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Superiority trial comparing intraoperative wound irrigation with aqueous 10% povidone–iodine to saline for the purpose of reducing surgical site infection after elective gastrointestinal surgery: study protocol for a randomised controlled trial

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ABSTRACT

Introduction Surgical site infection (SSI) is one of the most common complications after gastrointestinal surgery, with a reported incidence of approximately 10%–25%, which is higher than the rates after other types of surgery. Intraoperative wound irrigation (IOWI) is a simple intervention for SSI prevention, and recent studies have reported that IOWI with aqueous povidone–iodine (PVP-I) is significantly more effective at reducing the incidence of SSI than saline. However, the evidence level of previous trials evaluating the efficacy of aqueous PVP-I solution for preventing SSI has been low.

Methods and analyses We propose a single-institute, prospective, randomised, blinded-endpoint trial to assess the superiority of IOWI with aqueous 10% PVP-I solution compared with normal saline for reducing SSI in clean-contaminated wounds after elective gastrointestinal surgery. In the study group, IOWI with 40 mL of aqueous 10% PVP-I solution is performed for 1 min before skin suture, and in the control group, IOWI with 100 mL of saline is performed for 1 min before skin suture. We hypothesise that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSIs. The target number of cases is set at 950. The primary outcome is the incidence of incisional SSI up to postoperative day 30 and will be analysed in the modified intention-to-treat set.

Ethics and dissemination This trial was designed and is being conducted by Saitama Medical Center, Jichi Medical University, with approval from the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University. Participant recruitment began in June 2019. The final results will be reported in international peer-reviewed journals immediately after trial completion.

Trial registration number UMIN000036889.

Strength and limitations of this study

- ► Our inclusion and exclusion criteria strictly select homogenous patients with clean-contaminated wounds after gastrointestinal surgery.
- ► We are using the criteria established by the Centers for Disease Control and Prevention to diagnose surgical site infection (SSI), as the evidence levels of previous studies concerning the efficacy of intraoperative wound irrigation (IOWI) with aqueous povidone–iodine solution for preventing SSI have been low due to non-uniform definitions of SSI.
- ► In our sample size calculation, the number of expected dropout cases is expected to be accurate, as we can predict dropouts based on a previous large-scale randomised controlled trial (RCT) for SSI prevention conducted by our department.
- ► As significant attention should be paid to associated cost when developing measures for SSI prevention, our trial setting is novel, since the costs of IOWI in the study group and those in the control group were almost the same.
- ► One limitation is that multicentre RCTs will be necessary to generalise and substantiate the findings of this trial.

INTRODUCTION

Surgical site infection (SSI) is one of the most common complications after gastrointestinal surgery, with a reported incidence of around 10%–25% in recent studies.[1–3] A recent global survey revealed that the incidence of SSI after gastrointestinal surgery has remained at

9.4%, even in high-income countries.[1] The incidence of SSI after gastrointestinal surgery is higher than that after other types of surgery, including cardiac surgery, gynaecological surgery, neurosurgery and urological surgery.[4–7]

SSIs are harmful to patients, inducing incisional pain, and are associated with increased risks of morbidity and mortality.[8] SSIs have also been suggested to be associated with adverse long-term outcomes in patients undergoing oncological gastrointestinal surgery.[9–11] SSIs were reported to be associated with adverse oncological outcomes in patients who underwent liver resection for colorectal liver metastasis,[9] and postoperative infective complications, including SSI, reportedly affect the long-term survival after resection for gastric cancer[10] and colorectal cancer.[11]

Furthermore, SSIs dramatically increase medical costs.[12] Previous reports have shown that when SSIs occur, the excess hospitalisation duration and additional medical costs amounted to 6–10 days and US$1300–US$6000 per patient, respectively.[13–18] A recent cohort study from the UK also showed that the National Health Service cost associated with 12 months of care for an infected unhealed wound was approximately £8000 higher than the cost associated with care for a healed wound.[19] Thus, reducing the rate of SSI after gastrointestinal surgery is very important for improving patient outcomes and reducing medical costs, and reliable measures for SSI prevention are urgently needed.

