JOURNAL OF THE
ANUS, RECTUM AND COLON
dx.doi.org/10.23922/jarc.2021-030
http://journal-arc.jp

Trial Protocol

A Trial Protocol to Investigate the Incidence of Postoperative Bowel Obstruction after Laparoscopic Colorectal Cancer Surgery Using an Absorbable Adhesion Barrier Material (INTERCEED®) (Balsam CEED Study): A Prospective, Multicenter, Observational Study

Hiromichi Sonoda[1], Takeshi Yamada[1], Keiji Hirata[2], Nobuhisa Matsuhashi[3], Daisuke Ichikawa[4], Norio Yukawa[5], Ken Eto[6], Keiji Koda[7], Suguru Hasegawa[8], Akihisa Matsuda[1], Shingo Ito[9], Yasuyuki Yokoyama[10], Hiroshi Yoshida[1] and Soichiro Ishihara[11]

1) Department of Gastrointestinal Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, Tokyo, Japan
2) Department of Surgery 1, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan
3) Department of Surgical Oncology, Graduate School of Medicine, Gifu University, Gifu, Japan
4) First Department of Surgery, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan
5) Department of Surgery, Yokohama City University, Yokohama, Japan
6) Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan
7) Department of Surgery, Teikyo University Chiba Medical Center, Chiba, Japan
8) Department of Gastroenterological Surgery, Fukuoka University Faculty of Medicine, Fukuoka, Japan
9) Department of Surgery, Kawasaki Saiwai Hospital, Kawasaki, Japan
10) Department of Digestive Surgery, Nippon Medical School Musashikosugi Hospital, Kanagawa, Japan
11) Department of Surgical Oncology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Abstract

Background: Some studies have reported that adhesion prevention barriers (APBs) reduce adhesion after abdominal surgery; however, evidence showing that APBs reduce the incidence of postoperative small bowel obstruction (SBO), one of the most serious complications after abdominal surgery, is little. One concern is that APBs are usually applied only under the midline incision, although adhesion can occur at any place in the peritoneum where an incision is made during surgery. INTERCEED® is an APB that reportedly prevents postoperative SBO after surgery. This study aims to assess the clinical utility of INTERCEED® for the prevention of SBO after laparoscopic colorectal cancer surgery and determine whether the application site of INTERCEED® affects the incidence of SBO.

Methods/Design: This study is a prospective, multicenter, observational study conducted in Japan. The primary end point is the incidence of postoperative SBO 2 years after laparoscopic colorectal cancer surgery. The secondary end points include whether the site of the application of INTERCEED® affects the incidence of SBO. Each surgeon selects one of the following three procedures: 1) INTERCEED® is placed only under the midline incision; 2) INTERCEED® is placed at the site of bowel mobilization and/or lymph node dissection, but not under the midline incision; and 3) INTERCEED® is placed at both sites.

Discussion: This is the first study to assess whether the placement of APBs affects the incidence of SBO. The study results may lead to a subsequent randomized study.

Corresponding author: Takeshi Yamada, y-tak@nms.ac.jp
Received: April 27, 2021, Accepted: June 25, 2021

Keywords
adhesion prevention barrier, INTERCEED, colorectal cancer, laparoscopic surgery
J Anus Rectum Colon 2021; 5(4): 414-418

Background

Postoperative small bowel obstruction (SBO) is one of the most serious complications after colorectal cancer surgery; it often impairs patient quality of life. Intra-abdominal adhesions are thought to be one of the causes of SBO. Okabayashi et al.[1] demonstrated that the overall weighted mean formation rate of adhesions after abdominal surgery was 54% (95% confidence interval (CI): 40-68). A large retrospective cohort study demonstrated that the 5-year incidence rate of adhesive SBO was higher after open colectomy compared with laparoscopic colectomy (5.5% vs 2.8%, $p < 0.001$)[2]. To prevent abdominal adhesion, adhesion prevention barriers (APBs) have been developed. In Japan, three anti-adhesion barriers (Seprafilm®, INTERCEED®, and Adspray®) are now available. A systematic review and meta-analysis concluded that hyaluronate-carboxymethylcellulose membranes (Seprafilm®) can decrease abdominal adhesions but cannot reduce postoperative SBO after general surgery[3]. Furthermore, a single-center, randomized control trial involving open colon cancer surgery showed that Seprafilm® does not reduce postoperative SBO after open colon cancer surgery (Seprafilm group vs control group: 7.8% vs 10%, $p = 0.46$)[4]. Suto et al. conducted a prospective, randomized, single-blind study in patients who underwent laparotomy with ileostomy to clarify whether Adspray®, a newly developed spray-type APB, reduce the incidence of adhesion after open rectal anterior resection with ileostomy[5]. This study showed that the incidence of adhesions observed at the second-look surgery was significantly lower in the Adspray group than in the control group (52.7 vs 90.7%, $p < 0.001$). However, the incidence of postoperative SBO was similar in both Adspray and control groups (18% vs 13.1%, $p = 0.618$).

