Clinical Trial/Experimental Study

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Efficacy of an antiadhesive agent for the prevention of intra-abdominal adhesions after radical gastrectomy

A prospective randomized, multicenter trial

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Abstract

Background: Guardix-SG is a poloxamer-based antiadhesive agent. The aim of this study was to investigate its efficacy in preventing abdominal adhesions in gastric cancer patients undergoing gastrectomy. Few clinical studies have reported that antiadhesive agent reduces the incidence of adhesion after gastrectomy.

Methods: We conducted a multicenter trial from June 2013 and August 2015 in patients with gastric adenocarcinoma undergoing radical gastrectomy. Patients were randomly assigned to the Guardix treatment or control group. Postoperative adhesions were diagnosed based on postoperative symptoms, plain x-ray films, and computed tomography. The primary endpoint of the study was the incidence of small bowel obstruction in the first postoperative year. The secondary end-point was the safety of Guardix-SG.

Results: The study included 109 patients in the Guardix group and 105 patients in the control group. The groups were similarly matched with pathological stage, operation type, anastomosis method, midline incision length, and the extent of lymph node dissection. Eight in the Guardix group and 21 in the control group experienced intestinal obstruction during the 1-year follow-up period. The cumulative incidence of small bowel obstruction was significantly lower in the Guardix group compared to that seen in the control group (4.7% vs 8.6% at 6 months and 7.3% vs 20% at 1 year; $P = .007$, log-rank test). There were no differences in postoperative complications and adverse events.

Conclusion: Guardix-SG significantly decreased the incidence of intestinal obstruction without affecting the incidence of postoperative complications.

Abbreviation: CMC = carboxymethyl cellulose.

Keywords: gastric cancer, postoperative adhesions, radical gastrectomy

1. Introduction

Intra-abdominal adhesions often occur in patients who have undergone previous laparotomy. Intra-abdominal adhesions after abdominal surgery can cause small bowel obstruction, infertility, chronic pelvic pain, and may increase the technical difficulty of subsequent abdominal operations.[1] Additionally, adhesion formation and subsequent small bowel obstruction are a major health problem, negatively impacting patient quality of life postoperatively. In the United States in 1988, 1.2 billion dollars were spent to treat complications caused by adhesions after abdominal surgery.[2] Therefore, the prevention of adhesion

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formation after laparotomy has become an important issue in the management of laparotomy patients.

Gastric cancer is the most common malignancy in Korea, Japan, and China,[3] and postoperative adhesions are a frequent problem in patients undergoing gastrectomy for malignancy.[4] Adhesive small bowel obstruction is a major postoperative complication frequently associated with gastrectomy.[5–7] For this reason, the prevention of postoperative adhesion formation is particularly crucial in gastrectomy patients, and better modalities for the prevention of adhesion formation are needed.

Many different approaches have been used to prevent adhesion formation and its attendant complications.[8–10] These measures have included minimizing the size and number of wounds created during surgery, the administration of anti-inflammatory agents, and the pharmacological activation of tissue plasminogen to prevent fibrin formation.[11] Recent research has focused on the antiadhesion potential of various barrier membranes and materials. Ingredients used as adhesion prevention barriers include naturally-derived polysaccharides, such as oxidized regenerated cellulose, sodium carboxymethyl cellulose (CMC), dextran, and sodium hyaluronate. Synthetic polymers used for adhesion prevention include polyethylene glycol, poloxamer, and Gore-tex.[12]

Guardix-SG (Genewel, Dongsung Company, Seongnam, Korea) is a poloxamer-based, temperature-sensitive, antiadhesive agent that is a complex consisting of cross-linked poloxamer, alginate, and $CaCl_2$. Guardix-SG can transform from a solution to a gel at body temperature, which enhances its properties as a physical barrier. Guardix-SG acts as a thermosensitive barrier and has been shown in biodegradation studies to be initially stable. After 14 days, the amount of Guardix-SG begins to decrease, and it is completely degraded and eliminated from the body after 21 days.[13]

The aim of this study was to investigate the efficacy of Guardix-SG in the prevention of abdominal adhesions in patients undergoing radical gastrectomy for gastric cancer. We also aimed to assess the safety of the use of Guardix-SG in these patients.

