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The Effect of Simethicone on the Length of Hospital Stay of Patients Undergoing Laparotomy for Benign Gynecological Procedures with an Enhanced Recovery after Surgery Protocol: A randomized controlled trial

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ABSTRACT

Objectives: To evaluate the efficacy of simethicone in treating postoperative ileus symptoms assessed by length of hospital stay, for patients undergoing elective laparotomy for benign gynecological procedures in the setting of an enhanced recovery after surgery (ERAS) protocol and to identify factors associated with a decreased length of hospital stay.

Materials and Methods: A single-center randomized controlled trial (TCTR20210204012) was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, between February and June 2021. In all, 182 patients were randomized into 2 groups: an "immediate-simethicone-administration-group" (administered 160 mg of simethicone immediately after surgery; n = 91) and a "non-immediate-simethicone-administration-group" (no immediate simethicone used; n = 91). The lengths of stay and other hospital data were analyzed.

Results: No significant difference was observed in the lengths of stay of the immediate-simethicone-administration and non-immediate-simethicone-administration groups (p = 0.132), nor in their incidences of postoperative nausea/vomiting, abdominal discomfort, and diarrhea. A multivariate analysis found that the significant predictor of a decreased length of hospital stay was an estimated blood loss of < 500 mL (odds ratio 5.82, 95% confidence interval 1.20, 28.16, p = 0.029).

Conclusion: Immediately chewing simethicone after surgery had no effect on the length of hospital stay in cases of benign laparotomy for gynecological procedures in the setting of an ERAS protocol. An estimated blood loss below 500 mL was a predictor of early hospital discharge.

Keywords: ERAS, length of hospital stay, simethicone, benign surgery, laparotomy.

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การศึกษาผลของยาไซเมทิโคนต่อจำนวนวันในการนอนโรงพยาบาล ในผู้ป่วยที่เข้ารับการผ่าตัดเปิดหน้าท้องทางนรีเวชวิทยาที่ไม่ใช่มะเร็ง ตามแนวทางการส่งเสริมการฟื้นตัวหลังผ่าตัด (ERAS protocol), การทดลองแบบสุ่มและมีกลุ่มควบคุม

กานต์ชนก แตมามุ, สุชาดา อินทวิวัฒน์

บทคัดย่อ

วัตถุประสงค์: *ศึกษาผลของยาไซเมทิโคนในการรักษาภาวะลำไส้หยุดทำงานหลังผ่าตัด ที่มีผลต่อจำนวนวันในการนอนโรงพยาบาล ในผู้ป่วยที่เข้ารับการผ่าตัดเปิดหน้าท้องทางนรีเวชวิทยาที่ไม่ใช่มะเร็งตามแนวทางการส่งเสริมการฟื้นตัวหลังผ่าตัด (ERAS protocol) และเพื่อศึกษาปัจจัยที่ช่วยลดจำนวนวันในการนอนโรงพยาบาลหลังผ่าตัด*

วัสดุและวิธีการ: *การวิจัยจัดทำขึ้นที่ภาควิชาสูติศาสตร์นรีเวชวิทยา คณะแพทยศาสตร์ ศิริราชพยาบาล มหาวิทยาลัยมหิดล, ประเทศไทย ระหว่างเดือนกุมภาพันธ์ถึงมิถุนายน พ.ศ.2564 โดยผู้ป่วยทั้งหมด 182 คน ถูกแบ่งเป็น 2 กลุ่ม คือกลุ่มที่ได้รับยาไซเมทิโคนหลังผ่าตัดทันที (91 คน) และกลุ่มที่ได้รับยาไซเมทิโคนทีหลัง (91 คน) โดยเก็บข้อมูลจำนวนวันที่นอนโรงพยาบาลหลังผ่าตัดและข้อมูลอื่นๆ ระหว่างนอนโรงพยาบาล*

ผลการศึกษา: *จำนวนวันในการนอนโรงพยาบาลหลังผ่าตัดไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มที่ได้รับยาไซเมทิโคนหลังผ่าตัดทันที และ กลุ่มที่ได้รับยาไซเมทิโคนทีหลัง ($p = 0.132$) อีกทั้งความชุกในการเกิดอาการคลื่นไส้อาเจียน, ท้องอืด, และท้องเสียก็ไม่มีความแตกต่างกันระหว่าง 2 กลุ่ม แต่จากการวิจัยพบว่าอัตราการเสียเลือดในห้องผ่าตัดที่น้อยกว่า 500 มิลลิลิตร เป็นตัวแปรสำคัญที่ลดจำนวนวันในการนอนโรงพยาบาลหลังผ่าตัด (OR 5.82 [1.20, 28.16]; $p = 0.029$).*

สรุป: *การได้รับยาไซเมทิโคนเคี่ยวทันทีหลังผ่าตัดไม่มีผลต่อจำนวนวันในการนอนโรงพยาบาลหลังผ่าตัดในผู้ป่วยที่เข้ารับการผ่าตัดเปิดหน้าท้องทางนรีเวชวิทยาที่ไม่ใช่มะเร็งตามแนวทางการส่งเสริมการฟื้นตัวหลังผ่าตัด (ERAS protocol) แต่อัตราการเสียเลือดในห้องผ่าตัดที่น้อยกว่า 500 มิลลิลิตร เป็นตัวแปรที่บ่งชี้การกลับบ้านได้เร็วขึ้นหลังผ่าตัด*

