

Impact of intra-abdominal absorbable sutures on surgical site infection in gastrointestinal and hepato-biliary-pancreatic surgery: results of a multicenter, randomized, prospective, phase II clinical trial

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Abstract

Background The use of absorbable sutures in wound closure has been shown to reduce the incidence of surgical site infection (SSI); however, there is no evidence that the intra-abdominal use of absorbable rather than silk sutures reduces the incidence of SSI after gastrointestinal surgery. We report the findings of a phase II trial, designed to evaluate the impact of the intra-abdominal use of absorbable sutures on the incidence of SSI.

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Methods At 19 Japanese hospitals, 1147 patients undergoing elective gastrectomy, colorectal surgery, hepatectomy, or pancreaticoduodenectomy (PD) were randomly assigned to absorbable or silk intra-abdominal suture groups. The primary efficacy endpoint was the incidence of SSI. The secondary efficacy endpoints were the locations of SSI, time to resolution of SSI, length of hospital stay, and the incidence of bile leakage in hepatectomy and pancreatic fistula.

Results The incidence of SSI was 11.3%, 15.5%, 11.3%, and 36.9% after gastrectomy, colorectal surgery, hepatectomy, and PD, respectively. The incidence of SSI was

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higher in the absorbable suture group than in the silk suture group for all the surgical procedures, but the difference was not significant.

Conclusion The intra-abdominal use of absorbable sutures did not have enough of an effect on the reduction of SSI in this phase II trial to justify the planning of a large-scale phase III trial.

Keywords Surgical site infection · Absorbable suture · Silk suture · Surgery · Randomized prospective clinical trial

Introduction

Surgical site infection (SSI) is the most common nosocomial infection in surgical patients [1], with a reported incidence of 10–30% after gastrointestinal and hepato-biliary-pancreatic surgery [2, 3]. SSI causes physical and psychological distress to patients, is a burden to medical staff, and incurs additional costs to healthcare services.

Many studies have reported a decreasing incidence of SSI. In 1970, the Centers for Disease Control and Prevention (CDC) in the US set up the National Nosocomial Infection Surveillance (NNIS) system and established guidelines for the prevention of SSI [4–6]. The CDC reported that surveillance plays an important role in decreasing the incidence of SSI. The CDC NNIS risk index for SSI has three components: the American Society of Anesthesiologists (ASA) classification, the wound classification, and the length of the operation [7–9]. Other reported significant

risk factors for SSI are body mass index (BMI) [2], diabetes mellitus [10], smoking [11], emergency surgery [12], preoperative hair removal [4], perioperative blood glucose level [13], and perioperative oxygen administration [14]. Good surgical technique and perfusion of the surgical site are also important for the prevention of SSI [7].

Suture material is a foreign body and the presence of a foreign body increases the risk of infection. The placement of any foreign body should, therefore, be minimized, and absorbable suture material may be preferable to non-absorbable suture material such as silk. The number of *Staphylococcus aureus* bacteria required to produce infection was reported to be much lower when using silk sutures than when using non-absorbable sutures [15]. In an experimental infection model, electron microscopy showed more bacteria in the interstices of silk and multifilament nylon sutures than in monofilament nylon and polyglycolic acid sutures [16].

Most clinical trials on suture materials have focused on fascia closure. Since 1970, several studies have compared complication rates between wounds closed with silk and those closed with absorbable synthetic sutures. Studies of gastrointestinal fascia and neurosurgical wounds found that suture sinuses were more frequent when silk sutures were used for closure than when absorbable sutures were used, but these studies found no differences in wound infection rates among various suture materials [17–19]. In trauma surgery and auricular surgery, wound infection was more frequent with silk sutures than with absorbable sutures [20–22]. Several randomized studies and a meta-analysis found no difference in the incidence of wound infection between when absorbable and non-absorbable sutures were used, although the incidence of suture sinus was significantly higher when non-absorbable sutures were used [23, 24]. Because suture sinus was included in the CDC definition of SSI, the reported incidence of SSI was higher after the use of non-absorbable than absorbable sutures. However, the impact of the intra-abdominal use of absorbable sutures on SSI has not been clarified. Thus, we conducted a phase II trial to clarify the impact of the intra-abdominal use of absorbable sutures on the incidence of SSI after gastrointestinal and hepatobiliary surgery.

Methods

Study design and participants

This was a multicenter, randomized, open-label phase II study, designed to evaluate and compare the impact of intra-abdominal use of absorbable sutures and silk sutures on the incidence of SSI after gastrectomy, colorectal resection, hepatectomy, and pancreaticoduodenectomy (PD).

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The incidence of SSI was monitored and analyzed in 19 Japanese first-tier hospitals from February, 2009 to June, 2010, by the Clinical Study Promotion Committee of the Japan Surgical Society, according to the ethical guidelines for clinical studies published by the Ministry of Health, Labour and Welfare of Japan, the fifth revision of the Declaration of Helsinki, 2000, and the CONSORT guidelines. The protocol was approved by the institutional review board of each participating centre. All patients gave written informed consent prior to inclusion in the study. This study (UMIN 000001544) was registered in the University Hospital Medical Information Network clinical registry, which is one of the network members of the Japan Primary Registries Network, which meets WHO registry criteria (<http://www.umin.ac.jp/cir/index/him/>).