National and international health organisations, such as the Centers for Disease Control and Prevention (CDC),[20] WHO[21] and National Institute for Health and Care Excellence (NICE)[22] have proposed clinical guidelines based on systemic reviews and meta-analyses for SSI prevention. The pathogeneses of SSIs are complex; recommendations for SSI prevention thus include preoperative, intraoperative and postoperative measures. Intraoperative wound irrigation (IOWI) is a simple intervention to remove tissue debris, metabolic waste and tissue exudate from the surgical wound and to reduce bacterial effects before wound closure.[23 24] A recent Cochrane review concluded that the evidence base for IOWI was of a low quality,[25] but some recent meta-analyses showed that IOWI significantly reduced the rate of SSIs compared with no irrigation.[26–28]

Saline is an isotonic solution that does not interfere with wound healing and has been widely accepted as appropriate irrigation fluid for IOWI.[23 24] However, two recent meta-analyses reported that IOWI with saline was not effective in reducing SSIs[26 27] that IOWI with aqueous povidone–iodine (PVP-I) had a significant benefit in reducing SSIs compared with saline.[26 27] Previous trials to evaluate the efficacy of aqueous PVP-I solution to prevent SSI were mostly conducted in the 1970–1980s, and the evidence levels were low, as heterogeneous patients were included and non-uniform definitions were used for the diagnosis of SSI.[26–29] A meta-analysis after the exclusion of RCTs of low or uncertain quality showed that IOWI with aqueous PVP-I solutions was not associated with a significant decrease in the incidence of SSIs.[28] Thus, the evidence levels have been low, the clinical guidelines of the CDC and WHO weakly recommend IOWI with aqueous PVP-I for the prevention for SSI, thereby suggesting that IOWI with saline is not effective.[20 21] From the viewpoint of wound classification, recent meta-analyses showed that IOWI with aqueous PVP-I for the prevention of SSI had reproducible effects on clean wounds,[27 28] but the findings for clean-contaminated wounds were controversial.[28] The majority of wounds after gastrointestinal surgery are classified as clean-contaminated or contaminated; thus, at present, there is no established evidence supporting the effectiveness of IOWI with aqueous PVP-I for the prevention of SSI after gastrointestinal surgery. Furthermore, the clinical guideline of the NICE states that IOWI with aqueous PVP-I solution should be avoided in order to prevent local and systemic side effects.[22] Thus, the lack of uniformity in clinical guidelines from the CDC, WHO and NICE[20–22] as well as the lack of well-established evidence supporting the effectiveness of IOWI with aqueous PVP-I solution for SSI prevention[26–28] may confuse surgeons.

This single-centre, prospective, randomised controlled trial (RCT) is being performed to evaluate the superiority of IOWI with aqueous 10% PVP-I solution for reducing the incidence of SSI after gastrointestinal surgery compared with saline. We hypothesise that IOWI with aqueous 10% PVP-I solution will be more useful than saline for the prevention of SSI in clean-contaminated wounds.

METHODS

Trial design

This is a single-institute, prospective, randomised, blinded-endpoint trial being conducted to assess the superiority of IOWI with aqueous 10% PVP-I solution compared with normal saline for reducing SSI in clean-contaminated wounds after elective gastrointestinal surgery. This trial was designed and is being conducted by Saitama Medical Center, Jichi Medical University, and the present protocol follows the recommendations outlined in the Standard Protocol Items: Recommendations for Interventional Trials guidelines for RCTs.

Eligibility criteria

Patients who receive elective gastrointestinal surgery in the Department of Surgery, Saitama Medical Center, Jichi Medical University, and who are able to understand the extent and nature of this trial are eligible for inclusion in this study.

Inclusion criteria

1. Scheduled to undergo elective surgery for oesophagus, stomach, duodenum, jejunum, ileum, colorectal, pancreas, liver or biliary tract with a class II (clean-contaminated) surgical wound (table 1).
2. Age>20 years old at the time that consent is obtained by non-blinded investigators.
3. Provided written informed consent (online supplemental file).

