

Clinical Study of the Novel Antiseptic Olanexidine Gluconate in Gastrointestinal Cancer Surgery

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Abstract

Background

Surgical site infection (SSI) is a common complication of digestive surgery .Olanexidine gluconate (OLG) is a novel developed skin antiseptic and effective against a wide range of bacteria. The purpose of this study is to evaluate the bactericidal efficacy of OLG in gastrointestinal cancer surgery.

Methods

This retrospective study included a total of 281patients who underwent gastrointestinal cancer surgery (stomach or colon). There were two group: 223 patients were treated with OLG (OLG group), and 58 patients were treated with povidone-iodine (PVP-I) (control group). The efficacy and the safety outcomes were measured as the rate of surgical SSI within 30 days after surgery. In addition, we also conducted subgroups defined according to the surgical approach (open or laparoscopic) or primary lesion (stomach or colon).

Results

There was a significant difference in the rate of SSI between the control group and OLG group (10.3% vs. 2.7% ; p = 0.02). There was a significant difference in the SSI rate in superficial infection (8.6% vs. 2.2% ; p = 0.0345) but not in deep infection (1.7% vs. 0.5% ; p = 0.371). There was no significant difference between the control group and OLG group in the overall rate of adverse skin reaction (5.2% vs. 1.8% ; p = 0.157).

Conclusion

This retrospective study demonstrates that OLG is more effective than PVP-I for preventing SSI during gastrointestinal cancer surgery.

Background

Surgical site infection (SSI) is a postoperative complication of gastrointestinal cancer surgery that causes pain and psychological stress in patients, prolongs the hospital stay and increases medical costs. A high infection rate of 11.3–15.5 % has been reported after gastrectomy or colorectal surgery [1]. Several initiatives are aimed at reducing the risk of SSIs [2–4].

The skin is a major source of pathogens that cause SSIs. Therefore, preoperative skin antisepsis has the potential to decrease the risk of SSI [5]. Antiseptics prevent infection by decreasing the number of microorganisms, thereby decreasing the transmission of pathogens. Currently, povidone-iodine (PVP-I)

and chlorhexidine gluconate (CHG) are widely used to disinfect surgical sites [6–9]. However, PVP-I may not function well in the presence of organic materials, such as blood or pus, which can rapidly neutralize its bactericidal activity [10], and CHG also does not have sufficient activity to eradicate some pathogens, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) [11].

Olanexidine gluconate (OLG), a novel biguanide antiseptic agent, was introduced in 2015 in Japan for use as a skin disinfectant for surgical sites [12]. OLG exerts strong and fast-acting bactericidal activity against a wide range bacteria [10]. In both in vitro and in vivo models, the efficacy against MRSA and VRE was higher for OLG than CHG and PVP-I [13], and OLG has a broad spectrum of antibacterial activity against bacterial strains, including clinical isolates [10]. At present, few reports have explored whether OLG reduces the risk of SSIs after surgery. We retrospectively studied the efficacy of OLG in the surgical treatment of gastrointestinal cancer.

Materials And Methods

Study group

While PVP-I (Meiji Seika Pharma Co., Ltd., Tokyo, Japan) was previously used to disinfect surgical sites at our institution, OLG (Otuka Pharmaceutical Factory, In, Tokushima, Japan) was adopted for use in April 2016. Preoperative antiseptic use was completely changed from PVP-I to OLG at that time. Patients were assigned to preoperative skin antisepsis with OLG or PVP-I to evaluate the comparative effectiveness of the two preoperative skin preparations for the prevention of SSIs gastrointestinal cancer surgery. The medical records of patients who underwent surgery for primary colorectal cancer between April 2015 and May 2020 were retrospectively reviewed. Other than disinfection the methods were the same between the groups.

