Original Article

A Randomized Controlled Trial Comparing Chlorhexidine in Water and Povidone Iodine for Surgical Site Preparation in Abdominal Surgery

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Background: Surgical site infection (SSI) is the common complication after abdominal surgery. Proper use of antiseptic can decrease SSI. According to previous studies, chlorhexidine in alcohol is superior to povidone iodine when using as skin preparation before abdominal surgery. Due to alcohol is flammable substance, there are many reports shown usage of chlorhexidine in alcohol for skin preparation can cause skin burn. Our study will compare whether chlorhexidine in water superior to povidone iodine as effective antiseptic agent for skin preparation before abdominal surgery.

Objective: The aim of the present study is to compare SSI rate between using chlorhexidine in water and povidone iodine in patient undergoing abdominal surgery.

Materials and Methods: Patients undergoing abdominal surgery by single surgeon (WS) between 1 July 2017 to 30 June 2018 in Ramathibodi Hospital were randomized to use skin preparation with chlorhexidine in water or povidone iodine. The inclusion criteria were elective clean-contaminated abdominal surgery, patient's age between 18 to 75 years, and patients who signed consent form. Exclusion criteria were history of allergic to antiseptic agents, previous skin infection at surgical site, refused to participate in study and cannot follow-up. The primary outcome was SSI rate within 30 days after surgery.

Results: A total of 87 subjects (38 in the chlorhexidine in water group and 49 in the povidone iodine group) were enrolled. There are 19 males (50%) and 19 females (50%) in chlorhexidine in water group while there are 19 males (38.8%) and 30 females (61.2%) in povidone iodine group. The overall rate of SSI was 10.5% in chlorhexidine in water group and 16.3% in povidone iodine group (p-value=0.463).

Conclusion: Preoperative skin preparation with chlorhexidine in water tend to had lower SSI rate compared to povidone iodine, even without statistically significant. Future study with larger sample size may reveal any difference.

Keywords: Surgical site infection; Povidone iodine; Chlorhexidine in water

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Surgical site infections (SSIs) are the most common complications which occur after surgical procedures[1,2]. SSI is associated with increased hospital stay, morbidity, mortality and healthcare cost[3,4]. Colorectal operation is associated with the highest SSI rate among other elective surgical procedures, reported to be as high as 10 to 25%[5,6]. Multiple factors were contributed to SSI such as duration of surgery, wound classification, ASA classification and surgical site bacterial flora[7]. In gastrointestinal tract surgery, both luminal pathogens and skin flora play a role for developing of SSI. The risk of SSI from these pathogens can be reduced by using proper antiseptic for skin preparation before the procedure. The results of prior randomized controlled trial shown the superiority of chlorhexidine in alcohol compared with povidone iodine for the prevention of SSI in clean contaminated surgery[8]. However, the study by Swenson, et al[9] both iodine- alcohol preparations (iodine povacrylex-isopropyl alcohol and povidone iodine- isopropyl alcohol) were more effective than chlorhexidine-alcohol in preventing of SSI following general surgical procedures. Recent study by Tuuli, et al[10] demonstrated superior result of chlorhexidine- alcohol compared to iodine- alcohol for preventing SSI after caesarian sections. These conflicting reports in different surgical patient populations, lead to difficulty to conclude which skin preparations may be the most effective for prevention of SSI. Although alcohol based solutions have been shown to significantly reduce SSI, there is weakness in alcohol property[11]. Alcohol- based skin preparation are known to be flammable substance. The prior study shown fire or burn after using alcohol based antiseptic solution, which can cause morbidity and mortality[12,13].

To reduce risk of operating room fires, using of nonalcohol-based skin preparations is recommended[14].

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There was no previous published randomized study comparing the effect aqueous based antiseptic agent to another on incidence of SSI. The aim of this study was to compare the effectiveness of chlorhexidine in water and povidone iodine as surgical site skin preparation in clean contaminated surgery.

Materials and Methods

Study design

This single center, prospective, randomized controlled trial designed to evaluate whether skin preparation with chlorhexidine in water is noninferior to that with povidone iodine in clean- contaminated surgery was conducted at the Department of Surgery, Ramathibodi Hostpital, Bangkok, Thailand between July 2017 to June 2018. Ethic committee approved study protocol before enrollment of all patients (No. MURA2019/686) (Figure 1). This study was registered in Thailand Clinical Trial Registry (TCTR20210426003).

