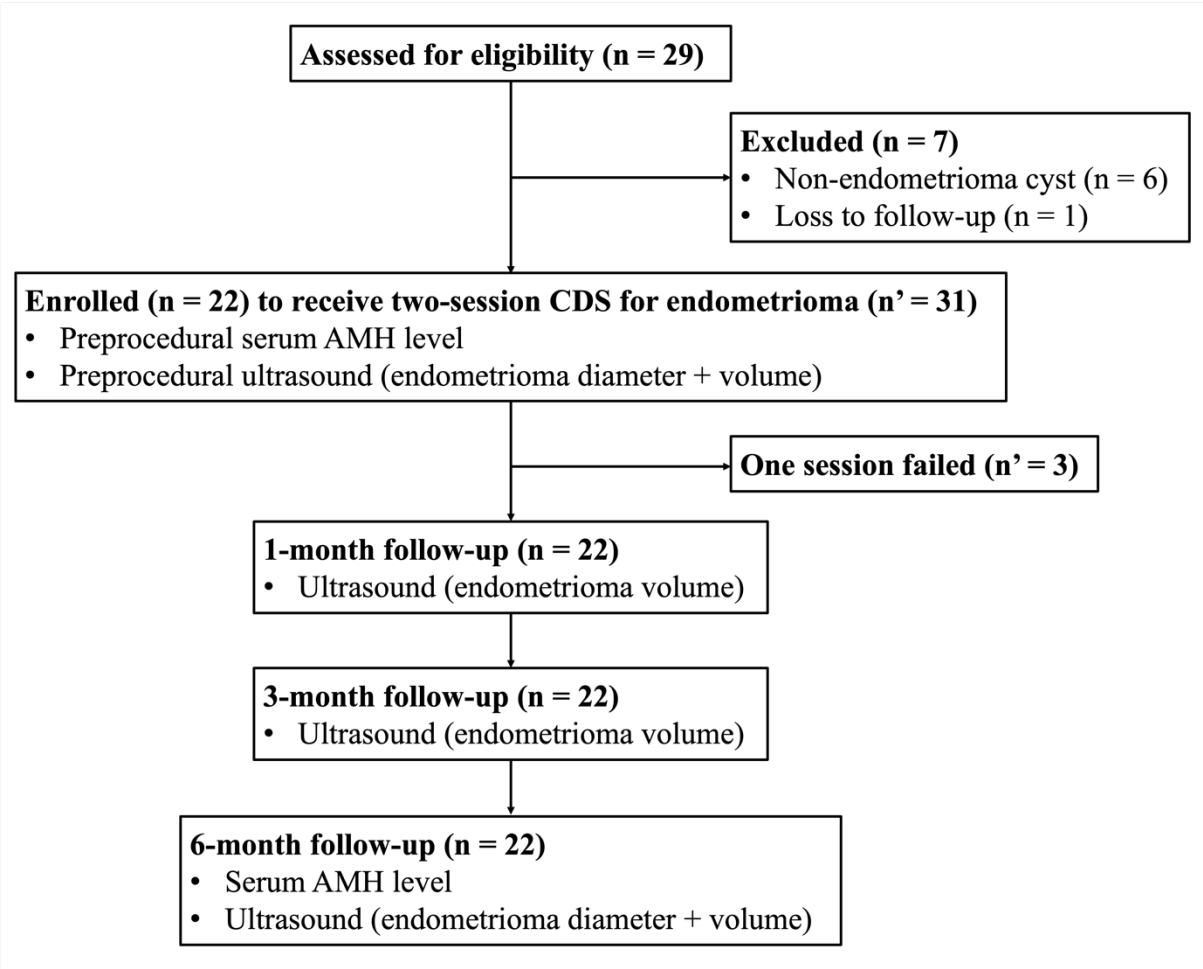

Figure 1. Study flowchart. CDS, catheter-directed sclerotherapy; AMH, anti-Müllerian hormone.

Procedural details

All procedures were performed by an over-20-year-experienced interventional radiologist. Transvaginal ultrasound (HM70A, Samsung Medison, Seoul, Korea) was used given its high diagnostic accuracy for endometrioma [25, 26]. Intravenous sedoanalgesia was achieved using 25 mg pethidine hydrochloride (Hana Pharm. Co., Seoul, Korea) and 50 μg fentanyl (Hanlim Pharm. Co., Seoul, Korea). After placing the participant in a lithotomy position, the vagina was sterilized with chlorhexidine gluconate 0.5% solution (Hexitane 0.5%; Firson, Cheon-an, Chungcheongnam-do, Korea). Then, the ultrasound probe, to which an in-plane endocavitary needle guide (EVN4-9, Aspen Surgical, Caledonia, MI, USA) was attached for precise targeting, was inserted into the vagina. Once the endometrioma was located, it was punctured by an 18-gauge, 20-cm Chiba biopsy needle (Cook, Bloomington, IN, USA). Next, a 0.035-inch hydrophilic guidewire (Terumo, Tokyo, Japan) was advanced into the endometrioma under fluoroscopy, and the needle was exchanged for a 7- or 8.5-F pigtail catheter (Dawson-Mueller Drainage Catheter; Cook) over the guidewire. Following complete aspiration of the chocolate-colored content, the cyst was filled with 5–20 mL, depending on the endometrioma size, of a water-soluble non-ionic contrast medium (iobitridol, Xenetix 300 [300 mg I/mL], Guerbet, Villepinte, France) to rule out rupture or spillage into the pelvic cavity. After the contrast medium was aspirated, the cyst was infused with 99% ethanol (30–80% of the aspirated volume; maximum 100 mL for patient safety) depending on the patient's pain tolerance or sense of fullness. Then, the participant was asked to change the positions (i.e., supine, bilateral decubitus, and prone) every 5 minutes with the catheter clamped to warrant a maximized contact between ethanol and the endometrioma wall [21]. After 20 minutes, the ethanol was aspirated as thoroughly as possible. The catheter was clamped and left *in situ* overnight for the second session the next day, and the patient was monitored in the patient ward. Any discomfort, such as pain or tenderness in the pelvic region, that the patient experienced

