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ORIGINAL ARTICLE

Randomized controlled trial of olanexidine gluconate and povidone iodine for surgical site infection after gastrointestinal surgery

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Abstract

Aim: Antiseptics used at surgical sites are vital to preventing surgical site infections (SSI). In this study, a comparative investigation of the novel antiseptics olanexidine gluconate (OG) and povidone-iodine (PI) was conducted to determine whether OG is more effective than PI against SSI after gastrointestinal surgery.

Methods: This prospective, randomized, single-blind, interventional, single-center study was conducted between August 2018 and February 2021. Patients scheduled for large-scale gastrointestinal surgeries were randomized into two groups and administered OG (OG group) or PI (PI group) as preoperative antiseptics. The primary endpoint was the SSI occurrence rate within 30 days after surgery.

Results: In total, 525 patients were enrolled in this study, of whom 256 and 254 were in the OG and PI groups, respectively. The total SSI occurrence rate in the OG group (10.8%; $n=26$) and the PI group (13.0%; $n=33$) was not significantly different ($p=0.335$). The occurrence rate of superficial incisional SSI and organ/space SSI did not significantly differ between the groups; however, that of deep incisional SSI showed a significant difference, with 0.4% ($n=1$) in the OG group and 4.3% ($n=11$) in the PI group ($p=0.003$).

Conclusion: OG, as a preoperative skin antiseptic, did not reduce the occurrence rate of total SSI. However, deep incisional SSI may be reduced using OG.

KEYWORDS
antiseptic, gastrointestinal surgery, olanexidine gluconate, povidone iodine, surgical site infection

1 | INTRODUCTION

Antiseptics used at surgical sites are vital for preventing surgical site infections (SSI). Notably, several studies have reported bacteria that exhibit resistance to antiseptics, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and *Pseudomonas aeruginosa*.[1–6] An antiseptic containing olanexidine gluconate (OG) (Olanedine Antiseptic Solution 1.5%®; Otsuka Pharmaceutical Factory, Inc.) has been developed as a novel antiseptic against these bacteria

and approved for clinical use in Japan; however, its effectiveness in reducing SSI remains unknown.

Olanedine Antiseptic Solution 1.5%® is a novel biguanide-based antiseptic containing OG as its active ingredient. It acquired marketing approval for skin disinfection at surgical sites (fields of operation) in Japan in July 2015. It is a sterile, transparent, or slightly yellow liquid containing 1.5% OG (1-(3,4-dichlorobenzyl)-5-octylbiguanide mono-D-gluconate, formula: $C_{17}H_{27}Cl_2N_5 \cdot C_6H_{12}O_7$) and suitable additives, including polyoxyethylene polyoxypropylene glycol, gluono-δ-lactone (as a pH adjuster), sodium hydroxide (as a pH adjuster), and purified water. It is a pharmaceutical product that acquired marketing approval for the first time in 50 years as a novel active ingredient-containing antiseptic, proven effective against antiseptic-resilient bacteria after a series of in vivo trials in bacteria-infected mouse skin.[7] Reportedly, OG exerts sterilizing effects by destroying bacterial cell walls and membranes and inducing protein denaturation in their intracellular components.[8] It exhibits slightly different effects from chlorhexidine gluconate (CG) and has been reported to have a higher sterilizing effect against MRSA and VRE than 0.5% CG or 10% povidone-iodine (PI).[7] Furthermore, the sterilizing effects of OG are unaffected by blood contamination.[9] Moreover, the fast-acting sterilizing effect of OG was comparable with that of alcohol-containing CG, and the duration of the sterilizing effects was longer in the former than in the latter.[10] OG has also been proven to be as safe as PI in phase III clinical trials.[11]

Another conventional antiseptic, PI Solution 10% MEIJI® (Meiji Seika Pharma Co., Ltd.), contains PI as the active ingredient. It is also widely used to disinfect surgical sites. PI is a complex of 1-vinyl-2-pyrrolidone polymer (polyvinylpyrrolidone) and iodine, commonly used as an antiseptic in an approximately 10% solution.

This study was conducted to determine whether the novel antiseptic Olanedine Antiseptic Solution 1.5%® is more effective than the conventional antiseptic PI Solution 10% MEIJI® against SSI through a comparative investigation at the clinical sites of gastrointestinal surgery.

2 | METHODS

2.1 | Trial design

This was a prospective, randomized, single-blind, interventional, single-center study. Patients who provided informed consent before the participant limit was reached were also enrolled in the trial after the limit was met. No significant changes were made to the trial methods during the study.

2.2 | Participants

The eligibility criteria were as follows: (1) patients scheduled for admission to Shiga University of Medical Science Hospital (SUMSH) to undergo surgery during the trial period; (2) those scheduled to undergo upper gastrointestinal tract surgery (excluding gastrostomy/enterostomy), lower gastrointestinal tract surgery (excluding colostomy/stoma closure), or hepatopancreatobiliary surgery (excluding laparoscopic cholecystectomy) under general anesthesia; (3) patients over 20 years of age (an upper age limit was not set); (4) patients were enrolled regardless of their sex; and (5) those who expressed their free will to participate in the trial by providing written informed consent.