Patients

All eligible patients completed informed consent before enrollment. Eligible patients included those 18 years of age or above undergoing an elective clean- contaminated surgery. Exclusion criteria were patients who had history of allergic to chlorhexidine and iodophors, previous infection or dirty wound classification, women who were pregnant or breast feeding and patients who were unable to come back for follow-up. Patients were recruited into the study by attending surgeons at the outpatient clinic after completion of the informed consent.

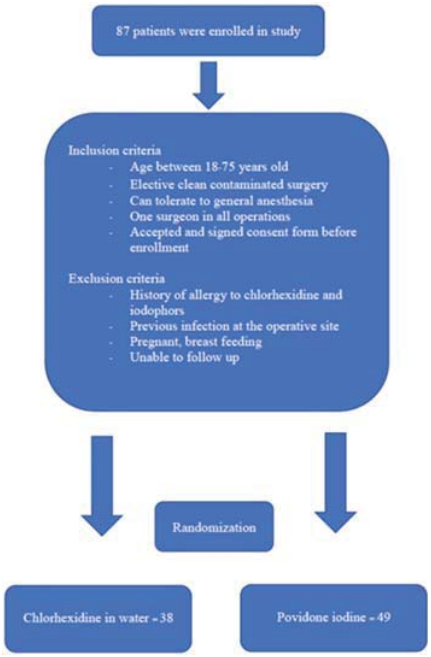

Figure 1. Study protocol.

Randomization and clinical procedures

All enrolled patients were randomized in 1: 1 ratio to undergo skin preparation with either chlorhexidine in water or povidone iodine. Randomization was performed using numbered and sealed envelopes that were opened before the operation started.

In preoperative phase, all patients had fasting after midnight. Preoperative parenteral antibiotic prophylaxis was administrated prior to skin incision in every patients. Enrolled patients in first group were scrubbed and painted with chlorhexidine in water. The control group received were scrubbed and painted with povidone iodine. All patients were operated by single surgeon (WS) according to standard operative technique.

After operation, surgical wounds were cleaned and inspected every day. If surgical site infections were diagnosed, data were collected. Treatment was performed up to level of infection until clinical improved. Patients were followed-up at 1 to 2 weeks and then 1 months after discharge.

Outcomes measures

The primary outcome of this study was the incidence of any SSI within first 30 day after surgery. These included both superficial and deep SSI. Other secondary outcomes were length of hospital stay and time to SSI. Diagnosis of SSI was confirmed using guideline from Centers for Disease Control and Prevention (CDC) definitions[15].

Statistical analysis

The data was verified and analyzed by STATA program version 14. Continuous variables were reported as mean$\pm$SD and categorical variables were reported as percentages. The Fisher's exact test and Chi-square test were used to compare the categorical data variables. The t-test was used to compare the continuous data variables. The Mann-Whitney test was used to compare the outcome variables. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

From 1 July 2017 to 30 June 2018, a total of 87 patients were randomly assigned to 2 study groups: 38 patients in the chlorhexidine in water group and 49 patients in the povidone iodine group. All patients were qualified for the intention to treat analysis. The first group, thirty eight patients were randomized to chlorhexidine in water group who are 19 males (50%) and 19 females (50%). The other group was povidone iodine group which are 19 males (38.8%) and 30 females (60.2%) in (p=0.295). The mean age at surgery was 60.9$\pm$10.4 years. For comparing between 2 groups, no statistically difference was found in preoperative variables such as diabetes mellitus, smoking, ASA class, hematocrit and serum albumin level. Mean operative time in chlorhexidine in water group is 2 hours (IQR 1.3, 3.3),

while in povidone iodine group is 2.3 hours (IQR 1.8, 3.0) (p=0.792). All patients underwent open surgery. Operative procedures performed included 64 (73.6%) colorectal operations, 14 (16.1%) small bowel resections, 3 (3.5%) gastrectomties and 6 (6.9%) other types of operations. All patients received preoperative parenteral antibiotic prophylaxis according to standard guidelines. There were no significant differences in type and number of antibiotics which patients received between two groups. All patients had clean contaminated wound classification. All other baseline characteristics did not vary significantly among study groups (Table 1).