A total of 298 patients diagnosed with primary gastric or colon cancer underwent gastrectomy or colectomy combined with lymphadenectomy. The exclusion criteria were emergency operations, involvement of other organs, reoperation within 30 days of the first surgery and major complications. Seventeen patients were excluded, and 281 patients were prospectively evaluated. Among the patients who met the inclusion criteria between April 2015 and May 2020, 58 patients who underwent conventional skin disinfection with PVP-I and 223 patients who underwent conventional skin disinfection with OLG were divided into two groups (control group or OLG group). The ins PVP-I was applied by wiping down the skin surface with gauze soaked with the drug, and OLG was applied using a sterile pre-packed applicator. All patients received antibiotic prophylaxis during and after surgery and mechanical bowel preparation, but not preoperative oral antibiotics. All patients were treated using a wound protector (Alexis wound protector, Applied Medical, Rancho Santa Margarita, CA, USA) during the operation.

We investigated the correlations between preoperative skin disinfection and the incidence of SSI, and estimated the risk factors for SSI.

Trial Outcome

The efficacy outcome was superficial or deep surgical-site infection within 30 days after the operation, according to the National Healthcare Safety Network definitions of the Centers for Disease Control and Prevention (CDC) [5]. All patients were checked daily for signs of infection. Skin or subcutaneous and deep tissue infections in purulent drainage, cultured organisms, procedural intervention due to pain, swelling, erythema, fever, or diagnosis made by the surgeon were generally considered as SSI. The safety outcome was defined as the rate of adverse skin reactions, such as skin irritation, erythema or pruritus, in the area of application of the disinfectant. We reviewed the patient records and collected data on patient sex, age, body mass index (BMI), operation time, amount of bleeding during the operation, comorbidities, approach (open or laparoscopy), site, tumor size, stage, postoperative complications, and postoperative length of hospital stay [14]. We conducted a subgroup analysis of the primary outcome in subgroups defined according to the surgical approach (laparotomy or laparoscopic) and the primary lesion (stomach or colon). This retrospective study was designed and independently done with approval from the ethics committee of Nagano Prefectural Shinshu Medical Center in accordance of the principles of the Declaration of Helsinki.

Statistical analysis

Statistical analyses were conducted using EZR (Saitama Medical Center, Jichi Medical University), which is a graphical user interface for R (The R Foundation for Statistical Computing, version 3.4.1). Correlations among patient characteristics, the antiseptics and SSI were evaluated using the chi-square test and Student's t test. Factors that predicted SSI development were estimated using multivariate analysis. Two-sided P values lower than 0.05 were considered to indicate statistical significance.

Results

Patient background

The characteristics of the patients and preoperative skin antisepsis are shown in Table 1. There were no significant differences in baseline patient characteristics between the two groups with regard to age, sex, BMI, diabetes mellitus, preoperative albumin level, respiratory disease, anticoagulant, primary lesion (stomach or colon), ASA, operation time, perioperative blood loss, transfusion, stage, leakage, complications other than SSI, or adverse skin reaction (Table 1). However, there were significant differences between the control and OLG groups for approach (laparotomy/laparoscopic: 42/16 vs. 91/117, p = 0.000171) and postoperative length of hospital stay (15.8 vs. 20.0 days, p = 0.0136).

Table 1
Patient and operative characteristics

Patient characteristics	OLG group (n = 223)	control group (n = 58)	P value
Mean age(range)	73.1 ± 10.7	73.9 ± 10.2	0.853
Gender			0.455
M	133 (59.6%)	31 (53.4%)	
F	90(40.4%)	27 (46.6%)	
Mean BMI ± SD	22.1 ± 3.5	22.4 ± 3.7	0.6
Diabetes mellitus (%)	66 (29.6%)	19 (32.8%)	0.634
Alb	3.89 ± 0.52	3.86 ± 0.57	0.752
Respiratory disease	39 (17.5%)	8 (13.8%)	0.56
Anticoagulant	41 (16.7%)	10 (17.2%)	1
Primary lesion			1
stomach	66 (29.6%)	17 (29.3%)	
colon	157 (70.4%)	144 (70.7%)	
ASA			0.495
1.2	171 (76.7%)	42 (72.4%)	
3	52 (23.3%)	16 (27.6%)	
Mean operation time ± SD	303.0 ± 108.8	297.2 ± 134.9	0.732
Bleeding (ml)	130.4 ± 244.5	133.3 ± 152.8	0.932
approach			0.000171
Open	91 (43.8%)	42 (72.4%)	
Laparoscopy	117 (56.2%)	16 (27.6%)	
Transfusion	5 (2.3%)	1(1.7%)	1
Stage			0.641
0,I,II	150 (67.3%)	37 (63.8%)	
III,IV	73 (32.7%)	21 (36.2%)	
Leakage	4 (1.8%)	5 (8.6%)	0.0205
Complication except SSI	51 (22.9%)	18 (31.0%)	0.232

