

ORIGINAL RESEARCH

Ethanol Sclerotherapy versus Laparoscopic Surgery in Management of Ovarian Endometrioma; a Randomized Clinical Trial

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Received: May 2022; Accepted: June 2022; Published online: 7 July 2022

Abstract: **Introduction:** A variety of therapeutic modalities are available in management of ovarian endometrioma. This study aimed to compare the effects of ethanol sclerotherapy and laparoscopic surgery on disease recurrence and ovarian factors of these patients. **Methods:** 70 women with ovarian endometrioma and chronic pelvic pain were randomly divided into two groups. The first group underwent sclerotherapy with a puncture needle (cook) and the second group underwent laparoscopic surgery. Both groups were followed up every three months to investigate the recurrence rate. In this regard, ultrasonography was performed 3 months and 12 months after treatment, and serum anti-Müllerian hormone (AMH) levels were also reassessed 12 weeks after the intervention. **Results:** 70 women with the mean age of 31.46 ± 4.71 years, and the mean body mass index (BMI) of 23.12 ± 1.01 were studied. The two groups were similar regarding age ($p = 0.770$), BMI ($p = 0.371$), history of gastrointestinal signs ($p = 0.794$), history of urinary diseases ($p = 0.324$), dysmenorrhea ($p = 0.403$), pelvic pain ($p = 0.454$), dyspareunia ($p = 0.448$), location of cyst ($p = 0.448$), and diameter of cyst ($p = 0.250$). In the laparoscopic group, a significant decrease in anti-Müllerian hormone (AMH) levels was observed after 12 weeks ($p < 0.0001$), while in the sclerotherapy group, no significant changes were found between pre-and post-operative AMH levels ($p = 0.120$). Cyst size decreased significantly in both groups three months ($p < 0.001$) and twelve months ($p < 0.0001$) after treatment. In the third month, 8 patients in the sclerotherapy group and 13 patients in the laparoscopic group had recurrences, and in the twelfth month, 17 patients in the sclerotherapy group and 15 patients in the laparoscopic group had recurrence of symptoms ($p > 0.05$). **Conclusion:** Although AMH level and mean cyst diameter were significantly lower one year after laparoscopy, recurrence rate of ovarian endometrioma was similar between ethanol sclerotherapy and laparoscopy methods.

Keywords: Endometriosis; Ethanol; Laparoscopy; Ovarian Cysts; Sclerotherapy

Cite this article as: Ghasemi Tehrani H, Tavakoli R, Hashemi M, Haghghat S. Ethanol Sclerotherapy versus Laparoscopic Surgery in Management of Ovarian Endometrioma; a Randomized Clinical Trial. Arch Acad Emerg Med. 2022; 10(1): e55. <https://doi.org/10.22037/aaem.v10i1.1636>.

1. Introduction

One of the most common medical conditions in women is endometriosis, defined as the growth of endometrial tissue outside the uterine cavity, which can respond to hormonal stimulation of the ovaries (1). Statistics have revealed that the presence of endometrial glands and stromal tissue outside

the uterine can cause infertility among women of reproductive age (2). Endometriosis is widely observed in the pelvic areas such as the ovaries, rectovaginal septum lesion, posterior cul-de-sac, and Sacro-uterine ligament (3).

Ovarian endometrioma is characterized by excessive proliferation of fibroblasts (4). A variety of therapeutic modalities are available in the management of women with ovarian endometrioma, based on medical criteria. For example, medical treatments can be useful for the relief of mild to moderate pain (5). However, surgical approaches are the gold standard in the treatment of infertility and severe pain caused by endometriosis (5). Currently, the conservative laparoscopy approach is used as a minimally invasive technique for the

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treatment of infertility related to ovarian endometrioma (6). During laparoscopy, either ovarian cyst excision or bipolar coagulation of the internal layer of the cyst wall is applied in most cases (7, 8). Regarding laparoscopic excision, after separation of adhesions, an incision is made, and endometriotic lesions are aspirated gently with minimal damage to the unaffected ovarian tissue (7). However, the mentioned methods for treating ovarian endometrioma have many disadvantages, which can affect ovarian function. Surgery-related damage to ovarian reserve following laparoscopy has become a central issue, and it seems clear that another option needs to be found (9). Therefore, various studies have been performed in order to use safer and less invasive methods to treat this medical condition. One of the newest treatment modalities is ultrasound-guided sclerotherapy (10).