Table 1 Definition of the wound classes

Class I (clean)	An uninfected operation wound in which no inflammation is encountered and respiratory, alimentary and genitourinary tract is not entered.
Class II (clean-contaminated)	An operative wound in which the respiratory, alimentary and genitourinary tracts are entered under controlled conditions and without unusual contamination provided no evidence of infection or major break in technique is encountered.
Class III (contaminated)	A wound in which gross contamination/spillage and a break in sterile technique occurs, and incision in which acute, non-purulent inflammation is encountered.
Class IV (dirty-contaminated)	A wound that is already considered infected, such as old traumatic wounds with retained devitalised tissue or perforated viscera.

Exclusion criteria

1. Identification of bacterial infection in the surgical field or the use antibiotic therapy prior to the operation.
2. Presence of a contaminated abdominal cavity due to stoma, intestinal fistula or drainage tube.
3. Synchronous operation for more than two targeted organs.
4. Open wound management for prior operation.
5. Pregnancy.
6. Allergy to PVP-I.
7. Conditions that make the patient unsuitable for inclusion (eg, thyroid disease, renal disease, cardiac disease, etc) according to the judgement of non-blinded investigators.

Intervention

- Study group: IOWI with 40 mL of aqueous 10% PVP-I solution with washing using surgical cotton balls is performed for 1 min before skin suture after elective gastrointestinal surgery.
- Control group: IOWI with 100 mL of saline with washing using surgical cotton balls is performed for 1 min before skin suture after elective gastrointestinal surgery.

Treatment protocol

Before skin suture, IOWI is performed for 1 min with 40 mL of aqueous 10% povidone–iodine (POVIDONE–IODINE solution 10% 'MEIJI'; Meiji Seika Pharma Co, Ltd, Tokyo, Japan) in the study group, and the same procedure is performed with 100 mL of saline (Isotonic Sodium Chloride Solution 'Hikari'; Hikari Pharmaceutical Co, Ltd, Tokyo, Japan) in the control group. The performance of IOWI with washing using surgical cotton balls is associated with additional benefits in preventing bacterial wound contamination and helps clean blood and necrotic tissue from the wound. The medical costs of 100 mL of saline and 40 mL of aqueous 10% PVP-I solution are almost the same (approximately JPY 40).

In addition, the following measures are used to prevent SSI in our protocol:

1. Surgical skin antisepsis with aqueous 10% PVP-I solution is performed before skin incision.
2. Standard antibiotic prophylaxis is administered 30 min before making the skin incision with additional doses every 3 hours for patients with normal renal function.
3. The use of a wound protector is recommended.
4. Surgical gloves are changed before skin suture.
5. Antimicrobial sutures coated with triclosan (PDS Plus; Ethicon, Johnson & Johnson, Somerville, New Jersey, USA) are used, the abdominal fascia and peritoneum are closed with interrupted sutures, and interrupted subcutaneous sutures are used for skin closure.
6. Intraoperatively and postoperatively, a normal body temperature is maintained using warming devices and appropriate oxygenation.
7. Perioperative glycaemic control is implemented with a blood glucose target level of <200 mg/dL.

Recruitment of study participants

This trial was approved by our institutional review board on 11 April 2019 and is registered in the University Hospital Medical Information Network Clinical Trial Registry (part of the WHO International Clinical Trial Registry Platform) under the identification number UMIN-CTR000036889. Patient recruitment for this trial was started in June 2019, and approximately 540 participants have been registered as of January 2021. Recruitment is scheduled to continue until 950 participants are recruited. All participants who meet the criteria will receive a participant information sheet from investigators before giving their written informed consent.

Randomization

Participants are being registered, randomised and allocated by non-blinded investigators. Participants' data will be password protected and will only be accessible by investigators. All access to the secure separate database will be monitored and logged. Permuted-block randomisation with an allocation ratio of 1:1 and a block size of 2 is used. Gender, surgical organ (upper gastrointestine, small bowel, colorectum, hepatobiliary–pancreas and others), and surgical approach (laparotomy or laparoscopy) are designated as allocation adjustment factors.