The exclusion criteria were as follows: (1) a history of allergy, hypersensitivity, or severe complications due to the ingredients of the antiseptics used in the trial, confirmed through clinical records or interviews; and (2) severe dysthyroidism. Data were collected at SUMSH, Japan, between August 2018 and February 2021.

2.3 | Intervention

Approximately 4 weeks before surgery, background factors and biochemical blood test results were evaluated to confirm eligibility, and eligible patients were enrolled after obtaining written informed consent. The principal investigator or co-investigator allocated the antiseptic after the patients were admitted to the hospital. The surgeon was informed whether the assigned antiseptic was Olanedine Antiseptic Solution 1.5%® or PI solution 10% MEIJI®.

All surgeries were performed under general anesthesia in the operating room of the SUMSH. The surgeon applied the assigned antiseptic to the surgical site after administering general anesthesia, and the skin incision was commenced after the antiseptic had dried naturally. Esophageal surgery requires skin incisions at several locations; the same antiseptic was used everywhere. The surgeon and assistant determined the extent of disinfection, and an additional disinfectant was administered if required.

Third-generation cephalosporin antibiotics (ceftriaxone sodium) were administered as perioperative prophylactic antibiotics during pancreaticoduodenectomy, total pancreatectomy, and hepatectomy with biliary reconstruction. Second-generation cephalosporin antibiotics (cefmetazole sodium) were administered during lower gastrointestinal surgery and esophagectomy with ileocolic reconstruction. First-generation cephalosporin antibiotics (cefazolin sodium) were administered for all other types of surgery. Antimicrobial-coated sutures and the product used for wound irrigation were the same in every surgery type.

Fascia closure was performed via the interrupted suture technique using absorbable braided yarn (Vicryl plus®; ETHICON, Inc.). Skin closure was also performed via the interrupted suture technique in every patient using absorbable monofilament yarn (PDS plus®; ETHICON, Inc.). The wound was completely covered with dressing material (OPSITE Post-Op Visible®; Smith & Nephew Medical, Ltd.), which was removed on postoperative day (POD) 3.

2.4 | Outcome

The primary endpoint was the occurrence rate of all SSIs evaluated using the Centers for Disease Control and Prevention (CDC) guidelines.[12] All SSIs were defined as events occurring within 30 days after surgery. Superficial incisional SSI was defined as an infection involving only the skin and subcutaneous tissue of the incision; deep incisional SSI was defined as an infection involving the deep soft tissues (fascia and muscle layers) at the incision site; and organ/space SSI was defined as an infection involving any body part deeper than the fascial/muscle layers that were opened or manipulated during the operative procedure. If the bacterial culture results were negative, the presence or absence of SSI was determined by doctors based on signs of infection such as purulent discharge, localized pain or tenderness, localized swelling, localized redness, and localized heat. A differential diagnosis of superficial incisional SSI from fat necrosis after surgery was made on the basis of the following observations: purulent wound discharge, wound discharge containing bacteria on bacterial culture, and inflammatory signs around the wound. Organ/space SSI and complications associated with surgical techniques, such as gastrointestinal anastomosis leakage, bile leakage, pancreatic fistula, and postoperative hemorrhage, were distinguished based on the presence of inflammation and bacterial culture results. For example, even among patients with pancreatic leakage, those with negative bacterial cultures in fluid drainage and no evidence of inflammation were not considered to have organ/space SSI.

The secondary endpoints included the occurrence rates of superficial incisional SSIs, deep incisional SSIs, and organ/space SSIs; the bacterial culture results of the patients with SSIs; and the occurrence rate of adverse skin reactions, such as erythema, pruritus, and dermatitis.

Patient backgrounds were considered preoperative factors. Postoperative findings were examined for the duration of hospitalization, gastrointestinal anastomosis leakage, bile leakage, pancreatic fistula, and postoperative hemorrhage. Regarding changes in inflammatory markers, WBC and CRP levels on POD 7, 14, and 21 were investigated. No changes were made to the endpoints after the trial initiation.

The presence of cardiovascular disease was defined as a history of heart failure, myocardial infarction, or valvular disease. Cerebrovascular disease was defined as the presence of cerebral infarction or hemorrhage. Similarly, the presence of respiratory diseases was defined as a history of tuberculosis, asthma requiring oral or inhalant treatment, or emphysema. A psychiatric disorder was defined as the presence of psychiatric or neurological therapy for depression, schizophrenia, Alzheimer's disease, or Lewy body dementia. Surgical history was categorized as the presence or absence of abdominal surgery. Bile leakage was determined according to International Study Group for Liver Surgery criteria. Pancreatic fistula was confirmed using the International Study Group of Pancreatic Fistula criteria.[13,14] The doctors in charge determined the gastrointestinal anastomosis leakage and postoperative hemorrhage criteria.

2.5 | Sample size

The primary endpoint of SSI occurrence rate was 18.0% in previous patients at our hospital using PI and 9.0% in patients using OG as an antiseptic (unpublished work). We predicted the number of patients necessary for statistical validity (two-sided), assuming from these results that using OG as an antiseptic on surgical sites would reduce the SSI occurrence rate from 18.0% to 9.0%, with the α offset at 0.05 and a β offset at 0.2, yielding a power of 80%. A total of 248 patients were required in each study arm, for a total population of 496. Anticipating approximately 5% (12 patients) dropout rate, the number of patients in the study was set at 260 patients per group, making a total of 520 patients.