Chemical sclerotherapy has been successfully performed in various organs, such as cystic lesions of the thyroid nodules, lymphatic malformations of the neck, liver, kidney, and spleen (11-14). Sclerotherapy is also used in ovarian endometrioma, and the overall recurrence rate is estimated at 13.8% (15). Various sclerosing agents have been used in sclerotherapy, including tetracycline, methotrexate, and ethanol (15). One of the main advantages of this technique, compared with the other techniques, is that it dramatically reduces pelvic pain related to endometriosis, while it has no negative effect on the number of oocytes retrieved and embryo quality (16).

However, due to the variety of treatment modalities and different types of surgery methods and their effects on disease recurrence and ovarian reserve, it is still not possible to decide on the best treatment method. The present study aimed to compare the effects of ethanol sclerotherapy and laparoscopic surgery on disease recurrence and ovarian factors of the mentioned patients.

2. Methods

2.1. Study design and setting

This clinical trial was conducted in Shahid Beheshti Hospital, Isfahan, Iran from December 2020 to January 2022. The study protocol was approved by the Ethical Committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1398.499) and registered on the Iranian Registry of Clinical Trial (IRCT Registration ID: IRCT20171030037093N31). Participants were informed about the objectives of the study, and informed consent was obtained from all patients before any intervention.

2.2. Participants

Women who had previously been diagnosed with ovarian endometrioma based on clinical examination or imaging were eligible for inclusion. Inclusion criteria were as follows: 1) In-

fertile women with ovarian endometrioma diagnosed by ultrasonography or magnetic resonance imaging (MRI); 2) Age range of 18 to 40 years old; 3) tumor marker CA125 <200 IU/mL; 4) chronic pelvic pain; 5) Ovarian endometrioma cysts of 4-10 cm in diameter. In this study, infertility was defined as the failure to achieve a clinical pregnancy after 12 months or more. Patients with incomplete information, women with non-endometrial ovarian masses, participants with a history of any malignancy, and patients who did not sign informed consent forms, were excluded from the study.

2.3. Data gathering

A standard form was designed in Microsoft Excel to extract information and patients' demographic and clinical characteristics, including age, the number of pregnancies, anti-Müllerian hormone (AMH), and any history of gastrointestinal diseases (Abdominal pain, nausea, bloating) were recorded. Data on pelvic pain was evaluated with the short-form McGill pain questionnaire (17).

2.4. Randomization

Before the start of the trial, a computer-generated random numbers table was used for randomization, and participants were randomly assigned to experimental groups.

2.5. Allocation concealment and blinding

Allocation concealment was performed using 70 identical, sequentially numbered, sealed envelopes. The study was a double-blind clinical trial. Patients and research assistants were blinded to treatment allocation.

2.6. Interventions

After obtaining consent, participants were randomly divided into two groups (35 cases/group): group 1) sclerotherapy group and group 2) laparoscopy group.

In the first group, a standardized approach was followed for sclerotherapy, as previously described by Yazbeck et al. (18). Transvaginal sclerotherapy was carried out under sedation and using ultrasound guidance in the lithotomic position, using needles of various sizes (Cook, Bloomington, Indiana). The Endometrioma lesion was observed and confirmed; following this, the needle tip was inserted into the lesions, and cyst content was aspirated. Approximately 80% of the cyst volume, was replaced with a maximum of 100 ml of 95% ethanol. Ethanol remained in the lesion for about 20 minutes, and then it was completely aspirated to eliminate the side effects of ethanol.

