The prevention of postoperative port-site adhesion following single-port access (SPA) laparoscopic surgeries

Joseph J. Noh, MD<sup>a</sup>, Myeong-Seon Kim, MD, PhD<sup>b</sup>, Soo-Young Jeong, MD<sup>a</sup>, Jun-Hyeok Kang, MD<sup>a</sup>, Byung-Kwan Park, MD, PhD<sup>c</sup>, Tae-Joong Kim, MD, PhD<sup>a</sup>,<sup>c</sup>

Abstract

No studies have examined the issue of intraabdominal port-site adhesion following single-port access (SPA) laparoscopic surgeries. The purpose of the present study was to investigate the clinical effects of temperature-sensitive adhesion barrier solution in preventing periumbilical adhesion in SPA laparoscopy. This was a prospective, single-arm study in which patients were given GUARDIX-SG™ after SPA laparoscopic surgery for benign gynecologic diseases. One gram of GUARDIX-SG™ was applied on the abdominal viscera just below the umbilical port site and adjacent abdominal wall prior to fascia closure. The primary endpoint was the incidence of postoperative adhesion evaluated by visceral sliding technique through transabdominal sonography after three months. Between June 2019 and March 2020, a total of 37 healthy patients without any history of previous abdominal surgery received SPA laparoscopic surgery by a single surgeon. No postoperative complications such as wound dehiscence or surgical site infection occurred during the follow-up period of three months. No postoperative adhesion around the umbilicus was noted in all 37 patients. The mean visceral movement measured by transabdominal sonography during maximal respiration was 4.9 cm (4.9 ± 1.9 cm). Using an adhesion barrier around the port site prior to fascia closure prevents postoperative adhesion in benign SPA laparoscopic gynecologic surgery.

Abbreviations: ASA = American Society of Anesthesiology, BMI = body mass index, BSA = body surface area, EBL = estimated blood loss, SPA = single-port access.

Keywords: adhesion barrier, gynecologic surgery, laparoscopic surgery, postoperative adhesion, single-port access (SPA)

1. Introduction

Postoperative surgical adhesion, which can be defined as abnormal fibrous connections joining tissue surfaces at non-anatomic locations, frequently occurs following abdominal surgery. There is now a growing body of consensus that it occurs whether it is performed through a laparotomy incision or via laparoscopy. Depending on their severity and position, postoperative adhesions may be silent or cause significant morbidity, including bowel obstruction, chronic abdominal pain, female infertility, and increased difficulty in subsequent surgeries, resulting in important consequences for patients and surgeons. The authors have investigated various aspects of single-port access (SPA) surgeries in previous studies, including suture techniques, postoperative hernia rates, retroperitoneal ligation of uterine arteries, and feasibility of operation for large tumors. These studies have consistently demonstrated the safety and feasibility of SPA surgeries in gynecology, and the literature agrees that the laparoscopic approach is now considered the standard surgical care for many benign gynecologic diseases. However, the majority of research investigating the healthcare and patient burdens of postoperative adhesion has focused on the consequences of laparotomy. Furthermore, no studies have been conducted to examine this issue in SPA laparoscopic surgery in which only one large incision is made at the umbilicus. It is not uncommon for surgeons to encounter periumbilical adhesion of the anterior abdominal wall with the omentum or small bowel when performing repeated entry through the umbilicus. Because the umbilicus is used the most often as the initial entry site for abdominal or pelvic laparoscopy, prevention of adhesion at this site is critical for future laparoscopic surgery, especially if a patient is likely to receive repeat surgery for disease recurrence.
adhesion-related morbidity.\[^{11}\] Adhesion barriers or anti-adhesive agents have come into the market that may help reduce the occurrence of adhesions. They range from membranes for selective coverage of certain areas to liquids for broad nonspecific coverage.

The aim of the present study was to evaluate the effectiveness of temperature-sensitive GUARDIX-SG\(^{\text{TM}}\) in the prevention of periumbilical de novo adhesion formation at the time of benign SPA laparoscopic gynecologic surgeries. We performed this study in patients with endometriosis and uterine leiomyoma because these two disease entities are with the highest recurrence rates among benign gynecologic diseases, therefore the patients were at high risk of receiving multiple surgical procedures, most often laparoscopically.