For all patients, the inclusion criteria were as follows: age 20–80 years, Eastern Cooperative Oncology Group performance status 0–1, written informed consent provided, white blood cell count 3000–10,000/mm³, neutrophil count >1500/mm³, hemoglobin level ≥9.0 g/dL, platelet count ≥70,000/mm³, serum total bilirubin level ≤1.5 mg/dL, serum aspartate aminotransferase level ≤100 IU/L, serum alanine aminotransferase level ≤100 IU/L, serum creatinine level <1.2 mg/dL, and serum albumin level >2.8 g/dL.

For gastrectomy, patients who underwent open partial gastrectomy (such as proximal or distal gastrectomy) or total gastrectomy for curative resection of gastric cancer were included. As for gastrectomy and colorectal resection, patients who underwent laparoscopically assisted resection were included, but those who underwent total laparoscopic gastrectomy were excluded. For hepatectomy, patients who underwent hepatic resection with biliary resection and reconstruction were excluded. For patients with liver cirrhosis, those with Child–Pugh class A or B liver function were included. For PD, patients with or without pyloric resection were included, but those who underwent combined hepatectomy were excluded.

Randomization and masking

Patients were recruited by the investigators and allocated preoperatively after eligibility was confirmed. Enrolment was done through a web-based system established for this trial, and randomization was done by a computer-generated permuted-block sequence with stratification. Patients were randomly assigned (1:1) to an absorbable suture group, in which polyglactin 910 or polydioxanone sutures were used, or a silk suture group, using the minimization method. For gastrectomy, the stratification was done according to the following factors: institution, partial or total gastrectomy, and open or laparoscopically assisted surgery. For colorectal resection, the stratification was done according to the following factors: institution, colonic resection or rectal

resection, and open or laparoscopically assisted surgery. For hepatectomy and PD, the stratification was done only by the institution. Investigator surgeons were informed of the suture material allocation via the internet and used absorbable suture materials or silk accordingly. Patients and investigators were not masked to the group assignment. The data centre, EPS Co., Ltd. (Tokyo, Japan) was responsible for allocation, central monitoring, and statistical analyses under the supervision of the statistician in charge.

Procedures

For patients assigned to the absorbable suture group, polyglactin 910 or polydioxanone was used for intra-abdominal ligations and knots and for patients assigned to the silk suture group, silk was used for intra-abdominal ligations and knots. For PD, there were no restrictions on the suture materials used for bowel, biliary, and pancreatic duct reconstruction. For hepatectomy and PD, there were no restrictions on the suture materials used for the hemostasis of large vessels. During the operation, the number of intra-abdominal sutures placed was counted.

All participating institutions were given recommendations to follow the guidelines about the CDC prevention of surgical site infections. Surgical gloves and instruments were changed before wound closure. Absorbable monofilament sutures were used for approximation of the fascia for wound closure and the method of closure, such as continuous or interrupted suturing, was decided by each institute. Intra-abdominal drain placement through a separate incision away from the operative incision was permitted, and the location and number of drainage tubes were decided according to each participating institution's respective standards.

Primary and secondary outcome

Our primary efficacy endpoint was the incidence of SSI after each type of surgery. Patients were monitored for any signs of SSI for 30 days after surgery. Patients in whom SSI developed were observed until the SSI resolved. The secondary efficacy endpoints were: the location of SSI according to the CDC classification (superficial incisional, deep incisional, or organ/space); the time to resolution of the SSI; the length of hospital stay; and the incidence of bile leakage in hepatectomy and pancreatic fistula in PD.

SSI was identified and classified according to the 1999 CDC guidelines. The CDC definition describes three levels of SSI:

1. Superficial incisional, affecting the skin and subcutaneous tissue. These infections may be indicated by localized (Celsian) signs, such as redness, pain, heat or

- swelling at the site of the incision or by the drainage of pus.
2. Deep incisional, affecting the fascial and muscle layers. These infections may be indicated by the presence of pus or an abscess, fever with tenderness of the wound, or a separation of the edges of the incision exposing the deeper tissues.
 3. Organ or space infection, which involves any part of the anatomy other than the incision that is opened or manipulated during the surgical procedure; for example, joint or peritoneum. These infections may be indicated by the drainage of pus or the formation of an abscess detected by histopathological or radiological examination or during re-operation.

Surgeons in participating institutions checked for signs of SSI every day during the hospital stay and at every outpatient visit until 30 days after surgery. The diagnosis of SSI was made by surgeons who knew the allocated arm. To ensure objectivity, more than one surgeon diagnosed the SSI, including deep SSI, during the hospital stay, according to a protocol. Surgeons checked the infected wound until the SSI resolved.

Statistical analysis

The primary objective of this study was to establish whether the intra-abdominal use of absorbable sutures reduced the incidence of SSI as compared with the use of silk sutures, to justify the planning of a large-scale phase III trial.