คำสำคัญ: *ERAS, ระยะเวลาพักรักษาตัวในโรงพยาบาล, ไซเมทิโคน, การฟื้นตัวหลังผ่าตัด, การผ่าตัดส่องกล้อง*

Introduction

Enhanced recovery after surgery (ERAS) protocols are multimodal, perioperative care pathways. The overriding aim of ERAS protocols is to improve postoperative recovery of patients undergoing major surgery. The concept of enhanced recovery programs was formulated by Professor Henrik Kehlet in the 1990s as part of European collaboration on colorectal surgery. The use of ERAS protocols for laparotomies and laparoscopies has since been widely studied, and they have proven to be safe for colorectal, vascular, and urological surgeries. The protocols were associated with comparable postoperative complications, shorter hospital stays, and reduced readmissions rates[1]. In an earlier study of gynecological surgery, the length of stay was significantly reduced after introducing ERAS protocols, declining from a mean of 2.6 days to 2.3 days, with no difference in complication, re-operation, or re-admission rates[2].

The ERAS pathways are comprised of many elements. They are preoperative counseling; preoperative bowel preparation; a venous thromboembolism prophylaxis; surgical-site infection reduction; standardized analgesic and anesthetic regimens; perioperative fluid management; perioperative nutrition; early mobilization; prevention of postoperative ileus; the avoidance of prolonged preoperative fasting, a large infusion volume, and extended Foley catheter usage; and a discharge pathway.

Postoperative ileus is an outcome of major abdominal surgery. The condition not only contributes to significant morbidity, but also prolongs length of hospital stay and increases treatment costs. The characteristics of ileus include reduced motility and intestinal dysfunction, resulting in an ineffective transit of intestinal contents. Postoperative ileus has a multifactorial pathogenesis that is only partially understood. It has been hypothesized that the pathogenesis is related to physical manipulation of the bowel; complex interactions between surgical stress and inflammatory mediators; the use of anesthetics; the analgesic methods employed; and perioperative fluid and electrolyte imbalances[3]. The reported incidence rate of postoperative ileus has differed between studies and surgical specialties; in the case of major abdominal surgery, it ranged between 10% and 30%[3] and affected about 14% of patients after laparotomies for gynecological procedures[4]. To date, there are few pharmacological interventions that shorten the duration of postoperative ileus. This is despite numerous studies having evaluated a range of pharmacological strategies to reduce ileus. The aims of those medications were to target the pathophysiology of ileus by minimizing sympathetic inhibition of gastrointestinal motility, inhibiting acetylcholinesterase activity, stimulating enteric motility, or decreasing inflammatory cascades[5]. For instance, numerous studies have investigated the chewing of gum. It is thought to stimulate the cephalon-vagal pathway, resulting in increased salivary and pancreatic secretions and an attendant improvement in gut motility[9]. The systematic and meta-analyses have found that the chewing of gum only minimally improves recovery from postoperative ileus[7, 10]. Nevertheless, the tested medications are not routinely used as they have not yet been adequately studied or they have not shown therapeutic efficacy.

Alternative agents (such as laxatives or antiflatulent drugs) are generally considered low-risk interventions to prevent ileus. One of these is simethicone. Simethicone is an activated dimethicone. Its large polymer consists of silicone, to which has been added silicon dioxide to increase the defoaming effects of simethicone. The drug is an inexpensive, readily available, and orally administered antifoaming agent comprised of polydimethylsiloxane and hydrated silica gel. It causes intestinal tract gas bubbles to coalesce, thereby facilitating their emission and preventing gas from forming at intestinal wall[6]. Simethicone coats the gastrointestinal tract and thus protects it from the harmful effects of gastric acid, acetylsalicylic acid, and biliary salts. In terms of its pharmacokinetics, simethicone is not absorbed by

the gastrointestinal tract; in addition, it does not disturb gastric acid secretion or mineral absorption. The drug is excreted in its original form in feces. The side effects of simethicone are nausea, vomiting, diarrhea, and headache, but they have been reported by only 2% - 5% of patients[6].

Few randomized controlled trials have evaluated the effects of simethicone on ileus, in terms of its impact on the length of hospital stay, following benign laparotomies for gynecological procedures in the setting of an ERAS protocol. The current investigation assessed simethicone's impact on the length of stay of Thai patients undergoing laparotomies for benign gynecological procedures with an ERAS protocol and also identified factors associated with a decreased length of hospital stay.