2.6 | Randomization

Written informed consent was obtained from all eligible patients. The principal investigator or co-investigator entered the relevant information based on the medical records into HOPE eACReSS (Fujitsu Limited), a web-based electronic data capture system, prior to the day before surgery. Patient assignment was performed one-to-one using the block randomization method with a block size of four. The assignment factors were age, sex, surgical procedure (upper gastrointestinal tract surgery, lower gastrointestinal tract surgery, and hepatobiliary pancreatic surgery), presence/absence of prolonged steroid use, and presence/absence of diabetes. The surgeon was notified of the results assigned by the system before surgery and performed disinfection according to the results.

2.7 | Blinding

The antiseptic assigned to each patient by randomization was not disclosed until the study was completed. Because of the color difference between the two antiseptics, the patients were blinded by completely removing the remaining antiseptic from the skin and using a dressing that obscured the wound.

The SSI assessment was performed by the doctor in charge of each patient and re-evaluated from each medical record by blinded doctors after the trial. In case of disparities in the assessments between the doctor-in-charge and the blinded doctor, consensus was reached through discussions among the doctors. In addition, blinded investigators performed the data entry for SSI diagnosis, and the data analyst was blinded.

2.8 | Statistical method

Patient age and body mass index (BMI) were presented as mean ± standard deviation. Other continuous variables are expressed as median values and quartile ranges. Among the primary and secondary endpoints, either Fisher's exact test or Pearson's

chi-squared test was used to compare nominal variables between groups, and the *t*-test or Mann–Whitney *U* test was used to compare continuous variables between groups. Interval estimation based on a binomial distribution was used to determine confidence intervals. In all statistical analyses, statistical significance was set at *p* values <0.05. All statistical analyses were performed using R statistical software version 4.0.2. (R Foundation for Statistical Computing, Vienna, Austria; https://cran.r-project.org/bin/macosx/). An interim analysis was not performed.

3 | RESULTS

Figure 1 shows the CONSORT diagram of the patients. Between August 2018 and February 2021, 594 patients met the eligibility criteria: 45 refused to participate in the study, 18 were excluded due to a history of allergic reactions to PI ingredients, and six patients were excluded due to severe thyropathy. The remaining 525 patients were randomly divided into OG and PI groups. Finally, 263 and 262 patients were assigned to the OG and PI groups, respectively. After the group assignment, some patients who requested withdrawal from the trial, those with a history of allergy to the PI ingredients, those who became inoperable, those who underwent unscheduled surgery, and those who died within 30 days postoperatively were excluded; the remaining patients in the OG and PI groups were analyzed (256 and 254, respectively) (Figure 1).

No significant differences were observed in patient background factors, such as age, sex, BMI, presence/absence of diabetes, hypertension, hyperlipidemia, hepatitis virus, cardiovascular diseases, cerebrovascular diseases, respiratory diseases, psychiatric disorders, and prolonged steroid use. However, a significant difference was observed in the presence/absence of past surgical history, with a surgical history rate of 51.2% in the OG group and 60.2% in the PI group ($p=0.041$). There were no significant differences in preoperative laboratory test findings (Table 1).

The total proportion of patients with SSI exhibited no significant difference: 10.2% (26 patients) in the OG group and 13.0% (33 patients) in the PI group ($p=0.335$). Among patients with SSI, those with superficial incisional SSI and organ/space SSI showed no significant differences between the groups. However, patients with deep incisional SSI showed a significant difference: 0.4% ($n=1$) in the OG group and 4.3% ($n=11$) in the PI group ($p=0.003$). Patients with gastrointestinal anastomosis leakage, bile leakage, pancreatic fistula, and postoperative hemorrhage, which are complications associated with surgical procedures and considered to strongly contribute to SSI, showed the same proportions in both groups. The proportion of superficial and deep incisional SSI in the OG group (2.3% [$n=6$]) was significantly smaller than that in the PI group (6.3% [$n=16$]; $p=0.03$). The frequency of adverse skin reactions to antiseptics, including erythema, pruritus, or dermatitis showed no significant differences between the groups. The postoperative hospitalization period did not differ significantly between the groups (Table 2).

Figure 2 shows the postoperative fluctuations in WBC and CRP levels in the OG and PI groups. The preoperative WBC levels were similar in both groups; however, the POD 7 result was $6.2\times10^3/\mu L$ in the OG group and $6.7\times10^3/\mu L$ in the PI group, showing a significantly lower value in the OG group ($p=0.041$). The CRP levels on POD 7 (OG, 2.51 mg/dL vs. PI, 3.06 mg/dL, $p=0.023$) and POD 14 (OG, 1.30 mg/dL vs. PI, 1.81 mg/dL, $p=0.02$) were also significantly lower in the OG group (Figure 2).

