

ORIGINAL ARTICLE

Chlorhexidine–Alcohol versus Povidone–Iodine for Surgical-Site Antisepsis

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ABSTRACT

BACKGROUND

Since the patient's skin is a major source of pathogens that cause surgical-site infection, optimization of preoperative skin antisepsis may decrease postoperative infections. We hypothesized that preoperative skin cleansing with chlorhexidine–alcohol is more protective against infection than is povidone–iodine.

METHODS

We randomly assigned adults undergoing clean-contaminated surgery in six hospitals to preoperative skin preparation with either chlorhexidine–alcohol scrub or povidone–iodine scrub and paint. The primary outcome was any surgical-site infection within 30 days after surgery. Secondary outcomes included individual types of surgical-site infections.

RESULTS

A total of 849 subjects (409 in the chlorhexidine–alcohol group and 440 in the povidone–iodine group) qualified for the intention-to-treat analysis. The overall rate of surgical-site infection was significantly lower in the chlorhexidine–alcohol group than in the povidone–iodine group (9.5% vs. 16.1%; $P=0.004$; relative risk, 0.59; 95% confidence interval, 0.41 to 0.85). Chlorhexidine–alcohol was significantly more protective than povidone–iodine against both superficial incisional infections (4.2% vs. 8.6%, $P=0.008$) and deep incisional infections (1% vs. 3%, $P=0.05$) but not against organ-space infections (4.4% vs. 4.5%). Similar results were observed in the per-protocol analysis of the 813 patients who remained in the study during the 30-day follow-up period. Adverse events were similar in the two study groups.

CONCLUSIONS

Preoperative cleansing of the patient's skin with chlorhexidine–alcohol is superior to cleansing with povidone–iodine for preventing surgical-site infection after clean-contaminated surgery. (ClinicalTrials.gov number, NCT00290290.)

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DESPITE THE IMPLEMENTATION OF preoperative preventive measures, which include skin cleansing with povidone-iodine, surgical-site infection occurs in 300,000 to 500,000 patients who undergo surgery in the United States each year.¹⁻⁶ Since the patient's skin is a major source of pathogens, it is conceivable that improving skin antiseptics would decrease surgical-site infections.⁷ The Centers for Disease Control and Prevention (CDC) recommends that 2% chlorhexidine-based preparations be used to cleanse the site of insertion of vascular catheters.⁸ However, the CDC has not issued a recommendation as to which antiseptics should be used preoperatively to prevent postoperative surgical-site infection in the 27 million operations performed annually in the United States.⁹ Furthermore, no published randomized studies have examined the effect of one antiseptic preparation as compared with another on the incidence of surgical-site infection. The main objective of this study was to compare the efficacy of chlorhexidine-alcohol with that of povidone-iodine for preventing surgical-site infections.

METHODS

STUDY DESIGN

We conducted this prospective, randomized clinical trial between April 2004 and May 2008 at six university-affiliated hospitals in the United States. The institutional review board at each hospital approved the study protocol, and written informed consent was obtained from all patients before enrollment. This investigator-initiated trial was conceived by the first author, who also acted as the study sponsor, recruited the sites, gathered the data, wrote the first and final versions of the manuscript, and decided in consultation with the other authors to submit the paper for publication. All authors vouch for the completeness and accuracy of the data. One of the authors, who is a statistician, analyzed the data. The single author from Cardinal Health (manufacturer of the antiseptic agents studied) substantially contributed to the design and conception of the study and critically revised the manuscript but played no role in data collection or analysis. All other authors had full access to the data and substantially contributed

to the analysis and interpretation of the data and the writing of the manuscript.

PATIENTS

Patients 18 years of age or older who were undergoing clean-contaminated surgery (i.e., colorectal, small intestinal, gastroesophageal, biliary, thoracic, gynecologic, or urologic operations performed under controlled conditions without substantial spillage or unusual contamination) were eligible for enrollment. Exclusion criteria were a history of allergy to chlorhexidine, alcohol, or iodophors; evidence of infection at or adjacent to the operative site; and the perceived inability to follow the patient's course for 30 days after surgery.