Materials and Methods

This single-center, randomized controlled trial compared the use and non-use of immediately simethicone in patients undergoing laparotomies for benign gynecological procedures with an ERAS protocol. The investigation was conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, between February and June 2021. The trial was registered at the Thai Clinical Trials Registry (TCTR20210204012). Before commencement of the research, its protocol was approved by the Siriraj Institutional Review Board (Si 089/2020). Written informed consent was obtained from all participants. Patients were enrolled if they were aged over 18 years and met neither of the exclusion criteria (a documented allergy to simethicone, or undergoing emergency surgery). The participants were consecutively recruited at the time of appointment for blood results before surgery at the outpatient unit and repeatedly on the day before surgery. However, patients were withdrawn if they were subsequently found to have injury to the bowel mucosa or a pathology report of cancer, or if they were admitted postoperatively to the intensive care unit.

The data that were collected were the characteristics of the patients and details of their operative procedures and hospitalization. The patient characteristics comprised age, body mass index, menopausal status, blood pressure, and heart rate. The operative data were collected from each participant's medical records. They consisted of the operation type, operating time, anesthetic method, type of incision, estimated blood loss, and postoperative diagnosis. During the participants' hospital stay, the research staff visited the patients between 7-8 AM daily. The staff assessed the following: abdominal distension, bowel movements, passage of flatus, and gastrointestinal symptoms (i.e., nausea, vomiting, diarrhea, and abdominal discomfort). In addition, the medical charts were reviewed to collect daily data on the patients' usage of simethicone and antiemetics, the presence of nausea/vomiting, the frequency of postoperative ileus, and average pain scores. The length of stay was also eventually recorded. In accordance with the ERAS protocol, its period was based on a discharge date that was determined by the clinical status of each patient, rather than a date desired by a patient. The discharge criteria are ability to tolerate regular diet without nausea or vomiting, oral anesthesia, and full mobilization.

Treatment allocation and trial medications

Using block of 2 randomization, a random number generator was employed to assign patient numbers for the experimental (simethicone) and non-drug regimen (non-simethicone) groups. A research assistant (a nurse) enclosed and sealed the computer-generated numbers, which were written on cards, in opaque envelopes. The nurse later opened the envelopes and dispensed the trial drugs to participants in accordance with the numbers.

After giving their consent to take part in the study, participants were randomized into either the immediately used simethicone or non- immediately used simethicone study arm. The patients randomized to the immediately used simethicone group were instructed to chew 2 simethicone tablets (80 mg in

total) immediately after their arrival at the postoperative floor. However, the participants in the non- immediately used simethicone group were not given this medicine. Although the participants and the research staff were not masked to the group assignments, the surgeons were.

Siriraj ERAS protocol

We followed the standardized Siriraj ERAS protocol for all patients. It involves fasting time, the mean tine of fasting is 10 hours which was reduced from the previous practice in Siriraj hospital. The mechanical bowel preparation with unison enema was performed in almost all elective patients, except some cases with difficult operation, Swiff solution was used instead. The administering of an intravenous antibiotic as a prophylaxis 1 hour before the skin incision. Typically, the antibiotic used was cephalosporins or ampicillin; if a patient was allergic to those drugs, clindamycin was given instead. The skin was cleaned with a chlorhexidine solution, with swabbing of the vagina prior to the insertion of a catheter and draping of the abdomen. Multimodal analgesia (such as patient-controlled epidural anesthesia combined with intravenous anesthesia) was utilized intraoperatively for some patients because of its ability to produce analgesic synergism and reduce adverse effects.

Early postoperative feeding with fluids commenced immediately upon regain of consciousness on the day after surgery. Feeding was later upgraded to a soft diet on the first day, and it was soon followed by a regular diet. However, if severe intraoperative abdominal adhesions, significant nausea and vomiting, or abdominal distension developed, oral feeding was withheld. It was restarted soon after resolution of the symptoms. An antifoaming agent and an iso-osmotic laxative were given if any gastrointestinal symptoms appeared. The fluid discontinued at 7-8 am day after surgery. Indwelling catheters were generally removed during day 1. If there was a need to continue the patient-controlled analgesia, though, the catheters were left in situ and removed soon after use of the analgesia stopped. All patients were encouraged to mobilize on day 1, for example, by lying on their side or sitting on the bed.

Sample size calculation

The estimation of the sample size was based on a prior investigation of gynecological surgery with an ERAS protocol that had been conducted at the Faculty of Medicine Siriraj Hospital. Data from that study showed that 60% of patients were discharged within 3 days of surgery. The current work assumed that 80% of patients would be discharged after receiving simethicone on the first postoperative day. The sample size was calculated for a power expectation of 80%, with a two-sided type I error of 0.05 to detect statistical significance. Using an anticipated dropout rate of 10%, the sample size was determined to be 182 patients (91 participants per group).

Statistical analysis

Data were analyzed using PASW Statistics for Windows (version 18.0; SPSS Inc., Chicago, IL, USA). Data are presented as mean and standard deviation (SD); number (n) and percentage (%); or median and interquartile range (IQR), as appropriate. Evaluation of the efficacy outcomes was based on per-protocol and modified intention-to-treat (ITT) analyses; in other words, all patients who took at least one dose of the trial medication were included in the analyses. As to patients who did not comply with the protocol, we applied the last-observation-carried-forward method for the ITT analysis. The normality of continuous data was tested using histogram plots and/or the Kolmogorov–Smirnov test of normality. Student's t-test (or the Mann-Whitney U test) and the chi-squared test (or Fisher's exact test) were used to analyze continuous and categorical data, respectively. To identify the factors associated with length of stay, univariate and multivariate logistic regressions were employed. All tests were two-tailed, and a p value < 0.05 was regarded as statistically significant.