was recorded. The next day, after ruling out leakage, the same procedure was repeated with the same volume of ethanol instilled for 20 minutes (**Figure 2**). After the second session was completed, the catheter was removed, and the patient was monitored for any procedure-related complications or discomfort and discharged the same day. If contrast medium spillage was identified or the patient complained about pain during the procedure, especially during ethanol injection, the session was discontinued immediately to minimize the risk of ethanol intoxication [8]. To rule out malignancy, the drained fluid was sent for a cytological examination to identify any atypical cells. Oral contraceptives (e.g., dienogest) were prescribed to control endometriosis-related pain where necessary [7].

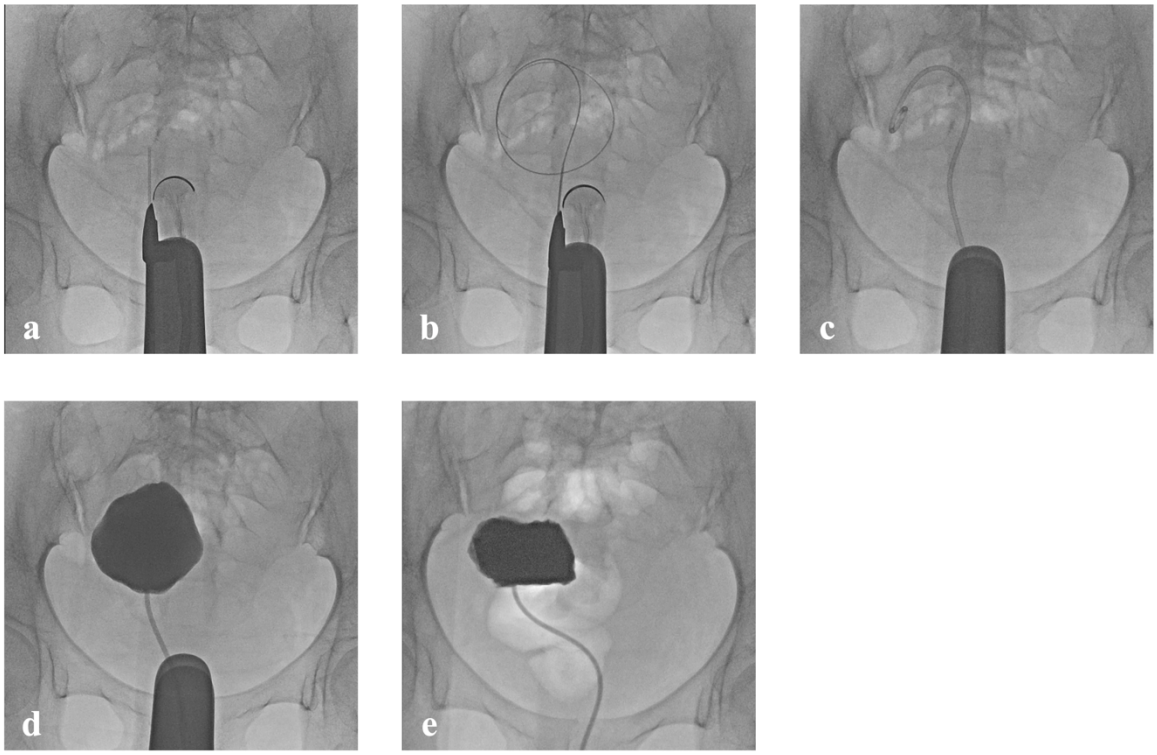

Figure 2. Technical steps of the two-session catheter-directed sclerotherapy for endometrioma. a) The endometrioma was punctured using an 18 G Chiba needle under transvaginal ultrasound guidance. b) A 0.035-inch guidewire was inserted into the endometrioma. c) A 7 F pigtail catheter was advanced over the guidewire. d) A contrast medium was injected to rule out leakage. e) The catheter was retained *in situ* for the second session performed the next day, and the same procedure was repeated.

Follow-up and definitions

Participants were routinely followed up with ultrasound by the performing physician at 1, 3, and 6 months after CDS to monitor changes in endometrioma diameter and volume as well as recurrence. The endometrioma volume was calculated using the formula:

$$V = \frac{4}{3}\pi r^3$$

where *d* indicated the diameter of the endometrioma measured by ultrasound. The change in endometrioma volume was expressed as the volume reduction ratio (VRR) and was calculated using the formula [27]:

$$Volume\ reduction\ ratio = \frac{(initial\ volume - final\ nodule\ volume)}{initial\ volume} \times 100\%$$

For patients with multiple endometriomas, the diameter and volume of each endometrioma were evaluated individually.