Subgroup analyses were conducted using factors considered to contribute to the total SSI incidence. Factors such as sex, presence/absence of obesity (BMI ≥ 25 kg/m^2), presence/absence of diabetes, presence/absence of surgical history, presence/absence of

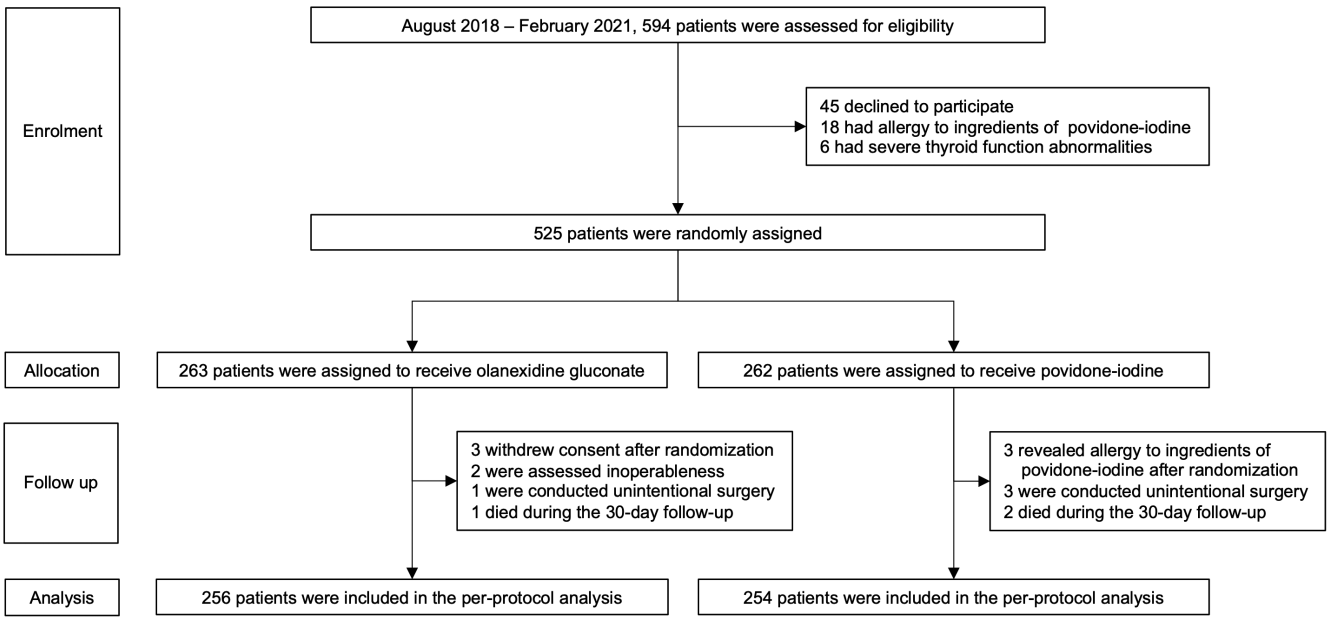


FIGURE 1 CONSORT diagram for the trial.

TABLE 1 Comparison of patients' background factors between OG group and PI group.

	OG group	PI group	
	n = 256	*n* = 254	*p*-value
Age	69.3 ± 11.5	68.6 ± 12.6	
Sex (%)			
Men	163 (63.7)	161 (63.4)	
Women	93 (36.3)	93 (36.6)	
BMI	22.6 ± 3.5	23.1 ± 4.8	
DM (%)	60 (23.4)	59 (23.2)	
Hypertension (%)	100 (39.1)	110 (43.3)	
Hyperlipidemia (%)	49 (19.1)	51 (20.1)	
HBV or HCV (%)	16 (6.2)	13 (5.1)	
Cardiovascular disease (%)	54 (21.1)	67 (26.4)	
Cerebrovascular disease (%)	12 (4.7)	11 (4.3)	
Respiratory disease (%)	52 (20.3)	49 (19.3)	
Psychiatric disorder (%)	7 (2.7)	10 (3.9)	
Steroid user (%)	10 (3.9)	8 (3.1)	
Surgical history (%)	131 (51.2)	153 (60.2)	0.041
Laparoscopic surgery (%)	192 (75.0)	173 (68.1)	
Surgical site (%)			
Upper gastrointestinal tract	70 (27.3)	71 (28.0)	
Lower gastrointestinal tract	81 (31.6)	76 (29.9)	
Hepatobiliary pancreatic	105 (41.0)	107 (42.1)	
Hb (g/dL)	12.8 [11.5, 13.8]	12.4 [10.9, 14.0]	
WBC (×1000)	5.4 [4.3, 6.5]	5.3 [4.4, 6.3]	
Lymphocyte	1365 [1069, 1724]	1390 [1080, 1810]	
PLT (×1000)	221 [171, 266]	219 [167, 264]	
ALB (g/dL)	3.9 [3.5, 4.2]	3.8 [3.6, 4.1]	
AST (IU/L)	22 [18, 29]	23 [18, 29]	
ALT (IU/L)	19 [14, 29]	19 [13, 27]	
T-BIL (mg/dL)	0.66 [0.50, 0.90]	0.67 [0.49, 0.94]	
BUN (mg/dL)	15.7 [12.3, 19.8]	15.9 [12.5, 18.8]	
CRE (mg/dL)	0.78 [0.65, 0.93]	0.79 [0.67, 0.94]	
PT-INR	0.97 [0.92, 1.03]	0.97 [0.93, 1.04]	
CRP (mg/dL)	0.11 [0.06, 0.36]	0.13 [0.06, 0.31]	
Operative time (min)	288 [220, 377]	294 [231, 389]	
Blood loss (mL)	70 [0, 250]	100 [0, 393]	

Note: Age and BMI are expressed as mean ± standard deviation. Other data are expressed as median with 25th and 75th percentiles.