The study sample size was calculated as follows: For gastrectomy and colorectal resection, the expected rate of SSI was 20% with silk sutures and 10% with absorbable sutures, as observed in a previous surveillance by one of the participating hospitals [25]. The same expected rates of SSI were used for hepatectomy [26, 27]. With one-sided $\alpha=0.1$, the study was expected to have 81% power to detect a relative risk reduction of 10% if 270 patients were included. For hepatectomy, the expected rates of SSI were 20% for the silk suture group and 7% for the absorbable suture group. With one-sided $\alpha=0.1$, the study was expected to have 81% power to detect a relative risk reduction of 10% if 320 patients were included. For PD, the expected rates of SSI were 20% for the silk suture group and 10% for the absorbable suture group [28]. With one-sided $\alpha=0.1$, the study was expected to have 76% power to detect a relative risk reduction of 10% if 240 patients were included; however, 10–20% of patients undergoing PD were ineligible because no sutures were placed in the abdominal cavity, so it was estimated that 290 PD patients would be needed.

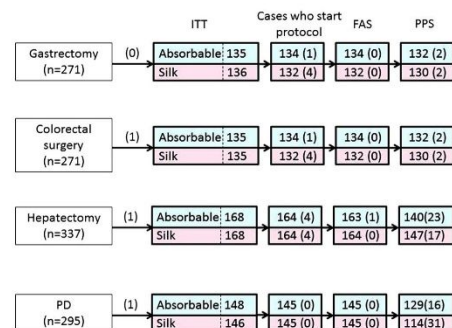


Fig. 1 Flow diagram of patient inclusion. *PD* pancreaticoduodenectomy, *ITT* intention-to-treat analysis, *FAS* full analysis set analysis, *PPS* per-protocol set analysis. The number of excluded cases are mentioned within parentheses

The full analysis set (FAS) was used for primary efficacy analysis. The FAS included data from all randomized subjects who underwent at least one of the included surgical procedures. The incidence of SSI was compared between groups using Fisher's exact test. This study investigated whether the incidence of SSI was significantly lower in the absorbable suture group than in the silk suture group. The null hypothesis was that the incidence of SSI in the absorbable suture group was equal to or higher than the incidence of SSI in the silk suture group. The alternative hypothesis was that the incidence of SSI was 10% or more lower in the absorbable suture group than in the silk suture group. Because the significance was not a major concern if absorbable sutures did not reduce the incidence of SSI, a one-tailed test with a significance level of 0.10 was used. Statistical analysis was performed using SAS ver 9.2 (SAS Institute Inc.).

Role of the funding source

This work was supported by a grant from the Japan Surgical Society Clinical Investigation Project Award and a Health Labour Science Research Grant (Rinsho-Ippan-006). The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Figure 1 shows a flow chart diagram of patient inclusion. For gastrectomy, no patients were excluded from the intention-to-treat (ITT) FAS analysis; however, five patients were excluded because the study could not be started according to the protocol, and four were excluded from the per-protocol set (PPS) analysis. For colorectal resection, one patient was excluded from the ITT analysis, and four were excluded because the study could not be started according to the protocol. Two patients were excluded from the FAS analysis and seven were excluded from the PPS analysis. For hepatectomy, one patient was excluded from the ITT analysis, and eight were excluded because the study could not be started according to the protocol. One patient was excluded from the FAS analysis and 40 were

excluded from the PPS analysis. For PD, one patient was excluded from the ITT analysis, and four were excluded because the study could not be started according to the protocol. No patients were excluded from the FAS analysis and 47 were excluded from the PPS analysis.

Background characteristics of the patients

1. Gastrectomy: A total of 266 patients were enrolled (absorbable suture group, $n=134$; silk suture group, $n=132$). There were no significant differences in peri-operative factors or the number of intra-abdominal ties between the absorbable suture and silk suture groups (Table 1 and Supplementary Table 1A).
2. Colorectal resection: A total of 264 patients were enrolled (absorbable suture group, $n=131$; silk suture

Table 1 Common clinical background characteristics of patients in the absorbable suture versus silk suture groups who underwent gastrectomy, colorectal surgery, hepatectomy, or pancreatico-duodenectomy

Factors	Gastrectomy		Colorectal surgery		Hepatectomy		PD	
	Absorbable ($n=134$)	Silk ($n=132$)	Absorbable ($n=131$)	Silk ($n=133$)	Absorbable ($n=163$)	Silk ($n=164$)	Absorbable ($n=145$)	Silk ($n=145$)
Age (years)	66 ± 10	65 ± 9	65 ± 11	65 ± 10	63 ± 13	61 ± 14	67 ± 9	66 ± 9
Sex (males/ female)	91:43 86:46	77/54	84/49	112/51	126/38	88/57	92/53	
ASA physiological status								
(Class 1/2/3/4/5)	97/35/2/0/0	89/40/3/0/0	75/53/3/0/0	70/63/0/0/0	113/46/4/0/0 96/63/5/0/0	74/63/8/0/0	72/66/7/0/0	
DM (no/yes)	119/15	117/15	110/21	114/19	121/42	122/42	107/38	106/39
BMI (kg/m ²)	22.6 ± 3.5	22.5 ± 3.1	22.6 ± 3.3	23.0 ± 3.8	22.7 ± 3.9	22.9 ± 3.4	22.3 ± 3.4	21.8 ± 3.2
Smoking status								
(Class 1/2/3/4)	44/24/8/0	33/19/6/0	88/24/12/7	80/21/21/11	82/57/16/8	96/63/5/0	78/50/10/7	77/54/10/4
Albumin (g/dl)	4.2 ± 0.4	4.2 ± 0.4	4.1 ± 0.4	4.0 ± 0.4	4.1 ± 0.8	4.1 ± 0.4	3.9 ± 0.6	3.9 ± 0.5
Hair removal (no/yes)	112/22	113/26	68/63	71/62	78/85	74/90	96/49	83/62
Blood loss (g)	369 ± 359	305 ± 328	210 ± 467	212 ± 359	656 ± 598	550 ± 663*	861 ± 679	931 ± 1251
Operation time (min.)	238 ± 94	235 ± 67	236 ± 93	236 ± 79	348 ± 135	328 ± 137	471 ± 151	483 ± 176
Vessel sealing system	70/64	59/73	41/90	50/83	95/68	107/57	32/113	31/114
Ultrasonic dissector (no/yes)								
Number of drainage tube (One ≥/two ≤)	70/64	76/56	121/ 10	119/ 14	92/71	94/70	35/110	39/106
Number of intra-abdom- inal sutures	35 ± 26	32 ± 23	20 ± 18	22 ± 21	71 ± 57	79 ± 86	102 ± 72	119 ± 83
Periods of drainage tube replacement (days)	7 ± 6	6 ± 6	7 ± 6	7 ± 6	7 ± 8	7 ± 7	18 ± 21	15 ± 20