2. Materials and methods

2.1. Patients

This was a prospective cohort study of women between 19 and 45 years old with the diagnosis of uterine leiomyoma or endometriosis who were scheduled to undergo SPA laparoscopic surgery. The study period was from June 2019 to March 2020 and it was taken at an urban tertiary academic medical center in Seoul, South Korea (Samsung Medical Center). Exclusion criteria were patients with any history of previous abdominal or pelvic surgery, history of medical disease such as pelvic inflammatory disease that might have caused abdominal or pelvic adhesion, and any radiologic evidence of abdominal or pelvic adhesion that was found prior to operation. These exclusion criteria were adopted to create a patient group with the minimum likelihood of the presence of adhesion prior to our surgery, therefore allowing us to accurately assess the clinical efficacy of the adhesion barrier. Patients under the age of 45 were selected because the recurrence rates of the diseases in this specific age group are higher than others, which implies that they are more likely to gain maximal benefit from the application of the adhesion barrier for future surgeries compared to other age groups. Approval from the Institutional Review Board at Samsung Medical Center was obtained (IRB number: SMC 2018-04-004).

2.2. Study design and protocols

The SPA laparoscopic myomectomy and endometriosis surgery were performed in the same surgical procedures and steps by one surgeon (TJK). After incising the skin at about 2.0 to 2.5 cm, subcutaneous tissue and anterior abdominal fascia were opened by Bovie electrocauterization (Bovie Medical Corporation, Inc., Melville, NY, USA) using the open Hasson technique. Entering the peritoneum, single-port access was created by inserting a polyurethane The One Port\(^{\text{TM}}\) (LapaKorea, Inc., Seoul, South Korea). The carbon dioxide pneumoperitoneum was kept at 13 mmHg throughout the operation. The instruments used during the operations included monopolar scissors, and laparoscopic energy devices such as ENSEAL\(^{\text{TM}}\) (Ethicon, Inc., Somerville, NJ, USA) or THUNDERBEAT\(^{\text{TM}}\) (Olympus, Inc., Tokyo, Japan). Prior to fascial closure, 1 g of GUARDIX-SG\(^{\text{TM}}\) was applied on the abdominal viscera just below the port insertion site. The anterior abdominal wall was lifted slightly with the Army-Navy retractors while the solution was placed on the visceral organs beneath it. It was also directly applied to the areas of the peritoneal and fascial layers that were about to be sutured. Fascial layers were closed in an interrupted manner using 2–0 Polysorb\(^{\text{TM}}\) (Ethicon, Inc., Somerville, NJ, USA). The peritoneum was not closed as a separate layer. The soft tissue was approximated with 4–0 Monocryl\(^{\text{TM}}\) (Ethicon, Inc., Somerville, NJ, USA) suture in an interrupted manner. The skin was closed with a clear adhesive bandage (Dermabond Mini\(^{\text{TM}}\), Ethicon, Inc., Somerville, NJ, USA).

2.3. Assessment

The primary endpoint was the incidence of postoperative adhesion observed by transabdominal sonography three months after the operations. Visceral slide sonography according to the technique that has been previously described was adopted.\[^{15}\] This technique is often used to detect periumbilical adhesions for its simplicity and reliability after pelvic surgeries.\[^{16,17}\] It was demonstrated in one study that it has a sensitivity of 83.3%, specificity of 100%, a positive predictive value of 100%, a negative predictive value of 98.5%, and diagnostic accuracy of 98.6%.\[^{18}\] The measurement was taken by the distance of the longitudinal excursion of the internal viscera to the fixed abdominal wall. Normal viscera sliding movement was defined as equal to or greater than 1.0 cm of longitudinal movement as normally defined in previous studies. Restricted viscera slide was defined as less than 1.0 cm of longitudinal movement during both normal and maximal respiration. The evaluation was performed by a single radiologist (BKP) who had more than 20 years of experience in gynecologic sonography.

