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ORIGINAL RESEARCH ARTICLE

Absorptive anti-adhesion barrier for the prevention of bowel obstruction after laparoscopic colorectal cancer surgery

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Abstract:

Objectives: The protective efficacy of an absorptive adhesion prevention product (Seprafilm®) against bowel obstruction (BO) during open surgery was demonstrated in a large-scale randomized controlled clinical trial in Europe and America. However, the efficacy of Seprafilm against BO in laparoscopic surgery remains uncertain. The objective of this study was to clarify the protective efficacy of Seprafilm against BO after laparoscopic surgery for colorectal cancer. Methods: From 2009 to 2016, 1328 laparoscopic colorectal resections were performed for colorectal cancer. From 2009, Seprafilm was used for preventing BO in laparoscopic colorectal surgery. The incidence of BO and short-term results were compared between the Seprafilm and non-Seprafilm groups after propensity score matching. Results: Propensity scoring generated 270 matched patients per group for the comparisons between the Seprafilm and non-Seprafilm groups. The two groups showed no significant differences regarding patients' backgrounds. Among all patients, 73.1% (19/26) of BO occurred within 30 days after the surgery. Significantly lower incidences of all grade (2.6% vs. 7.0%; $p = 0.016$) and grade 2 + 3a (1.5% vs. 5.2%; $p = 0.017$) BO were observed in the Seprafilm group than in the non-Seprafilm group; no significant difference regarding grade 3b BO (1.1% vs. 1.9%; $p = 0.476$) was found. A significant difference in BO within 30 days was also noted between the two groups (1.9% vs. 5.2%, $p = 0.036$). There were no significant differences between the groups regarding anastomotic leakage and deep surgical site infection. Conclusions: Seprafilm was useful for preventing BO, requiring decompression therapy of the bowel, after laparoscopic colorectal surgery without increasing adverse events.

Keywords:

bowel obstruction prevention, laparoscopic surgery, absorptive anti-adhesion barrier, colorectal cancer, propensity score matching

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Introduction

Bowel obstruction (BO) owing to postoperative peritoneal adhesion remains a major problem during abdominal surgery. Various products and postoperative management procedures have been used to prevent postoperative peritoneal adhesions[1-8)]. The usefulness of the absorptive anti-adhesion barrier film Seprafilm[9-14)] has been shown by many randomized control studies and meta-analysis, although studies with negative results do exist[15-18)]. Interestingly, the reports on

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peritoneal adhesion or BO associated with laparoscopic surgery, the use of which has rapidly spread in recent years, are few compared with reports on open surgery[11,19-23]. However, one report noted a lack of reduction in BO with laparoscopic surgery[24]. The prevention of BO is also an inevitable problem in laparoscopic surgery. Some studies have described a method of positioning Seprafilm in laparoscopic surgery to prevent BO and peritoneal adhesion[25-27]. However, reports concerning the usefulness of Seprafilm in laparoscopic surgery are few[28]. The aim of this study was to assess whether Seprafilm prevents BO after laparoscopic surgery for colorectal cancer.

Methods

Seprafilm has been used in laparoscopic colorectal surgery since 2009. Seprafilm, several quarter or eighth sheets in size, is inserted via an abdominal incision or 12-mm trocar. Seprafilm is applied to the organ around the abdominal incision and is occasionally used according to the judgment of the surgeon in charge. We examined patients who underwent laparoscopic colorectal surgeries for colorectal cancer at Chemotherapy Research Institute hospital, Teikyo University Hospital, and Yokohama City Medical Center from January 2009 to July 2016. All cases underwent elective surgery. The incidence of BO and early complications, except for BO, were compared between a Seprafilm arm and a non-Seprafilm arm of the study. Patients with non-resection surgeries, conversions to open surgery, follow-up period of <6 months, and improper data were excluded. Because this study was retrospective, the patients' backgrounds were significantly different. Thus, we conducted propensity score matching. The following variables were used to develop the logistic regression model for the determination of a propensity score: sex, age (≥75 years), American Society of Anesthesiologists score (≥2), history of laparotomy, diabetes, body mass index (≥2), tumor location (colon or rectum), operative time, stoma making, complete mesocolic excision (CME), preoperative chemoradiation, and pathological stage (≥2). The terminologies of complications used were according to the Common Terminology Criteria for Adverse Events version 4.0[29]. The definition of BO included all states in which the transportation of intestinal contents stopped at the distal side after the postoperative recovery of intestinal movement. Patients with no intestinal movement or defecation after the operation and those with the occurrence of a disease within 7 days after the operation were excluded as postoperative paralytic ileus. In addition, patients with silent bowel sounds were excluded. BO was graded according to the Clavien-Dindo classification system[30]. Total parenteral nutrition and a nasogastric tube insertion were classified as grade 2 BO, and a radiological insertion of a nasojejunal tube stent was classified as grade 3a BO. The treatment method of nasogastric tube or nasojejunal tube was selected on the basis of the judgment of the doctor in charge. Therapeutic criterion was not the one that was unified by each physician in charge at the three hospitals. Therefore, both grade 2 + 3a were analyzed as a conservative management for BO. Surgical adhesiotomy and intestinal resection were classified as grade 3b BO. Besides the BO grades, BO was investigated with respect to the time of occurrence: early (≤30 days) or late (>30 days) phase.