Data are expressed as the mean ± SD or number (%). ASA = American Society of Anesthesiologists. Smoking status: class 1: never, class 2: no smoking ≥ 30 days, class 3: no smoking < 30 days, class 4: smoking on admission. Blood loss in the silk suture group was significantly less than that in the absorbable suture group ($p=0.0250$)

- group, $n=133$). There were no significant differences in perioperative factors or the number of intra-abdominal ties between the absorbable suture and silk suture groups (Table 1 and Supplementary Table 1B).
- Hepatectomy: A total of 327 patients were enrolled (absorbable suture group, $n=163$; silk suture group, $n=164$). The blood loss was significantly greater in the silk suture group than in the absorbable suture group. There was no significant difference in the number of intra-abdominal ties between the two groups (Table 1 and Supplementary Table 1C).
 - PD: A total of 290 patients were enrolled (absorbable suture material, $n=145$; silk suture group, $n=145$). There were no significant differences in perioperative factors or the number of intra-abdominal ties between the absorbable suture and silk suture groups (Table 1 and Supplementary Table 1D).
- combined resection, blood loss ≥ 250.5 g, and ≥ 30.5 absorbable sutures (Table 2; Fig. 2). The incidence of SSI was 14.2% in the absorbable suture group and 8.3% in the silk suture group, without a significant difference between the groups.
- Colorectal resection: SSI developed in 41 of the 264 patients (15.4%). The incidence of SSI was significantly higher after rectal resection than after colonic resection ($p=0.0097$), but there were no other significant risk factors for SSI (Table 3). The incidence of SSI was 17.6% in the absorbable suture group and 13.5% in the silk suture group, without a significant difference between the groups (Fig. 2).
 - Hepatectomy: SSI occurred in 37 of the 327 patients (11.3%). SSI was significantly associated with blood loss ≥ 435 g and an operation time ≥ 320 min, but not with the intra-abdominal use of silk sutures (Table 4). The incidence of SSI was 12.9% in the absorbable suture group and 9.8% in the silk suture group. The incidence of SSI was higher in the absorbable suture group than in the silk suture group, without a significant difference between the groups (Fig. 2).
 - PD: SSI occurred in 107 of the 290 patients (36.9%). The significant risk factors for SSI were BMI ≥ 21.8 kg/m², placement of more than two drainage tubes, and

Primary efficacy endpoint

- Gastrectomy: SSI developed in 30 of the 266 patients (11.2%). The significant risk factors for SSI were BMI ≥ 22.45 kg/m², open surgery, total gastrectomy,

Table 2 Relationships between clinical factors and surgical site infection for patients who underwent gastrectomy

Factors	Subgroup	Number	SSI number	SSI incidence (%)	<i>p</i> values
Age (years)	65>	113	9	8.0	0.1716
	65≤	153	21	13.7	
BMI (kg/m ²)	22.45<	133	7	5.3	0.0031
	22.45≥	133	23	17.3	
Laparo-assisted	No	214	29	13.6	0.0138
	Yes	52	1	1.9	
Drainage tube	0–1	146	10	6.9	0.0187
	2≤	120	20	16.7	
Operation	Partial	190	15	7.9	0.0087
	Total	75	15	20.0	
Lymph node dissection	D0,1	106	7	6.6	0.0797
	D2, >D2	49	49	14.4	
Combined resection	No	217	18	8.3	0.0042
	Yes	49	12	24.5	
Blood loss (g)	250.5>	133	8	6.0	0.0107
	250.5≤	133	22	16.5	
Operative time (min)	225.5>	133	10	6.0	0.0797
	225.5≤	133	20	15.0	
Number of absorbable sutures	30.5>	67	4	6.0	0.0117
	30.5≤	67	15	22.4	
Number of silk sutures	28.5>	66	4	6.1	0.5308
	28.5≤	66	7	10.6	