Table 1. Baseline characte ristics

Variables	Total (n=87)	Chlorhexidine in water (n=38)	Povidone iodine (n=49)	p-value
Age (year), mean±SD	60.9±10.4	61.2±10.2	61.2±10.2	0.845
Gender, n (%)				
Male	38 (43.7)	19 (50.0)	19 (38.8)	0.295
Female	49 (56.3)	19 (50.0)	30 (61.2)	
Operative time (hr), median (IQR)	2.3 (1.5, 3.1)	2.0 (1.3, 3.3)	2.3 (1.8, 3.0)	0.344
Comorbidity, n (%)				
Diabetes mellitus				
No	71 (81.6)	29 (76.3)	42 (85.7)	0.262
Yes	16 (18.4)	9 (23.7)	7 (14.3)	
Laboratory values				
Hematocrit (%), mean±SD	36.4±5.8	35.0±6.4	37.4±5.1	0.059
Albumin (mg/dl), median (IQR), n=49	37 (33, 38)	34 (33, 38)	37 (34, 39)	0.249
Smoke, n (%)				
No	81 (93.1)	35 (92.1)	46 (93.9)	0.999
Yes	6 (6.9)	3 (7.9)	3 (6.1)	
ASA class, n (%)				
I	6 (6.9)	4 (10.5)	2 (4.1)	0.190
II	35 (40.2)	11 (28.9)	24 (49.0)	
III	44 (50.6)	22 (57.9)	22 (44.9)	
IV	2 (2.3)	1 (2.6)	1 (2.0)	
Type of operations, n (%)				
Colectomy	27 (31.0)	9 (23.7)	18 (36.7)	0.176
Rectum resecton (LAR/AR)	30 (34.5)	13 (34.2)	17 (34.7)	
APR	7 (8.1)	5 (13.16)	2 (4.1)	
Small bowel resection	14 (16.1)	9 (23.7)	5 (10.2)	
Gastrectomy	3 (3.5)	1 (2.6)	2 (4.1)	
Others	6 (6.9)	1 (2.6)	5 (10.2)	
Surgical approach, n (%)				
Laparoscopic approach	-	-	-	-
Laparoscopic and converted	-	-	-	-
Open surgery	87 (100)	38 (100)	49 (100)	-
Length of hospital stay(day), median (IQR)	6 (5, 7)	6 (5, 7)	7 (6, 7)	0.354
SSI, n (%)				
No	75 (86.2)	34 (89.5)	41 (83.7)	0.436
Yes	12 (13.8)	4 (10.5)	8 (16.3)	

SD = standard deviation; IQR = interquartile range; ASA = American Society of Anesthesiologist; LAR = low anterior resection; AR = anterior resection; APR = abdominoperineal resection; SSI = surgical site infection

Outcomes

The overall rate of SSI was 13.8%. In chlorhexidine in water group, there were 4 superficial SSI (10.5%) while in povidone iodine group, 8 patients (16.3%) developed SSI. The overall SSI rate was not significantly differed between chlorhexidine in water group (10.5%) and povidone iodine group (16.3%) (p=0.436). All of surgical site infections which existed are superficial SSI.

The secondary outcomes including length of hospital stay and time to diagnosis of SSI were analyzed. The median length of stay for patients in the chlorhexidine in water group was 6 (IQR 5, 7) days, compared with 7 (IQR 6, 7) days for patients in the povidone iodine groups, which was not statistically difference (p=0.354). Two patients in Povidone iodine groups had to readmit for diagnosis and treatment of SSI. The median time from surgery to diagnosis of SSI was comparable in both chlorhexidine in water and povidone iodine group (6 (IQR 5, 6) days vs. 6 (IQR 4, 9) days; p=0.730) (Table 2).

The result revealed wide range of times in both groups; there were SSI diagnosed as soon as 2 days postoperatively, and as long as 16 days after surgery. Most common type of operation associated with SSI was colorectal surgery. The diagnosis of patients who had SSI were colorectal cancer (Table 3).

Finally, we examined the bacteria identified from the cultured wounds. Overall, only 4 SSI wounds were cultured. In 2 wounds, 2 organisms were identified; in 1 wound, 1 organism was identified and, in 1 wound, no organism was found. The most common pathogens identified was *Enterobacter species*.