INTERVENTIONS

Enrolled patients were randomly assigned in a 1:1 ratio to have the skin at the surgical site either preoperatively scrubbed with an applicator that contained 2% chlorhexidine gluconate and 70% isopropyl alcohol (ChlorPrep, Cardinal Health) or preoperatively scrubbed and then painted with an aqueous solution of 10% povidone-iodine (Scrub Care Skin Prep Tray, Cardinal Health). More than one chlorhexidine-alcohol applicator was used if the coverage area exceeded 33 by 33 cm. To help match the two groups and address potential interhospital differences, randomization was stratified by hospital with the use of computer-generated randomization numbers without blocking.

EFFICACY OUTCOMES

The primary end point of the study was the occurrence of any surgical-site infection within 30 days after surgery. The operating surgeon became aware of which intervention had been assigned only after the patient was brought to the operating room. Both the patients and the site investigators who diagnosed surgical-site infection on the basis of criteria developed by the CDC⁹ remained unaware of the group assignments. Secondary end points included the occurrence of individual types of surgical-site infections. These were classified as superficial incisional infection (which involved only skin and subcutaneous tissue and excluded stitch-related abscesses), deep incisional infection (which involved fascia and muscle), or organ-space infection (which involved any organ or space other than

the incised layer of body wall that was opened or manipulated during the operation).⁹

CLINICAL ASSESSMENT

Preoperative evaluation included a medical history taking, physical examination, and routine hematologic and blood chemical laboratory tests. The surgical site and the patient's vital signs were assessed at least once a day during hospitalization, on discharge, at the time of follow-up evaluation, and whenever surgical-site infection occurred. After discharge, the investigators called the patients once a week during the 30-day follow-up period and arranged for prompt clinical evaluation if infection was suspected. Whenever surgical-site infection was suspected or diagnosed, clinically relevant microbiologic samples were cultured. Investigators who were unaware of the patients' group assignments assessed the seriousness of all adverse events and determined whether they were related to the study.