To assess the impact of CDS on ovarian reserve, serum anti-Müllerian hormone (AMH) was measured before and 6 months after the procedure. Procedure-related complications, fluoroscopy time, and dose area product were recorded in all cases.

Technical success was defined as the completion of both sessions by successfully retaining ethanol inside the endometrioma for 20 minutes during each session. Recurrence of endometrioma was defined, in the same ovary, as the occurrence of newly developed endometriomas on ultrasonography or an increase in size during follow-up and calculated using the formula [28]:

$$Recurrence\ rate = \frac{number\ of\ patients\ developing\ recurrence}{total\ number\ of\ patients\ treated} \times 100\%$$

Major complications were defined as procedure-related adverse events causing or prolonging hospitalization, requiring an invasive procedure to treat, or resulting in a change of functional status. Minor complications were defined as transient procedure-related adverse

events requiring nominal or no treatment with or without overnight hospitalization for observation and resolving spontaneously [29].

Statistical analyses

Continuous variables are presented as mean ± standard deviation. According to the variable's normality, either the paired *t*-test or Wilcoxon signed-rank test was used as appropriate. $P < 0.05$ was considered to indicate a statistically significant difference. All statistical analyses were performed using SPSS software (version 22; IBM, Chicago, IL, USA).

RESULTS

Baseline participant and endometrioma characteristics are presented in **Table 1**. From June 2020 to March 2023, a total of 29 patients were assessed for eligibility and seven were excluded. The reasons for exclusion were non-endometrioma cysts (n = 6) and loss to follow-up (n = 1). The final analysis included 22 participants at a mean age of 31.0 years (range, 19–44 years) with 31 endometriomas of an average size of 5.5 ± 1.7 cm (range, 2.7–10.0 cm). Among them, 14 patients (63.6%) had a single endometrioma, seven (31.8%) had two endometriomas (unilateral endometriomas in one patient and bilateral in six), and one (4.5%) had three endometriomas on both the right and left sides. The detailed clinical characteristics and treatment outcomes are listed in **Tables 2 & 3**. Twenty (90.9%) patients had primary endometriomas, including three patients who had contralateral pelviscopic ovarian cystectomy after 2 and 8 years or salpingo-oophorectomy after 20 years. Two (9.1%) patients had recurrent endometriomas 3 and 7 years after receiving ipsilateral pelviscopic ovarian cystectomy. The reasons for endometriomas being detected were pain (n = 12), including dysmenorrhea in nine patients and lower abdominal pain in three, incidental findings during routine ultrasound check-ups (n = 8), and follow-up after pelviscopic ovarian cystectomy (n = 2).

Table 1. Baseline characteristics and procedural details

Characteristic	Value
Age, yr (n = 22)	31.0 ± 6.0
Previous surgery for endometrioma	5 (22.7)
Initial AMH, ng/mL	1.37 ± 0.96
Number and location of endometrioma	
One	14 (63.6)
Two	
Unilateral	1 (4.5)
Bilateral	6 (27.3)
Three (Bilateral)	1 (4.5)
Initial endometrioma diameter, cm	5.5 ± 1.7
Initial endometrioma volume, cm^3	114.6 ± 113.0
Aspirated endometrioma volume, mL	65.0 ± 68.1
Volume of instilled ethanol, mL	
First session	28.1 ± 23.9
Second session	27.4 ± 24.7

Note: Data are presented as mean ± standard deviation and number (percentage). AMH, anti-Müllerian hormone.

Table 2. Clinical characteristics of patients with endometrioma

Patient #	Age	# of Endometriomas	Side	Reason for detection	Medication
1	28	1	R	Dysmenorrhea	N/A
2	33	2	R L	Dysmenorrhea	Dienogest after CDS
3	23	1	R	Recurrent EMA after PEL-LOC	Dienogest before/after CDS
4	30	1	R	Lower abdominal pain	Dienogest after CDS
5	38	2	R L	Dysmenorrhea	Dienogest after CDS
6	30	1	L	USG check-up	N/A
7	41	1	L	Dysmenorrhea	N/A
8	32	1	R	USG check-up	Oral contraceptives after CDS
9	29	1	R	Dysmenorrhea	Dienogest after CDS
10	41	1	R	USG check-up	N/A
11	32	2	R L	Lower abdominal pain	Dienogest before CDS
12	29	2	R L	USG check-up	Dienogest after CDS
13	26	1	L	Dysmenorrhea	Dienogest after CDS
14	29	1	L	Dysmenorrhea	N/A
15	27	3	R R L	USG check-up	N/A
16	33	2	L L	Dysmenorrhea	N/A
17	28	2	R L	USG check-up	Dienogest after CDS
18	34	1	R	USG check-up	N/A
19	44	2	R L	Recurrent EMA after PEL-LOC	N/A
20	19	1	L	Lower abdominal pain	N/A
21	25	1	L	USG check-up	N/A
22	31	1	R	Dysmenorrhea	N/A

Note: R, right; L, left; EMA, endometrioma; PEL-LOC, pelviscopic left ovarian cystectomy; USG, ultrasonography; CDS, catheter-directed sclerotherapy; NA, not applicable.