Blinding

Patients will be blinded to their assigned group. However, the operating surgeons cannot be blinded, as there is a difference in colour between aqueous 10% PVP-I solution and saline. The assessors will be blinded, as they will not

Table 2 Schedule and data collection of this trial

	Study period					
	Enrollment	Allocation	Postallocation			Close-out
TIMEPOINT	**–1–2 days**	**Surgery**	**POD1**	**POD3**	**POD4-29**	**POD30**
ENROLLMENT	**X**					
Informed consent	X					
Inclusion and exclusion criteria	X					
Allocation		X				
INTERVENTIONS		**X**				
Intervention A (PVP-I)		X				
Intervention B (saline)		X				
ASSESSMENTS						
Demographic data	X					
Medical history	X					
Physical examination	X					
Blood sample*	X		X	X		
Type of operation		X				
Time of operation		X				
Wound classification		X				
Estimated blood loss		X				
Blood transfusion		X				
Stoma creation		X				
Documentation of SSI			X	X	X	X
Wound swab microbiology			X	X	X	X
Documentation of reoperation			X	X	X	X
Documentation of AE			X	X	X	X
Duration of hospital stay						X

*Includes white blood cell count, red blood cell count, haemoglobin, haematocrit, platelets, lymph cell count, total protein, albumin, bilirubin, AST, ALT, urea nitrogen, creatinine, Na, K, Cl, glucose.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cl, chloride; K, potassium; Na, sodium; POD, postoperative day; PVP-I, povidone–iodine; SSI, surgical site infection.

be in the operating room and cannot access the randomisation results. The data on SSIs and analyses will be entered by blinded investigators.

Trial visits

Non-blinded investigators who received ethics education and were approved by the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University will obtain informed consent for surgery and inclusion in the clinical trial after admission, 1–2 days before surgery. We will confirm and record each patient's medical history, allergies (including povidone–iodine) and physical examination results. After their written informed consent has been obtained, patients eligible for this trial will be randomised into two groups before surgery. The period of observation will be 30 days after surgery. Table 2 shows a summary of the schedule and the data collected for this trial.

Risks

No additional risks for study patients are anticipated. IOWI with aqueous 10% PVP-I solution is a manner of usage that is in line with the pharmaceutical affairs law and is generally performed and recommended by several guidelines as a measure to prevent SSI. Adverse effects may be expected in the improbable event of unknown hypersensitivity to PVP-I. The potential benefits of a reduced risk of SSI outweigh the negligible potential adverse effects of PVP-I. Each participant will receive informed consent about notification and follow-up of adverse events and will be provided with medical care for any potential harm stemming from their participation in the trial. The Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University agree that a data monitoring and safety committee is unnecessary.

Outcome measures

The non-blinded investigators will check the surgical wound and describe the medical records during hospitalisation. If an SSI is suspected based on the clinical findings, non-blinded investigators will collect microbiological cultures from wounds and record the treatment details and wound depth in the medical record. After discharge, participants will be referred to the outpatient department at approximately 30 days after surgery. Participants will be recommended to contact us and visit the outpatient department soon if they experience any symptoms suggesting an SSI. The non-blinded investigators will examine the patients in the same way as during hospitalisation. The blinded assessors will determine the presence or absence of an SSI according to the clinical findings and microbiological cultures. The primary outcome is the incidence of incisional SSI up to postoperative day 30. The secondary outcomes are the length of postoperative hospital stay, positive wound bacterial test rate, and bacterial strains.

Definitions

SSI is defined according to the standard criteria devised by the CDC (table 3). Incisional SSI includes superficial and deep incisional SSI that develops during the first 30 days after surgery. Superficial incisional SSI involves the skin or subcutaneous tissue at the site of the incision, and deep incisional SSI affects the more internal structures of the abdominal layer (such as the fascia or muscle).

Data collection

The investigators will obtain the participants' information from medical records and collect the information in a password-protected file in the hospital database. The participants' hospital identification will be anonymised. Patient characteristics, such as sex, age, body mass index, serum albumin level, comorbidities, American Society of Anesthesiologists-physical status classification and preoperative treatment, will be collected. In addition, surgical data, such as surgical procedures, operative time, estimated blood loss, wound classification, and length of postoperative hospital stay, will also be collected.

Data management

The study will be conducted according to good clinical practice standards and legal regulations. Prior to inclusion, patients will be informed that any patient-related data and materials will be appropriately pseudonymised and that these data may be used for analysis and publication purposes. All information required by the study protocol and collected during this trial will be entered in the electronic case report form (CRF; encrypted Excel database) by investigators. The progress of the trial will be updated on the web page of UMIN-CTR every 6 months, and the president of Jichi Medical University and the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University will monitor progress approximately every year.