STATISTICAL ANALYSIS

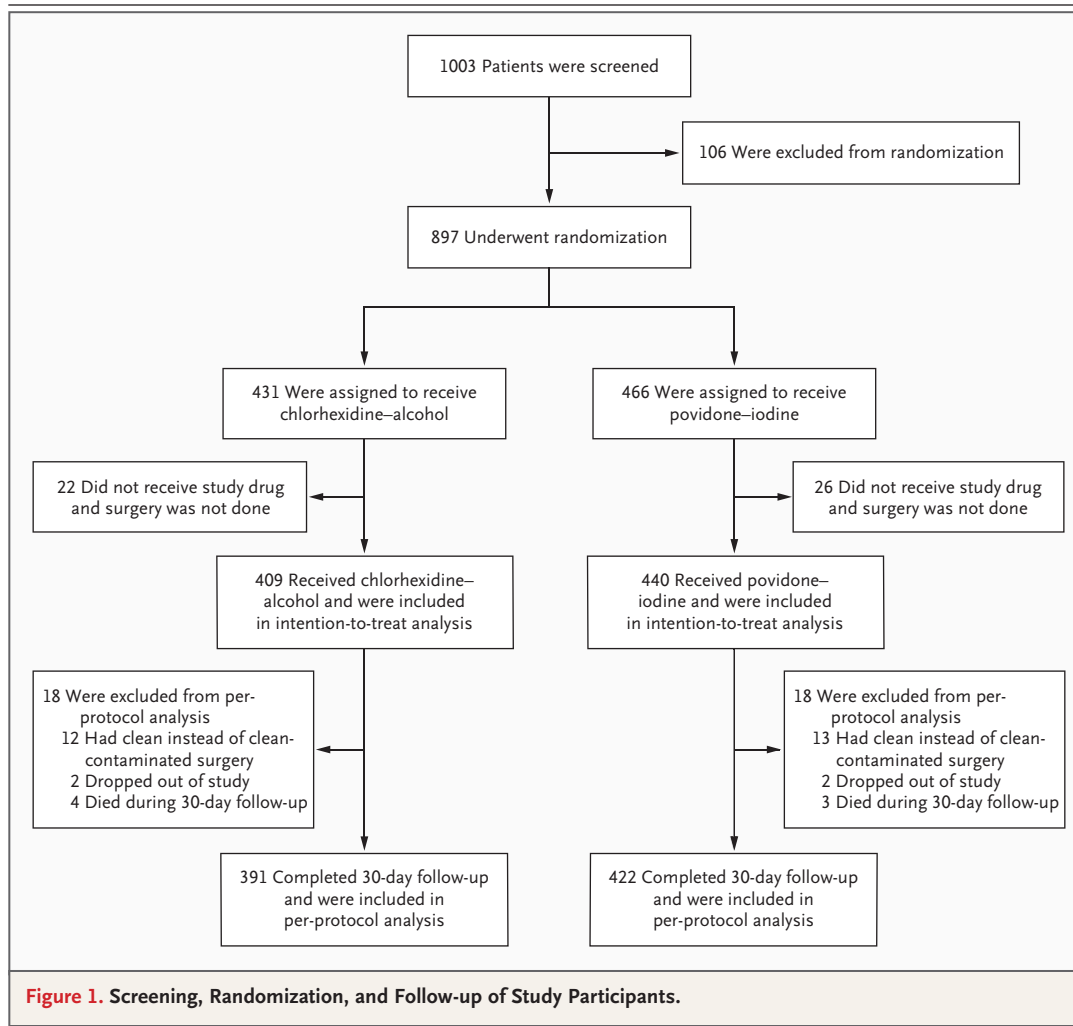
The average baseline rate of surgical-site infection at the six participating hospitals was 14% after clean-contaminated surgery with povidone-iodine skin preparation, and we estimated that substituting chlorhexidine-alcohol for povidone-iodine would reduce this rate to 7%. Therefore, we planned to enroll approximately 430 patients in each study group who could be evaluated in order for the study to have 90% power to detect a significant difference in the rates of surgical-site infection between the two groups, at a two-tailed significance level of 0.05 or less.

The criteria for including patients in the intention-to-treat analysis included randomization and the possibility of applying each of the study antiseptic preparations (which required performance of surgery). Inclusion in the per-protocol analysis required the application of the study preparation before clean-contaminated surgery and completion of the 30-day follow-up. An independent data and safety monitoring board composed of an infectious-disease physician, a surgeon, and a statistician met annually to review the conduct of the study. No formal criteria were set for stopping the study.

The significance of differences between the two study groups in terms of patient characteristics was determined with the use of the Wilcoxon

rank-sum test for continuous variables and Fisher's exact test for categorical variables. For efficacy outcomes, we compared the proportions of patients in the two study groups who could be evaluated and who had any type of surgical-site infection, using Fisher's exact test and calculating the relative risk of infection and 95% confidence intervals. The consistency of the effects of the study intervention on infections across different types of surgery was examined with the use of an interaction test. To determine whether the results were consistent across the six participating hospitals, a prespecified Breslow-Day test for homogeneity was performed. To compare the proportions of patients in the two study groups who were free of surgical-site infection as a function of the length of time since surgery, we performed log-rank tests on Kaplan-Meier estimates based on analyses in which data for patients who did not have infections were censored 30 days after surgery. Both the frequency of isolating certain organisms and categories of organisms and the incidence of adverse and serious adverse events were compared between the study groups with the use of Fisher's exact test. All reported P values are based on two-tailed tests of significance and were not adjusted for multiple testing.