Abbreviations: ALB, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CRE, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; HBV, hepatitis B virus; HCV, hepatitis C virus; Hb, hemoglobin; OG, olanexidine gluconate; PI, povidone-iodine; PLT, platelet count; PT-INR, prothrombin time-international normalized ratio; T-BIL, total bilirubin; WBC, white blood cell count.

laparoscopic surgery, long operative time (operative time ≥ 300 min), and surgery sites (upper gastrointestinal tract surgery, lower gastrointestinal tract surgery, and hepatobiliary pancreatic surgery) were investigated. The analysis results did not indicate any significant difference; however, all subgroups, except patients with diabetes, exhibited a higher SSI frequency in the PI group. The patients, particularly those with obesity, that is, BMI ≥ 25 (risk ratio, 2.54), and those with lower gastrointestinal tract surgery (risk ratio, 2.26), exhibited a higher tendency of SSI occurrence in the PI group (Figure 3).

In this study, six of the 26 SSI cases in the OG group had no bacterial culture tests, and two had no bacteria detected in the bacterial culture tests. The remaining 18 bacterial cultures included four

TABLE 2 Results of SSI, Non-STR-SSI, complications related to surgical techniques, or adverse skin reactions compared between OG group and PI group.

	OG group	PI group	
	n = 256	*n* = 254	*p*-value
SSI total (%)	26 (10.2)	33 (13.0)	0.335
Superficial incisional (%)	5 (2.0)	5 (2.0)	>0.999
Deep incisional (%)	1 (0.4)	11 (4.3)	0.003
Organ/space (%)	22 (8.6)	30 (11.8)	0.245
Superficial + deep incisional (%)	6 (2.3)	16 (6.3)	0.03
Complications related to surgical techniques			
Leakage of gastrointestinal anastomosis (%)	8 (3.1)	8 (3.1)	>0.999
Bile leakage (%)	7 (2.7)	5 (2.0)	0.772
Pancreatic fistula (%)	10 (3.9)	17 (6.7)	0.172
Postoperative hemorrhage (%)	4 (1.6)	5 (2.0)	0.751
Adverse skin reaction	4 (1.6)	2 (0.8)	0.373
Erythema	3 (1.2)	1 (0.4)	0.623
Pruritus	1 (0.4)	1 (0.4)	>0.999
Dermatitis	0	0	>0.999
Postoperative hospitalization (days)	12 [9, 17]	12 [9, 20]	0.272

Note: Postoperative hospitalization is expressed as median with 25th and 75th percentiles.

Abbreviations: Non-STR-SSI, non-surgical technique related to surgical site infection; OG, olanexidine gluconate; PI, povidone-iodine; SSI, surgical site infection.

cases of *Enterobacter cloacae*, three of *Staphylococcus epidermidis*, two of *Enterococcus faecium*, two of *Klebsiella pneumoniae*, two of Methicillin-resistant *S. aureus* (MRSA), two of *Candida albicans*, one of *Escherichia coli*, one of *Klebsiella oxytoca*, one of *P. aeruginosa*, and one of *Streptococcus anginosus*. Of the 33 SSI cases in the PI group, seven had no bacterial culture tests, and two had no bacteria detected in the bacterial culture tests. The remaining 24 bacterial cultures included six cases of *E. cloacae*, four of Methicillin-susceptible *S. aureus* (MSSA), three of MRSA, three of *Enterococcus faecalis*, two of *Candida glabrata*, two of *E. coli*, one of *Acinetobacter baumannii*, one of *C. albicans*, one of *K. oxytoca*, and one of *P. aeruginosa*.