2.4. Sample size estimation

No studies have investigated the incidence of postoperative umbilical adhesion in SPA laparoscopic gynecologic surgeries yet. Therefore, we had to extrapolate the incidence from pertinent literature. The Cochrane Database of Systematic Reviews estimated that between 1.6% and 51.0% of gynecologic laparoscopic surgeries would result in the development of postoperative adhesion.\[^{11}\] A substantial variation is seen in the estimated incidence due to different study designs and modalities of confirming adhesion formation. Perhaps, the most accurate way of diagnosing postoperative adhesion is achieved by second-look laparoscopic surgery. Researchers have noted a 12% incidence rate of postoperative adhesion development after laparoscopic surgeries by second-look laparoscopy.\[^{19}\] It has also been postulated that the risk of developing postoperative adhesion doubles if the size of trocar insertion increases by two times.\[^{20}\] In general, SPA laparoscopic surgery utilizes a 2.0 to 2.5 cm umbilical incision, which is about twice bigger than the conventional 5 to 12 mm trocar sites. Therefore, we estimated that the risk of developing postoperative adhesion would be around 24% without the use of an adhesion barrier. The Cochrane Database of Systematic Reviews also estimated that the use of an adhesion barrier would decrease the risk of developing postoperative adhesion by an odds ratio of 0.09 to 0.20.\[^{11}\] Therefore, we assumed that the incidence of postoperative adhesion with the application of adhesion barrier would be around 3%. The sample size required to allow the detection of at least one patient with postoperative adhesion in this study at a probability of ≥95% with 91% statistical power was calculated to be ≥34. Based on this result, the target sample size was decided at 42 in consideration of 20% of drop-outs.
2.5. Statistical analysis

The data for the present study are expressed as mean ± standard deviation for continuous variables. Statistical significance was determined using the Fisher exact test for dichotomous variables and by the independent Student t test for continuous variables. P values less than .05 were considered significant. Statistical calculations were carried out with R 3.6.2. (Vienna, Austria; http://www.R-project.org/).

3. Results

Between June 2019 and March 2020, a total of 42 patients were enrolled in the study. Among them, 17 patients received SPA laparoscopic myomectomy while 20 patients received endometriosis surgery including ovarian cystectomy. Two patients converted to multiport laparoscopic surgery during the operations due to inadequate exposure to the surgical field and difficulties in surgical manipulation. Another three patients completed their surgeries by SPA laparoscopy but were lost to follow-up for postoperative sonography (Fig. 1). Table 1 shows the baseline characteristics of the patients. The mean age of the patients was 33.7 years (36.2 ± 6.5 years for myomectomy and 31.8 ± 7.0 years for endometriosis surgery) all without a history of previous abdominal surgery. All patients reported no history of pelvic inflammatory disease, which could raise the possibility of abdominal or pelvic adhesion formation prior to their operations. Adhesiolysis was performed in 13 patients in which various extent of pelvic adhesion was noted likely due to endometriosis. Postoperative period was uneventful in all participating patients.

The incidence of postoperative adhesion was zero within the three-month follow-up period. No surgical site infection or wound dehiscence was reported. The mean visceral movement during tidal respiration measured by transabdominal sonography three months after the operation was 1.2 ± 0.6 cm (1.3 ± 0.7 cm for patients who received myomectomy and 1.1 ± 0.6 cm for patients who received endometriosis surgery). The same measure during the maximal respiration was 4.9 ± 1.9 cm (5.7 ± 1.7 cm for patients who received myomectomy and 4.3 ± 1.9 cm for patients who received endometriosis surgery) (Table 2). These results support that no postoperative adhesion formed from benign SPA laparoscopic gynecologic surgery in the present study.

4. Discussion

The present study demonstrated the clinical efficacy of GUARDIX-SGTM, a temperature-sensitive adhesion barrier, in preventing postoperative periumbilical adhesion in SPA laparoscopic surgery for benign gynecologic diseases. It was also found to be safe to apply the adhesion barrier directly on the suture sites without increasing the risk of developing wound dehiscence or infection. The present study was the first to investigate postoperative adhesion in SPA surgeries.

A number of different approaches have been developed to reduce adhesion formation after abdominal surgery.[2] These measures include minimizing the size and number of wounds, the administration of anti-inflammatory agents, and the application of adhesion barrier membranes and materials. Components often included in adhesion barriers are naturally derived polysaccharides such as oxidized regenerated cellulose, sodium carboxymethyl cellulose, dextran, sodium hyaluronate, polyethylene glycol, and poloxamer.[21] GUARDIX-SGTM (Genewel, Dong-sung Company, Seongnam, South Korea) is a poloxamer-based, temperature-sensitive anti-adhesive agent that consists of cross-linked poloxamer, alginate, and calcium chloride (CaCl2). It remains in a solution form at 20°C but transforms to a gel form once applied to surfaces at body temperature (above 30°C), which enhances its properties as a physical barrier. Hyaluronate/carboxy cellulose membrane (SeprafilTM) is one of the most extensively studied anti-adhesive agents in gynecologic surgery.[21] Several studies have reported that it effectively decreases the formation of postoperative surgical adhesion.[23,24] However, an important drawback of the available membranous adhesion barriers, such as SeprafilmTM, is the difficulty of handling them during laparoscopic procedures. Therefore, an anti-adhesive agent in solution or gel form is favored in many laparoscopic surgeries. It is easy to deliver the agent through small port sites, and its viscous characteristic allows it to remain on the site where it is initially applied.