We conducted univariate and multivariate analyses to assess whether risk factors contributed to the occurrence of surgical-site infection. The univariate analysis for categorical factors was performed with the use of Fisher's exact test. For continuous factors, we used a single-variable logistic-regression model that involved generalized estimating equations (GEE) to account for hospital site as a random effect. A multivariate logistic-regression analysis that also adjusted for the hospital site as a random effect (by means of GEE) was performed to assess factors deemed significant ($P \leq 0.10$) by univariate analysis or considered clinically important. The assessed risk factors were prespecified in the protocol, and the statistical methods were preplanned except for the inclusion of hospital site as a random effect. Since some types of surgery did not result in infection in either study group, a dichotomous variable — "abdominal" surgery (including colorectal, biliary, small intestinal, and gastroesophageal operations) versus "nonabdominal" surgery (including thoracic, gynecologic, and urologic operations) — was created for the GEE logistic-regression model.



RESULTS

PATIENTS

A total of 897 patients were randomly assigned to a study group: 431 to the chlorhexidine-alcohol group and 466 to the povidone-iodine group (Fig. 1). Of the 849 patients who qualified for the intention-to-treat analysis, 409 received chlorhexidine-alcohol and 440 received povidone-iodine. Thirty-six patients were excluded from the per-protocol analysis: 25 underwent clean rather than clean-contaminated surgery, 4 dropped out of the study 1 or 2 days after surgery, and 7 died before completion of the 30-day follow-up (4 in the chlorhexidine-alcohol group and 3 in the povidone-iodine group). Therefore, 813 patients (391 in the chlorhexidine-alcohol group and 422 in the povidone-iodine group) were included in the per-protocol analyses.

The patients in the two study groups were similar with respect to demographic characteristics, coexisting illnesses, risk factors for infection, antimicrobial exposure, and duration and types of surgery (Table 1, and Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). All patients received systemic prophylactic antibiotics within 1 hour before the initial incision, and there were no significant differences in the type or number of antibiotics given to the two study groups, even when only patients who underwent colorectal surgery were considered (Table 2 in the Supplementary Appendix).

RATES OF INFECTION

For the patients in the intention-to-treat population, the overall rate of surgical-site infection was

Table 1. Baseline Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Chlorhexidine–Alcohol (N = 409)	Povidone–Iodine (N = 440)	P Value
Male sex (%)	58.9	55.9	0.40
Age (yr)	53.3+14.6	52.9+14.2	0.87
Systemic antibiotics			
Initiated preoperatively (%)	100	100	>0.99
Duration of preoperative administration (days)			
Mean	1.1±1.2	1.1±0.8	>0.99
Range	1–20	1–11	
Received postoperatively (%)	51.7	48.9	0.41
Duration of surgery (hr)	3.0±1.5	3.0±1.5	>0.99
Abdominal surgery (%)	72.6	70.0	0.41
Colorectal	45.5	43.4	0.58
Biliary	10.8	12.3	0.52
Small intestinal	10.0	7.7	0.28
Gastroesophageal	6.4	6.6	0.89
Nonabdominal surgery (%)	27.4	30.0	0.41
Thoracic	10.8	13.0	0.34
Gynecologic	10.3	9.1	0.56
Urologic	6.4	8.0	0.42
Preoperative shower (%)	26.7	27.0	0.94
With 4% chlorhexidine gluconate (%)	16.1	18.9	0.32
With 10% povidone–iodine (%)	7.3	5.2	0.26
With 0.6% triclocarban soap bar (%)	3.2	3.0	>0.99

* Plus–minus values are means ±SD.

significantly lower in the chlorhexidine–alcohol group (9.5%) than in the povidone–iodine group (16.1%, $P=0.004$) (Table 2). The relative risk of any surgical-site infection among patients whose skin was preoperatively cleansed with chlorhexidine–alcohol versus povidone–iodine was 0.59 (95% confidence interval [CI], 0.41 to 0.85). Similarly, chlorhexidine–alcohol was associated with significantly fewer superficial incisional infections (relative risk, 0.48; 95% CI, 0.28 to 0.84) and deep incisional infections (relative risk, 0.33; 95% CI, 0.11 to 1.01). However, there were no significant differences between the two study groups in the incidence of organ-space infection (relative risk, 0.97; 95% CI, 0.52 to 1.80) or sepsis from surgical-site infection (relative risk, 0.62; 95% CI, 0.30 to 1.29).

