

Original Article

Ethanol Sclerotherapy versus Laparoscopic Surgery for Endometrioma Treatment: A Prospective, Multicenter, Cohort Pilot Study

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ABSTRACT **Study Objective:** To compare the cost-effectiveness of ultrasound (US)-guided aspiration and ethanol sclerotherapy versus laparoscopic surgery for benign-appearing ovarian endometrioma.

Design: Prospective, cohort pilot study.

Setting: Multiple centers, Spain.

Patients: Forty patients with suspected ovarian endometrioma identified by US, with a maximum diameter of 35 to 100 mm, of whom 33 met inclusion criteria.

Interventions: The study group (n = 17) underwent US-guided aspiration plus sclerotherapy with ethanol, and the control group (n = 14) underwent laparoscopic cystectomy.

Measurements and Main Results: Recurrence, complications, and direct costs were compared. One of 17 sclerotherapy patients recurred (5.9%) compared with 4 of 14 laparoscopic surgery patients (28.6%) (odds ratio 0.18, 0.01–1.53). No serious adverse effects (Clavien-Dindo \geq III) were observed in the sclerotherapy group; 1 patient in the surgery group had a Clavien-Dindo IIIb complication. Median hospital direct costs were significantly lower in the sclerotherapy group than those in the surgery group—266 euros versus 2189 euros.

Conclusion: Ethanol sclerotherapy seems to be cost-effective for endometrioma and also appears to reduce complications. In this pilot study, recurrence was not higher than with conventional surgery. Journal of Minimally Invasive Gynecology (2020) 27, 1133–1140. © 2020 AAGL. All rights reserved.

Keywords: Complications; Cost-effectiveness; Laparoscopic cystectomy; Recurrences; Stripping

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The estimated prevalence of endometriosis in fertile females is around 6.1% [1] and can have a profound impact on quality of life, causing pain and infertility that can interfere with daily life, sexual relationships, and livelihood and can significantly affect healthcare costs [2]. Ovarian endometrioma occurs in 17% to 44% of patients with endometriosis [3]. Although the risk of malignancy is 0.3% to 0.8% [4], laparoscopic stripping is the standard treatment for patients who are symptomatic or patients with cysts > 50 mm [5,6]. Two years after resection, recurrence ranges between 6% and 30% [6–8]. Furthermore, surgery has a deleterious effect on ovarian reserve [9,10].

To avoid postoperative complications and reduce the impact on fertility, other minimally invasive therapies need to be developed. Medical therapies have not proved effective [11,12]. Depending on the ultrasound (US)-guided aspiration and sclerotherapy technique used for the management of benign-appearing ovarian cysts, recurrence has been reported at 0% to 62.5% [13–22] after 12 to 24 months of follow-up. This conservative treatment may achieve symptomatic cure and reduce costs.

After our previous positive experience with ethanol sclerotherapy in endometriomas [13,21], we designed a multicenter study to compare ethanol sclerotherapy with standard surgical therapy for endometriomas. Before starting the randomized study, a prospective observational multicenter pilot study was performed to evaluate ethanol sclerotherapy and assess viability to compare cost-effectiveness of US-guided aspiration and ethanol sclerotherapy with laparoscopic surgery for select patients with benign-appearing ovarian endometriomas.

Materials and Methods

Forty patients with a suspicion of ovarian endometrioma on US were recruited in Barcelona, Girona, and Tarragona, Spain, between February 2016 and March 2018.

Treatment Cohorts

Two independent cohorts were established. Patients in the study group underwent US-guided aspiration plus ethanol sclerotherapy; patients in the control group underwent laparoscopic cystectomy. The treatment for each patient was determined according to the clinical practice of each center, not according to the physician or the patient. In accordance with each center's protocol, all patients were in the study group or the control group. Hospitals that included patients in the study group were Bellvitge University Hospital, Consorci Sanitari Integral, Sant Joan de Déu de Sant Boi Hospital, Viladecans Hospital, and Sant Joan de Déu d'Esplugues University Hospital. Hospitals that included patients in the control group were Vall d'Hebron University Hospital, Doctor Josep Trueta University Hospital, Joan XXIII University Hospital, and Verge de la Cinta Hospital.