The failure of APBs to prevent SBO may reflect the manner in which they are applied rather than its ineffectiveness. In previous studies, Seprafilm® and Adspray® were used only under the midline incision. However, SBO occurred most often at sites other than the midline incision. Thus, we hypothesize that the incidence of SBO can be reduced by applying APBs at sites of bowel mobilization and lymph node dissection.

Seprafilm® is difficult to position with trocars because it is highly adhesive to wet tissue. In contrast, INTERCEED® (Johnson & Johnson, New Brunswick, NJ, USA), which is a woven sheet of oxidized, regenerated cellulose, is more readily manipulated during surgery because of its softness and pliability. Some previous studies have reported that INTERCEED® is useful for preventing postoperative SBO at short term (6 months) after laparoscopic colorectal surgery[6,7]. This multicenter, prospective, observational study aims to assess the clinical utility of INTERCEED® for preventing long-term postoperative SBO after laparoscopic colorectal cancer surgery and determine whether the site of attachment, i.e., under the midline incision, at the site of bowel mobilization or lymph node dissection, or both, affects the incidence of SBO.

Methods/Design

This study is designed as a prospective, multicenter, observational study. Patients will be recruited from 20 institutions in Japan. Patients can decline participation in this study on the websites of the participating hospitals. This trial is organized by the Department of Gastrointestinal and Hepato-Biliary-Pancreatic Surgery, Nippon Medical School, Tokyo, Japan. The study protocol (B-2019-086) was approved by the Ethics Committee of Nippon Medical School (Tokyo, Japan) on September 2, 2020, and was registered to the University Hospital Medical Information Network (UMIN000040969). Each researcher is committed to implementing obligations in accordance with provisions of the Helsinki Declaration. A total of 400 patients with colorectal cancer who undergo laparoscopic surgery between September 2020 and August 2022 will be registered.

Patient selection criteria and registration

The inclusion and exclusion criteria for this study are shown in Table 1. Briefly, we include patients with histologically verified colorectal carcinoma, without metastasis or invasion of adjacent organs, who underwent laparoscopic curative surgery. We exclude patients with previous abdominal surgery.

This prospective, observational study includes only patients who underwent curative surgery, because approximately 75% of those patients are observed for ≥5 years. If we register patients before surgery, we would inadvertently include some patients who underwent non-curative surgery. Therefore, participants are registered within 3 days after surgery to minimize selection bias.

Table 1. Inclusion/Exclusion Criteria for This Study.

<Inclusion criteria>
1. Histologically confirmed colorectal carcinoma
2. Without metastasis and/or invasion of adjacent organs
3. Laparoscopic surgery performed
4. Curative surgery performed
5. INTERCEED® used as an anti-adhesion barrier during surgery
6. Patient with age between 20 and 80 years
7. Patient with an Eastern Cooperative Oncology Group Performance Status of 0 or 1
8. Registered until postoperative day 3
9. Exhibiting sufficient organ function within 1 month prior to enrollment in the study with the following parameters considered:
•Leukocyte count ≥3,500/mm^3
•Hemoglobin level ≥8.0 g/dL
•Platelet count ≥75,000/mm^3
•Total bilirubin level ≤1.5 mg/dL
•Serum creatinine level ≤1.5 mg/dL
<Exclusion criteria>
1. Contraindications for INTERCEED® use
2. History of previous abdominal surgery, except for appendectomy performed >5 years prior
3. The treating physician did not feel that the use of INTERCEED® was appropriate
4. Patients who were not followed up for at least 2 years and were excluded from statistical analyses

Procedure

At the final step of the surgery, complete hemostasis is achieved before using INTERCEED®. *(Two sheets of INTERCEED® are permitted to use.)* Each surgeon selects one of the following three procedures: 1) INTERCEED® is placed only under the midline incision; 2) INTERCEED® is placed at the site of bowel mobilization and/or lymph node dissection, but not under the midline incision; and 3) INTERCEED® is cut to the appropriate size and placed at the site of bowel mobilization and/or lymph node dissection in addition to under the midline incision. INTERCEED® was moistened with a little physiological saline after attachment to the tissue. Each researcher decides whether patients are registered or not in consideration of macroscopic curativity immediately after surgery and sent the registration form to the research organizer within 3 days after the surgery.