Results

A flowchart of the participants is presented in Fig. 1. Of the 182 participants who consented, 3 were excluded after assignment to the simethicone group because they had pathology reports confirming malignancy. A further 2 were removed from the control group because of injury to the bowel mucosa. The remaining 177 patients were included in the analyses. All received routine postoperative care in an ERAS setting. Half (88 women) had been assigned to chew simethicone immediately after surgery, while the other half (89 women) had been placed in the control group (no use of simethicone).

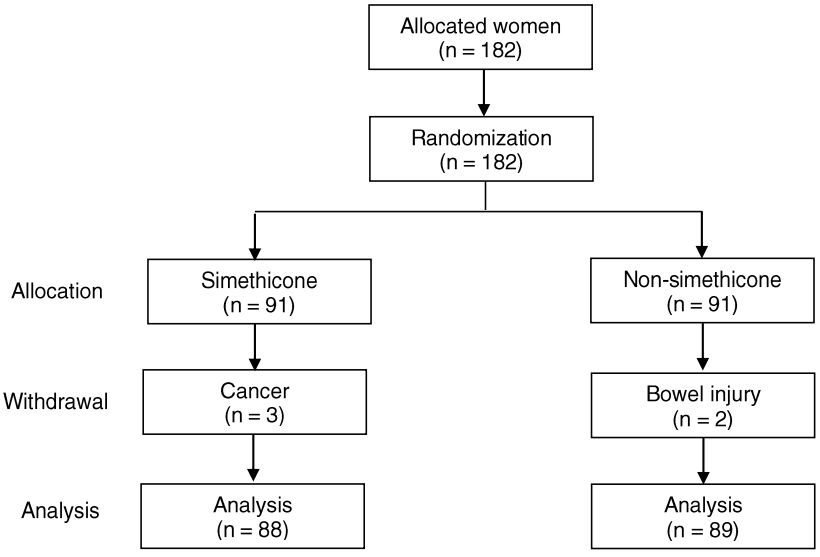

Fig. 1. Flow chart of participants.

The characteristics of the 182 participants are detailed in Table 1. Their ages ranged from 18 to 77 years (mean ± SD, 44.0 ± 8.3 years). Thirty-five women (19.2%) had natural menopause. The mean body mass index (BMI) was 25.1 ± 4.8 kg/m^2, with most participants having a BMI > 23 kg/m^2 (63.7%). The median (IQR) length of hospital stay was 3.0 (3, 3) days. The average nothing-per-oral (NPO) interval was 10.8 ± 2.6 hours, while the mean duration of urinary catheterization after surgery was 22.4 ± 9.6 hours. The most common gynecological disease was myoma uteri (60.4%), and the most frequent procedure was total abdominal hysterectomy with bilateral salpingo-oophorectomy (74.7%). Pfannenstiel incision was the most prevalent incision type (73.1%). Most patients received regional anesthesia (67.0%); only 18.7% had general anesthesia, and 14.3% were administered general endotracheal anesthesia with an epidural. The median estimated intraoperative blood loss was 360.7 (100.0, 462.5) mL, with 12.1% patients receiving blood transfusions. The mean operative duration was 128.6 ± 45.8 minutes.

Intraoperative complications occurred in 4 (2.1%) patients: 2 had small bowel mucosa injuries, one had bladder injury, and one had ureter injury. All were treated surgically during the primary operative procedure. Postoperatively, 49 (26.9%) patients received narcotics drugs to manage pain; 42 (23.1%) had non-steroidal inflammatory drugs (NSAIDs); 31 (17.0%) were given a combination of painkiller medications; and 60 (33.0%) did not utilize any painkiller. Antiemetics were required by 66 (36.3%) patients. Simethicone usage was noted in 102 (56.0%) patients who developed abdominal discomfort on postoperative day 2.

Table 1. Baseline characteristics of patients undergoing laparotomy for benign gynecological diseases.