Patient Selection

The inclusion criteria were female patients aged ≥ 18 or ≤ 40 years; US features predictive of endometrioma: homogeneous appearance involving diffuse internal echoes on a hypoechoic background, according to the International Ovarian Tumor Analysis (IOTA) group criteria [23]; maximum cyst diameter between 35 and 100 mm when symptomatic and between 50 and 100 mm when asymptomatic; cyst persistence ≥ 3 months from diagnosis; tumor marker CA125 < 200 IU/mL and HE4 < 70 pM; no symptoms of extraovarian endometriosis; and written informed consent. The exclusion criteria were females aged < 18 or > 40 years; previous oophorectomy; cyst size < 35 mm or > 100 mm; US features suggestive of dermoid cysts (fat-fluid levels, globular calcifications, or hyperechoic mural plug), anechoic cysts, cysts with a solid component, internal septation, a fluid-fluid level, or any sign indicating a high risk of malignancy according to the IOTA criteria; serum CA125 or HE4 levels greater than 200 IU/mL and 70 pM, respectively; abnormal coagulation test results; a personal history of gynecologic cancer; pregnancy; menopausal women; and patients who declined participation in the study or those with a mental disability. When extraovarian endometriosis was suspected, magnetic resonance imaging (MRI) was performed to determine patient inclusion. When the MRI confirmed the presence of extraovarian endometriosis, the patient was excluded.

Procedures

A gynecologist trained in interventional procedures performed a transvaginal or a transabdominal US-guided aspiration plus ethanol sclerotherapy. A transabdominal aspiration was indicated in the absence of previous sexual intercourse and US evidence of high vascularization in the vaginal puncture trajectory, to avoid vessel injury. The abdominal wall or the vagina was disinfected with iodine solution. Under direct US guidance, a sterilized 17-gauge spinal follicle puncture needle was aimed toward the center of the cyst, and the endometrioma was aspirated with saline when dense intracystic fluid was present. Next, several intracystic saline washes were performed before introducing ethanol as the sclerosing agent. Sterile, 100% pure ethanol was administered for sclerotherapy, dispensed in a 10-mL vial. The volume of ethanol was equal to two-thirds of the volume aspirated from the endometrioma and never more than 100 mL. The ethanol remained in the cyst for 15 minutes and was removed to allow for further washing with saline, until completely dry. The drained fluid was routinely collected, measured using a syringe, and sent for cytologic examination to confirm the absence of atypical cells. All procedures were outpatient, without anesthesia, sedation, or prophylactic antibiotics, as described in our previous publication [13] and in accordance with recommendations of Noma and Yoshida [24].

All laparoscopic cystectomies were performed under general anesthesia by an expert team. The surgeons tried to

reduce damage to the healthy parts of the ovary in accordance with international recommendations [10]. Adhesiolysis and mobilization of the ovaries were performed when necessary. To excise endometriomas, an incision was performed at the antimesenteric site of the affected ovary using monopolar electrosurgery; then, the endometrioma was drained with aspiration, and the pseudocapsule was dissected by gentle traction and countertraction using two 5-mm grasping forceps (stripping). Bleeding was stopped by bipolar electrosurgery only when necessary.

Variables Recorded

The clinical characteristics of the patients (age, body mass index, previous surgery for endometriosis, pregnancy history, sterility [more than 1 year], symptomatology [visual analog scale of pain before and after the procedures], antimüllerian hormone level before and 6 months after the procedure, and hormonal therapy after the procedure) and of the cysts (US size and localization) were recorded. Complications directly related to the procedures were assessed according to the Clavien-Dindo classification [25] during the first 6 weeks: grades I to II were considered minor complications, and grades III to V were considered major complications.