There were no adverse events attributed to both skin preparations during the study. Other major complication other than SSI was 1 contained anastomosis leakage in chlorhexidine in water group patient which was resolved with conservative treatment and 1 colocutaneous fistula which was healed up in 32 days without further intervention.

Discussion

One of the most important measures for SSI prevention in patients undergoing gastrointestinal tract surgery is optimal skin preparation. There are many studies examining the efficacy of numerous types of antiseptic skin preparation in neurosurgery[16], obstetrics procedures[17,18] and orthopedics procedures[19-22]. However, most recent studies examining SSI in abdominal surgery are retrospective in nature with few number of randomized controlled trial[8,23,24].

One large scale study to compare the effect of

Table 2. Surgical site infection (SSI), n=12 and related outcomes

Variables	Total (n=12)	Chlorhexidine in water (n=4)	Povidone iodine (n=8)	p-value
Overall SSI rate, n (%)	12	4 (10.5)	8 (16.3)	0.436
Length of hospital stay (day), median (IQR)	6 (5, 7)	6 (5, 7)	7 (6, 7)	0.354
Readmission within 30 days, n (%)	2	0 (0)	2 (4.1)	0.502
Diagnosis of SSI at day, median (IQR), n=12	6 (5, 7)	6 (5, 6)	6 (4, 9)	0.730
Operation type, n (%), n=12				
Anterior resection	3 (25.0)	0	3 (37.5)	0.143
Closure ileostomy	3 (25.0)	2 (50.0)	1 (12.5)	
Exploratory laparotomy	2 (16.7)	0	2 (25.0)	
Low anterior resection	1 (8.3)	1 (25.0)	0	
Right hemicolectomy	1 (8.3)	1 (25.0)	0	
Sigmoidectomy	2 (16.7)	0	2 (25.0)	
Cultures, n (%), n=12				
No	8 (66.7)	3 (75.0)	5 (62.5)	0.999
Yes	4 (33.3)	1 (25.0)	3 (37.5)	
Arcanobacterium bernadiae	1 (1.2)	0	1 (2.0)	
Citrobacterium freundii	1 (1.2)	1 (2.6)	0	
Enterobacter cloacae	1 (1.2)	1 (2.6)	0	
Enterobacter species	1 (1.2)	0	1 (2.0)	
No growth	1 (1.2)	0	1 (2.0)	
Staphylococcus aureus coag. negative	1 (1.2)	0	1 (2.0)	

SSI = surgical site infection; IQR = interquartile range

Table 3. Characteristic of 12 patients with superficial SSI

Patient No.	Groups	Operation	Length of hospital stay (days)	Time to diagnosis of SSI (at postoperative day)
1	Chlorhexidine in water	Closure ileostomy	7	4
2	Chlorhexidine in water	Right hemicolectomy	8	6
3	Chlorhexidine in water	Closure ileostomy	22	6
4	Chlorhexidine in water	Low anterior resection	19	5
5	Povidone iodine	Anterior resection	38	3
6	Povidone iodine	Anterior resection	9	2
7	Povidone iodine	Closure ileostomy	41	16
8	Povidone iodine	Sigmoidectomy	9	5
9	Povidone iodine	Explore laparotomy with biopsy peritoneum (CA rectum)	15	5
10	Povidone iodine	Anterior resection	11	6
11	Povidone iodine	Explore laparotomy (CA rectum)	3	8
12	Povidone iodine	Sigmoidectomy	15	9

different skin preparation between chlorhexidine in alcohol and povidone iodine in the general surgery population was conduct by Swenson, et al[9]. They reported significantly lower rates of SSI in patients prepared with iodophor-based compounds. Contrary to Swenson's study, in a randomized controlled trial by Darouiche, et al[8] evaluated skin antisepsis (Chlorhexidine-alcohol vs. Povidone-iodine for clean-contaminated surgery, the overall rate of SSI was significantly lower in the chlorhexidine in alcohol group than in povidone iodine group (9.5% vs. 16.1%; p=0.004; relative risk 0.59; 95% CI 0.41 to 0.85). These superior clinical efficacy of chlorhexidine-alcohol in the present study correlated well with previous studies showing that chlorhexidine-based antiseptic preparations are more effective than iodine-containing solution in prevention of SSI for caesarean section[17,18] and orthopedic surgery[19-22].