Table 3. Treatment outcomes of catheter-directed sclerotherapy for endometrioma

Patient #	Side	Aspirated volume (cm^3)	Ethanol injection (cm^3)		Session failed	Diameter (cm)		Volume (cm^3)				VRR (%)			AMH (ng/mL)	
			1st	2nd		Before	6 mo.	Before	1 mo.	3 mo.	6 mo.	1 mo.	3 mo.	6 mo.	Before	6 mo.
1	R	80	25	25	N/A	5.4	2.0	80.1	4.2	4.2	4.2	94.8	94.8	94.8	1.46	1.84
2	R	130	40	40	N/A	7.0	2.7	179.5	20.6	20.6	10.3	88.5	88.5	94.3	2.57	1.71
	L	30	15	15	N/A	4.0	0.7	33.5	0.3	0.2	0.2	99.1	99.4	99.4		
3	R	30	20	20	N/A	5.0	1.0	65.4	1.1	1.1	0.5	98.3	98.5	99.2	0.03	0.08
4	R	100	40	40	N/A	6.0	2.4	113.0	31.8	7.8	7.2	71.9	93.1	93.6	2.55	1.89
5	R	25	15	15	N/A	4.3	2.0	40.2	6.4	5.2	4.0	84.1	87.1	90.0	1.00	0.66
	L	35	20	20	N/A	4.2	2.3	39.3	9.6	8.0	6.4	75.6	79.6	83.7		
6	L	235	80	80	N/A	8.5	3.4	322.0	33.5	22.4	21.1	89.6	93.0	93.4	5.70	N/A
7	L	30	15	15	N/A	5.2	0.8	71.6	3.1	0.8	0.3	95.7	98.9	99.6	0.18	0.25
8	R	51	25	25	N/A	5.7	0.6	98.0	0.1	0.1	0.1	99.9	99.9	99.9	N/A	0.40
9	R	20	8	N/A	1st	4.3	0.6	42.5	4.5	0.3	0.1	89.4	99.3	99.8	3.75	2.72
10	R	25	20	20	N/A	5.6	2.6	91.9	28.7	20.6	9.2	68.8	77.6	90.0	0.01	0.01
11	R	10	5	5	2nd	4.2	0.8	38.8	2.1	0.3	0.3	94.5	99.3	99.3	0.78	0.07
	L	210	70	70	N/A	7.2	0.8	195.3	50.9	4.2	0.3	73.9	97.9	99.9		
12	R	25	15	15	N/A	4.6	1.2	50.9	20.6	2.6	0.9	59.6	95.0	98.2	2.20	1.98
	L	100	50	50	N/A	7.6	1.2	229.7	17.1	14.1	0.9	92.5	93.8	99.6		
13	L	40	20	20	N/A	4.6	0.8	50.9	5.6	0.5	0.3	89.1	99.0	99.5	0.72	1.61

14	L	70	30	30	N/A	6.8	2.5	164.6	61.6	9.2	8.2	62.6	94.4	95.0	1.61	0.87
	R	33	15	15	N/A	3.9	1.0	31.0	1.8	0.5	0.5	94.3	98.3	98.3		
15	R	5	3	3	N/A	2.7	0.6	10.3	0.9	0.2	0.1	91.2	98.3	98.9	1.01	0.81
	L	8	5	5	N/A	3.7	0.7	26.5	1.8	0.7	0.2	93.3	97.4	99.3		
16	L	12	8	8	N/A	4.7	0.6	54.3	9.2	0.3	0.1	83.1	99.5	99.8	1.16	0.75
	L	36	20	20	N/A	6.3	3.0	130.9	18.8	14.1	14.1	85.6	89.2	89.2		
17	R	265	90	90	N/A	10.0	0.5	523.3	5.6	1.1	0.1	98.9	99.8	100.0	2.00	3.22
	L	27	13	13	N/A	4.5	0.4	47.7	4.8	1.8	0.0	89.8	96.3	99.9		
18	R	90	45	20	1st	7.7	1.8	238.9	15.6	4.2	3.1	93.5	98.2	98.7	1.59	0.87
19	R	11	5	5	N/A	3.3	1.8	18.8	11.5	3.1	3.1	38.9	83.8	83.8	0.10	0.10
	L	22	10	10	N/A	5.6	1.6	91.9	17.1	6.4	2.1	81.3	93.1	97.7		
20	L	140	70	70	N/A	8.4	1.1	310.2	73.6	15.6	0.7	76.3	95.0	99.8	1.49	0.81
21	L	20	15	15	N/A	4.2	1.0	38.8	10.3	2.6	0.5	73.4	93.4	98.7	1.43	1.51
22	R	100	60	60	N/A	6.1	2.2	121.1	17.1	8.2	5.6	85.8	93.2	95.4	1.73	1.90

Note: VRR, volume reduction ratio; AMH, anti-Müllerian hormone; mo, month; R, right; L, left; NA, not applicable.

A technical success rate of 90.3% (28/31 endometriomas) was achieved. The technical failure rate was 9.7%. To be specific, suspicious minimal or extensive contrast medium leakage was identified during the first session in one endometrioma of one patient having bilateral endometriomas (#11) and during the second session in two having a single endometrioma (#9 and 18). For patient #9, the second session failed because extensive contrast medium was observed, and ethanol injection followed by 20-minute retention could not be completed (**Figure 3**). During the first session of patient #11's right ovary, suspicious minimal contrast medium leakage was seen. From the perspective of patient safety, 5 mL of ethanol washing was attempted and immediately aspirated without retaining ethanol inside for 20 minutes. A 20-minute instillation with position change was completed after ruling out leakage during the second session the day after. This patient did not complain about intolerable pain throughout the whole experience. During patient #18's second session, suspicious minimal contrast medium leakage was observed. After 20 mL of ethanol was infused, the patient's complaint about pain prevented further injection of ethanol (45 mL injected during the first session) and 20-minute retention; thus, the procedure was terminated with catheter removal, and the patient was monitored in the patient ward.