Follow-Up

Patients were followed up every 6 months in the first year and annually thereafter. Recurrence was defined as the presence of an adnexal cyst suggestive of endometrioma with a maximum diameter ≥ 30 mm in either ovary on US examination. Spontaneous pregnancies were also recorded at follow-up.

Cost Calculation

For each patient, hospitalization costs were extracted from the Bellvitge University Hospital financial information system. Direct in-hospital medical costs were based on a fixed internal hospital fee schedule for services and consisted of an operating room fee and staff labor costs (gynecologist, anesthesiologist, nurses, and others), materials (consumables), medications (ethanol and nonantibiotic drugs), inpatient costs (nursing service and ward-bed occupation), and miscellaneous item costs (pathologic study and others). Indirect medical costs, which mostly refer to a loss of income owing to absenteeism and intangible costs caused by pain and suffering, were excluded. Hospital length of stay and complications were also included in the cost for these patients. All cost data were obtained in euros.

Statistical Analyses

Categorical variables were described according to the number of cases and the proportions. Continuous variables following a normal distribution were described with means

and standard deviation. Continuous variables that did not follow a normal distribution were described by medians and the first and third quartiles. For recurrence, a univariate analysis according to logistic regression was performed. A p -value $< .05$ was considered statistically significant. All analyses were performed using R statistical software, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) [26].

Ethics Statement

This study was reviewed and approved by our hospital's institutional review board (reference PR314/15), and the procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. The trial was registered on ClinicalTrials.gov (NCT02669628). All data were recorded in the electronic medical record and were monitored by an external professional (C.F.) who was not involved in the experimental study. The confidentiality of the personal data of the subjects participating in the study was preserved.

Results

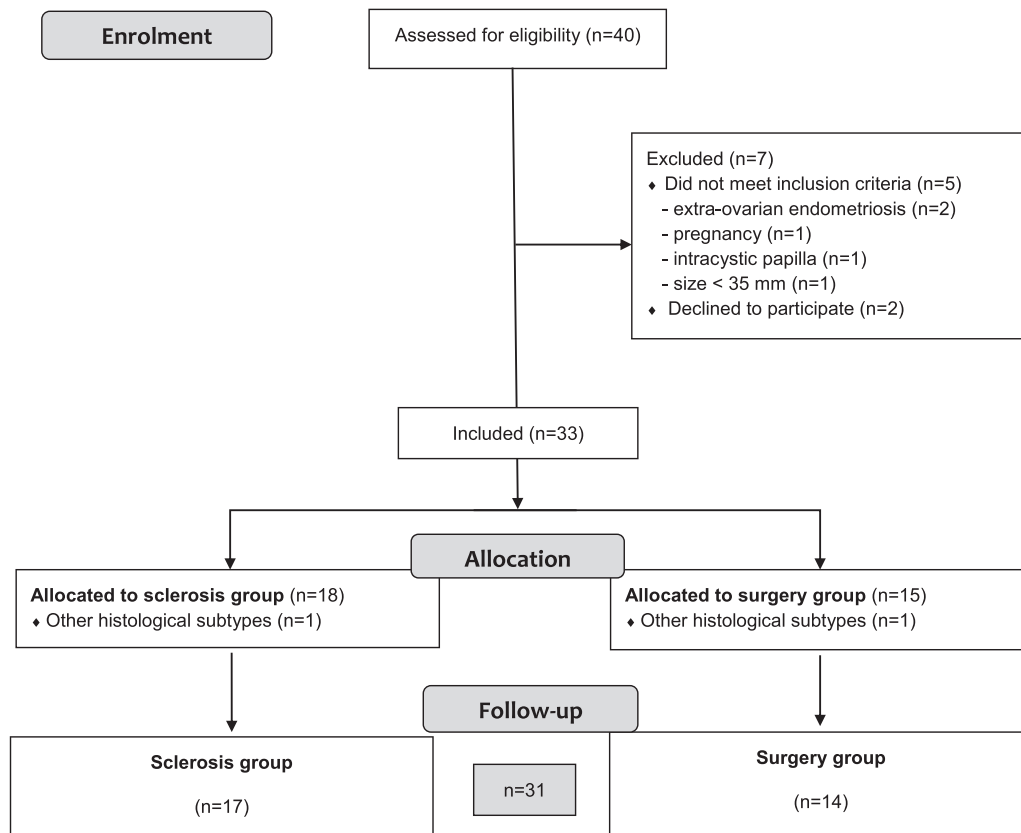
Of the 40 patients with low-risk adnexal cysts predictive of endometriomas who were referred for treatment during the study period, 33 met inclusion criteria (Fig. 1), 2 patients with a definitive diagnosis other than endometrioma were excluded after the procedure. No patients were lost at the 6-month follow-up. The clinical characteristics of the patients, cysts, and procedures are shown in Table 1.