Baseline characteristics	Mean ± SD, or n (%), or median (interquartile range, IQR)
Age (years)	44.0 ± 8.3
≥ 50	35 (19.2%)
Menopause	22 (12.1%)
Body mass index (kg/M2)	25.1 ± 4.8
≥ 23	116 (63.7%)
≥ 27.5	53 (29.1%)
Length of hospital stay (days)	3 (3, 3)
Intravenous fluid volume (mL)	2,060.6 ± 781.0
Duration of urinary catheterization (hours)	22.4 ± 9.6
Blood loss (mL)	200.0 (100.0, 462.5)
Blood transfusion, yes	22 (12.1%)
Preoperative factor	
Comorbidity, yes	73 (40.1%)
Previous abdominal surgery, yes	81 (44.5%)
ASA class 1	94 (51.6%)
Duration of NPO (hours)	10.8 ± 2.6
Benign gynecological disease	
Myoma	110 (60.4%)
Adenomyosis	39 (21.4%)
Ovarian cyst	24 (13.2%)
Other	9 (4.9%)
Intraoperative factor	
Intraabdominal adhesion, yes	65 (35.7%)
Duration of operation (minutes)	128.6 ± 45.8
Type of surgery	
Myomectomy	32 (17.6%)
Cystectomy	6 (3.3%)
Salpingo-oophorectomy	5 (2.7%)
TAH with BSO	136 (74.7%)
Other	3 (1.6%)
Type of anesthesia	
General	34 (18.7%)
Regional	122 (67.0%)
Combined	26 (14.3%)
Type of incision	
Midline	38 (20.9%)
Pfannenstiel	133 (73.1%)
Maylard	11 (6.0%)
Postoperative factor	
Pain killer, yes	122 (67.0%)
Narcotic drugs	49 (26.9%)
NSAIDs	42 (23.1%)
Combination	31 (17.0%)
Antiemetic medicine, yes	66 (36.3%)
Simethicone addition	102 (56.0%)
Complication	
Bowel injury	2 (1.1%)
Bladder injury	1 (0.5%)
Ureter injury	1 (0.5%)

Data are mean ± SD; number (n) and percentage (%); or median and interquartile range (IQR). BSO: bilateral salpingo-oophorectomy, NPO: nothing per oral, TAH: total abdominal hysterectomy

Table 2 lists the outcomes of the ITT population. The mean ± SD ages were 43.9 ± 8.1 years for the control participants, and 44.1 ± 8.4 years for the simethicone group. There was no statistically significant difference in the ages, menopausal status, or BMI values of the 2 groups. The groups had similar surgical variables: intravenous fluid volume, duration of urinary catheterization, blood transfusion volume, the type of benign gynecological disease, and the surgery duration and type. Although the proportion of participants who were discharged from the hospital within 2 days of surgery was higher for the control group than the simethicone group, there was no significant difference. Analysis using the ITT and per protocol data revealed similar results (data not shown).

The average length of hospital stay was 3 days. Patients were admitted 1-2 days before surgery, depending on their ability to optimize preoperative care. For our data analysis, we only considered the nights spent in hospital after surgery. This seemed to be more accurate, and its use eliminated any bias induced by individual patients' circumstances. The average number of postoperative days was 3.0 (3, 3) for both groups, with no statistical significance (p = 0.869). Sixteen (17.6%) control group patients were discharged within 2 days, whereas 9 (9.9%) simethicone-group patients were.

Table 2. Baseline parameters and outcomes of intention to treat (ITT) population.

Parameters	Control group (n = 91)	Simethicone group (n = 91)	p value
Age (years)	43.9 ± 8.1	44.2 ± 8.4	0.865
≥ 50	16 (17.6%)	19 (20.9%)	0.573
Menopause	12 (13.2%)	10 (11.0%)	0.649
Body mass index (kg/M2)	25.1 ± 4.7	25.1 ± 4.9	0.982
≥ 23	42 (46.2%)	44 (48.4%)	1.000
≥ 27.5	27 (29.7%)	26 (28.6%)	0.870
Length of hospital stay	3 (3, 3)	3 (3, 3)	0.869
≤ 2 day	16 (17.6%)	9 (9.9%)	0.132
Intravenous fluid volume (mL)	2,044.7 ± 692.2	2,076.5 ± 864.4	0.785
Duration of urinary catheterization (hours)	23.4 ± 12.5	21.5 ± 5.2	0.190
Blood loss (mL)	200 (100, 400)	250 (100, 500)	0.247
Blood transfusion, yes	10 (11.0%)	12 (13.2%)	0.649
Preoperative factor			
Comorbidity, yes	40 (44.0%)	33 (36.3%)	0.290
Previous abdominal surgery, yes	44 (48.4%)	37 (40.7%)	0.296
ASA class 1	46 (50.5%)	48 (52.7%)	0.767
Duration of NPO (hours)	10.8 ± 2.5	10.7 ± 2.6	0.784
Benign gynecological disease			0.432
Myoma	50 (54.9%)	60 (65.9%)	
Adenomyosis	21 (23.1%)	18 (19.8%)	
Ovarian cyst	15 (16.5%)	9 (9.9%)	
Other	5 (5.5%)	4 (4.4%)	
Intraoperative factor			
Intraabdominal adhesion, yes	30 (33.0%)	35 (38.5%)	0.439
Duration of operation (minutes)	128.7 ± 50.4	128.5 ± 41.1	0.983

Table 2. Baseline parameters and outcomes of intention to treat (ITT) population. (Cont.)