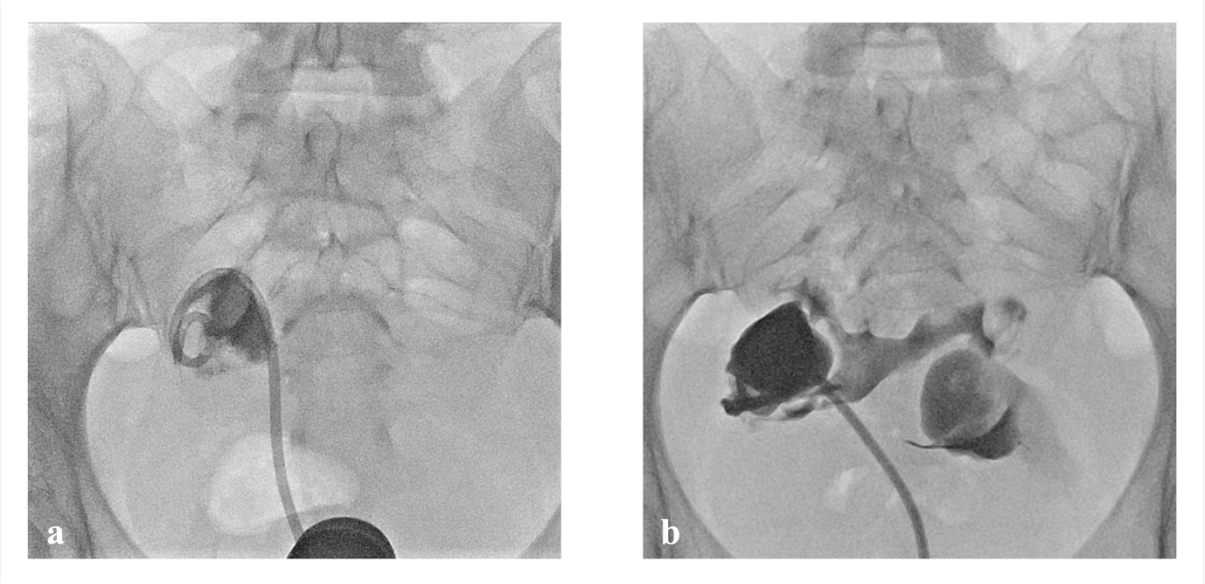

Figure 3. Extensive contrast medium leakage in patient #9 with a unilateral (right) endometrioma. a) No contrast medium leakage occurred during the first session. b) Extensive contrast medium leakage was observed during the second session, and the procedure was immediately terminated to ensure the patient's safety.

An average of 65.0 ± 68.1 mL (range, 5–265 mL) of fluid was aspirated, and the mean volume of alcohol instilled was 28.1 ± 23.9 mL (range, 3–90 mL) and 27.4 ± 24.7 (range, 3–90 mL) for the first and second sessions, respectively. The mean fluoroscopy time was 3.5 ± 1.5 minutes for the first session and 0.6 ± 0.3 minutes for the second session. The mean dose area product was 4.9 ± 2.9 and 0.7 ± 0.4 $Gycm^2$ for the first and second sessions, respectively. No atypical cell was discovered in the aspirated fluid. The clinical course of one participant is described in **Figure 4**.

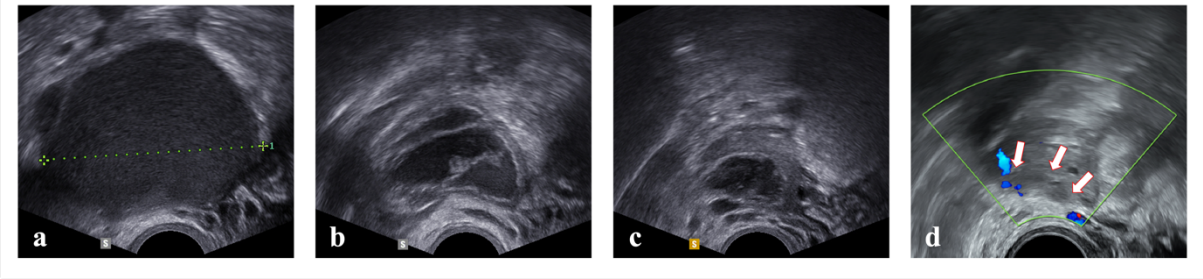

Figure 4. The clinical course of a 30-year-old woman with primary endometrioma in the right ovary. a) The endometrioma was measured to be 6 cm in diameter and 113 cm^3 in volume on ultrasound before the procedure. b) The endometrioma shrunk to 3.8 cm and 31.8 cm^3 at 1-month follow-up, and the volume reduction ratio (VRR) was 71.9%. c) At the 3-month follow-up, the endometrioma shrunk to 2.1 cm in diameter and 7.8 cm^3 in volume, and VRR was 93.1%. d) The endometrioma (arrows) further shrunk to 1.2 cm and 0.9 cm^3 at the 6-month follow-up, and VRR was 99.2%.