Meta-analysis by Lee, et al included 3,614 patients from 9 RCTs which examined SSI rate both from clean and clean-contaminated operations[25]. From seven studies in this meta-analysis comparing SSI following skin antisepsis with chlorhexidine preparation and following povidone iodine preparation revealed that chlorhexidine decreased the SSI rate by 36% compared with povidone iodine (p<0.0001).

Nearly all the published studies of chlorhexidine use it in combination with some form of alcohol. Sidhwa, et al[26] recommended that the skin preparation should include an alcohol component, because alcohol is inexpensive, safe, and effective. Previous published guidelines for the prevention of SSI by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) gave the consensus that alcohol-based preparations were associated with reduced risk of SSI compared to aqueous-based solution[27,28]. However, there were previous reports of risk of fire in the operating theatre after using alcohol in skin preparation because the flammable property of alcohol[12,13]. Only previous study on mechanism of fires in operating room was conducted by Jone, et al[14]. This study use standardized, ex vivo model of clipped porcine dermis and compared nonalcohol-based skin preparations (chlorhexidine gluconate 4%, Povidine-iodine 1%) with alcohol-based skin preparation (chlorhexidine-isopropyl alcohol and iodine-isopropyl alcohol). Ignition of fire was performed by monopolar "Bovie" pencil activated for 2 seconds on 30 Watt (coagulation mode) which was the common setting in clinical use. The test with Bovie pencil were applied at 3 situations, immediately after application of skin preparation (0 minute), after 3-minute delay and in pooling of skin preparation. The result of this study showed that no fires occurred with nonalcohol-based preparations compared with alcohol-based preparation (p<0.001). The incidence of fire from using alcohol-based preparations occurred at 0 minute in 22% and at 3 minutes in 10% of tests. When examining pooling of alcohol-based preparations, fires events increased to 38% at 0 minute and 27% at 3 minute. This study mentioned that even following the guideline from manufactures to allow 3 minutes for drying of alcohol-based preparations, the surgical fires were still occur in 10% of cases without pooling and more than one-quarter of cases with pooling. So surgeons should consider using of nonalcohol-based skin preparations or avoid pooling of the preparation solution.

Due to the risk of fires from alcohol-based skin preparations, our study try to evaluate efficacy of aqueous-based chlorhexidine (chlorhexidine in water) to povidone iodine for skin preparation in clean-contaminated surgery. The type of surgery were colorectal, small bowel and gastric surgery. According to those mentioned surgery type, there was no difference in surgical procedure in both group (p=0.504). Most of the operations are colorectal surgery (75.9%). All patients received preoperative parenteral

antibiotic prophylaxis. Surgical site infection rate in chlorhexidine in water group is 10.5% and in povidone iodine group is 16.3% (p-value=0.436). Our study showed that chlorhexidine in water did not superior to povidone iodine in terms of prevention of SSI following clean-contaminated surgery. The rate of SSI in this study was comparable with other prospective studies[8,23]. However, patients who developed SSI significantly had longer hospital stay compared to those who did not (median 13 (3, 41) days vs. 6 (1, 26) days, p<0.01). These will be explained from requirement of further wound care and prolonged antibiotic. Fortunately, most SSIs were diagnosed while patients were still in the hospital. So the treatment of SSIs were not delayed.

The strength in this study is study design which is prospective randomized study and all operations were did by the same surgeon with exactly the same surgical technique. However, this trial has several limitations. First, the sample size was relatively small because the recruitment time was limited. Second, the heterogeneity of the operation might had some effect to the result. Moreover, the variation in patient's physical status and comorbidities could contribute some effect to the result.

Conclusion

Based on evidences of our study, the use of chlorhexidine in water as surgical site skin preparation before clean-contaminated abdominal surgery did not significantly showed superior result over povidone iodine in terms of SSI rate. However, there was a trend that using chlorhexidine in water had a lower SSI rate compared to povidone iodine. Further prospective randomized controlled trials with larger sample sizes are required to determine the true efficacy of chlorhexidine in water as alternative preoperative skin antiseptic before abdominal operation.

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