The umbilicus is often used as the initial entry site for abdominal or pelvic laparoscopic surgeries. Therefore, the formation of postoperative periumbilical adhesion will subsequently obstruct the entry of future abdominal or pelvic laparoscopic surgeries and increase the risk of inadvertent enterotomy or vessel injuries. Furthermore, postoperative adhesion carries significant social, personal, litigious, and economic consequences. Therefore, it is important to prevent and reduce the chance of postoperative surgical adhesion formation, especially in patients who are likely to receive repeat surgeries. Patients with endometriosis or uterine leiomyoma have a high risk of disease recurrence and often receive additional surgeries. A population-based cohort study revealed that, among 628 women who had already received uterine myomectomy, 127 (21.8%) had a second surgery, and 95 (17.8%) of which were hysterectomies. The cumulative incidence of second surgery was 23.5% at 5 years and 30% at 7 years.[21] A higher incidence of repeat surgery in endometriosis compared to age-matched women was also demonstrated by another large population-based cohort study from Scotland.[24]
|                                      | Myomectomy (n = 17) | Endometriosis surgery (n = 20) | Total (n = 37) |
|--------------------------------------|---------------------|------------------------------|---------------|
| Age (years old)                      | 36.2 ± 6.5          | 31.8 ± 7.0                   | 33.7 ± 7.1    |
| Sexual history                       |                     |                              |               |
| Yes                                  | 16 (94.1%)          | 18 (90.0%)                   | 34 (91.9%)    |
| No                                   | 1 (5.8%)            | 2 (10.0%)                    | 3 (8.1%)      |
| Previous vaginal deliveries          |                     |                              |               |
| 0                                    | 13 (76.5%)          | 15 (75.0%)                   | 28 (75.7%)    |
| 1                                    | 1 (5.8%)            | 2 (10.0%)                    | 3 (8.1%)      |
| 2                                    | 3 (17.6%)           | 3 (15.0%)                    | 6 (16.2%)     |
| Height (cm)                          | 161.8 ± 4.6         | 162.5 ± 4.8                  | 162.2 ± 4.6   |
| Weight (kg)                          | 59.2 ± 7.4          | 54.7 ± 7.6                   | 56.6 ± 7.8    |
| BMI                                  | 22.6 ± 2.7          | 20.7 ± 2.6                   | 21.5 ± 2.8    |
| BSA (m²)                             | 1.6 ± 0.1           | 1.6 ± 0.1                    | 1.6 ± 0.1     |
| Chief complaint about surgery        |                     |                              |               |
| Dysmenorrhea                         | 0 (0%)              | 13 (65.0%)                   | 13 (35.1%)    |
| Menorrhagia                          | 6 (40.0%)           | 1 (5.0%)                     | 7 (18.9%)     |
| Abdominal discomfort                 | 7 (46.7%)           | 6 (30.0%)                    | 13 (35.1%)    |
| Urinary frequency                    | 2 (13.3%)           | 0 (0%)                       | 2 (5.4%)      |
| ASA physical status classification   |                     |                              |               |
| 1                                    | 14 (82.4%)          | 16 (80.0%)                   | 30 (81.1%)    |
| 2                                    | 2 (11.8%)           | 4 (20.0%)                    | 6 (16.2%)     |
| 3                                    | 1 (5.8%)            | 0 (0%)                       | 1 (2.7%)      |
| Medical conditions                   |                     |                              |               |
| Hypertension                         | 0 (0%)              | 0 (0%)                       | 0 (0%)        |