Sclerotherapy of the cyst was performed transvaginally in 15 patients (88.2%) and transabdominally in 2 (11.8%). The sclerotherapy procedures were performed without incident in 15 of 17 patients (88.2%); of the other 2, 1 patient presented a small leak of ethanol into the peritoneum causing pain and requiring a shortening of sclerotherapy time, and the other presented vasovagal syncope after the procedure, which resolved spontaneously. Stripping of the cyst was performed laparoscopically in 13 of 14 patients from the surgery group (93%). Unilateral adnexectomy was performed in 1 patient owing to technical difficulties presented during surgery. Although there were 2 patients with extraovarian endometriosis (14%), 1 peritoneal and 1 in the uterosacral ligament, they were not treated specifically (because they were superficial and not symptomatic), and no other additional procedures were needed during surgery. In the surgery group, only 4 patients could be treated on an outpatient basis (Table 2).

No serious adverse effects (Clavien-Dindo \geq III) were observed in the sclerotherapy group (Table 2). One patient in the surgery group had a Clavien-Dindo IIIb complication, an intestinal occlusion 1 week after laparoscopy requiring a second intervention, in which a bilateral adnexectomy was performed by emergent open surgery. Cytology and pathologic analyses were benign in all patients in both groups.

Fig. 1

Flow chart diagram.



After a median follow-up of 20 months (Q1–Q3; 13–27 months), recurrences were higher in the surgery group, although not statistically significant (odds ratio 0.18, 0.01–1.53). Endometrioma recurrence was observed in 1 of 17 patients in the sclerotherapy group (5.9%), in the treated ovary, not in the contralateral ovary. Four of 14 patients in the surgery group (28.6%) had recurrence, 2 in the contralateral ovary. All recurrences were smaller than the initial size (median 35.5 mm, range 30–50); 3 appeared after a 9-month follow-up and 1 at 16 months; none required additional surgery. One patient who experienced recurrence in the study group underwent sclerotherapy once more during follow-up. No other variables were significant with regard to the increase in recurrence (Table 3).

Three patients became pregnant during follow-up, all in the sclerotherapy group. Symptoms were resolved or improved in most patients in both groups following the procedures (14 of 17 in the sclerotherapy group [82.4%] and 11 of 14 in the surgery group [78.6%]).

The median hospital direct costs were significantly lower in the sclerotherapy group than those in the surgery group: 266 euros (Q1: 266; Q3: 266) versus 2189 euros (Q1: 1944; Q3: 2189) (Table 4). Most costs in the surgical group were

from the operating room, staff costs, consumables, and length of stay, which was avoided in the sclerotherapy group.

Discussion

In this pilot study, there were no more recurrences with ethanol sclerotherapy than with conventional surgery, and ethanol sclerotherapy seemed to result in fewer complications and lower cost.

Recurrence of 28.6% after laparoscopy in the current series was similar to previous reports of 15% to 30% [7,8]. In contrast, after sclerotherapy, endometrioma reappeared in only 1 patient (5.9%). This was even lower than other studies [13,19,22,24,27] that reported recurrence of 0% to 62.5%. The risk of recurrence was significantly higher in females treated with ethanol washing than in those treated with ethanol retention [22]. Recurrence was 62.5% when ethanol was left for < 10 minutes, but 9.1% when left for > 10 minutes [24]. In the current study, ethanol was washed after 15 minutes because ethanol retention allows ethanol extravasation into the abdominal cavity, increasing postoperative abdominal pain and favoring peritoneal adhesions.