Patient characteristics	OLG group (n = 223)	control group (n = 58)	P value
Postoperative length of hospital stay (days)	15.8 ± 10.4	20.0 ± 15.8	0.0136
adverse skin reaction (all)	4 (1.8%)	3 (5.2%)	0.157
Skin irritation	2 (0.9%)	0 (0%)	1
Erythema	3 (1.3%)	3 (5.2%)	0.105
Pruritus	1 (0.4%)	1 (1.7%)	0.371

Surgical Site Infection

The overall incidence of SSI was 4.3% (n = 12). Six patients in the control group (10.3%) and 6 in the OLG group (2.7%) developed SSIs (Table 2), and a significant difference was observed between the two groups ($p = 0.02$). In the control and OLG groups, the rates of superficial infection were 8.6% and 2.2%, respectively ($p = 0.0345$), and the rates of deep infection were 1.7% and 0.5%, respectively ($p = 0.371$).

Table 2
Effect of surgical site infection

All	OLG group (n = 223)	Control group (n = 58)	P value
Surgical site infection	6(2.7%)	6 (10.3%)	0.02
Superficial incisional	5 (2.2%)	5 (8.6%)	0.0345
Deep incisional	1 (0.5%)	1 (1.7%)	0.371
open	OLG group (n = 91)	Control group (n = 42)	
Surgical site infection	2 (2.2%)	4 (9.5%)	0.0789
Superficial incisional	2 (2.2%)	4 (9.5%)	0.0789
Deep incisional	0 (0%)	0 (0%)	
Laparoscopy	OLG group (n = 132)	Control group (n = 16)	
Surgical site infection	4 (3.0%)	2(12.5%)	0.127
Superficial incisional	3 (2.3%)	1 (6.3%)	0.37
Deep incisional	1 (0.8%)	1 (6.3%)	0.205
Stomach	OLG group (n = 66)	Control group (n = 17)	
Surgical site infection	0 (0%)	1(5.9%)	0.205
Superficial incisional	0 (0%)	1 (5.9%)	0.205
Deep incisional	0 (0%)	0 (0%)	
Colon	OLG group (n = 157)	Control group (n = 41)	
Surgical site infection	6 (3.8%)	5(12.2%)	0.0523
Superficial incisional	5 (3.2%)	4 (9.8%)	0.0904
Deep incisional	1 (0.6%)	1 (2.4%)	0.372

In the subgroup analysis, the incidence of SSI was 4.5% for laparotomy and 4.1% for laparoscopy. However, among patients treated with laparotomy, 4 in the control group (9.5%) and 2 in the OLG group (4.8%) developed an SSI (Table 2), no significant difference between the two groups ($p = 0.0789$). In the same way, among patients treated with laparoscopy, 2 in the control group (12.5%) and 4 in the OLG group (3.0%) developed an SSI (Table 2), but no significant difference between the two groups ($p = 0.127$). In the primary lesion, the incidence of SSI was 1.2% for stomach and 5.6% for colon. Both among patients performed gastrectomy, 1 in the control group (5.9%) and 0 in the OLG group (0%), and patients performed colectomy, 5 in the control group (12.2%) and 6 in the OLG group (3.8%) developed an SSI (Table 2), but no significant difference between the two groups ($p = 0.205/0.0523$)

The factors found to be associated with SSI are shown in Table 3. Diabetes, ASA and the use of OLG significantly influenced the incidence of SSI. The rates of OLG use in patients with and without a SSI were 50.0% and 90.4%, respectively ($p = 0.02$). Multivariate analysis also demonstrated that the use of OLG was the only significant risk factor for the development of SSI (OR of 0.142, 95% CI 0.0332-0.610, $p = 0.00862$) (Table 4).