2. Materials and methods

2.1. Patients

Between June 2013 and August 2015, patients with histologically confirmed gastric adenocarcinoma by endoscopic biopsy who were scheduled to undergo open radical gastrectomy were enrolled in the study. This multicenter trial was conducted by 13 surgeons from 7 hospitals. Patients were excluded if they were <20 years old or >80 years old, were pregnant, had ascites or distant metastasis, had a history of previous abdominal surgery, refused to participate in the clinical trial, took drugs that might impact the evaluation of efficacy, or had diabetes. Written informed consent was obtained from all patients before surgery. The study protocol was approved by the Ministry of Food and Drug Safety and the Institutional Review Board of The Catholic University of Korea (IRB Approval No: XC13DDMT0061D) and was registered at ClinicalTrials.gov (NCT02198898).

2.2. Randomization and masking

Patients were randomized to 1 of 2 groups at the completion of surgery just before abdominal closure. Using sequential sealed envelopes containing computer-randomized treatment assignments, the enrolled patients were assigned to the Guardix or the nontreatment group (Fig. 1). Investigators were not masked as to the treatment allocation.

2.3. Study design

Standard operations for stomach cancer were employed in all patients. Patients received open gastrectomy, omentectomy, and lymph node dissection (D1+ or D2). After distal gastrectomy, Billroth I or II reconstruction was performed. For patients with proximal lesions, total gastrectomy and Roux-en-Y anastomosis were performed. Peritoneal irrigation was performed with 35°C saline before closure. In the Guardix-SG group, 6 to 10 mL of Guardix-SG was applied to the lymph node dissection site and the small bowel below the abdominal wound just before wound closure. No Guardix-SG was applied in the nontreatment group. The abdominal fascia was closed with 1-0 coated Vicryl (Ethicon, Inc, Somerville, NJ) in a single layer, and the skin was closed with staples. Both groups received the same postoperative treatment.

2.4. Data collection

Patient demographic findings including body mass index, perioperative findings, and operative information were documented. Pathologic stage, perioperative complications, and the occurrence of postoperative paralytic ileus before discharge were also documented. Patients visited the out-patient clinic

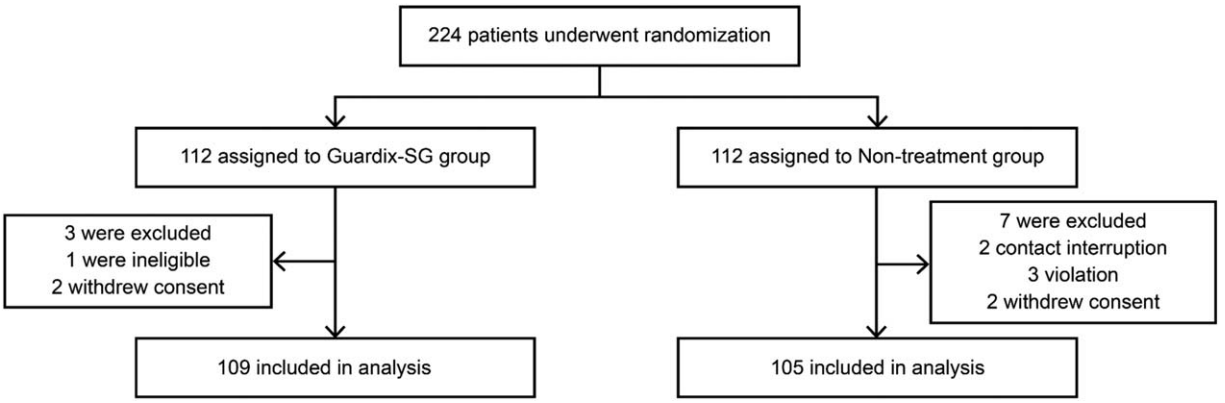

Figure 1. Flowchart of the study.

postoperatively at defined time intervals (1, 3, 6, 9, and 12 months). At every visit, the investigators questioned the patients regarding the presence of clinical symptoms and signs suggestive of bowel obstruction and recorded their responses. The investigators also performed physical examinations and documented their findings.