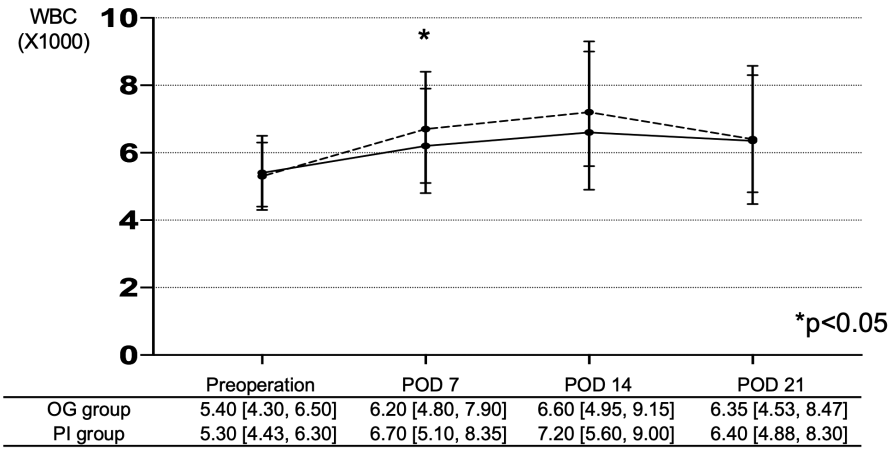
4 | DISCUSSION

The results of this study demonstrate that the use of OG as an antiseptic at gastrointestinal surgery sites did not reduce the occurrence rate of all SSI incidents to a greater extent than the use of PI. However, it could reduce the occurrence rate of deep-incisional SSI. The CDC guidelines define deep incisional SSI as an incident in which the superficial incisional SSI is aggravated to involve the fascia. Therefore, deep and superficial incisional SSI do not coexist at the same incision site. When the total SSI incidents of deep and superficial incisional SSI were defined as overall incisional SSI, a significantly lower occurrence rate was noted in the OG group (OG, 2.3% vs. PI, 6.3%, $p = 0.03$). The occurrence rate of organ/space SSI was similar in both groups, showing that OG can successfully reduce the occurrence rate at incised sites. These antiseptics are applied to incised sites and have no effect on the intra-abdominal cavity where organ/space SSI occur, suggesting their effects at the incised sites, which is a logical outcome. We also discuss the mechanism from the viewpoint of causative bacteria. In this study, the bacterial culture results of the superficial and deep incisional SSI cases in the PI group were as follows: five cases of *E. cloacae*, two cases of MSSA, one case of MRSA, one case of *E. coli*, and one case of *Enterococcus faecalis*. Five cases had no bacterial culture tests, and one case had no bacteria detected in the bacterial culture tests. In contrast, the bacterial culture results of the superficial and deep incisional SSI cases in the OG group were as follows: one case of *E. cloacae* and one case of *P. aeruginosa*. Four patients had no bacterial culture results. Among the superficial and deep incisional SSI cases, MSSA, MRSA, and bacteria from the skin flora were not detected in the OG group. From these results, the reason why the overall incisional SSI decreased in the OG group might be that OG has a greater effect on the skin flora, including MRSA, than PI.

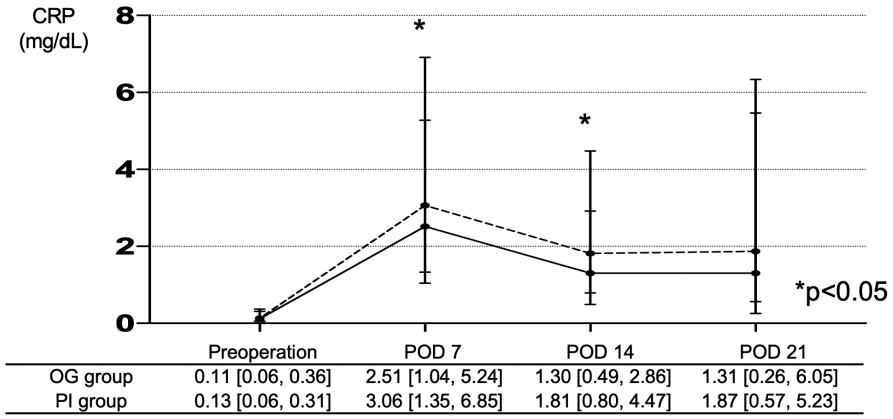
Prevention of SSI incidents is essential because these incidents extend the hospitalization period and incur expensive treatment costs.[15,16] Antiseptics, such as PI and CG, have been conventionally used for disinfection at surgical sites. Several randomized controlled trials (RCTs) have been conducted using these antiseptics. Darouiche et al. reported that alcohol-containing CG significantly reduced SSI incidents to a greater extent than PI.[17] However, that study included patients who underwent gastrointestinal surgery as well as those who underwent thoracic, gynecologic, or urologic surgery. A similar investigation including only gastrointestinal surgery patients was conducted by Srinivas et al. and Park et al.; however, neither study included patients with lower gastrointestinal tract surgery, and their results did not indicate any significant difference in the SSI occurrence rate between CG and PI.[18,19] Another study on inguinal hernia surgery, which is classified as a clean wound in the wound classification for gastrointestinal surgery, did not indicate any significant difference between the use of PI and CG.[20]

The Japanese SSI prevention guidelines published in 2018 suggested that CG may be effective in preventing SSI incidents in gastrointestinal surgery. This suggestion was made based on meta-analyses including several RCTs. However, because the concentration of CG differed in the studies included in the meta-analysis and because CG contains alcohol, which is inflammable, PI is still frequently used in Japan.

The effects of OG and PI on SSI in gastrointestinal surgery have been proven in a multicenter RCT initiated during the same period as this study.[21] The results indicated a total SSI occurrence rate of 7.0% in the OG group and 13.0% in the PI group ($p = 0.002$). This



	Preoperation	POD 7	POD 14	POD 21
OG group	5.40 [4.30, 6.50]	6.20 [4.80, 7.90]	6.60 [4.95, 9.15]	6.35 [4.53, 8.47]
PI group	5.30 [4.43, 6.30]	6.70 [5.10, 8.35]	7.20 [5.60, 9.00]	6.40 [4.88, 8.30]



	Preoperation	POD 7	POD 14	POD 21
OG group	0.11 [0.06, 0.36]	2.51 [1.04, 5.24]	1.30 [0.49, 2.86]	1.31 [0.26, 6.05]
PI group	0.13 [0.06, 0.31]	3.06 [1.35, 6.85]	1.81 [0.80, 4.47]	1.87 [0.57, 5.23]