In the second group, laparoscopic cystectomy was performed under general anesthesia. In all patients, after the incision was made into the cyst wall, the content was completely aspirated, and then endometrioma was stripped from the healthy ovarian parenchyma. Finally, all endometrial lesions excised



Table 1: Comparing the demographic and clinical baseline characteristics between the groups

Variable	Sclerotherapy N= 35	Laparoscopy N= 35	p-value
Age (year)	32.17 ± 4.76	30.80 ± 4.63	0.770
Body mass index	23.01 ± 1.17	23.22 ± 0.79	0.371
History of Gastrointestinal Signs	10 (28.57)	11 (31.42)	0.794
History of urinary diseases	7 (20.00)	4 (11.42)	0.324
Dysmenorrhea	25 (71.42)	28 (80.00)	0.403
Pelvic pain	24 (68.57)	21 (60.00)	0.454
Dyspareunia	16 (45.71)	9 (25.71)	0.081
Location of Cyst			
Right	7 (20.00)	11 (31.42)	
Left	22 (62.85)	17 (47.58)	0.448
Bilateral	6 (17.15)	7 (20.00)	
Mean Longest Cyst Diameter (mm)	6.92 ± 1.85	8.67 ± 8.69	0.250

Data are presented as mean ± standard deviation or frequency (%).

Table 2: Comparing the outcomes between the two groups

Outcome	Sclerotherapy N= 35	Laparoscopy N= 35	p-value
Mean longest cyst diameter (mm)			
Before	6.92 ± 1.85	8.67 ± 8.69	0.250
3 months after	3.30 ± 2.52	1.22 ± 1.80	<0.001
12 months after	5.45 ± 1.65	3.19 ± 1.98	<0.001
Recurrence rate (%)			
3 months after	8 (22.8)	13 (28.8)	0.192
12 months after	17 (48.57)	15 (42.85)	0.631

Data are presented as mean ± standard deviation or frequency (%).

from the abdominal cavity were sent for histological analysis.

2.7. Outcomes

All patients were hospitalized and monitored for at least 24 hours. Both groups were followed up every 12 weeks to investigate the recurrence rate. In this regard, ultrasonography was performed 3 months and 12 months after treatment, and serum AMH levels were also reassessed 12 weeks after the intervention.

2.8. Statistical analysis

The sample size (35/group) was calculated based on the results of previous studies (16, 19) using the formula for estimating the sample size, with a confidence level of 95% ($Z = 2 - \alpha/1 = 1.96$), and a test power coefficient of 84%.

Statistical analysis was performed using the SPSS software version 24. The descriptive data were presented as mean ± standard deviation (SD) or frequency (percentage). Data were analyzed using chi-square, independent t-test, and Pearson correlation statistical test. A p-value <0.05 was considered to be statistically significant.

3. Results

3.1. Participant flow

Figure 1 demonstrates details of the enrollment, allocation, follow-up, and analysis of participants through the trial based on the CONSORT criteria (20). 10 women were excluded from the study due to not meeting the inclusion criteria ($n = 4$), declining to participate ($n = 3$), not receiving the allocated intervention ($n = 1$), and being lost to follow up ($n = 2$). Finally, a total of 70 women who had previously been diagnosed with ovarian endometriosis were included in the study.

3.2. Baseline characteristics of patients

In the present study, 70 women with ovarian endometrioma were randomly divided into two groups. The mean age of the participants was 31.46 ± 4.71 years, and their mean BMI was 23.12 ± 1.01 . Demographic and clinical baseline characteristics of the study population are illustrated in Table 1. There was no significant difference between groups regarding age ($p = 0.770$), BMI ($p = 0.371$), history of gastrointestinal signs ($p = 0.794$), history of urinary diseases ($p = 0.324$), dysmenorrhea ($p = 0.403$), pelvic pain ($p = 0.454$), dyspareunia ($p = 0.448$), location of cyst ($p = 0.448$), and diameter of cyst ($p = 0.250$). The mean cyst volume aspirated and the mean volume of alcohol instilled in the sclerotherapy group were