2.5. Definition of intestinal obstruction

Intestinal obstruction was defined by the presence of at least 3 of the following symptoms: nausea or vomiting, cramping abdominal pain, abdominal distension, and the absence of defecation or flatus in the previous 24 hours along with an abnormal physical examination (abdominal tenderness, accentuation of bowel sounds, and tympanic sounds on percussion) and imaging studies (plain abdominal x-ray or computed tomography) showing signs of intestinal obstruction or failing to rule out small bowel obstruction. These criteria are similar to those used by Fazio et al and Hayashi et al.[14,15] Radiographic studies were conducted if intestinal obstruction was suspected based on symptoms and physical examination findings. The obstruction was confirmed by a case review by researchers at all institutions through a meeting of researchers.

2.6. Objectives

The primary endpoint of this study was to compare the incidence of intestinal obstruction between the 2 groups during the first year of follow-up. The secondary end-point was to evaluate the safety of Guardix-SG when used as an adhesion barrier after gastrectomy. Poloxamer is metabolized in the liver and excreted through the kidneys. Therefore, liver and renal function tests were evaluated. Moreover, blood coagulation time was measured since coagulation failure may increase adhesion formation. Laboratory examinations were performed on the seventh postoperative day. The occurrence of postoperative complications, including anastomotic leakage, intra-abdominal abscess formation, pancreatitis, atelectasis, pneumonia, pulmonary thromboembolism, and wound infection, were documented.

2.7. Sample size and statistical analysis

Based on previous studies of the prevalence of small bowel obstruction after gastrectomy (11.7%–38.5%), the treatment efficacy of the control and the Guardix groups was estimated. The incidence of intestinal obstruction in the control group for this study was estimated to be 25%, which is the mean of the incidences reported in previous studies.[5,6,15] We assumed that the incidence of small bowel obstruction in the Guardix group would be 15% lower than that in the control group. We calculated that a total of 100 patients would be required in each group to detect a significant difference between the groups with a 2-tailed type 1 error of 5% and a statistical power of 80%. If 10% of patients withdrew from the study, the number of patients needed for each group would be 112 and the total number of patients taking part in this study would be 224.

Continuous variables including demographic and patient characteristics were analyzed using Student t test. Categorical variables including pathological stage, operative data, and complications were analyzed using the χ^2 test and the Fisher exact test. The cumulative incidence of small bowel obstruction was calculated using the Kaplan–Meier method, and the curves were compared by means of the log-rank test. P-values of $<.05$ were considered to indicate statistical significance. All statistical analyses were performed according to the intention to treat. All analyses were carried out with SPSS version 11 (IBM Corp, Chicago, IL) software.

3. Results

3.1. Study populations

The patient flow diagram is shown in Figure 1. Of the 112 patients enrolled in the Guardix group, 3 patients were excluded from the clinical trial, including 1 unqualified patient and 2 patients who withdrew consent. Among the 112 patients in the control group, 7 were excluded from the clinical trial, including 2 patients who were lost to follow-up, 3 patients who violated the protocol, and 2 patients who withdrew consent. Subsequently, a total of 214 patients were evaluated (109 in the Guardix group and 105 in the nontreatment group), and both groups were well matched after randomization (Table 1). There were also no significant differences between the 2 groups with regard to operative data including pathological stage, operation types, methods for anastomosis, length of the midline incision, and extent of lymph node dissection (Table 2). There was a tendency towards a shorter postoperative hospital stay in the control group, but this difference was not statistically significant between the groups (Guardix group 11.9 ± 8.2 days vs control group 10.2 ± 4.9 days, $P = .054$).

3.2. Incidence of the intestinal obstruction

Eight patients in the Guardix group developed intestinal obstruction, and 21 patients in the nontreatment group developed intestinal obstruction during the 1-year follow-up period. The cumulative incidence of small bowel obstruction was significantly lower in the Guardix group than that seen in the control group (4.7% vs 8.6% at 6 months and 7.3% vs 20% at 1 year, respectively; $P = .007$, log-rank test). The Kaplan–Meier plot for postoperative intestinal obstruction demonstrated a higher frequency of small bowel obstruction in the nontreatment group compared with that seen in the Guardix group. This difference was statistically significant ($P = .007$) (Fig. 2). All patients with intestinal obstruction recovered with conservative treatment.

3.3. Adverse events

We compared the incidence of immediate postoperative complications, such as gastric stasis, fever, intra-abdominal

Table 1

General characteristics.