The study was approved by the Ethics Committees of Teikyo University, Yokohama City University Medical Center, and International University of Health and Welfare, Japan.

Statistical analysis

Continuous variables were presented as means, and categorical variables were presented as frequencies and percentages (%). Chi-square test was used to evaluate the significance of differences in proportions, and *t*-test was used to evaluate the significance of differences in continuous variables. These methods were used to consider the propensity score matching. A p value of <0.05 was considered to be statistically significant. The IBM SPSS Statistics software version 21 for Windows (IBM, NYC, NY, USA) was used for all statistical analyses.

Results

During the study period, 2109 patients underwent surgery for colorectal cancer, of which 731 patients underwent open surgery, nine underwent robotic surgeries, and 41 patients underwent a local excision without abdominal surgery. Of 1328 laparoscopic surgeries, 52 patients were converted to open surgery. Two surgeries were non-excision type, and data of 152 surgeries were not appropriate for the analysis. Of 1122 patients, 534 underwent surgery with Seprafilm and 588 underwent surgery without Seprafilm. There were some significant differences between both the groups with regard to the following items: history of laparotomy, tumor stage, operative procedure, formation of end colostomy, CME, and operative time (Table 1). After matching 270 patients in each group based on their propensity scores, no statistically significant differences were found between the two groups regarding background characteristics (Table 2).

A summary of the study characteristics is shown in Figure 1.

Occurrence of BO

Significant differences were noted between the Seprafilm and non-Seprafilm groups regarding all grades and grade 2 + 3a of BO, and no difference regarding grade 3b BO was noted.

Among all cases, 73.1% (19/26) of BO occurred in the

Table 1. Patients' Backgrounds at Pre-matching.

	Seprafilm (n=534)	Non-Seprafilm (n=588)	*p* value
Patients' characteristics			
Age: years (y.o.)	66.1±12.6	65.7±11.1	0.532
Sex: Male	323 (60.5)	349 (59.4)	0.699
Female	211 (39.5)	239 (40.6)	
ASA score: 1	186 (34.8)	175 (29.8)	0.069
2 or more	348 (65.2)	413 (70.2)	
Diabetes	92 (17.2)	83 (14.1)	0.151
Body mass index	22.8±3.9	22.9±3.4	0.807
History of laparotomy	143 (26.8)	115 (19.6)	0.004
Tumor location:			0.923
Right colon	149 (27.9)	156 (26.5)	
Left colon	173 (32.4)	188 (32.0)	
Bilateral colon	5 (0.9)	5 (0.9)	
Rectum	207 (38.8)	239 (40.6)	
p-Stage:			0.002
0	22 (4.1)	20 (3.4)	
I	134 (25.1)	210 (35.7)	
II	155 (29.0)	149 (25.3)	
III	176 (33.0)	175 (29.8)	
IV	47 (8.8)	34 (5.8)	
Therapeutic characteristics			
Operative procedure			0.005
Right colectomy	137 (25.7)	138 (23.5)	
Transverse colectomy	12 (2.2)	23 (3.9)	
Left colectomy	173 (32.4)	181 (30.8)	
Anterior resection	188 (35.2)	187 (31.8)	
Intersphincteric resection	7 (1.3)	27 (4.6)	
Abdominoperineal resection	10 (1.9)	26 (4.4)	
Hartmann	3 (0.6)	2 (0.3)	
Total colectomy	4 (0.7)	4 (0.7)	
Formation of stoma	65 (12.2)	95 (16.2)	0.057
End colostomy	13 (2.4)	28 (4.8)	0.038
Diverting ileostomy	52 (9.7)	67 (11.4)	0.368
Complete mesocolic excision	412 (77.2)	485 (82.5)	0.026
Preoperative chemoradiation	28 (5.2)	28 (4.8)	0.711
Operative time (min)	208±86	240±90	<0.001
Blood loss (ml)	63±130	85±238	0.056
Follow-up period (mo.)	33±19	33±14	0.653