Objectives

Primary end point

The primary end point is the incidence of postoperative SBO within 2 years after laparoscopic colorectal cancer surgery. In this study, bowel obstruction is defined as meeting all of the following criteria:

i) Clinically diagnosed bowel obstruction treated upon admission;
ii) Fasting for more than 1 day;
iii) Patients with or without insertion of a nasal gastric tube, a nasal long decompression tube, or a trans-anal decompression tube;
iv) Patients with bowel obstructions due to cancer recurrence are excluded; and
v) Exclusive diagnosis by computed tomography is preferred.

Secondary end point

- Incidence of postoperative SBO within 5 years after laparoscopic colorectal cancer surgery
- Association between the site of INTERCEED® use and the development of postoperative SBO
- Association between surgical procedures (right-side colon surgery, left-side colon surgery, or rectal surgery) and the development of postoperative SBO
- Association between patient background (age, sex, duration of the operation, or intraoperative hemorrhage) and the development of postoperative SBO

Data collection

1) Patient characteristics: gender, performance status, and comorbidity
2) Surgical procedures: degree of lymph node dissection and the site(s) of INTERCEED® application
3) Tumor characteristics: tumor location, depth of tumor invasion, lymph node metastatic status, histological findings, lymphatic invasion, and vascular invasion
4) Blood examination: white blood cell, neutrophil, and platelet counts, and hemoglobin, albumin, creatinine, and c-reactive protein levels
5) Tumor markers: CEA and CA19-9
6) Prognostic information: presence or absence of postoperative SBO, interval between surgery and onset of

postoperative SBO, treatment for postoperative SBO (only fasting, intervention with or without surgery), survival, cause of death, recurrence or non-recurrence, treatment for cancer recurrence, or cancerous lesion(s) other than colorectal cancer

Researchers at each hospital maintain individual patient data, including images, laboratory data, and other records. All data are collected by the Nippon Medical School Data Center. The data center oversees the data sharing process during the trial. Clinical data entry, central monitoring, and data management are performed. All data aggregation and statistical analysis are performed at Nippon Medical School Data Center. Only clinical data managers at Nippon Medical School Data Center can access the reported case data.

Dissemination policy

The results of the present study will be submitted for publication in peer-reviewed journals, and important findings will be presented at domestic and international conferences. Authorship will be assigned in accordance with the guidelines of the International Committee of Medical Journal Editors.

Statistical analysis plan

A meta-analysis showed that the incidence of SBO after laparoscopic colorectal surgery was 11.8%[8]. We hypothesized that APB has a potential to prevent SBO if the incidence of SBO after laparoscopic colorectal surgery with APB is lower than 8%. Thus, we defined the expected value as 5% and planned to include 400 patients. If 20 patients develop SBO, the incidence of SBO is 5%, and the upper limit of 95% confidence interval is 7.64%.

Discussion

This is the first multicenter, prospective, observational study to investigate the incidence of postoperative SBO with the use of APB. Although numerous clinical studies have examined the use APBs, most have applied APBs just beneath the small midline incision, and few studies have investigated the incidence of postoperative SBO when applying APBs at surgical incision sites, including the sites of bowel mobilization and lymph node dissection. Several studies demonstrated that APB helps in reducing adhesions to the midline incision but does not reduce the incidence of postoperative SBO[3,4,7]. Thus, we hypothesized that adhesion to sites other than the midline incision (the site of bowel mobilization and lymph node dissection) is involved in postoperative SBO and that the attachment of APB around the site of bowel mobilization and lymph node dissection can decrease the incidence of postoperative SBO.

Because of the lack of reports showing the utility of APB application at sites of surgical incision, we conducted a non-randomized study. However, we believe that this study will help promote surgery with lower rates of postoperative SBO.

Seprafilm® has been used in many previous studies of anti-adhesion barriers. However, Seprafilm®, which is made of hyaluronate-carboxymethylcellulose, is difficult to insert into the abdominal cavity through trocars and is not suitable for laparoscopic surgery[6]. On the other hand, INTERCEED® is easy to use during laparoscopic surgery because its softness and pliability facilitate intraoperative manipulation[6,9].

INTERCEED® is an absorbable adhesion barrier that is composed of 100% oxidized, regenerated cellulose and comprised glucuronic acid and glucose with β-linkages. Macrophages/mononuclear phagocytes contain lysosomal enzymes (β-glucuronidase and β-glucosidase), which are capable of degrading these β-linkages. Previous reports on the use of INTERCEED® for laparoscopic colorectal surgery have demonstrated its utility for the prevention of postoperative SBO[6,9].