Variable	Guardix group (n = 109)	Control group (n = 105)	P
Age, yr	62.2 ± 11.0	58.2 ± 11.2	.786
Gender			.425
Male	86 (78.9%)	78 (74.3%)	
Female	23 (21.1%)	27 (25.7%)	
BMI, kg/m^2	23.1 ± 3.1	23.0 ± 3.0	.896
Stage			.444
I	40	41	
II	23	30	
III	43	32	
IV	3	2	

BMI = body mass index.

Table 2

Operative and postoperative clinical data.

Variable	Guardix group (n = 109)	Control group (n = 105)	*P*
Gastrectomy			.755
Total	49	44	
Distal	58	60	
Other	2	1	
Anastomosis			.450
Roux Y	44	44	
Billroth I	12	6	
Billroth II	41	46	
Other	12	9	
LN dissection			.499
D2	93	86	
D1+	16	19	
Incision length, cm	21.7 ± 3.1	21.7 ± 3.3	.632
Hospital stay (POD)	11.9 ± 8.2	10.2 ± 4.9	.054
First flatus (POD)	4.0 ± 1.3	3.6 ± 1.0	.583

LN = lymph node, POD = postoperative day.

Table 3

Immediate postoperative complications.

	Guardix group (n = 109)	Control group (n = 105)	*P*
Gastric stasis	3	0	.089
Fever	3	1	.336
Intra-abdominal abscess	1	1	.979
Ileus	2	3	.625
Hernia	1	0	.326
Myocardial infarction	1	0	.326
Anastomosis leakage	0	2	.150
Postoperative bleeding	0	1	.308
Bile duct injury	1	0	.326
Pancreatitis	2	0	.165
Pleural effusion	0	1	.308
Ascites	1	1	.979
Total	15 (13.8%)	10 (9.5%)	.365

abscess, early postoperative ileus, herniation of the small bowel, myocardial infarction, anastomotic leakage, postoperative bleeding, bile duct leakage, pancreatitis, pleural effusion, and ascites, in both groups (Table 3). The overall complication rate was 13.8% in the Guardix group and 9.5% in the nontreatment group ($P = .365$). There were no device-related complications. There were no in-hospital deaths in either group. Laboratory data obtained on postoperative day 7 was not significantly different between the 2 groups. Aspartate aminotransferase, alanine aminotransferase, total bilirubin, prothrombin time, activated partial thromboplastin, blood urea nitrogen, and creatinine levels were measured and the mean values of all parameters were within the normal ranges (Table 4). Three patients died of cancer during the follow-up period. All 3 patients were in the Guardix group. One patient with stage III cancer died from recurrent gastric cancer, 1 patient with stage II cancer died from hepatic metastasis, and 1 patient with stage III cancer died from lung cancer.

4. Discussion

In this randomized study, there was a significant difference in the incidence of postgastrectomy small bowel obstruction between the Guardix group and the control group. The cumulative incidence of small bowel obstruction was 4.7% in the Guardix group and 8.6% in the control group at 6 months and 7.3% and 20% at 1 year, respectively ($P = .007$). The overall incidence of obstruction in the control group was 20% and this was comparable to the incidence found in previous reports (11.7%–38.5%). To the best of our knowledge, this is the first prospective multi-center randomized study to evaluate the protective effect of Guardix-SG on the development of intra-abdominal adhesions after gastrectomy.