All data will be collected by the investigators in an anonymous and encrypted database. The confidentiality of the participants will be maintained at all times. The investigator will maintain all study-related information, including medical records, CRFs, written informed consent documents and other pertinent data, for 5 years after trial termination. After the study, all individual participant data required during the trial will be available from the corresponding author in an anonymized fashion on reasonable request.

Sample size calculation

In a retrospective cohort of patients who underwent gastrointestinal surgery and IOWI with saline at our department in 2017, the incidence of SSI was 9.4%. In this trial, we hypothesise that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSI. The expected SSI rates of the study and control groups are 4.7% and 9.4%, respectively. With a two-sided alpha level of 0.05, it is estimated that a total of 930 patients will be needed in order for the trial to have 80% power to detect superiority in the reduction of the frequency of SSI. Twenty dropout cases are expected, so the total target number of cases is set at 950.

Patient and public involvement

Neither patients nor the public are involved in this trial.

Statistical analyses

All analyses will be performed after the termination of the main part of the trial, that is, after the last 30-day follow-up visit has taken place. The primary and secondary outcomes will be analysed in the modified intention-to-treat set, from which participants who do not undergo surgery or who withdraw their consent before the assessment of the primary endpoint will be excluded. The safety analysis will be performed on the safety set, which will consist of all participants randomised into the treatment group who received the actual treatment. Student's t-test or the Mann-Whitney U test will be used to compare continuous variables with a normal or non-normal distribution. The χ^2 test or Fisher's exact test will be used to compare categorical variables between the study group and control group.

P values of <0.05 are considered to indicate statistical significance. All statistical analyses will be conducted using EZR.[30]

Ethics and dissemination

This trial was approved by the Bioethics Committee for Clinical Research, Saitama Medical Center, Jichi Medical University (S18-138), and the trial protocol was registered in the UMIN-CTR. Participant recruitment was started in June 2019. The final results will be reported in international peer-reviewed journals immediately after the trial is completed.

DISCUSSION

Recent meta-analyses have suggested that IOWI with aqueous PVP-I solution has a benefit for SSI

Table 3 Definition of SSI

Superficial incisional SSI	Date of event occurs within 30 days after any NHSN operative procedure (where day 1=the procedure date) **AND** involves only skin and subcutaneous tissue of the incision **AND** patient has at least one of the following: 1. Purulent drainage from the superficial incision. 2. Organism(s) identified from an aseptically obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture-based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (eg, not Active Surveillance Culture/Testing (ASC/AST)). 3. Superficial incision that is deliberately opened by a surgeon, physician* or physician designee and culture or non-culture-based testing of the superficial incision or subcutaneous tissue is not performed **AND** patient has at least one of the following signs or symptoms: localised pain or tenderness; localised swelling; erythema; or heat. 4. Diagnosis of a superficial incisional SSI by a physician* or physician designee. * The term physician for the purpose of application of the NHSN SSI criteria may be interpreted to mean a surgeon, infectious disease physician, emergency physician, other physician on the case or physician's designee (nurse practitioner or physician's assistant).
Deep incisional SSI	The date of event occurs within 30 or 90 days after the NHSN operative procedure (where day 1=the procedure date) **AND** involves deep soft tissues of the incision (eg, fascial and muscle layers) **AND** patient has at least one of the following: 1. Purulent drainage from the deep incision. 2. A deep incision that spontaneously dehisces, or is deliberately opened or aspirated by a surgeon, physician* or physician designee. **AND** organism(s) identified from the deep soft tissues of the incision by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST)) or culture or non-culture-based microbiologic testing method is not performed. A culture or non-culture based test from the deep soft tissues of the incision that has a negative finding does not meet this criterion. **AND** patient has at least one of the following signs or symptoms: fever (>38°C); localised pain or tenderness. 3. An abscess or other evidence of infection involving the deep incision that is detected on gross anatomical or histopathologic exam, or imaging test. * The term physician for the purpose of application of the NHSN SSI criteria may be interpreted to mean a surgeon, infectious disease physician, emergency physician, other physician on the case, or physician's designee (nurse practitioner or physician's assistant).
Organ/space SSI	Date of event occurs within 30 or 90 days after the NHSN operative procedure (where day 1=the procedure date) **AND** involves any part of the body deeper than the fascial/muscle layers that is opened or manipulated during the operative procedure **AND** patient has at least one of the following: 1. Purulent drainage from a drain that is placed into the organ/space (for example, closed suction drainage system, open drain, T-tube drain, CTguided drainage). 2. Organism(s) identified from fluid or tissue in the organ/space by a culture or non-culture-based microbiologic. testing method which is performed for purposes of clinical diagnosis or treatment (for example, not Active Surveillance Culture/Testing (ASC/AST)) 3. An abscess or other evidence of infection involving the organ/space that is detected on gross anatomical or histopathologic exam, or imaging test evidence suggestive of infection.