Table 3
Patient characteristics and the incidence of SSI

Patient characteristics	SSI- (n = 269)	SSI+ (n = 12)	P value
Mean age(range)	72.9 ± 10.6	77.4 ± 11.3	0.151
Gender			0.37
M	155(57.6%)	9 (75.0%)	
F	114 (42.4%)	3 (25.0%)	
Mean BMI ± SD	22.2 ± 3.5	22.9 ± 3.9	0.485
Diabetes mellitus (%)	78 (29.0%)	7 (58.3%)	0.0489
Alb ± SD	3.89 ± 0.53	3.71 ± 0.52	0.244
Respiratory disease	43 (16.0%)	4 (33.3%)	0.122
Anticoagulant	28 (17.1%)	5 (45.5%)	0.032
ASA			0.0434
1.2	207 (77.0%)	6 (50.0%)	
3	62 (23.0%)	6 (50.0%)	
Mean operation time ± SD	300.1 ± 110.0	339.7 ± 191.8	0.242
Bleeding (ml)	128.4 ± 222.6	188.6 ± 340.0	0.373
approach			1
Open	127 (50.0%)	6 (50.0%)	
Laparoscopy	127 (50.0%)	6 (50.0%)	
Transfusion	6 (2.2%)	0 (0%)	1
Use of Olanexidine	217 (90.4%)	6 (50.0%)	0.02
Primary lesion			0.118
stomach	82 (34.2%)	1(8.3%)	
colon	187 (65.8%)	11 (91.7%)	
tumor size (cm)	4.65 ± 2.56	4.25 ± 2.13	0.595
Stage			0.543
0,I,II	180 (66.9%)	7 (58.3%)	
III,IV	89 (33.1%)	5 (41.7%)	
Complication except SSI	63 (23.5%)	6 (50.0%)	0.0782

Patient characteristics	SSI- (n = 269)	SSI+ (n = 12)	P value
Adverse skin reaction(all)	7 (2.6%)	0(0%)	1

Table 4
Multivariate analysis of risk factors for developing SSI

Factor	Effect size (95% CI)	P value
Age	1.08 (0.983-1.2000)	0.106
Male gender	2.47 (0.529–11.600)	0.25
Diabetes mellitus	3.5 (0.879–13.900)	0.0756
Anticoagulant	1.56 (0.351–6.970)	0.558
ASA(1.2 or 3)	1.92 (0.440–8.350)	0.387
Site (stomach or colon)	0.224 (0.0215-2.340)	0.212
Approach(open or laparoscopy)	0.605 (0.1380–2.640)	0.504
Use of Olanexidine	0.142 (0.0332-0.610)	0.00862

In 7 of the 12 patients with SSI, the culture specimens were positive for bacterial growth. Table 5 summarizes the distribution of organisms isolated from the patients with SSI in both groups. The most organism was Enterococcus faecalis in OLG group, Streptococcus constellatus in control group.

Table 5
Organisms isolated from surgical sites (percentage)

Organisms	OLG group (n = 6)	Control group (n = 6)
Enterococcus faecalis	2 (33.3%)	0 (0%)
Enterococcus avium	1(16.7%)	0 (0%)
Enterobacter aerogenes	1(16.7%)	0 (0%)
Enterobacter cloacae	1(16.7%)	0 (0%)
Pseudomonas aerginosa	1(16.7%)	0 (0%)
Klebsiella pneumoniae	1(16.7%)	0 (0%)
Escherichia coli	1(16.7%)	1(16.7%)
Streptococcus constellatus	0 (0%)	2 (33.3%)
MSSA	0 (0%)	1(16.7%)
Citrobacter freundii	0 (0%)	1(16.7%)
Corynebacterium sp	0 (0%)	1(16.7%)
γ-streptococcus	0 (0%)	1(16.7%)
MSSA: methicillin-sensitive Staphylococcus aureus		

Conclusion

In this retrospective analysis, we found that the risk of SSI after gastrointestinal cancer surgery was significantly lower when OLG was used for preoperative skin preparation than when was used. The incisional SSI rate were 2.7% in OLG group and 10.3% in the control group. This result could directly imply the efficacy of olanexidine for surgical skin antisepsis in gastrointestinal surgery.