The per-protocol analysis yielded similar efficacy results. The Kaplan–Meier estimates of the

risk of surgical-site infection (Fig. 2) showed a significantly longer time to infection after surgery in the chlorhexidine–alcohol group than in the povidone–iodine group ($P=0.004$ by the log-rank test).

The interaction between treatment group and type of surgery (abdominal vs. nonabdominal) was included in a logistic-regression model with the main effects of group and surgery type and was found not to be significant ($P=0.41$). When considered separately in a subgroup analysis (Table 3), the rate of infection after abdominal surgery was 12.5% in the chlorhexidine–alcohol group versus 20.5% in the povidone–iodine group (95% CI for the absolute difference [chlorhexidine–alcohol minus povidone–iodine], –13.9 to –2.1 percentage points). For patients undergoing nonabdominal surgery, the rate of infection was 1.8% in the chlorhexidine–alcohol group versus 6.1% in the

Table 2. Proportion of Patients with Surgical-Site Infection, According to Type of Infection (Intention-to-Treat Population).

Type of Infection	Chlorhexidine- Alcohol (N = 409) <i>no. (%)</i>	Povidone-Iodine (N = 440) <i>no. (%)</i>	Relative Risk (95% CI)*	P Value†
Any surgical-site infection	39 (9.5)	71 (16.1)	0.59 (0.41–0.85)	0.004
Superficial incisional infection	17 (4.2)	38 (8.6)	0.48 (0.28–0.84)	0.008
Deep incisional infection	4 (1.0)	13 (3.0)	0.33 (0.11–1.01)	0.05
Organ-space infection	18 (4.4)	20 (4.5)	0.97 (0.52–1.80)	>0.99
Sepsis from surgical-site infection	11 (2.7)	19 (4.3)	0.62 (0.30–1.29)	0.26

* Relative risks are for chlorhexidine-alcohol as compared with povidone-iodine. The 95% confidence intervals were calculated with the use of asymptotic standard-error estimates.

† P values are based on Fisher's exact test.

povidone-iodine group (95% CI for the absolute difference, -7.9 to 2.6 percentage points).

Both the intention-to-treat analysis (Table 3) and the per-protocol analysis showed lower rates of surgical-site infection in the chlorhexidine-alcohol group than in the povidone-iodine group for each of the seven types of operations studied. Although the trial was not powered to compare the rates of infection for subcategories of patients, infection occurred significantly less often in the chlorhexidine-alcohol group than in the povidone-iodine group in the intention-to-treat analysis for patients who underwent small intestinal surgery ($P=0.04$) or abdominal surgery ($P=0.009$) or who did not shower preoperatively ($P=0.02$).

The Breslow-Day tests indicated homogeneity in showing no significant differences between hospitals with respect to the incidence of either any type of surgical-site infection ($P=0.35$) or individual types of infection ($P\geq 0.19$). Even so, we accounted for hospital site in all logistic-regression models by including this term as a random effect through the use of GEE.

ANALYSES OF RISK FACTORS

The multivariate logistic-regression analysis identified the following risk factors for surgical-site infection in the intention-to-treat population: use of povidone-iodine, abdominal surgery, alcohol abuse, liver cirrhosis, cancer, diabetes mellitus, malnutrition, gastrointestinal disease, longer duration of surgery, longer duration of placement of surgical drain, and preoperative shower with povidone-iodine (Table 3 in the Supplementary Ap-

pendix). Since an analysis of risk factors other than the assigned intervention constitutes an exploratory analysis, which involves multiple simultaneous statistical tests, it could inflate the probability of a false positive finding (type II error).