CDS was well tolerated in general, and intraprocedural pain was conservatively managed with analgesics. No patient complained about intolerable discomfort from carrying the catheter overnight, and no catheter migration was observed between the two sessions. Minor procedure-related complications were detected in four patients, with one patient developing a mild fever and three experiencing mild pain, and resolved spontaneously before discharge on the same day of the second session. The patient who developed a fever had a history of contralateral pelviscopic ovarian cystectomy, while the other three patients who experienced mild pain did not have a history of previous surgery for endometrioma. As shown in **Table 4**, the mean diameter of endometrioma significantly decreased from 5.5 ± 1.7 cm at baseline to 1.4 ± 0.9 cm at 6 months after the procedure ($P < 0.001$). In addition, the mean volume of endometrioma significantly decreased from 114.6 ± 113.0 cm^3 to 3.4 ± 4.9 cm^3 at 6-month follow-up ($P < 0.001$), and VRR was 84.3 ± 13.7%, 94.3 ± 5.8%, and 96.4 ± 4.7% at 1-, 3-, and 6-month follow-up, respectively (**Figure 5**). No recurrence was identified in any of the participants. No significant difference was found in the serum AMH level before and 6 months after the procedure ($P = 0.170$).

Of the 12 patients who experienced pain before the procedure, one (#9) had no change, four (#1, 2, 4, and 7) had less pain, and the pain disappeared in seven (#5, 11, 13, 14, 16, 20, and 22). One patient received dienogest (i.e., a progestin) before the procedure whereas one continued it and seven started it after the procedure. One patient started oral contraceptives (i.e., a combination of estrogen and progestin) after the procedure.

Table 4. Comparison between baseline and treatment outcomes

Characteristic	Before CDS	6 months after CDS	*P*
Endometrioma diameter (cm)	5.5 ± 1.7	1.4 ± 0.9	< 0.001
Endometrioma volume (cm^3)	114.6 ± 113.0	3.4 ± 4.9	< 0.001
AMH (ng/mL)	1.37 ± 0.96	1.18 ± 0.92	0.170

Note: Data are presented as mean ± standard deviation. CDS, catheter-directed sclerotherapy; AMH, anti-Müllerian hormone.

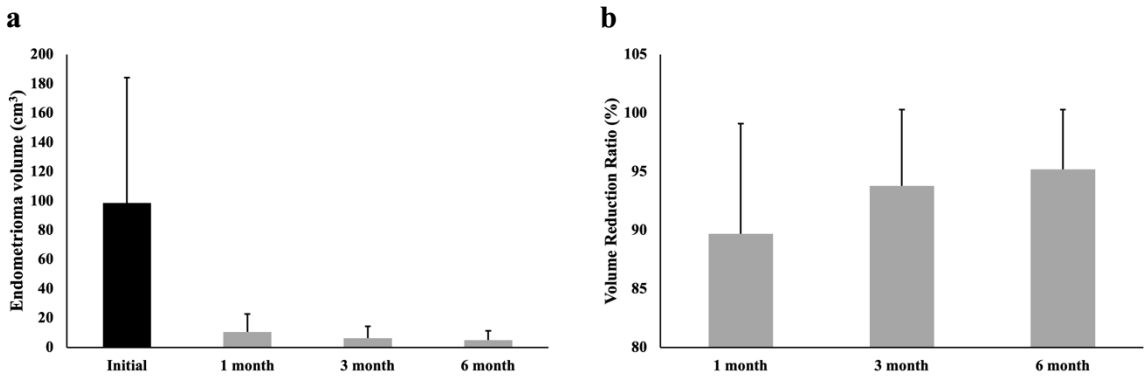

Figure 5. Changes in endometrioma volume. a) The endometrioma volume was significantly reduced at 1-, 3-, and 6-month follow-ups (all $P < 0.001$). b) The volume reduction ratio steadily increased over a follow-up duration of 6 months.

DISCUSSION

This prospective study analyzed the safety and clinical outcomes of two-session CDS using 99% ethanol for endometrioma in 22 patients with 31 endometriomas. Both sessions were successfully performed for 28 endometriomas, and at least one session was successful in the remaining three endometriomas. This finding indicated the feasibility of this modified sclerotherapy with a high technical success rate of 90.3%. Minor procedure-related complications developed in four patients and resolved spontaneously without prolonging hospitalization. The mean endometrioma diameter significantly decreased from 5.5 ± 1.7 cm to 1.4 ± 0.9 cm and VRR reached 96.4 ± 4.7% at 6-month follow-up. A decrease in the serum AMH level was detected 6 months after the procedure at a nonsignificant level.

Since a cleavage plane between the endometrioma wall and the ovarian cortex is absent, cystectomy may result in a significant loss of cortex and ovarian parenchyma bleeding, leading to impaired ovarian reserve, which was evidenced by significantly reduced serum AMH levels in previous studies [30, 31]. In this regard, for five patients who previously received ipsi- or contralateral ovarian cystectomy or salpingo-oophorectomy, transvaginal sclerotherapy was performed to minimize the risk of further impairing ovarian reserve. In this present study, among the three patients who developed primary endometrioma, the serum AMH level increased in two of them after the procedure and remained constant in one. For the two patients with recurrent endometriomas, the serum AMH level decreased in one patient and remained the same in the other. Overall, the nonsignificant change in the AMH level demonstrated a well-preserved ovarian function after two-session CDS. Meanwhile, adding a second session of ethanol instillation did not considerably increase radiation exposure (first and second session: 3.5 ± 1.5 and 0.6 ± 0.3 minutes, respectively) or prolong hospitalization given that all patients were discharged 2 days after admission (i.e., the same day as the second session), while a single

session required an average hospitalization of 2.6 days reported in a previous study [16]. These findings were important as they substantiated the overall safety of this modified technique.