Parameters	Control group (n = 91)	Simethicone group (n = 91)	p value
Type of surgery			0.742
Myomectomy	18 (19.8%)	14 (15.4%)	
Cystectomy	4 (4.4%)	2 (2.2%)	
Salpingo-oophorectomy	3 (3.3%)	2 (2.2%)	
TAH with BSO	65 (71.4%)	71 (78.0%)	
Other	1 (1.1%)	2 (2.2%)	
Type of anesthesia			0.928
General	18 (19.8%)	16 (17.6%)	
Regional	60 (65.9%)	62 (68.1%)	
Combined	13 (14.3%)	13 (14.3%)	
Type of incision			0.163
Midline	24 (26.4%)	14 (15.4%)	
Pfannenstiel	61 (67.0%)	72 (79.1%)	
Maylard	6 (6.6%)	5 (5.5%)	
Postoperative factor			
Pain killer, yes	65 (71.4%)	57 (62.6%)	0.544
Narcotic drugs	26 (28.6%)	23 (25.3%)	
NSAIDs	24 (26.4%)	18 (19.8%)	
Combination	15 (16.5%)	16 (17.6%)	
Antiemetic medicine, yes	33 (36.3%)	33 (36.3%)	1.000
Simethicone addition	53 (58.2%)	49 (53.8%)	0.550
Complication			0.287
Bowel injury	2 (2.2%)	0(0%)	
Bladder injury	0 (0%)	1 (1.1%)	
Ureter injury	1 (1.1%)	0 (0%)	

Data are mean ± SD, number (n) and percentage (%), or median and interquartile range (IQR).
BSO: bilateral salpingo-oophorectomy, NPO: nothing per oral, NSAIDs: non-steroidal anti-inflammatory drugs, TAH: total abdominal hysterectomy

The adverse events are presented in Table 3. The most common were nausea, vomiting, abdominal or stomach discomfort, and diarrhea. Chart reviews revealed postoperative nausea in 25 (27.5%) patients. Postoperative emesis was reported for only 6 (6.6%) patients. Abdominal discomfort was noted in 6 (6.6%) patients, and diarrhea in 6 (6.6%). There were no statistical differences in the adverse effects of the 2 groups. None of the reported events were regarded as serious, and no participants withdrew from the study because of them.

Two cases of bowel injury were reported. One (1.1%) patient was diagnosed intraoperatively, with general surgery required for definitive management. The second case (1.1%) underwent repeat surgery for a right loop transverse colostomy. With the latter case, sigmoid diverticulitis and perforation were diagnosed on postoperative day 3. This followed the development of fever and abdominal pain, and the subsequent detection of an intra-abdominal collection by a computerized tomography study of the whole abdomen. With both patients, the initial gynecological procedure involved extensive dissection of the rectosigmoid off the posterior uterus because of severe adhesion. Although both of the patients with bowel complications were from the simethicone group, there was no statistical difference from the control group (p = 0.287).

Table 3. Adverse events of intention to treat (ITT) population.

Adverse events	Control group (n = 91)	Simethicone group (n = 91)	p value
Overall	24 (26.4%)	16 (17.6%)	0.152
Nausea	14 (15.4%)	11 (12.1%)	0.518
Vomiting	3 (3.3%)	3 (3.3%)	1.000
Abdominal or stomach discomfort	4 (4.4%)	2 (2.2%)	0.682
Diarrhea	4 (4.4%)	2 (2.2%)	0.682

Data are number (n) and percentage (%). Some patients had more than one adverse event.

The study revealed no significant differences between the groups in terms of their levels of patient satisfaction (p = 0.507) or their pain scores (p = 0.811; Table 4).

Table 4. Satisfaction and pain scores of patients undergoing laparotomy for benign gynecologic surgery.

Factors	N	Control group (n=91)	Simethicone group (n=91)	p value
Patient satisfaction	182	7.70±1.04	7.80±0.96	0.507
Pain scores				0.811
1-3	2	1(1.1%)	1(1.1%)	
4-6	25	14(15.4%)	11(12.1%)	
7-10	155	76(83.5%)	79(86.8%)	

Data are mean ± SD, or number (n) and percentage (%).

The results of the univariate analysis to identify the predictive characteristics of a hospital discharge within 2 postoperative days are given in Table 5. No significant correlation was found between discharge by the end of postoperative day 2 and the following factors: age, menopausal status, BMI, intravenous fluid volume, duration of urinary catheterization, estimated blood loss, blood transfusion, perioperative factors, anesthetic method, incision type, or other postoperative factors (pain killer, antiemetic drugs, and complications).

Table 5. Factors associated with length of stay following benign gynecological surgery.

Factors	Length of stay			p value
	Within Day 2 (n/N) (n=25)	More than Day 2 (n/N) (n=157)	OR (95% CI)	
Clinical				
Age (years)				0.420
≥ 50	3 (12.0%)	32 (20.4%)	1.00	
< 50	22 (88.0%)	125 (79.6%)	1.88 (0.53, 6.67)	
Menopausal status				0.319
Yes	1 (4.0%)	21 (13.4%)	1.00	
No	24 (96.0%)	136 (86.6%)	3.71 (0.48, 28.86)	
BMI (kg/M^2)				0.976
≥ 23	16 (64.0%)	100 (63.7%)	1.01 (0.42, 2.4)	
< 23	9 (36.0%)	57 (36.3%)	1.00	

Table 5. Factors associated with length of stay following benign gynecological surgery. (Cont.)