FIGURE 2 Postoperative fluctuations in the WBC and CRP levels in the OG and PI groups. The preoperative WBC and CRP levels exhibited similar values in both groups; however, POD 7 indicated lower values of WBC ($p=0.041$) and CRP levels ($p=0.023$) in the OG group. Moreover, the CRP level was lower in the OG group on POD 14 ($p=0.02$). They returned to the same levels on POD 21. CRP, C-reactive protein; OG, olanexidine gluconate; PI, povidone iodine; POD, postoperative day; WBC, white blood cell.

study's results demonstrated the same result as a previous report of 13.0% in the PI group; however, that in the OG group was 10.0%, without showing any significant difference. The occurrence rates of organ/space SSI and deep incisional SSI did not significantly differ in the previous report; however, the superficial incisional SSI incidence rate was significantly different. Conversely, this study showed a significant difference in the occurrence rates of deep incisional SSI and no significant difference in the occurrence rates of organ/space and superficial incisional SSI. Both studies reported similar organ/space SSI occurrence rates in the OG and PI groups. It is challenging to precisely distinguish between superficial incisional SSI and deep incisional SSI; therefore, the overall incisional SSI occurrence rate, combining the incidence of superficial and deep incisional SSIs, was significantly reduced in both studies using OG. The results of bacterial cultures in the initial study showed a positivity rate of 6.0% in the OG group and 11.0% in the PI group. In comparison, the study's results were 7.0% in the OG group and 9.8% in the PI group, indicating similar positive rates of bacterial culture to the initial study. *E. cloacae* was the dominant bacterium in both groups, as reported in a previous study.

One of the differences between the present and previous studies was that among gastrointestinal surgeries, laparoscopic cholecystectomy, a minor surgery, was excluded in this study since the SSI occurrence rate in laparoscopic cholecystectomy is low.[22–24] Another difference is that surgeries such as gastrostomy, enterostomy, colostomy, and stoma closure were excluded to exclusively investigate patients who underwent relatively highly invasive surgery involving gastrointestinal tract resection/reconstruction, hepatectomy, pancreatectomy, and choledochectomy. This study suggests that the effects of antiseptics may be reduced in highly invasive surgeries with long operation times. However, because the previous study did not describe the operative time, a comparison with this is impossible, and there is no clear evidence for the above.

Antiseptic-induced skin disorders are important adverse events. One retrospective study reported that the OG group exhibited significantly more skin erythema or eruption incidents than the PI group.[25] However, the previous and present RCTs reported a similar rate of skin disorders in the OG and PI groups.

The series of subgroup analyses conducted was prompted by factors considered to be related to SSI occurrence, such as sex, BMI, presence/absence of diabetes, presence/absence of surgical history, operation time, and surgical sites.[26–29] No significant differences were observed; however, it was suggested that using OG should reduce the SSI occurrence rate in patients with a high BMI of 25 kg/m^2 and undergoing lower gastrointestinal tract surgery.

The results of this study suggest that OG may suppress overall incisional SSIs. Due to the nature of the antiseptic solution, it is not expected to be effective for organ/space SSI. When organ/space SSI occurs, albumin levels decrease because of systemic inflammation if drainage is ineffective. Therefore, organ or space SSI may cause