ASA, American Society of Anesthesiologists.

early phase. The incidence of early phase BO was higher than that of late phase BO in both the groups (Seprafilm group, 5/7; non-Seprafilm group, 14/19). The non-Seprafilm group had higher incidences of early phase BO than late phase BO (Table 3).

In stage 4, peritoneal metastases were six cases (13.6%) by 44 patients. BO occurred in one patient (2.3%) with stage 4 hepatic metastasis.

Short-term results except BO

There were no significant differences between the Seprafilm and non-Seprafilm groups regarding grade ≥3a anastomotic leakage and deep surgical site infection. In addition, there were no significant differences between the groups regarding the length of postoperative stay (Table 4).

Discussion

New products or postoperative management procedures for reducing adhesions have been reported in abdominal surgery[31-37]. However, almost all reports assessed the reduction of adhesions in open surgery, with only one report referring

Table 2. Patients' Backgrounds after Matching.

	Seprafilm (n=270)	Non-Seprafilm (n=270)	*p* value
Patients' characteristics			
Age: years (y.o.)	65.4±12.5	65.9±11.3	0.583
Sex: Male	160 (59.3)	166 (61.5)	0.598
Female	110 (40.7)	104 (38.5)	
ASA score 1	75 (27.8)	76 (28.1)	0.924
2 or more	195 (72.2)	194 (71.9)	
Diabetes	50 (18.5)	49 (18.1)	0.911
Body mass index	23.0±3.3	22.8±3.9	0.575
History of laparotomy	57 (21.1)	50 (18.5)	0.450
Tumor location:			0.088
Right colon	65 (24.1)	68 (25.2)	
Left colon	96 (35.6)	74 (27.4)	
Bilateral colon	1 (0.4)	5 (1.9)	
Rectum	108 (40.0)	123 (45.6)	
p-Stage:			0.347
0	16 (5.9)	7 (2.6)	
I	80 (29.6)	86 (31.9)	
II	65 (24.1)	72 (26.7)	
III	85 (31.5)	85 (31.5)	
IV	24 (8.9)	20 (7.4)	
Therapeutic characteristics			
Operative procedure			0.115
Right colectomy	61 (22.6)	61 (22.6)	
Transverse colectomy	3 (1.1)	10 (3.7)	
Left colectomy	95 (35.2)	73 (27.0)	
Anterior resection	95 (35.2)	95 (35.2)	
Intersphincteric resection	4 (1.5)	14 (5.2)	
Abdominoperineal resection	9 (3.3)	14 (5.2)	
Hartmann	2 (0.7)	2 (0.7)	
Total colectomy	1 (0.4)	1 (0.4)	
Formation of stoma	45 (16.7)	50 (18.5)	0.572
End colostomy	12 (4.4)	15 (5.6)	0.554
Diverting ileostomy	33 (12.2)	35 (13.0)	0.795
Complete mesocolic excision	229 (84.8)	228 (84.4)	0.905
Preoperative chemoradiation	11 (4.1)	13 (4.8)	0.676
Operative time (min)	231±94	222±81	0.224
Blood loss (ml)	62±143	91±246	0.094
Follow-up period (mo.)	30±15	32±12	0.054

ASA, American Society of Anesthesiologists.

to laparoscopic surgery[28]. Tsuruta et al. reported regarding the efficacy of Seprafilm on adhesion prophylaxis in laparoscopic colorectal surgery and recommended the intraabdominal three-layered pasting technique, i.e., the multilayer comprised the deepest area of the abdominal cavity, the space around the mesentery, and the area below the incision. However, this technique is a little difficult to perform, and whether it is suitable for generalized use is doubtful. The study design was retrospective, and the sample size was small (n = 167). Therefore, the patients' backgrounds had some differences between the Seprafilm and non-Seprafilm groups. Our study examined the efficacy of preventing BO by simply pasting Seprafilm under the incision in laparoscopic surgery. Our study design was also retrospective. Therefore, there were many differences between the two groups. A matched case-control design with propensity score matching was used in large-scale retrospective studies to reduce the confounding effects of covariates on the treatment results. We compared the two groups after matching the patients' and therapeutic background variables to equate the two groups in this study.