Factors	Length of stay			p value
	Within Day 2 (n/N) (n=25)	More than Day 2 (n/N) (n=157)	OR (95% CI)	
Intravenous fluid volume (mL)				0.110
≥ 1,000	22 (88.0%)	151 (96.2%)	1.00	
< 1,000	3 (12.0%)	6 (3.8%)	3.43 (0.80, 14.72)	
Duration of urinary catheterization (hours)				1.000
≥ 12	25 (100%)	156 (99.4%)	–	
< 12	0 (0.0%)	1 (0.6%)		
Blood loss (mL)				0.066
≥ 500	2 (8.0%)	43 (27.4%)	1.00	
< 500	23 (92.0%)	114 (72.6%)	4.34 (0.98, 19.19)	
Blood transfusion				0.319
Yes	1 (4.0%)	21 (13.4%)	1.00	
No	24 (96.0%)	136 (86.6%)	3.71 (0.48, 28.86)	
Preoperative factor				
Comorbidity, no	17 (68.0%)	92 (58.6%)	1.50 (0.61, 3.69)	0.373
Previous abdominal surgery, no	11 (44.0%)	90 (57.3%)	0.58 (0.25, 1.37)	0.213
ASA class < 2	17 (68.0%)	77 (49.0%)	2.21 (0.90, 5.41)	0.078
Duration of NPO < 6 hours	1 (4.0%)	11 (7.0%)	0.553 (0.07, 4.45)	1.000
Type of surgery				0.009
Myomectomy	10 (40.0%)	22 (14.0%)	1.00	
Cystectomy	2 (8.0%)	4 (2.5%)	1.10 (0.17, 7.03)	
Salpingo-oophorectomy	1 (4.0%)	4 (2.5%)	0.55 (0.05, 5.57)	
TAH with BSO	12 (48.0%)	124 (79.0%)	0.21 (0.08, 0.55)	
Other	0 (0.0%)	3 (1.9%)	–	
Type of anesthesia				0.225
General	4 (16.0%)	30 (19.1%)	1.00	
Regional	20 (80.0%)	102 (65.0%)	1.47 (0.47, 4.64)	
Combined	1 (4.0%)	25 (15.9%)	0.30 (0.03, 2.86)	
Type of incision				0.155
Midline	3 (12.0%)	35 (22.3%)	1.00	
Pfannenstiel	22 (88.0%)	111 (70.7%)	2.31 (0.65, 8.19)	
Maylard	0 (0.0%)	11 (7.0%)	–	
Postoperative factor				
Pain killer				0.289
None	9 (36.0%)	51 (32.5%)	1.00	
Narcotic drugs	6 (24.0%)	43 (27.4%)	0.791 (0.26, 2.40)	
NSAIDs	3 (12.0%)	39 (24.8%)	0.44 (0.11, 1.72)	
Combination	7 (28.0%)	24 (15.3%)	1.65 (0.55, 4.97)	
Antiemetic medicine, no	17 (68.0%)	99 (63.1%)	1.25 (0.51, 3.06)	
Simethicone addition	12 (48.0%)	90 (57.3%)	1.00	0.383
No simethicone addition	13 (52.0%)	67 (42.7%)	0.69 (0.29, 1.60)	
Complication, no	25 (100%)	152 (96.8%)	–	1.000

Data were analyzed using multiple logistic regression (enter method).

The findings of a subsequent multivariate analysis are summarized in Table 6. There appeared to be an increased likelihood for early discharge of patients with a low blood loss (< 500 mL; OR 5.82 [1.20, 28.16]; p = 0.029). Interestingly, the intravenous fluid volume, ASA classification 1, and other types of surgery were not identified as significant factors.

Table 6. Multivariate logistic regression of factors associated with hospital discharge within 2 days of benign gynecological surgery.

Factors	p value	Adjusted OR (95% CI)
Intravenous fluid volume (mL) < 1,000	0.121	3.84 (0.70, 21.01)
Blood loss < 500 mL	0.029	5.82 (1.20, 28.16)
ASA class 1	0.412	1.53 (0.55, 4.26)
Type of surgery		
Myomectomy	0.023	1.00
Cystectomy	0.529	0.52 (0.07, 3.91)
Salpingo-oophorectomy	0.539	0.46 (0.04, 5.40)
TAH with BSO	0.002	0.192 (0.066, 0.557)

Data were analyzed using multiple logistic regression (enter method). TAH with BSO: total abdominal hysterectomy with bilateral salpingo-oophorectomy.

Discussion

Postoperative ileus is one of the reasons for a prolonged hospital stay after abdominal surgery[4, 6]. Numerous studies have evaluated pharmacological strategies and methods to reduce the occurrence of ileus. Simethicone, an antifoaming agent, has been proposed as a low-risk intervention to prevent ileus. Only 2, relatively old, randomized controlled trials demonstrated an early passage of flatus, reduced gas pain, and a decreased rate of ileus[11, 12].