| Diabetes mellitus                    | 0 (0%)              | 0 (0%)                       | 0 (0%)        |
| Allergy                              | 1 (6.7%)            | 0 (0%)                       | 1 (2.7%)      |
| Social conditions                    |                     |                              |               |
| Past smokers                         | 0 (0%)              | 1 (5.0%)                     | 1 (2.7%)      |
| Current smokers                      | 0 (0%)              | 2 (10.0%)                    | 2 (5.4%)      |
| Alcohol drinkers                     | 3 (20%)             | 6 (30.0%)                    | 9 (24.3%)     |
| Operation time (minutes)             | 116.8 ± 29.6        | 93.8 ± 29.3                  | 103.7 ± 31.2  |
| Final pathology diagnosis            |                     |                              |               |
| Uterine leiomyoma                    | 17 (100%)           | 0 (0%)                       | 17 (45.9%)    |
| Endometriosis                        | 0 (0%)              | 20 (100%)                    | 20 (54.1%)    |
| Size of the largest mass (cm)        | 7.1 ± 2.1           | 5.8 ± 2.3                    | 6.4 ± 2.3     |
| Side of the mass (for adnexal surgery)| Not applicable     | Not applicable                | Not applicable|
| Anterior                             | 7 (41.2%)           |                              |               |
| Fundus                               | 5 (29.4%)           | Not applicable                | Not applicable|
| Posterior                            | 4 (23.5%)           |                              |               |
| Others (cervical leiomyoma)          | 1 (5.8%)            |                              |               |
| Weight of leiomyoma (g)              | 195.1 ± 101.4       | Not applicable                | Not applicable|
| Adhesiolysis                         |                     |                              |               |
| Performed during operation           | 1 (5.8%)            | 12 (60.0%)                   | 13 (35.1%)    |
| Not performed                        | 16 (94.1%)          | 8 (40.0%)                    | 24 (64.9%)    |
| EBL (mL)                             | 70.7 ± 42.2         | 118.5 ± 63.7                 | 98.0 ± 59.8   |
| Hemoglobin (g/dL)                    | 13.1 ± 1.2          | 13.0 ± 1.0                   | 13.0 ± 1.0    |
| Pre-operative                        | 11.8 ± 1.1          | 11.3 ± 1.0                   | 11.5 ± 1.1    |
| Post-operative                       | −1.3 ± 0.8          | −1.7 ± 0.9                   | −1.5 ± 0.9    |
| White blood cell counts (per µL)     |                     |                              |               |
| Pre-operative                        | 5765 ± 1382         | 6978 ± 1576                  | 6458 ± 1595   |
| Post-operative                       | 8611 ± 2420         | 9265 ± 2273                  | 8984 ± 2325   |
| Differences between pre-op. and post-op. | −39.6 ± 33.9         | −32.6 ± 45.3                 | −35.6 ± 40.4  |
| Platelet counts (x 10³ per µL)       |                     |                              |               |
| Pre-operative                        | 261.3 ± 69.0        | 280.6 ± 58.6                 | 272.3 ± 63.0  |
| Post-operative                       | 221.7 ± 70.6        | 248.0 ± 50.3                 | 236.7 ± 60.3  |
| Differences between pre-op. and post-op. | −39.6 ± 33.9         | −32.6 ± 45.3                 | −35.6 ± 40.4  |
| Total hospital stays after operation (days) |                     |                              |               |
| 1                                    | 0 (0%)              | 20 (100%)                    | 20 (54.1%)    |
| 2                                    | 17 (100%)           | 0 (0%)                       | 17 (45.9%)    |