SSI, surgical site infection.

prevention,[26–28] and the clinical practice guidelines of the CDC[20] and WHO[21] weakly recommend IOWI with aqueous PVP-I for SSI prevention. However, previous clinical trials evaluating the efficacy of aqueous PVP-I solution for SSI prevention were largely conducted in the 1970s and 1980s[26–28], and since then, many control measures for preventing SSIs other than IOWI have been developed.[20–22] Nowadays, preoperative surgical skin antisepsis, the administration of standard antibiotic prophylaxis, maintaining a normal body temperature, proper oxygenation during surgery, perioperative serum blood sugar control and other measures are strongly recommended for SSI prevention in many clinical guidelines.[20–22] With the development of surgical technology, surgical procedures have progressed from open surgery to laparoscopic surgery since the 1990s, and many clinical studies have shown that laparoscopic surgery is associated with a significantly lower incidence of SSI than open surgery in many types of gastrointestinal surgery.[31–33] Thus, it may be difficult to directly introduce clinical guidelines related to IOWI with aqueous PVP-I for SSI prevention into current surgical practice based on evidence obtained from studies from the 1970s and 80s.

High-quality studies adhere to methodological principles to minimise errors in surgical trials, including adequate randomisation, concealment of allocation, blinding, performance of an intention-to treat analysis, complete follow-up, reliable accurate outcome measures and a priori sample size calculation.[34] The present trial is designed according to these principles. RCTs in single centres tend to include more homogeneous populations (highly selected) and follow outcomes more completely than multicentre RCTs.[35] Our inclusion and exclusion criteria for participants aim to select homogenous patients with clean-contaminated wounds. SSIs are diagnosed according to the definition of the CDC guidelines.[20] A recent meta-analysis showed that IOWI with aqueous 10% PVP-I solution was associated with a 59% reduction in the incidence of SSI in patients undergoing elective surgical procedures.[28] Thus, in the present trial, we hypothesise that IOWI with aqueous 10% PVP-I solution will achieve a 50% reduction in the incidence of SSI and calculated the target number of cases for such an outcome. In addition, the number of expected dropout cases was able to be predicted based on a previous large RCT for SSI prevention that was conducted by our department.[36] Thus, we are confident that the total target number of cases is accurate. As mentioned above, we use multiple perioperative measures for SSI prevention, according to the clinical guidelines.[20–22] The ratio of participants undergoing open surgery or laparoscopic surgery reflects the surgical practice at present. Thus, our RCT using homogenous patient recruitment, a standardised definition of SSI, precise sample size calculation and current measures other than IOWI will clearly establish evidence to support the efficacy of IOWI with aqueous 10% PVP-I solution in preventing SSI in current surgical practice.