Table 1

Baseline patient characteristics			
Characteristic	Surgery n = 14	Sclerotherapy n = 17	p-value
Mean age, yr (SD)	32.1 (5.64)	32.8 (6.36)	NS
Mean BMI, kg/m ² (SD)	23.2 (2.82)	23 (2.91)	NS
Median FSH, IU/L (Q1–Q2)	6.12 (3.89–8.42)	6.55 (5.35–9.04)	NS
Missing	6	1	
Median AMH, ng/mL (Q1–Q3)	1.09 (0.82–3.33)	2.20 (1.23–3.74)	NS
Missing	4	1	
Prior hormonal therapy, n (%)			
Yes	2 (14.3)	2 (11.8)	NS
No	12 (85.7)	15 (88.2)	
Nulliparity, n (%)	7 (50)	10 (58.8)	NS
Sterility, n (%)	1 (7.14)	2 (11.8)	NS
Symptomatology, n (%)			
Pain	14 (100)	11 (73.3)	NS
Others	0	4 (23.5)	
Missing	0	3	
Endometrioma features			
Median size by US (Q1–Q3), mm	61 (55.5–63)	60 (46–78)	NS
Localization			
Bilateral	6 (42.9)	0	.004
Right	3 (21.4)	7 (41.2%)	NS
Left	5 (35.7)	10 (58.8%)	

AMH = antimüllerian hormone; BMI = body mass index; FSH = follicle-stimulating hormone; IU = international units; NS = not significant; Q1–Q3 = quartile 1–3; SD = standard deviation; US = ultrasound.
All data were available in all cases except when missing data are specified.

Half of recurrences occurred in the contralateral ovary, though all recurrences should be classified equally because they have the same impact on a patient's quality of life [28]. Curiously, contralateral ovary recurrences occurred only in the surgery group. This led to the hypothesis that cells that spread through the peritoneum during surgery may be implanted in the contralateral ovary, favoring the formation of endometrioma in this site.

Miranda and Carvajal [29] reported overall complications in 17 of 2140 (0.79%) and major complications in 10 of 2140 (0.46%) after laparoscopy in a retrospective study. Adhesions involving endometriosis may increase the risk of complications as in the current study. The surgical group included 1 severe complication (Clavien-Dindo IIIb) in a patient who needed a radical reintervention some days after surgery, whereas no major complications were observed in the sclerotherapy group.

The current study demonstrates the first prospective evaluation of complications in patients with endometriomas, although a larger number of patients are warranted to obtain more conclusive results. The most important limitation of this study is the number of patients included. Sources of potential bias included the involvement of different surgeons, multicenter scenario, the nonrandomized design, and the fact that the procedure was determined according to the hospital where the patient was treated. However, this pilot study is an

important preliminary step to designing randomized, multicenter studies.

Naturally, the cost of the procedures and hospital length of stay were significantly lower for the sclerotherapy group ($p < .001$), which avoided general anesthesia that is required for laparoscopy.

A limitation of ethanol sclerotherapy is that it does not provide a definitive pathology specimen. Therefore, sclerotherapy should not be used when there is a risk of malignancy and patient selection must be carried out with great care. Nevertheless, no malignancy was observed in either group. The sensitivity and specificity of US in benign cysts suggestive of endometriomas according to IOTA are very high [30].

An additional feature of endometriomas is their association with other endometriotic implants that should be treated at the same time. It has been reported that 99% of patients with ovarian endometriomas have concomitant disease at other sites, mostly intestinal or pelvic [3]. In our series, we observed only 2 patients in the surgery group with superficial extraovarian endometriosis who were not specifically treated, by decision of the surgeon, because they were not symptomatic. In any case, symptoms resolved in approximately 80% of patients in both groups.