This study includes some concerns. First, the follow-up period (2 years) may be too short. Previous studies have demonstrated that the majority of cases of adhesive postoperative SBO continue to develop for many years after surgery, usually occurring within 4 years[4,10,11]. However, we desire to show the utility of applying anti-adhesion barriers around the site of bowel mobilization and lymph node dissection as early as possible. Thus, the incidence of postoperative SBO was set as a secondary end point. Based on the results of the present study, we will conduct a randomized study. Second, we allow participants to register each case until 3 days after surgery. Thus, patients with some trouble, such as bleeding or long operative time, during the operation or 1-3 days after operation could be excluded; thus, another bias might occur.

Acknowledgements

We thank all the patients and coworkers for their participation and cooperation in the Balsam CEED study.

Conflicts of Interest

Ken Eto and Suguru Hasegawa received honoraria from Johnson & Johnson.

Author Contributions

H.S., T.Y., and A.M. wrote the manuscript. All 14 authors contributed in developing the study protocol.

Disclaimer

Soichiro Ishihara is the Editor-in-Chief of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. Takeshi Yamada is one of the Associate Editors of Journal of the Anus, Rectum and Colon and on the journal's Editorial Board. They were not involved in the editorial

evaluation or decision to accept this article for publication at all.

Approval by Institutional Review Board (IRB)

IRB approval number: B-2019-086, Ethics Committee of Nippon Medical School

Trial registration information

Registry name: A prospective, multicenter study on the incidence of postoperative bowel obstruction after laparoscopic colorectal cancer surgery using an absorbable adhesion barrier (INTERCEED) (Balsam CEED study)

Trial ID: UMIN000040969

URL:https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000046784

References

1. Okabayashi K, Ashrafian H, Zacharakis E, et al. Adhesions after abdominal surgery: a systematic review of the incidence, distribution and severity. Surg Today. 2014 Mar; 44(3): 405-20.
2. Udelsman BV, Chang DC, Parina R, Talamini MA, Lillemoe KD, Witkowski ER. Population level analysis of adhesive small bowel obstruction: sustained advantage of a laparoscopic approach. Ann Surg. 2020 May; 271(5): 898-905.
3. Zeng Q, Yu Z, You J, Zhang Q. Efficacy and safety of Seprafilm for preventing postoperative abdominal adhesion: systematic review and meta-analysis. World J Surg. 2007 Nov; 31(11): 2125-31; discussion 2132.
4. Saito G, Sadahiro S, Ogimi T, et al. Preventive effects of a synthetic absorbable antiadhesive film (seprafilm) on small bowel obstruction in patients who underwent elective surgery for colon cancer: a randomized controlled trial. J Surg Oncol. 2019 Nov; 120 (6): 1038-43.
5. Suto T, Watanabe M, Endo T, et al. The primary result of prospective randomized multicenter trial of new spray-type bio-absorbable adhesion barrier system (TCD-11091) against postoperative adhesion formation. J Gastrointest Surg. 2017 Oct; 21(10): 1683-91.
6. Naito M, Ogura N, Yamanashi T, et al. Prospective randomized controlled study on the validity and safety of an absorbable adhesion barrier (Interceed®) made of oxidized regenerated cellulose for laparoscopic colorectal surgery. Asian J Endosc Surg. 2017 Feb; 10(1): 7-11.
7. Kusunoki M, Ikeuchi H, Yanagi H, et al. Bioresorbable hyaluronate-carboxymethylcellulose membrane (Seprafilm) in surgery for rectal carcinoma: a prospective randomized clinical trial. Surg Today. 2005 Nov; 35(11): 940-5.
8. Yamada T, Okabayashi K, Hasegawa H, et al. Meta-analysis of the risk of small bowel obstruction following open or laparoscopic colorectal surgery. Br J Surg. 2016 Apr; 103(5): 493-503.
9. Watanabe J, Ishida F, Ishida H, et al. A prospective multi-center registry concerning the clinical performance of laparoscopic colorectal surgery using an absorbable adhesion barrier (INTERCEED®) made of oxidized regenerated cellulose. Surg Today. 2019 Oct; 49(10): 877-84.
10. Strik C, Stommel MW, Schipper LJ, van Goor H, ten Broek RP. Long-term impact of adhesions on bowel obstruction. Surgery. 2016 May; 159(5): 1351-9.
11. Parker MC, Ellis H, Moran BJ, et al. Postoperative adhesions: ten-year follow-up of 12,584 patients undergoing lower abdominal surgery. Dis Colon Rectum. 2001 Jun; 44(6): 822-29; discussion 829.