The overall recurrence rate of endometriomas after sclerotherapy is 13.8% [32]. Similar to Han *et al.*'s study [21], no recurrence was observed in the current study, demonstrating the efficacy of this modified technique. This may result from the sufficiently long ethanol retention inside the endometrioma during the two 20-minute sessions. As previously reported, the recurrence rate can be significantly lowered if the sclerosing agent is retained for > 10 minutes compared to ≤ 10 minutes (odds ratio, 0.2; $P = 0.015$) in a single session [32, 33]. However, the existing data can hardly prove the superiority of two sessions to a single session, requiring comparative research in the future. Also, it might be of interest to compare a single session > 10 minutes and two sessions ≤ 10 minutes each to discover the possible role of ethanol retention duration and/or number of sessions performed in treating endometrioma.

No major procedure-related complications were observed in this present trial. Also, performing a second session was found to increase the probability of, at least, one successful session. This was because even a few patients experienced one failed session, no patients experienced failure for both sessions. The recurrence rate was explored to decrease as the duration of ethanol washing increased [32, 34]; the underlying theory is that increased contact between the sclerosing agent and cyst wall helps to denature proteins and induce necrosis in the endometrial lining cells. This process creates aseptic inflammation and fibrosis, which impairs their secretory function, prevents cyst refilling, and ultimately eliminates the cyst [35, 36]. However, there exist different opinions that in Aflatoonian *et al.*'s comparison between the aspiration and retention approaches, no significant difference in recurrence was detected (aspiration vs. retention, 52.0% vs. 46.2%; $P = 0.500$) [37]. Furthermore, when comparing irrigation and retention of ethanol, both postprocedural serum AMH level and total pregnancies were lower in the retention group than in the irrigation group (both $P < 0.05$) [24]. A possible

explanation was that ethanol could persistently destroy ovarian tissue when left *in situ*, while ethanol irrigation generally caused less damage. Also, long-term ethanol retention may cause ethanol extravasation into the abdominal cavity, increasing postoperative abdominal pain, forming peritoneal adhesion, and causing severe reactions including infection and abscess [12, 38]. On the other hand, when leaving ethanol *in situ* for a long time, continuous intravascular absorption of ethanol by the cyst wall may increase the risk of high blood alcohol levels, leading to ethanol intoxication or even more lethal conditions [8]. Therefore, implementing the second session was anticipated to minimize the risk of deteriorating ovarian reserve due to ethanol retention and reduce the recurrence of endometrioma.

At present, there is no standard on the maximum volume of ethanol injection, and the mean volume of ethanol injection varies across studies focusing on endometriomas of different sizes. In most studies published by far, the volume of ethanol injection was based on the initial volume of the aspirated cyst volume. One Italian cohort reported the use of 95–100% of the initial volume of the aspirated content [39]; however, refilling a cyst with 100% of the initial volume, in others' opinion, was risky and challenging because preventing spillage was almost not possible [39]. Han *et al.* injected 25% of the aspirated volume at a maximum of 100 mL for patient safety [21]. In Miquel *et al.*'s 8-year experience in treating endometrioma using ethanol, 60% of the initial volume of ethanol was injected [8]. Whilst most studies relate the volume of ethanol injection to the initial volume of the endometrioma, some suggest the volume of ethanol injection refers to the patient's weight because blood alcohol levels show a direct correlation to the patient's weight [8, 40]. However, there is no evidence showing the association between the patient's weight and the size/volume of the endometrioma, and whether the maximum volume of ethanol injection should depend on the patient's weight rather than the endometrioma condition is appropriate and reliable remains unclear. Taken together, how the volume of ethanol injection affects treatment outcomes and complications is

inconclusive and worth investigating. The maximum volume of ethanol injection needs to be further tested and verified in a larger cohort of patients with various weights.

Serum cancer antigen 125 (CA-125) was often used to measure therapeutic efficacies in previous work, but direct visualization of the cyst and histopathological confirmation remain the gold standard for diagnosing endometrioma [41]. Since tumor markers are inconclusive for diagnosing endometrioma [42], CA-125 was not included in this study protocol; instead, the drained fluid was cytologically examined to identify atypical cells [37]. Considering the positive correlation between serum AMH level and endometrioma, the serum AMH level was monitored to assess ovarian reserve [43]. As a relatively new biomarker of ovarian reserve, serum AMH has recently gained increasing attention due to its relatively stable level throughout the menstrual cycle, even if hormonal treatment is prescribed [44]. This current study detected a nonsignificant decrease in serum AMH after the procedure (1.37 ± 0.96 vs. 1.18 ± 0.92 ng/mL, $P = 0.170$), indicating well-preserved ovarian reserve that likely resulted from the safer, less invasive features of the procedure compared to surgical procedures [45]. Also, this finding was consistent with previous studies, in which an initial decrease was identified followed by gradual recovery to a slightly lower level at post-procedural 6 months than that at baseline [24, 44]. In Ghasemi Tehrani *et al.*'s study, in the sclerotherapy group, no significant changes were found between pre- and 12 months for postoperative AMH levels (2.12 ± 1.05 versus 2.09 ± 1.01; $P = 0.120$) [45]. Serum AMH level is affected by many factors, such as age, previous surgery, autoimmune condition, and family history. Some patients enrolled in this trial presented with a low serum AMH level and were referred by the gynecology department due to gynecological conditions. Also, they tended to be of a higher age or have a surgical history for endometrioma. Although maintaining fertility is a main goal of procedures likewise, fertility rate before and after the procedure was not evaluated in this

current study because some patients did not have a sexual intercourse history and pregnancy was not their purpose of the treatment.