We did not evaluate the impact on fertility in this study because most patients were not contemplating pregnancy,

Table 2

Outcomes and follow-up			
Outcome measure	Surgery n = 14	Sclerotherapy n = 17	p-value
Median follow-up, mo (Q1–Q3)	20 (13–27)	21 (18–25)	NS
Length of stay, d, n (%)			.001
0	4 (28.6)	17 (100)	
1	8 (57.1)	–	
2	2 (14.3)	–	
Complications,* n (%)			NS
None	10 (71.4)	15 (88.2)	
Grade I–II	3 (21.5)	2 (11.8)	
Grade III	1 (7.1)	0 (0)	
Grade IV–V	–	–	
Hormonal therapy after procedure, n (%)			NS
No	6 (42.9)	12 (70.6)	
Yes	8 (57.1)	5 (29.4)	
Median FSH at 6 mo, IU/L (Q1–Q3)	7.10 (1.70–8.45)	7.05 (3.95–8.05)	NS
Missing	7	5	
Median AMH at 6 mo, ng/mL (Q1–Q3)	1.35 (0.60–1.61)	2.02 (0.90–3.14)	NS
Missing	5	5	
Pregnancies, n (%)	0 (0)	3 (17.6)	NS
Recurrences, n (%)	4 (28.6)	1 (5.9)	NS
Symptomatology at 6 mo, n (%)			NS
None	2 (22.2)	9 (56.2)	
Improved	4 (44.4)	4 (25)	
Persistence	3 (33.3)	3 (18.8)	
Missing	5	1	

AMH = antimüllerian hormone; FSH = follicle-stimulating hormone; IU = international units; NS = not significant; Q1–Q3 = quartile 1–3.
All data were available in all cases except when missing data are specified.
* Complications according to Clavien-Dindo classification.

although 3 spontaneous pregnancies were observed in the sclerotherapy group and none in the surgery group. Anti-müllerian hormone levels pre- and postprocedure varied widely in both groups; therefore, larger studies are needed to establish the impact on fertility preservation. A literature review revealed that sclerotherapy does not affect the number of pregnancies, term pregnancies, abortions, or extracted

oocytes when compared with infertile females without ovarian cysts [16,31].

Conclusions

Ethanol sclerotherapy for endometrioma treatment seems to reduce healthcare costs and could also reduce

Table 3

Univariate analysis of recurrence				
Measure	No Recurrence n = 26	Recurrence n = 5	OR (95% CI)	p-value
Procedure, n (%)				
Sclerotherapy	16 (61.5)	1 (20)	0.18 (0.01–1.53)	NS
Surgery	10 (38.5)	4 (80)		
Mean age, yr (SD)	32.8 (6.2)	30.7 (4.6)	0.94 (0.79–1.11)	NS
Mean BMI, kg/m ² (SD)	23.0 (2.9)	23.5 (2.8)	1.07 (0.75–1.52)	NS
Mean endometrioma size, mm (SD)	61.7 (16.7)	76.6 (15.2)	1.05 (0.99–1.11)	.089
Hormonal therapy after procedure, n (%)				
No	15 (57.7)	3 (60)	1.10 (0.16–7.74)	NS
Yes	11 (42.3)	2 (40)		

BMI = body mass index; CI = confidence interval; NS = not significant; OR = odds ratio; SD = standard deviation.

Table 4

Direct medical cost estimate of patients in both groups

Item	Surgery	Sclerotherapy	Difference
Staff labor costs	536.90	105.83	431
Operating room occupation	459.73	0	460
Consumables	350.43	70.46	280
Medication	67.09	2.99	64
Ultrasound amortization	0	12.3	-12
Inpatient costs	362.55	0	363
Miscellaneous costs	412.41	74.66	338
Total in-hospital direct costs	2189.10	266.24	1923

Cost estimates are expressed in euros.

complications because it is a simple technique, performed in ambulatory patients without anesthesia. In this pilot study, there were no more recurrences with ethanol sclerotherapy than with conventional surgery. Further multicenter randomized studies with larger sample sizes are warranted to demonstrate this hypothesis conclusively.

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