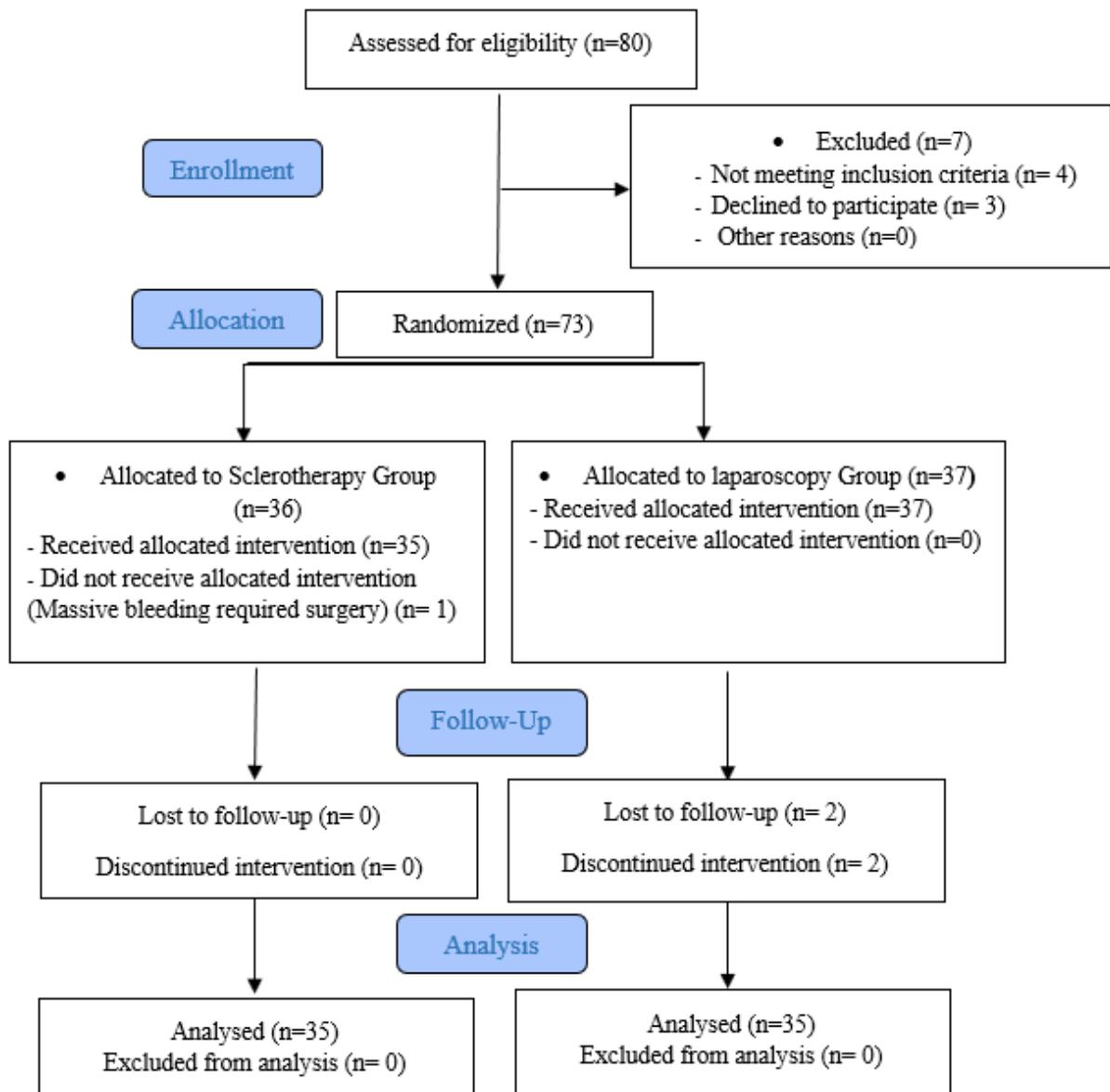


Figure 1: The CONSORT flow diagram of the studied population.