Seprafilm is used as an insurance against developing BO

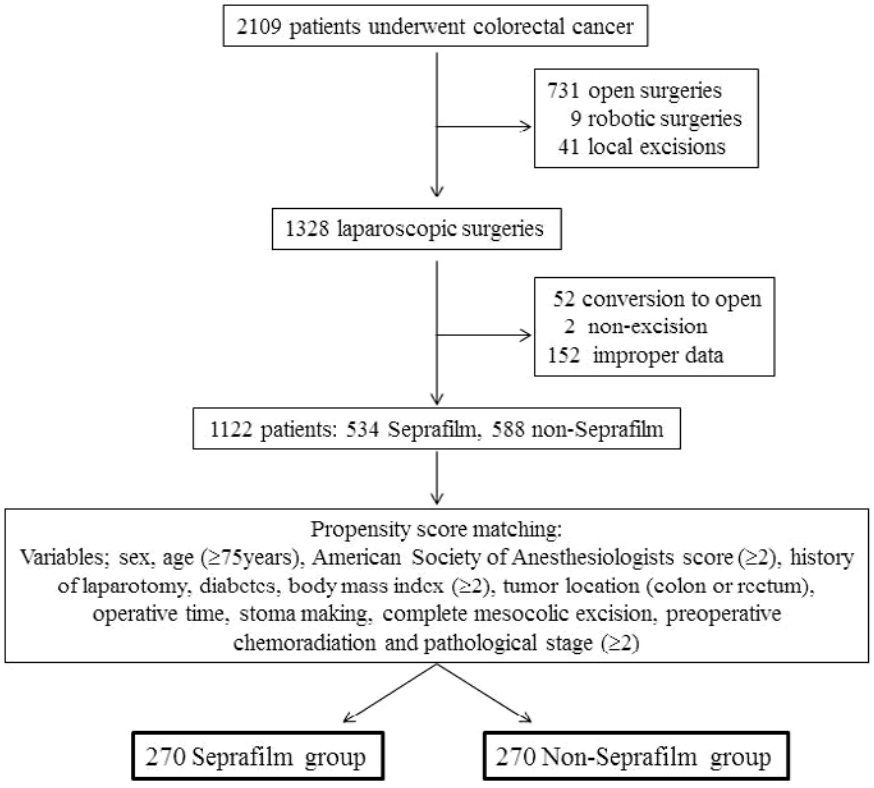

Figure 1. Study profile. From January 2009 to July 2016, 1328 patients underwent laparoscopic surgeries. Patients with conversion to open surgery, non-excision surgery, and improper data were excluded. After exclusion, 534 and 588 patients remained in the Seprafilm and non-Seprafilm groups, respectively. Following propensity score matching, each group comprised 270 patients.

Table 3. Incidence of BO.

	Seprafilm (n=270)	Non-Seprafilm (n=270)	*p* value
Grade of BO			
All grade	7 (2.6)	19 (7.0)	0.016
Grade 2+3a	4 (1.5)	14 (5.2)	0.017
Grade 3b	3 (1.1)	5 (1.9)	0.476
Time of BO occurrence			
Early BO	5 (1.9)	14 (5.2)	0.036
Late BO	2 (0.7)	5 (1.9)	0.254

BO, bowel obstruction.

after all abdominal surgeries in Japan and therefore is widely used as an anti-adhesion product. Seprafilm is made up of hyaluronate-carboxymethylcellulose and has bioresorbablilty properties. It changes to a gel-like form in 24-48 h and acts as a physical barrier between injured sites of the peritoneum and the abdominal wall for approximately 7 days. It is then reabsorbed via the peritoneum and is subsequently discharged in the urine within 28 days.

In this study, differences were observed between the Seprafilm and non-Seprafilm groups regarding grade 2 + 3a BO; however, no difference was observed regarding grade 3b BO. The low incidence of grade 3b BO noted was similar to that reported in several previous studies[19-21], which described few incidences of postoperative BO in laparoscopic surgery. In this study, the efficacy of Seprafilm in preventing BO requiring decompression therapy was demonstrated. The anti-adhesive effect of Seprafilm is considered to reduce the incidence of BO, even in laparoscopic surgery.