SSI can occur as a complication after surgery for gastrointestinal cancer and causes pain and psychological stress in patients, prolongs hospital stays and increases healthcare costs [15]. A high infection rate of 11.3–15.5 % has been reported after gastrectomy or colorectal surgery [1]. Several initiatives are aimed at reducing the risk of SSIs [2–4]. Many perioperative measures to reduce SSI have been reported, including enhanced nutritional support, perioperative oxygenation, different surgical techniques, wound dressing and the use of an antimicrobial agent [13].

The skin is a major source of pathogens that cause SSIs. Therefore, preoperative skin antisepsis may reduce the risk of SSI [5]. Antiseptics prevent infection by decreasing the number of microorganisms and thereby reduce the transmission of pathogens [10]. Currently, PVP-I, CHG and other alcohol-based preparations are widely used to disinfect surgical sites. The CDC guidelines recommend that skin preparation should be performed with an alcohol-containing agent only if there are no contraindications

to its use, and other guidelines do not favor one antiseptic agent over another for skin preparation [16]. PVP-I and CHG both have broad-spectrum antibacterial effectiveness. However, PVP-I may not function well in the presence of organic materials, such as blood or pus, which can rapidly neutralize its bactericidal activity [10]. CHG also does not have sufficient activity to eradicate some pathogens, such as MRSA and VRE[11]. Furthermore, alcohol-based products are highly flammable and can burn the skin if not allowed sufficient time to dry [17–19]. Therefore, it is necessary to identify more effective antiseptics for surgical site preparation.

OLG, a novel biguanide antiseptic agent, has been commercially available since 2015 in Japan for use as a skin disinfectant for surgical sites [12]. It disrupts membrane integrity by binding to the cell membrane, resulting in irreversible leakage of intracellular components, which is the mechanism underlying its bactericidal and fungicidal activities [13]. OLG exerts strong and fast-acting bactericidal activity against a wide range of bacteria [10]. OLG might have higher bactericidal activity against MRSA and VRE both in vitro and in vivo animal models than those of CHG and PVP-I [13]. However, few clinical investigations have explored the use of OLG as a preoperative disinfectant in digestive surgery.

While Asukai et al performed a retrospective study in the field of orthopedics, but found no significant difference between OLG and PVP-I [14]. On the other hand, Obara et performed a randomized study in clean contaminated gastrointestinal and hepatobiliary pancreatic surgery, found significant difference between OLG and PVP-I, which were nearly equivalent to our study [20]. Almost all clean surgeries performed in the orthopedic department were included in this study, and the rate of SSI was low; therefore, it was difficult to identify a difference. However, the risk of SSI is higher in gastrointestinal surgery than in orthopedic surgery, and it is therefore possible to identify a significant difference in this group. Thus, the use of OLG may be more effective in surgery with a high risk of SSI.

Many factors affect SSI and have been previously reported in digestive surgery. Known risk factors for SSI include ASA stage, operation time, diabetes, BMI, and intraoperative blood transfusion. Laparoscopic surgery is considered to reduce SSI. Other reports include age, sex, use of prophylactic antibiotics, ostomy, preoperative use of nonabsorbable oral antibiotics, smoking ,type of skin closure, and total nutrition [21–29]. However, few common risk factors were identified in our surveillance data. This finding suggests that the risk factors for SSI may vary in accordance with the changing conditions experienced during surgery. The widespread use of laparoscopic surgery is a condition that changed markedly during the study period. While laparoscopic surgery is minimally invasive and usually performed with less blood loss than is observed during open surgery, its operation time is longer. The advantageous features of laparoscopic surgery may contribute to a decreased risk of SSI, as suggested in a previous study [30]. In our study, although the difference was not significant between laparoscopic surgery and open surgery in the rate of SSI, that might be due to the very low number of laparoscopic surgery in the control group. Since patients who underwent laparoscopic surgery were mainly included in the OLG group, it is possible that the rate of SSI was significantly lower in the OLG group, and this effect was therefore further examined for each approach in a subgroup analysis. The results showed that there was no significant difference, but the rate of SSI was lower in the OLG group than control group in both the open and