There were some limitations to this study. First, despite its prospective nature to minimize potential confounders, this investigation represented a single-arm trial that lacked a control group to confirm its superior efficacy. In addition, all procedures were performed by a single experienced interventional radiologist. Subsequent randomized controlled multicentric trials comparing this two-session design, performed by operators with different skill levels, with single-session CDS or ethanol retention are warranted to promote the generalizability of the modified technique. Second, the sample size was small, and the follow-up period was relatively short. Third, only the serum AMH level was assessed, and other markers (i.e., antral follicle count) or factors that could affect ovarian reserve (i.e., the use of dienogest or oral contraceptives for polycystic ovary syndrome) were not considered. Lastly, the change in pain was not assessed as a treatment outcome because it was difficult to quantify considering that some patients initially had no pain but received medications for amenorrhea/pain after the procedure. However, the change in pain is worth investigating and needs to be included in subsequent studies.

CONCLUSION

In this limited series, the two-session CDS with 99% ethanol 1 day apart is safe, feasible, and effective, showing a steady reduction in the volume of endometrioma over 6 months and well-preserved ovarian function. Whether it is superior to previously reported single-session CDS needs to be further validated in subsequent studies.

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국문요약

배경: 자궁내막종은 오래된 생리혈과 조직으로 구성된 난소에 형성된 낭성 병변이다. 이는 가임 연령의 여성에게서 흔히 볼 수 있으며, 이는 즉각적이거나 미래에 임신을 원하는 여성의 생식 능력을 어렵게 만든다. 현재 치료 옵션에는 약물치료, 복강경 낭종절제술, 배액 및 열치료술이 포함되지만 각 옵션에는 한계가 있다. 초음파 유도 하에 고농도 에탄올을 사용하는 질경유 경화요법은 낭종 벽을 보호하면서 낭종 내부의 자궁내막 조직을 파괴하여 주변 난모세포를 손상으로부터 보호하는 것을 목표로 한다. 그러나 최적의 보존 기간은 여전히 논란의 여지가 있다. 장기간 에탄올을 내부에 남기지 않고 체류 기간을 늘리기 위해 1 일 간격으로 두 세션을 시행하는 2 세션 카테터 유도 경화요법(catheter-directed sclerotherapy, CDS)을 제안했으며, 본 연구의 목적은 99% 에탄올을 사용한 2 세션 CDS 의 안전성과 임상 결과를 평가하는 것이다.

재료 및 방법: 이 전향적 연구는 모든 참가자로부터 서면 동의를 얻어 연구 윤리위원회의 승인을 받았으며, Clinicaltrial.gov 에 등록되었다. 2020 년 6 월부터 2023 년 3 월 사이에 난소 자궁내막종에 대해 2 세션 CDS 치료를 받은 환자를 전향적으로 평가했다. 자궁내막종의 질경유 초음파 유도 천자 후, 흡인 및 에탄올 주입을 위해 생검 바늘을 7 또는 8.5F 카테터로 교체했다. 카테터는 다음날 두 번째 세션을 위해 제자리에 유치하였다. 자궁내막종의 부피는 CDS 전, 1 개월, 3 개월, 6 개월 후에 초음파로 측정하였고 부피감소율(VRR)을 계산하였다. 난소 예비력을 평가하기 위해 CDS 전과 후 6 개월에 혈청 항뮬러리안 호르몬(AMH)을 측정했다.

결과: 22 명의 환자(평균 연령, 31.0 세, 범위, 19~44 세)의 31 건의 자궁내막종이 치료되었다. 28 개의 자궁내막종은 2 세션 CDS 로 성공적으로 치료되었으며, 3 명의 환자 중 3 개의 자궁내막종에서는 조영제 누출 또는 통증으로 인해 한 세션이 불완전했다.

4 명의 환자에서 경미한 시술 관련 합병증이 발생했으며 두 번째 세션 당일 퇴원하기 전에 자발적으로 호전되었다. 추적관찰 중 재발은 확인되지 않았다. 6 개월 추적 관찰에서 자궁내막종의 평균 직경은 5.5 ± 1.7 cm 에서 1.4 ± 0.9 cm 로 감소하였고(P < 0.001), 혈청 AMH 수치는 감소하였으나 통계적 유의성은 없었다(1.37 ± 0.96 ng/mL 대 1.18 ng/mL). ± 0.92ng/mL, P = 0.170). CDS 후 1 개월, 3 개월, 6 개월 후 VRR 은 각각 84.3±13.7%, 94.3±5.8%, 96.4±4.7%였다.

결론: 99% 에탄올을 사용한 2 세션 CDS 는 자궁내막종 치료에 안전하고 실행 가능하며 효과적이고 난소 기능을 잘 보존한다.

Abbreviation

AMH	Anti-Müllerian hormone
CA-125	Cancer antigen 125
CDS	Catheter-directed sclerotherapy
NDS	Needle-directed sclerotherapy
VRR	Volume reduction ratio