BMI = body mass index, BSA = body surface area, ASA = American Society of Anesthesiology, EBL = estimated blood loss.
The size of the incision in SPA laparoscopic surgery is usually between 2.0 and 2.5 cm. It is made directly on the umbilicus vertically, thereby minimizing visible scar after the operation. Despite its advantage in providing less visible postoperative scar, its size is generally larger than the conventional 5 and 12 mm trocar incision site. After incising the skin, the subcutaneous tissue and abdominal fascia are opened in a similar manner to the procedures taken during laparotomy. It is also closed similar to how the laparotomy incision site is closed. Anterior abdominal fascia is identified first and sutured with delayed absorbable materials in an interrupted manner. Because of this method, the risk of developing postoperative adhesion at this port insertion site is higher than that of smaller trocar insertion sites, even though they are considered the same in terms of using the laparoscopy in a minimally invasive way. Therefore, the prevention of potentially higher risk of developing postoperative adhesion at the umbilicus by SPA laparoscopy is further emphasized.

Various methods have been proposed to detect the presence of adhesions in the abdominal cavity in previous literature. While the most accurate way of confirming abdominal adhesion and evaluating the extent to which it is formed is by performing laparoscopy, this is not feasible in most clinical settings unless the patients are needed to undergo additional laparoscopy for therapeutic purposes. Gerner-Rasmussen et al reviewed the literature to investigate the usefulness of non-invasive diagnostic methods for the detection of intraabdominal adhesions. A total of 25 studies were reviewed in which 18 of them used ultrasonography, 5 used magnetic resonance imaging, one used computed tomography, and one used both ultrasonography and magnetic resonance imaging. All ultrasonography studies used the visceral slide technique, which depends on the natural excursion of internal organs to the abdominal wall when the diaphragm displaces them during a respiratory cycle. The authors concluded that ultrasonography is the most accurate modality in the diagnosis of adhesions between viscera and the abdominal wall through the use of the visceral slide technique. Although there was a large variance in study results when it came to sensitivity and specificity, 5 of 6 ultrasonography studies with a patient population of more than 100 found a sensitivity of 90% to 100%. The visceral slide technique was first proposed by Sigel et al and refers to a technique by sliding motion of the abdominal contents for detection of the intraabdominal adhesion. According to previous studies, normal viscera sliding movement is defined as equal to or greater than 1 cm of longitudinal movement. This definition is applied for both normal and exaggerated respirations. Restricted viscera slide is defined as less than 1 cm of longitudinal movement during both normal and exaggerated respirations.

One limitation the present study carries is that it was performed with no control arm to directly compare the results. Nevertheless, the present study was conducted as a pilot study mainly to evaluate the safety of the application of the adhesion barrier solution to the port insertion site and periumbilical area. Studies have proven the safety of the use of adhesion barriers in pelvic and abdominal visceral organs. However, no data have been available to investigate its safety when applied directly to the abdominal wall which undergoes complex biochemical processes of wound healing after suture. Given the positive evidence of adhesion barrier in preventing intraabdominal adhesion reported by numerous studies, it was also ethically not feasible to try a randomized trial. Single-arm trials are best utilized when the natural history of the disease is well understood when placebo effects are minimal and when a placebo control is not ethically desirable. Therefore, we have decided to perform a single-arm prospective cohort study to evaluate the clinical safety and efficacy of the agent. Based on the results shown by the present study, it can safely be assumed that the anti-adhesive agents are not likely to cause surgical complications such as wound dehiscence or inflammation when directly applied to laparoscopic port insertion sites. Another limitation of the present study is that the ultrasound studies using the visceral slide technique only determined whether there were adhesions between viscera and bowel. The techniques did not detect the presence of postoperative adhesions in the pelvis in which most of the surgical procedures had been performed. Nonetheless, the purpose of the present study was to evaluate the efficacy of applying adhesion barriers for the prevention of umbilical port sites, which is larger than conventional trocar sites thereby increasing the probability of creating adhesions after closure.

In conclusion, the application of an adhesion barrier just below the umbilical port site effectively prevented postoperative surgical adhesion in the periumbilical area after SPA laparoscopic surgery. Furthermore, it was shown to be safe to use the adhesion barrier in terms of postoperative complications such as wound dehiscence or surgical site infection. This agent should be considered as another modality to minimize postoperative periumbilical adhesion for patients undergoing SPA gynecologic surgery. The importance of the results found in the present study is further emphasized for those who are likely to receive surgeries repeatedly for recurrence. However, further studies are warranted to overcome the limitation of the present study. Comparison with a historical control group or the utilization of other methodologies to assess postoperative adhesion may be considered.

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### Author contributions

Conceptualization: Tae-Joong Kim.
Data curation: Joseph Noh, Byung-Kwan Park.

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| Table 2 |
|----------------|----------------|----------------|
| **Results of follow-up transabdominal sonography three months after operations.** | **Myomectomy (n = 17)** | **Endometriosis surgery (n = 20)** | **Total (n = 37)** |
|----------------|----------------|----------------|
| Visceral movement during tidal respiration (cm) | 1.3 ± 0.7 | 1.1 ± 0.6 | 1.2 ± 0.6 |
| Visceral movement during maximal respiration (cm) | 5.7 ± 1.7 | 4.3 ± 1.9 | 4.9 ± 1.9 |
Formal analysis: Joseph Noh, Myeong-Seon Kim, Soo-Young Jeong, Byung-Kwan Park, Tae-Joong Kim.

Funding acquisition: Tae-Joong Kim.

Investigation: Byung-Kwan Park.

Methodology: Soo-Young Jeong, Jun-Hyeok Kang, Byung-Kwan Park.

Project administration: Joseph Noh, Myeong-Seon Kim, Soo-Young Jeong, Jun-Hyeok Kang, Byung-Kwan Park, Tae-Joong Kim.

Supervision: Byung-Kwan Park.

Writing – original draft: Joseph Noh.

Writing – review & editing: Joseph Noh, Tae-Joong Kim.

Writing manuscripts: [N, TJK; data analysis: MSK, SYJ, JHK; data collection: BKP.

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