125.88 ± 110.66 ml and 71.66 ± 30.91 ml, respectively

3.3. Outcomes and estimation

Table 2 compares the outcomes between groups before and after the intervention. In the laparoscopic group, a significant decrease in AMH levels was observed after 12 months (2.48 ± 1.34 vs, 1.62 ± 1.22; $p < 0.001$), while in the sclerotherapy group, no significant changes were found between pre- and 12-months post-operative AMH levels (2.12 ± 1.05 vs. 2.09 ± 1.01; $p = 0.120$). Cyst size significantly decreased in both groups three months ($p < 0.001$) and twelve months ($p < 0.001$) after treatment. In the third month, 8 patients in

the sclerotherapy group and 13 patients in the laparoscopic group had recurrences, and in the twelfth month, 17 patients in the sclerotherapy group and 15 patients in the laparoscopic group had recurrence of symptoms. Based on the statistical analysis, no significant differences were found in terms of recurrence rate between the two groups.

4. Discussion

Based on the findings of the present study, although AMH level and mean cyst diameter were significantly lower one year after laparoscopy, recurrence rate of ovarian endometri-

oma was similar between ethanol sclerotherapy and laparoscopy methods. Endometriosis is a benign disease characterized by the growth of endometrial tissue outside the uterine cavity (21). The most common affected sites for endometriosis are ovaries (1). In the management of ovarian endometriosis, the patient's symptoms, fertility status, and the extent of lesion, are of particular importance. The best method to evaluate the severity and extent of the lesion is laparoscopic surgery, which is preferable to laparotomy for treatment because it creates little adhesion (22). However, the laparoscopic procedure was associated with problems, including surgery-related damage to ovarian reserve and a high recurrence rate of endometrioma after treatment (23). In this regard, sclerotherapy was introduced as a new method for the management of ovarian endometrioma. In the present study, a significant decrease in AMH levels was observed after 12 weeks in the laparoscopy group. This lends support to the previous findings in the literature (23-26). A comprehensive study by Raffi et al. showed that laparoscopic surgery of endometrioma lesions reduced anti-Müllerian hormone levels, which may be one of the reasons for the reduced fertility rate in these women after surgery (23). On the other hand, in line with the report by Huang et al. (27), the serum level of AMH in the sclerotherapy group had not changed in our study, so our experiments demonstrate that sclerotherapy might be safer and less invasive than laparoscopy.

In this research, recurrence was defined as the presence of a typical cystic mass with a minimum diameter of 20 mm, detected by transvaginal ultrasonography within three months after the surgery. Although studies have suggested that ethanol sclerotherapy could be an effective strategy for the treatment of ovarian endometrioma from the standpoint of recurrence (28, 29), we did not find a significant difference in recurrence rates between the two groups in this study. This difference in findings may be due to several different factors, such as methodological differences. However, it seems that the chances of pregnancy will increase due to the improvement of AMH levels in the sclerotherapy group.

Cyst size significantly decreased in both groups three months and twelve months after treatment, compared to before treatment. Our results share a number of similarities with Chang et al.'s (30) findings, in which the authors showed that cyst size was consistently decreased until six months after sclerotherapy.

Based on our study, ethanol sclerotherapy seems to be an effective alternative in the management of ovarian endometrioma and also appears to decrease surgery-related damage to ovarian reserve.

5. Limitations

The current study was limited by a small sample size and possible selection bias because of the specificity of the study design, so further studies are needed to increase the generalizability of its findings. In addition, the result might be affected by the involvement of different surgeons and the different laboratory conditions.

6. Conclusion

Based on the findings of present study, although AMH level and mean cyst diameter were significantly lower one year after laparoscopy, recurrence rate of ovarian endometrioma was similar between ethanol sclerotherapy and laparoscopy methods. Therefore, ethanol sclerotherapy seems to be an effective alternative for laparoscopic surgery in management of ovarian endometrioma.

7. Declarations

7.1. Acknowledgments

This research was made possible by a grant from Isfahan University of medical science.

7.2. Availability of Data and Materials

All data supporting the findings of the article and materials used in this work were publicly available.

7.3. Data availability

The data is at the disposal of the corresponding author of the article and it can be made available to the researchers upon request.

7.4. Authors' contributions

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7.5. Funding and supports

This study was supported by grants from Isfahan University of Medical Sciences (398662).

7.6. Conflict of interest

The authors declare that there is no conflict of interest.

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