SSI surgical site infection

Fig. 2 Incidence of SSI for each type of surgery

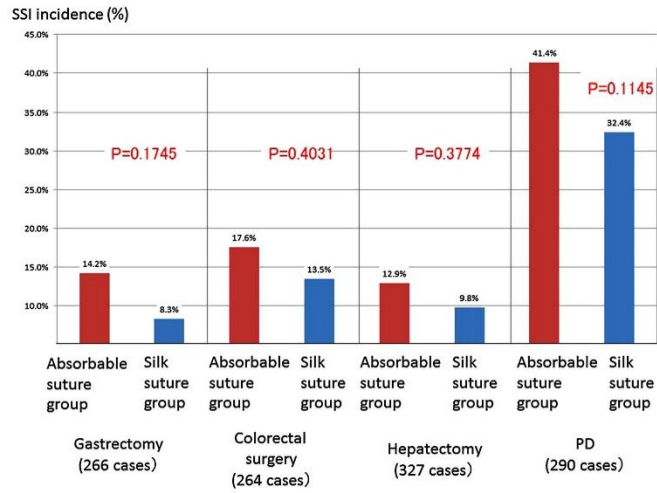


Table 3 Relationships between clinical factors and SSI in patients who underwent colorectal resection

Risk factor	Subgroups	Number	SSI number	SSI incidence (%)	p values
Age (years)	67>	125	18	14.4	0.7341
	67≤	139	23	16.5	
BMI (kg/m ²)	22.65>	132	21	15.9	1.0000
	22.65≤	132	20	15.2	
Laparo-assisted	Open	146	24	16.4	0.7355
	Yes	118	17	14.4	
Number of drainage tube	0–1	240	35	14.6	0.2312
	2≤	24	6	25.0	
Operative procedures	Colon	178	20	11.2	0.0097
	Rectum	83	20	24.1	
Lymph nodes dissection	D0,1,2	104	13	12.5	0.3012
	D3, >D3	160	28	17.5	
Combined resection	No	242	37	15.3	0.7579
	Yes	22	4	18.2	
Blood loss (g)	88.5>	132	17	12.9	0.3079
	88.5≤	132	24	18.2	
Operation time (min)	228>	132	22	16.7	0.7343
	228≤	132	19	14.4	
Number of absorbable sutures	10>	65	11	16.9	1.0000
	10≤	66	12	18.2	
Number of silk sutures	10.5>	66	12	18.2	0.1358
	10.5<	67	6	10.6	

Table 4 Relationships between clinical factors and SSI in patients who underwent hepatectomy

Factors	Subgroups	Numbers	SSI numbers	SSI incidence (%)	<i>p</i> values
Age (years)	65>	161	13	8.1	0.0812
	65≤	166	24	14.5	
BMI (kg/m ²)	22.8>	163	17	10.4	0.7275
	22.8≤	164	20	12.2	
Laparo-assisted	Open	316	37	11.7	0.6205
	No	11	0	0	
Number of drainage tube	0–1	186	16	8.6	0.0807
	2≤	141	21	14.9	
Operative procedures	Segment≥	241	28	11.6	0.8387
	Bisegment≤	79	8	10.1	
Combined resection	No	15	0	12.7	0.4892
	Yes	177	18	10.2	
Blood loss (g)	435>	162	10	6.2	0.0047
	435≤	165	27	16.4	
Operation time (min)	320>	162	10	6.2	0.0047
	320≤	165	27	16.4	
Number of absorbable sutures	34>	81	11	13.6	0.8193
	34≤	82	10	12.2	
Number of silk sutures	36.75>	82	7	8.5	0.7933
	36.75≤	82	9	11.0	

Table 5 Relationships between clinical factors and SSI in patients who underwent pancreaticoduodenectomy

Factors	Subgroups	Number	SSI number	SSI incidence (%)	<i>p</i> values
Age (years)	68>	138	47	34.1	0.3839
	68≤	152	60	39.5	
BMI (kg/m ²)	21.8>	143	41	28.7	0.0051
	21.8≤	147	66	44.9	
Laparo-assisted	Open	285	107	37.5	0.1617
	Yes	5	0	0	
Number of drainage tube	0–1	74	18	24.3	0.0117
	2≤	216	89	41.2	
Combined resection	No	52	20	38.5	0.8742
	Yes	238	87	36.6	
Blood loss (g)	615>	145	42	29.0	0.0073
	615≤	145	65	44.8	
Operation time (min)	470>	145	52	35.9	0.8078
	470≤	145	55	37.9	
Number of absorbable sutures	67>	71	32	45.1	0.4030
	67≤	74	28	37.8	
Number of silk sutures	75>	71	24	33.8	0.8593
	75≤	74	23	31.1	

blood loss ≥ 615 g (Table 5). The incidence of SSI was 41.4% in the absorbable suture group and 32.4% in the silk suture group, without a significant difference between the groups (Fig. 2).

Secondary efficacy endpoints

In the patients who underwent gastrectomy, colorectal resection, or PD, the incidence of organ/space SSI was higher in the absorbable than in the silk suture group, although the difference was not significant (Fig. 3). The rates of bile leakage [29] after hepatectomy and pancreatic fistula [30] after PD in the absorbable and silk suture groups did not differ significantly (Fig. 4). The mean time to resolution of the SSI and the mean length of hospital stay for any of the surgical procedures did not differ significantly between the two suture groups (Table 6).