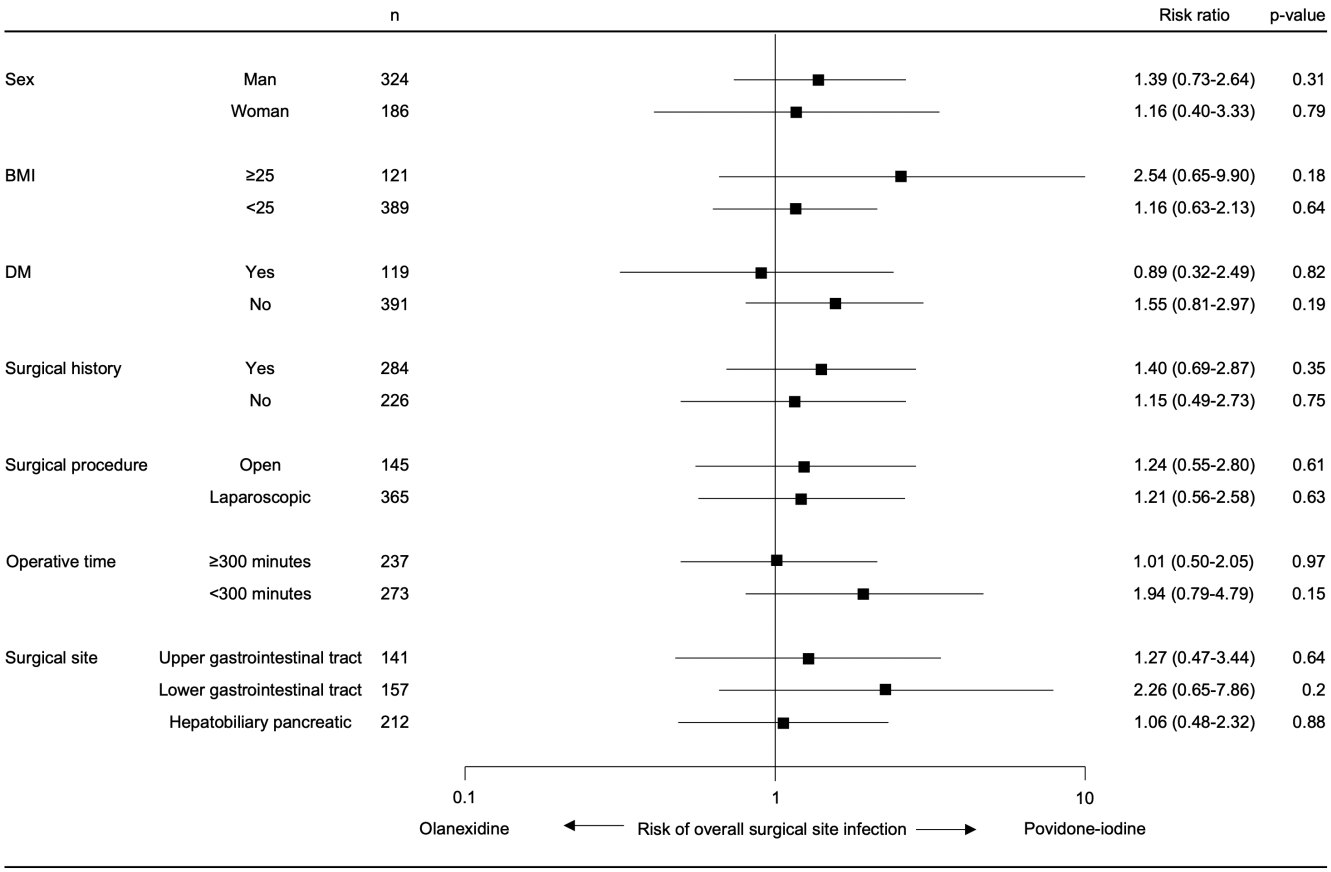


FIGURE 3 Sub-group analysis using factors considered to contribute to postoperative SSI. A series of sub-group analyses were conducted using factors of sex, presence/absence of obesity (BMI ≥ 25 kg/m^2), presence/absence of diabetes, presence/absence of surgical history, presence/absence of laparoscopic surgery, long operation time (operation time ≥ 300 min), and surgical sites (upper gastrointestinal tract surgery, lower gastrointestinal tract surgery, and hepato-pancreato-biliary surgery). The PI group exhibited higher SSI frequencies except for the sub-group with diabetes, especially in cases of obesity, that is, with BMI ≥ 25 (risk ratio, 2.54), and those of lower gastrointestinal tract surgery (risk ratio, 2.26). BMI, body mass index; DM, diabetes mellitus; SSI, surgical site infection.

anastomotic failure. Therefore, it is vital to identify intervention methods to suppress organ/space SSI.

The limitations of this study are that it was conducted at a single facility and included only Japanese patients. Inclusion of patients undergoing different surgeries, including esophagectomies, gastrectomies, hepatectomies, pancreatectomies, and colectomies, is another limitation. Both blinded and unblinded doctors conducted the SSI assessments. When these doctors' diagnoses differed, the assessment of unblinded doctors was often adopted because blinded doctors diagnosed SSI based on the patients' medical records. Regarding the presence or absence of skin reactions as an adverse incident, it is difficult to establish the difference between an allergic reaction to perioperative prophylactic antibiotics and the effects of skin disinfection at surgical sites. We did not examine the frequency of SSI in asymptomatic MRSA carriers because we did not perform a preoperative screening test for MRSA using nasal bacterial cultures. In this study, five factors were used for randomization: age, sex, surgical procedure (upper and lower gastrointestinal tract surgeries and hepatobiliary pancreatic surgery), presence/absence of prolonged steroid use, and presence/absence of diabetes. Only the presence/absence of a surgical history demonstrated a significant difference among the patients' background factors. If the number of assignment factors had increased, the number of cases per stratification would have decreased, and the number of cases between the groups might have become uneven. Therefore, surgical history was not used as a randomization factor. The present study is the second comparative investigation on the effects of OG and PI against SSI, globally. However, the trial was initiated during the same period as the initial study, and the study was novel at the time of trial initiation.

In conclusion, using OG as a preoperative skin disinfectant during gastrointestinal surgery did not reduce the total SSI occurrence rate. However, the results suggest that the deep incisional SSI occurrence rate may be reduced by using OG.

AUTHOR CONTRIBUTIONS

HI designed the research and analyzed the patient data. HI, HM, SK, KT, TM, and MT performed data collection. HI drafted the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

DATA AVAILABILITY STATEMENT

The protocol or datasets used during the current study are obtainable from the corresponding author upon reasonable request.

ETHICS STATEMENT

Approval of the research protocol: This randomized controlled trial conformed to the clinical research guidelines and was approved by the ethical committee of SUMSH (approval number: S2019-027). This trial was also registered with UMIN-CTR (identification number: UMIN000032108).

Informed consent: Written informed consent was obtained from all patients.

Registry and registration number: N/A.

Animal studies: N/A.

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