laparoscopic surgery. Therefore, OLG may reduce SSI regardless of the selected approach (open or laparoscopic).

On the other hand, there was no significant difference between the OLG group and the control group for both gastric cancer and colorectal cancer. But in the colorectal cancer cases in which the rate of SSI was high, while the rate of SSI was originally low in the gastric cancer, the rate of SSI considerably lowered in the OLG group. This result also shows that the use of OLG may be more effective in surgery with a high risk of SSI.

Our study has several limitations. First, this was a single-center retrospective study in which the number of cases with SSI was small. It would have been useful to compare data within the same operative method, if possible, but this study was performed using the described methods for primary gastric or colorectal cancer since the case number is small in this middle sized general hospital in Japan. The content was nearly uniform since the operative procedure and perioperative management used during surgery and the preoperative and postoperative periods were always performed by the same individuals(three surgeons). However, because the groups were divided into two groups according to the disinfection method used during the study period, the ration of cases performed using laparoscopy increased over time, and a bias existed in the surgical approach between the two groups. Second, the skin of the surgical field was generally disinfected by dipping a sterilized coating material, such as a cotton ball, in sterilized disinfectant and then applying the dipped material to the skin using sterile forceps. PVP-I disinfection was performed using this method. OLG disinfection was instead performed using an applicator in which the disinfectant and the coating material were aseptically integrated. The use of an applicator reduces the burden of medical workers during disinfection procedures, and it may also reduce the risk of bacterial contamination and contribute to the reduction of SSI because it is sterilized and packaged. For a precise comparison of the efficacy of the disinfectant itself, it may be necessary to perform disinfection using a similar approach in both groups. Finally, several evidence-based guidelines for the prevention of SSIs were updated during the study period; these included recommended antisepsis for preoperative surgical skin preparation according to the World Health Organization (WHO) and CDC and included chlorhexidine-alcohol-based (CHG-AL) agents but not aqueous PVP-I[15, 31]. Furthermore, one trial in which CHG-AL was demonstrated to be superior to PVP-I for pre-operative topical antisepsis in clean-contaminated surgery was followed by a meta-analysis and systematic review that confirmed this result[8, 32, 33]. Therefore, further studies aimed at comparing OLG with an alcohol-based agent such as CHG-AL, are needed to verify the effectiveness of OLG.

In conclusion, in this retrospective study, we demonstrate that OLG is more effective than PVP-I for preventing SSIs during gastrointestinal cancer surgery. Particularly, the use of OLG may also be more effective in surgeries with a high risk of SSI as colorectal cancer. This result indicates that OLG may be useful in reduction SSI in patients undergoing gastrointestinal surgery.

Abbreviations

surgical site infection
SSI, Povidone-iodine:PVP-I, CHG:chlorhexidine gluconate, Olanexidine gluconate:OLG, Centers for Disease Control and Prevention:CDC, methicillin-resistant Staphylococcus aureus:MRSA, vancomycin-resistant enterococci:VRE

Declarations

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Authors' contributions

All authors made substantial contributions to the conception and design of the study protocol. NK designed the study and wrote the protocol. NFDT, SI,KU and MT assisted with the development of the study design ad protocol and contributed to data collection. NK drafted the manuscript and all authors read and approved the final manuscript.

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Availability of data and materials

The datasets used during the current study available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The ethics committee of Nagano Prefectural Shinshu Medical Center approved our study (reference number. No.R2-4). All patients gave a written, informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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