The incidences of anastomotic leakage and abdominal abscess were increased in a large-scale randomized controlled clinical trial and meta-analysis[18,38]. However, there were no differences between the Seprafilm and non-Seprafilm groups regarding grade 3a anastomotic leakage and deep surgical site infection. A previous large-scale randomized controlled clinical trial revealed that wrapping an anastomotic region increased the risk of an anastomotic leakage[38]. Therefore, we avoided applying Seprafilm on an anastomotic area. Moreover, Seprafilm was not applied to the pelvis because it tended to be stuck around small incisions in laparoscopic surgery.

The efficacy of Seprafilm in preventing postoperative adhesion or BO has been previously demonstrated by several randomized control studies and meta-analyses[9-11,13,14]. How-

Table 4. Short-term Results Except BO.

	Seprafilm (n=259)	Non-Seprafilm (n=254)	*p* value
Anastomotic leakage (Grade 3a or more)	3 (1.2)	7 (2.8)	0.191
	Seprafilm (n=270)	Non-Seprafilm (n=270)	*p* value
Deep surgical site infection	4 (1.5)	5 (1.9)	0.737
Postoperative hospital stay (days)	15.9±10.5	14.8±12.7	0.272

BO, bowel obstruction.

ever, several studies have reported negative results of Seprafilm[15-18]. Studies have described how Seprafilm was not useful in preventing BO, although it was effective in preventing adhesion[15,18]. In our study, Seprafilm was effective in preventing BO after colorectal cancer surgery. Similarly, several studies have reported regarding the efficacy of Seprafilm in preventing BO or abdominal adhesions after gastrointestinal or colorectal surgery[9,10,14]. On the other hand, other studies have shown increased adverse events and a negative effect of Seprafilm in preventing BO after gynecological surgery[39,40]. Further studies are required to verify whether Seprafilm is effective in preventing BO and to identify the most suitable procedure.

In this study, ≥70% of BO occurred within 30 days after the surgery. The incidence of early phase BO was higher in the current study than in a previous large-scale randomized study for open surgery[9]. In that study, 50% of BO occurred within 6 months, with nearly 30% occurring within 30 days. Therefore, there is a possibility that adhesion prevention at the early phase is effective in preventing BO because BO mostly occur in the early stages after laparoscopic colorectal surgery.

Peritoneal metastases were six patients (13.6%) by 44 patients of stage 4.

BO did not occur in all cases with peritoneal metastasis, and peritoneum metastasis was hypothesized to not influence BO.

No difference was noted in the length of postoperative stay between both the groups. This reason was speculated that BO was not a main factor for deciding the postoperative stay because the incidence of it was 4.8% in all cases. Moreover, and the regulations of leaving the hospital were not unified among the physicians in charge.

Seprafilm could not reduce the occurrence of BO that needed surgical therapy. BO requiring surgical therapy may be adhesive to the deep portion of the abdominal cavity or intestinal tract. Future studies are warranted to assess the prevention of adhesion of those parts.

The major limitation of this study was its retrospective design. First, Seprafilm was not used for all patients. The use of Seprafilm depended on the judgment of the doctor in charge. However, the reason was not described in the operative note in many cases. Second, there was a possibility that a small portion of the paralytic ileus was included. We excluded patients who had no intestinal movement or defecation, those in whom the disease occurred within 7 days after the operation, and those with silent bowel sounds. However, it is uncertain whether to be able to exclude all the paralytic ileus by those methods really. This appears to be a limitation of a retrospective research. Finally, there were a lot of between the two groups with regard to the patients' backgrounds. Therefore, we attempted to overcome several weak points by propensity score matching. If the study was conducted as a prospective randomized controlled design, the sample size was set at 435 cases in one arm because of the hypothesis with 80% statistical detection power that Seprafilm reduced BO by half from 10% according to past report[28]. The number of cases in this study was sufficient for the analysis before propensity score matching. However, it became each of 270 patients by the match, and power was dissatisfied. Ouaïssi et al. described that the routine use of anti-adhesion products should not be recommended without high-level evidence regarding their efficacy and safety[15]. It is also important to use an anti-adhesion product only for patients at high risk of BO to prevent the wastage of a medical resource.

In conclusions, Seprafilm showed efficacy for preventing BO, requiring decompression therapy, after laparoscopic colorectal surgery without increasing adverse events. Therefore, we recommend the use of Seprafilm in colorectal surgery.

Conflicts of Interest

There are no conflicts of interest.

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