The current investigation was the first to assess whether shorter hospital stays result from using simethicone to promote the return of bowel function after open benign gynecological surgery. Simethicone demonstrated no significant effect on the length of stay (p = 0.869), postoperative nausea (p = 0.518), vomiting (p =1.000), or abdominal discomfort (p = 0.682). Additionally, the simethicone and non-simethicone groups had comparable adverse events as well as similar postoperative pain and patient satisfaction levels. Our results differed from those of a study in which the patients chewed gum after completing staging surgery for gynecological malignancies. That work found that the mean length of hospital stay was significantly reduced for the patients who chewed gum compared with controls (5.9 ± 1 and 7.0 ± 1.4 days, p < 0.001)[13]. The discrepancy can be explained by differences in the study methods. In our work, the patients in the simethicone group were given only one dose of simethicone (80 mg) immediately after surgery. However, additional, variable doses of simethicone were given to patients in both the immediate-simethicone-administration and non-immediate-simethicone-administration groups, depending on patients' symptoms or as an abdominal distension prophylaxis by surgeons. Another consideration is that postoperative ileus is self-limiting. Recovery often begins in the small intestine (about 8 - 12 hours postoperatively), then the stomach (about 1 - 2 days), and finally the colon (about 3 - 5 days)[10]. Our study only assessed patients undergoing benign gynecological surgery, which is less likely to involve intense bowel manipulation. Hence, not all participants in the present work developed postoperative ileus, or the ileus may have improved by itself without the need for simethicone.

The secondary aim of this study was to identify factors influencing the duration of hospital stay. Our findings showed that an estimated blood loss below 500 mL was significantly associated with a short hospital admission (p = 0.029, OR 5.82, 95%CI 1.20,

28.16). In contrast, no statistical differences were found for many other factors. They were age, menopausal status, BMI, intravenous fluid or blood transfusion volume, duration of NPO or urinary catheterization, presence of comorbidities, previous abdominal surgery, ASA classification, type of surgery, anesthesia, or incision, painkiller usage, and postoperative complications. The results showed the lesser blood loss (< 400 ml, 90th percentile) was associated with a decreased hospital stay, major postoperative complications, reoperation, and readmission[14]. We assume that the undifferentiated of surgical indication, population age, and BMI may produce the same outcomes, however, further study is required to confirm this.

A retrospective review of patients undergoing open gynecological surgery with ERAS protocols revealed that a vertical midline incision, perioperative complications, malignancy, advanced stage disease, and intensive care unit admission were significantly associated with prolonged hospital stays[15]. Our results differed from those of that study. It found that 73.8% of patients were successfully discharged in 3 days or less (mean 3.5 days [3.3, 3.8]), compared with 86.8% of our patients (mean 3.0 days [3, 3]). The difference may be due to our patients having benign conditions and not undergoing lymphadenectomies or omentectomies, with midline incisions being used in only 20.9% of cases. The absence of lymphadenectomies and the much lower usage of vertical midline incisions in our study may explain why vertical midline incisions were not associated with a prolonged hospital stay.

Our results showed no significant difference in the lengths of stay for the 2 predominant types of abdominal incision used in the current investigation (Pfannenstiel and vertical midline). This result differs from a retrospective review on open gynecological surgery in the setting of an ERAS protocol[15]. We hypothesize that our results differ from that finding because all of our patients had benign conditions. By contrast, the patients in the other review had both benign and malignant conditions, and the rate of vertical incision was higher. On the other hand, our results were similar to those of a randomized controlled trial comparing abdominal hysterectomies performed by vertical midline versus low transverse incisions. It found no significant difference in the lengths of stay for the 2 incisions[16]. The similarity of our study and previous reported may be the same condition of patient and operation (simple hysterectomy).

There had several limitations of our analysis. Our study focused on the effects of simethicone, for which we employed subjective and imperfect measurements. Unlike previous studies, we chose to measure postoperative nausea, vomiting, and abdominal discomfort rather than the time to flatus or the time to passing stoo[6, 10, 13, 17]. An additional limitation was the variability of the administered doses. All of the patients in the immediate-simethicone-administration group received 80 mg of simethicone within 2 hours of their surgery. However, some patients in both groups received extra doses of simethicone (40 mg) after surgery, this was done in accordance with their surgeons' orders to stimulate the bowel function. Unfortunately, we could not control this variable. There were other factors that may have influenced the lengths of stay. These included several operators in this study (residents and gynecological surgeons), and variability in the operative techniques employed and the postoperative care provided.

Additionally, there was a lack of blinding in this study. This may have led to bias by the patients. The participants received full information about simethicone, including its efficacy and side effects, upon admission. However, a placebo could not be prepared due to limitations related to its manufacture. Unfortunately, the Department of Pharmacology of the Faculty of Medicine Siriraj Hospital can prepare drugs in capsule form, but not in tablet form. Crushed simethicone losses its efficacy and has a specific smell and taste. The use of a placebo and the blinding of the participants would have lent weight to the findings of the study.

With the advent of ERAS protocols, patients are encouraged to resume normal eating after surgery. The current work demonstrated that simethicone did not enhance bowel recovery following gynecological

surgery, and it had no effect on the length of hospital stay. Patients who were following an ERAS protocol took simethicone immediately after laparotomies for benign gynecologic procedures did not shorten the length of hospital stay.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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