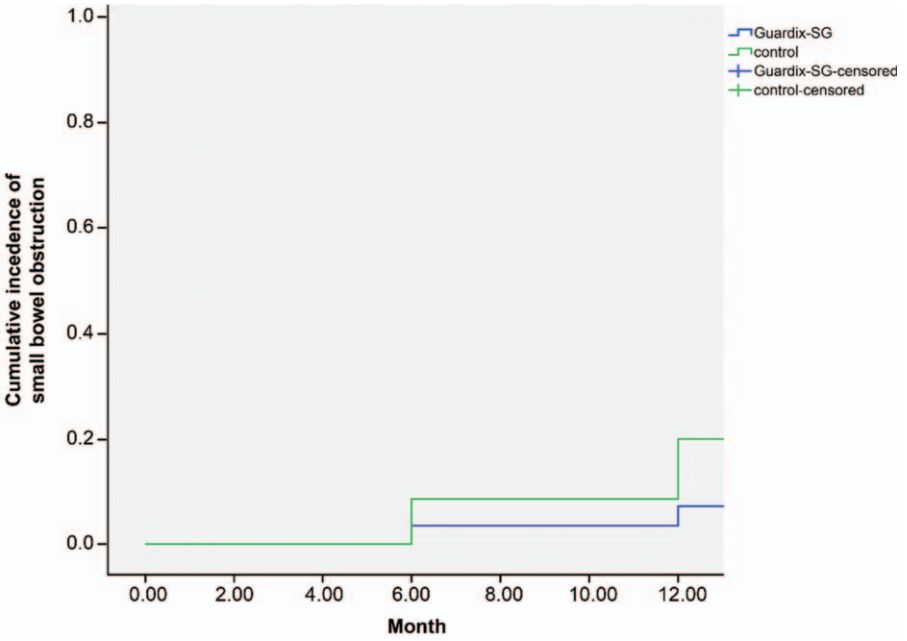

Figure 2. Cumulative incidence of small bowel obstruction in the Guardix group and the control group (log-rank = 0.007).

Table 4

Liver and renal function test results on postoperative day 7.

	Guardix group (n = 109)	Control group (n = 105)	Normal value	*P*
AST, U/L	22.7 ± 12.6	21.7 ± 13.2	0–50	.55
ALT, U/L	22.1 ± 17.2	20.4 ± 16.2	0–50	.47
Total bilirubin, mg/dL	0.7 ± 0.3	0.7 ± 0.3	0.2–1.4	.98
Prothrombin time, s	11.34 ± 0.91	11.38 ± 0.81	10.8–13.8	.96
aPTT, s	27.29 ± 4.05	26.91 ± 3.58	20.7–34.7	.46
Blood urea nitrogen, mg/dL	14.8 ± 5.4	14.9 ± 4.2	8.0–20.0	.91
Serum creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.2	0.67–1.17	.89

Data are mean ± SD.

ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase.

Hyaluronic acid/CMC (Seprafilm) is the most widely studied adhesion-prevention barrier in general surgery. Two clinical trials have reported the results obtained with the use of Seprafilm after gastrectomy in gastric cancer patients. In one randomized controlled trial of 150 gastric cancer patients, the use of Seprafilm did not significantly reduce the incidence of small bowel obstruction.[15] However, another retrospective study of 282 patients statistically proved the effectiveness of Seprafilm in reducing the incidence of adhesive obstruction after distal gastrectomy.[7]

Guardix-SG is a temperature-sensitive antiadhesive poloxamer/alginate mixture. Nagakura et al demonstrated that alginate solution reduced scar formation by forming a physical barrier against fibroblast invasion, and that it also stimulated wound healing in the surrounding tissues.[16] The antiadhesion effect of Guardix-SG has been previously demonstrated. Hong et al compared the effects of Guardix-sol and Guardix-SG in decreasing pericardial adhesions in an animal experiment. They found that both substances effectively decreased pericardial adhesion, although Guardix-SG was more effective.[17] Using an esophageal motility assay, Park et al showed the efficacy of Guardix-SG in preventing adhesions without clinical complications after thyroidectomy.[18]

In our study, a secondary endpoint was to assess the safety of Guardix-SG in patients with gastric cancer who were undergoing radical gastrectomy. The incidence of immediate postoperative complications was not significantly different between the 2 groups. The overall complication rate was 13.8% in the Guardix-SG group and 9.5% in the control group ($P = .365$). There were no device-related complications. Based on the results of the laboratory tests and the incidence of postoperative complications, the use of Guardix-SG in gastric cancer patients after radical gastrectomy was safe.

The present study has several limitations. First, there is no overall agreement on the criteria used to establish a diagnosis of small bowel obstruction; however, we used the criteria that were used in previous studies. However, patient symptomatology does not always reflect the degree of adhesion. Second, the follow-up period was shorter in our study than in the previous studies. Some studies have shown that there was an increased number of complications associated with adhesions over time. If the length of the follow-up period was increased, the rate of small bowel obstruction after surgery might have also increased in this study. Third, this study requires a subgroup analysis to determine if there is a difference in the results between the institutions. But there were few cases for subgroup analysis.

5. Conclusion

The incidence of intestinal obstruction in the Guardix-SG group was significantly lower than that of the control group. Additionally, Guardix-SG was safe to use in terms of postoperative complications. Guardix-SG should be considered effective and safe in the prevention of adhesions and small bowel obstruction in gastric cancer patients undergoing radical gastrectomy.

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