IOWI with aqueous 10% PVP-I solution is generally performed and recommended by several guidelines as a measure to prevent SSI.[20 21] In the past, there has been concern about the potential negative effects of PVP-I on tissue regeneration and serum iodine toxicity; however, these adverse effects were not substantiated in clinical trials of IOWI with aqueous 10% PVP-I solution.[26–28] Furthermore, no serious harm was reported in a large meta-analysis, even when PVP-I was used for other internal tissues (eg, irrigation of the intraperitoneal cavity, pericardial cavity or bladder).[29 37 38] In previous RCTs, IOWI with aqueous PVP-I solution showed no dose–response effect in reducing the incidence of SSI, and the concentration of aqueous PVP-I solution most frequently used for IOWI was 10%. Aqueous 10% PVP-I solution is easy to access in a ready-to-use fashion for preoperative surgical skin antisepsis in Japan. We will also use aqueous 10% PVP-I solution for surgical skin antisepsis before skin incision in this RCT, as chlorhexidine-alcohol at >2%, which is recommended by international clinical guidelines,[20–22] is not commercially available in Japan. In the cohort prior to this RCT in our department, the standard duration of IOWI with saline was approximately 1 min. PVP-I can induce antimicrobial activity within 30 s after application,[38] and the duration of IOWI with aqueous PVP-I solution most frequently used in previous RCTs was 1 min.[27–29] Therefore, in the present study, the duration of IOWI has been set to 1 min for both groups.

SSI is associated with increased medical costs and imposes a huge burden on healthcare systems worldwide.[12–19] When designing measures for SSI prevention, significant attention should be paid to its medical cost. A recent meta-analysis revealed that the introduction of absorbable antimicrobial sutures reduced the risk of SSI, and the mean savings per surgical procedure from using antimicrobial sutures was found to be significant across all wound types.[39] In the present RCT, 40 mL of aqueous 10% PVP-I solution is being used for IOWI in the study group, and 100 mL of saline is being used for IOWI in the control group; the costs of IOWI in the two groups are almost the same. Because IOWI with aqueous PVP-I solution showed no dose–response effect,[27] we will set the volume of aqueous 10% PVP-I solution used for IOWI at 40 mL (approximately JPY 40), which is in line with the price of 100 mL of saline (approximately JPY 40). There is novelty in our trial setting in that the cost of IOWI for SSI prevention is being carefully considered. If this trial reveals that IOWI with aqueous 10% PVP-I solution is more useful for SSI prevention than saline, the result will also be supported from a medical cost perspective.

Several limitations associated with the present study warrant mention. First, all patients undergoing gastrointestinal surgery, irrespective of the organ, diagnosis or procedure, which are all associated with differing incidences of SSI, are being considered for inclusion. Second, this trial is being conducted at a single centre, and RCTs at single centres typically show larger treatment effects than multicentre RCTs.[35] Well-designed multicentre RCTs will

be necessary to generalise and substantiate the findings of this trial. Third, the evidence level is low. A meta-analysis suggested that IOWI with antibiotic solutions seems to be more effective than that with aqueous PVP-I solution.[26] Should the present study reveal that IOWI with aqueous 10% PVP-I solution is effective for SSI prevention, it might be worth planning an RCT to compare IOWI with aqueous 10% PVP-I solution to that with antibiotic solutions in patients with clean-contaminated wounds after gastrointestinal surgery.

The results of the present RCT will provide high-level evidence regarding the effectiveness of IOWI with aqueous 10% PVP-I solution for SSI prevention for clean-contaminated wounds after gastrointestinal surgery. Should this trial reveal the superior efficacy of IOWI with aqueous 10% PVP-I solution for SSI prevention compared with saline, the evidence will strongly support the clinical CDC and WHO guidelines for SSI prevention as well as current surgical practice. The implementation of multidisciplinary care for SSI prevention after gastrointestinal surgery has been increasingly shown to be effective since the 2010s, and IOWI with aqueous PVP-I solution is being increasingly frequently incorporated as an important component of multidisciplinary care.[40–42] Even if this trial produces negative results, our findings will contribute to the modification of future clinical guidelines in relation to IOWI for SSI prevention and support future RCTs exploring the development of effective IOWI methods.

Trial status

Recruitment is continuing steadily, and as of January 2021, 540 participants have been enrolled. The current protocol is in operation at V.1.4 (11 June 2020).

Contributors RM and HN contributed equally to this study. RM, HN, KI and ST made substantial contributions to conception and trial design. KI, RK, EM, NK, RS, HA, TF, NK, YM, MI, RF, FW, TK, MS, ST and YM were responsible for the protocol development. RM, HN and KI contributed the data management. RM and HN performed statistical analyses, and all authors interpreted the analytical results. RM and HN wrote the manuscript. HN and TR critically revised the manuscript. All authors made critical revisions and approved the final version of the manuscript.

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