Discussion

This was a multicenter, randomized, phase II trial, with the primary efficacy endpoint of the incidence of SSI. The main goal of this study was to prove the hypothesis that the intra-abdominal use of absorbable sutures would

significantly reduce the incidence of SSI compared with using silk sutures. To prove such a hypothesis, a large-scale phase III trial is usually necessary. However, as there are no prospective data for evaluating this hypothesis, a pilot study is necessary to estimate the difference in the incidence of SSI with use of absorbable vs. silk sutures. When the effect size has been established, a large-scale phase III trial can be conducted. This study evaluated the effect size in a multicenter, randomized, clinical trial, using silk sutures for the control group. This study was conducted in Japanese first-tier hospitals and the incidence of SSI was revealed to be 11.3%, 15.5%, 11.3%, and 36.9% after gastrectomy, colorectal resection, hepatectomy, and PD, respectively. These incidences are acceptable when compared with those of previous reports [2, 3].

According to SSI surveillance data for Japan in 2004, non-absorbable sutures were used for seromuscular closure and silk was commonly used for intra-abdominal sutures [25]. This may be because silk sutures are cheaper than absorbable sutures in Japan, and because silk sutures are technically easier for surgeons to tie and ligate vessels with than absorbable sutures. Retrospective SSI surveillance data from 27 Japanese hospitals showed that the intra-abdominal use of absorbable sutures rather than silk sutures significantly reduced the incidence of SSI after colorectal surgery, with incidences of SSI of 13.9 vs. 22.4%, respectively ($p=0.03$). Togo and colleagues [27] reported that

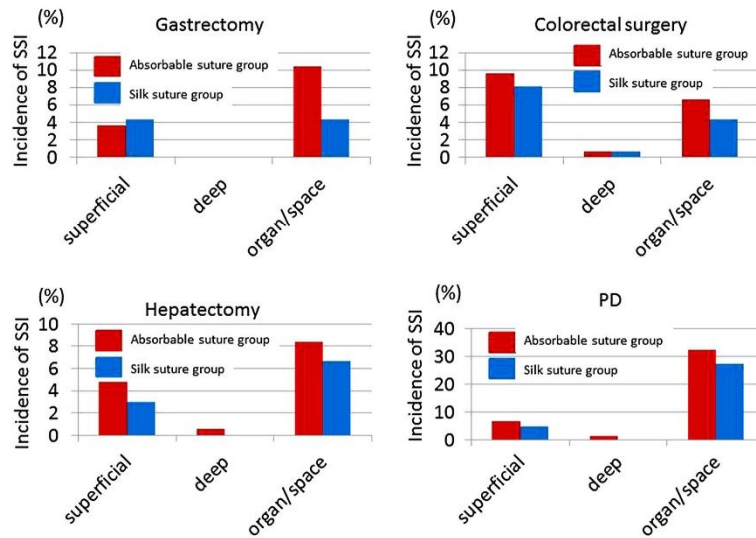


Fig. 3 The incidence of superficial, deep and organ/space SSI after surgery

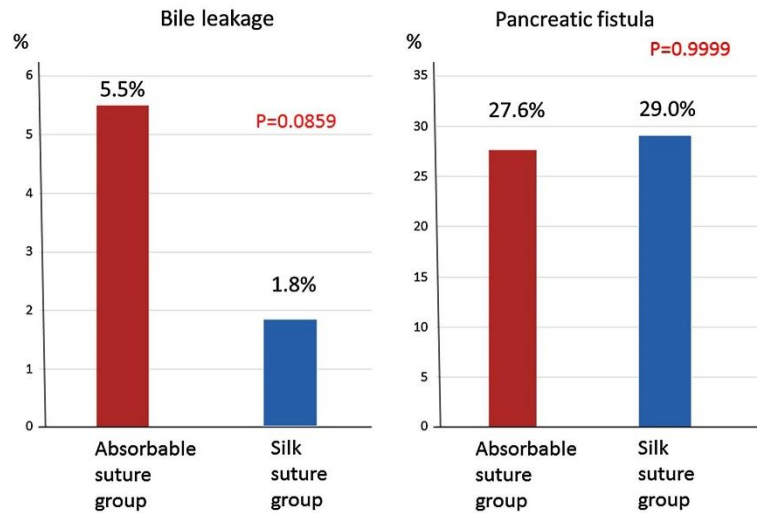


Fig. 4 *Left* The incidence of bile leakage after hepatectomy in the absorbable and silk suture group is shown. *Right* The incidence of pancreatic fistula after PD between the two groups is shown

Table 6 The secondary endpoints: days to resolution of SSI and the length of hospital stay were compared between silk and absorbable suture groups in ITT analysis

	Silk suture group	Absorbable suture group	<i>p</i> values
Gastrectomy	(<i>n</i> = 12)	(<i>n</i> = 19)	
Days to resolution of SSI	22.2 ± 16.8	17.2 ± 10.0	0.3107
The length of hospital stay (days)	24.8 ± 13.3	24.6 ± 11.7	0.9649
Colorectal surgery	(<i>n</i> = 18)	(<i>n</i> = 23)	
Days to resolution of SSI	17.1 ± 8.1	17.1 ± 10.5	0.9949
The length of hospital stay (days)	25.1 ± 11.2	24.4 ± 10.2	0.8543
Hepatectomy	(<i>n</i> = 16)	(<i>n</i> = 23)	
Days to resolution of SSI	22.1 ± 20.3	25.1 ± 21.0	0.6517
The length of hospital stay (days)	25.4 ± 15.8	31.2 ± 19.0	0.3197
PD	(<i>n</i> = 47)	(<i>n</i> = 23)	
Days to resolution of SSI	30.6 ± 36.2	27.9 ± 19.5	0.6183
The length of hospital stay (days)	41.0 ± 44.2	41.0 ± 44.2	0.8856

There were no statistically significant differences between two groups in gastrectomy, colorectal surgery, hepatectomy and PD

the intra-abdominal use of absorbable sutures significantly reduced the incidence of SSI after hepatectomy. However, because these findings were based on retrospective data rather than randomized prospective data, there is still no consensus regarding the optimal suture materials to use.

Based on these previous retrospective studies, we calculated the number of patients needed for the present study. The number had to be large enough to allow us to examine

our hypothesis. The primary efficacy endpoint was selected as SSI, including superficial, deep incisional, and organ or space SSI. Theoretically, the intra-abdominal use of absorbable suture may reduce organ or space SSI. Nevertheless, previous studies have found that the intra-abdominal use of absorbable suture reduced the incidence of total SSI, including superficial, deep incisional, and organ or space SSI. Thus, the total SSI was selected as the primary

efficacy endpoint in this study. In this kind of exploratory study, the effects of absorbable sutures on organ or space SSI would be examined after the stratification of whole data.

Although the incidence of SSI tended to be higher in the absorbable suture group for all types of surgery, the differences were not significant. For gastrectomy, the incidence of SSI was significantly higher in the subgroup with a larger number of absorbable sutures than the subgroup with a smaller number of absorbable sutures. For hepatectomy, the incidence of bile leakage and organ/space SSI tended to be higher in the absorbable suture group than in the silk suture group. These data suggest that the use of absorbable sutures may be related to the occurrence of SSI, which may be because ties using absorbable sutures are more technically challenging and the knots may slip more easily. However, these results are unlikely to be attributed to the surgeons' skill, because this study was conducted in 19 Japanese first-tier hospitals, all of which have an acceptable incidence of SSI. The greater blood loss in the absorbable suture group may reflect such technical difficulties. To compare the effects of the suture material itself, some training on the tying of absorbable sutures may be necessary to lower the incidence of SSI following their use. However, the results after special training cannot be applied to the general clinical setting and, clearly, the aim of this study is to clarify the benefit and effectiveness of absorbable sutures for preventing SSI in the general clinical setting. Therefore, the results of the present study, without training, might be acceptable. Another possibility is that the body's response to absorbable suture materials may contribute to the incidence of SSI. The reasons for these findings remain unclear.

Examining all the patients as one group, the incidence of SSI was 16.1% (93 of 577 patients) in the silk suture group and 21.4% (123 of 575 patients) in the absorbable suture group. This difference was significant ($p=0.0235$); however, the aim of this study was to clarify whether the use of intra-abdominal use of absorbable rather than silk sutures would reduce the incidence of SSI after gastrointestinal surgery. Furthermore, an independent randomized prospective study was designed for each of the fields examined, namely gastrectomy, colorectal surgery, hepatectomy, and PD. Therefore, to provide the beneficial effects of using silk sutures to reduce the incidence of SSI, another prospective study would be necessary.

The weakness of this study might be that more than 10% of the patients were excluded from the PPS analysis of hepatectomy and PD, although most of these patients had only a few sutures applied, sometimes using other materials. Nevertheless, the results were statistically the same, even after ITT, FAS, and PPS analysis.

In conclusion, the results of this study show that the intra-abdominal use of absorbable sutures did not reduce the incidence of SSI after gastrointestinal surgery. The statistical null hypothesis that "the incidence of SSI in the absorbable suture group was equal to that in silk group (or the incidence in the absorbable group was higher than that in the silk group)" was not denied but the intra-abdominal use of absorbable sutures did not have a sufficient effects on the reduction of SSI to justify the planning of a large-scale phase III trial.

Compliance with ethical standards

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Conflict of interest We declare that we have no conflicts of interest.

References

- Katayama H, Kurokawa Y, Nakamura K, Ito H, Kanemitsu Y, Masuda N, et al. Extended Clavien-Dindo classification of surgical complications: Japan Clinical Oncology Group postoperative complications criteria. *Surg Today*. 2016;46:668–85.
- Smith RL, Bohl JK, McElearney ST, Friel CM, Barclay MM, Sawyer RG, et al. Wound infection after elective colorectal resection. *Ann Surg*. 2004;239:599–607.
- Sørensen LT, Hemmingsen U, Kallehave F, Wille-Jørgensen P, Kjaergaard J, Møller LN, et al. Risk factors for tissue and wound complications in gastrointestinal surgery. *Ann Surg*. 2005;241:654–8.
- Emori TG, Culver RDH, Horan TC, Jarvis WR, White JW, Olson DR, et al. National nosocomial infection surveillance system (NNISS) description of surveillance methods. *Am J Infect Control*. 1991;19:19–35.
- Cruse PJ, Foord R. The epidemiology of wound infection: A 10-year prospective study of 62,939 wounds. *Surg Clin North Am*. 1980;60:27–40.
- Mangram AJ, Horan TC, Pearson ML, Silver LC, Jarvis WR. Guideline for prevention of surgical site infection, 1999. *Infect Control Hosp Epidemiol*. 1999;20:247–78.
- Culver DH, Horan TC, Gaynes RP, Martone WJ, Jarvis WR, Emori TG, et al. Surgical wound infection rates by wound class, operative procedure, and patient risk index. National Nosocomial Infections Surveillance System. *Am J Med*. 1991;91:1525–7S.
- Gayne RP, Culver DH, Horan TC, Edwards JR, Richards C, Tolson JS. Surgical site infection (SSI) rates in the United States, 1992–1998: the National Nosocomial Infections Surveillance System basic SSI risk index. *Clin Infect Dis*. 2001;33(Suppl 2):S69–77.
- Roy MC, Herwaldt LA, Embrey R, Kuhns K, Wenzel RP, Perl TM. Does the center for disease control's NNIS system risk index stratify patients undergoing cardiothoracic operations by their risk of surgical-site infection? *Infect Control Hosp Epidemiol*. 2000;21:1865–90.
- Melton GB, Vogel JD, Swenson BR, Remzi FH, Rothenberger DA, Wick EC. Continuous intraoperative temperature measurement and surgical site infection risk: analysis of anesthesia

- information system data in 1008 colorectal procedures. *Ann Surg.* 2013;258:606–12.
11. Sørensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. *Ann Surg.* 2003;238:1–5.
 12. Lizan-Garcia M, Garcia-Caballero J, Assensio Vegas A. Risk factors for surgical-wound infection in general surgery: a prospective study. *Infect Control Hosp Epidemiol.* 1997;18:310–5.
 13. Zerr KJ, Furnary AP, Grunckenmeier GL, Bookin S, Kanhere V, Starr A. Glucose control lowers the risk of wound infection in diabetics after open heart operation. *Ann Thro Surg.* 1997;63(2):356–61.
 14. Greif R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. *N Engl J Med.* 2000;342:161–7.
 15. Merritt K, Hitchins VM, Neale AR. Tissue colonization from implantable biomaterials with low numbers of bacteria. *J Biomed Mater Res.* 1999;44:261–5.
 16. Otten J-E, Wiedmann-Al-Ahmad M, Jahnke H, Pelz K. Bacterial colonization on different suture materials—a potential risk for introral dentoalveolar surgery. *J Biomed Mater Res B Appl Biomater.* 2005;74:627–35.
 17. Kronborg O. Polyglycolic acid (DEXON) versus silk for fascial closure of abdominal incisions. *Acta Chir Scand.* 1976;142:9–12.
 18. Blomstedt GC. Infection in Neurosurgery: A randomized comparison between silk and Polyglycolic acid. *Acta Neurochir.* 1985;76:90–3.
 19. Iwase K, Higaki J, Tanaka Y, Kondoh M, Yoshikawa M, Kamiike W. Running closure of clean and contaminated abdominal wounds using a synthetic monofilament absorbable looped suture. *Surg Today.* 1999;29:874–9.
 20. Sortino F, Lombardo C, Sciacca A. Silk and polyglycolic acid in oral surgery: a comparative study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2008;105:e15–8.
 21. Adams IW, Bell MS, Driver RM, Fry WG. A comparative trial of polyglycolic acid and silk suture materials for accidental wounds. *Lancet.* 1977;2(8050):1216–7.
 22. Willatt DJ, Durham L, Ramadan MF, Bark-Jones N. A prospective randomized trial of suture material in aural wound closure. *J Laryngol Otol.* 1988;102:788–90.
 23. Hodgson NC, Malthaner RA, Østbye T. The search for an ideal method of abdominal fascial closure, a meta-analysis. *Ann Surg.* 2000;231:436–42.
 24. van't Riet M, Steyerberg EW, Nellensteyn J, Bonjer HJ, Jeekel J. Meta-analysis of techniques for closure of midline abdominal incisions. *Br J Surg.* 2002;89:1350–6.
 25. Watanabe A, Kohnoe S, Shimabukuro R, Yamanaka T, Iso Y, Baba H, et al. Risk factors associated with surgical site infection in upper and lower gastro-intestinal surgery. *Surg Today.* 2008;38:404–12.
 26. Okabayashi T, Nishimori I, Yamashita K, Sugimoto T, Yatabe T, Maeda H, et al. Risk factors and predictors for surgical site infection after hepatectomy. *J Hosp Infect.* 2009;73:47–53.
 27. Togo S, Matsuo K, Tanaka K, Matsumoto C, Shimizu T, Ueda M, et al. Perioperative infection control and its effectiveness in hepatectomy patients. *J Gastroenterol Hepatol.* 2007;22:1942–8.
 28. Ueno T, Yamamoto K, Kawaoka T, Takashima M, Oka M. Current antibiotics prophylaxis in pancreatoduodenectomy in Japan. *J Hepatobiliary Pancreat Surg.* 2005;12:304–9.
 29. Yamashita Y, Hamatsu T, Rikimaru T, Tanaka S, Shirabe K, Shimada M, et al. Bile leakage after hepatic resection. *Ann Surg.* 2001;233:45–50.
 30. Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, Falconi M, et al. Pancreatic fistula after pancreatic resection. The importance of definitions. *Dig Surg.* 2004;21:54–9.