MICROBIOLOGIC CAUSES OF INFECTION

Culture of the surgical site in 60 of 61 infected patients yielded growth of organisms (a total of 107 isolates), and similar proportions of infected patients in the two study groups (23 of 39 [59%] in the chlorhexidine-alcohol group and 37 of 71 [52%] in the povidone-iodine group) had an identifiable microbiologic cause of infection (Table 4 in the Supplementary Appendix). Gram-positive aerobic bacteria (63 isolates) outnumbered gram-negative aerobic bacteria (25 isolates) by a factor of 2.5, and 38% of cultures were polymicrobial. There were no significant differences in the frequency of isolating certain categories of organisms or particular organisms in the chlorhexidine-alcohol group (total of 44 isolates) as compared with the povidone-iodine group (total of 63 isolates), with the exception of streptococci, which were less common in the former group (1 of 44 [2.3%] vs. 10 of 63 [15.9%], $P=0.03$).

ADVERSE EVENTS

In the intention-to-treat analysis, adverse events occurred in equal proportions among the patients in the chlorhexidine-alcohol group and the povidone-iodine group (228 of 409 [55.7%] and 256 of 440 [58.2%], respectively), as did serious adverse events (72 of 409 [17.6%] and 70 of 440 [15.9%],

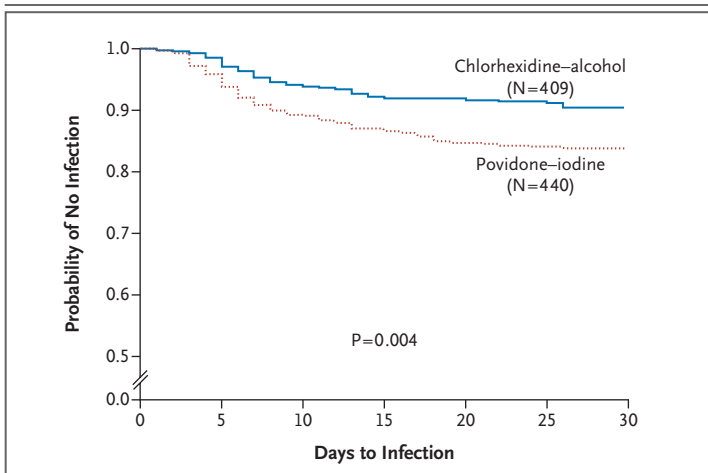


Figure 2. Kaplan-Meier Curves for Freedom from Surgical-Site Infection (Intention-to-Treat Population).

Patients who received chlorhexidine-alcohol were significantly more likely to remain free from surgical-site infection than were those who received povidone-iodine ($P=0.004$ by the log-rank test). In the chlorhexidine-alcohol group, 39 patients had events (9.5%) and data from 370 patients (90.5%) were censored; in the povidone-iodine group, 71 patients had events (16.1%) and data from 369 patients (83.9%) were censored.

respectively) (Table 4, and Table 5 in the Supplementary Appendix). Findings were similar in the per-protocol analysis. Three patients (0.7%) in each study group had an adverse event (pruritus, erythema, or both around the surgical wound) that was judged to be related to the study drugs; however, no serious adverse events were judged to be related to the study drugs. There were no cases of fire or chemical skin burn in the operating room. A total of seven patients died: four (1.0%) in the chlorhexidine-alcohol group who did not have surgical-site infections and three (0.7%) in the povidone-iodine group who died from sepsis due to organ-space infection.

DISCUSSION

Randomized studies have compared the efficacy of different types¹⁰⁻¹³ or doses^{14,15} of systemic antibiotics for preventing surgical-site infection but not the effect of preoperative skin antisepsis. In this randomized study, the application of chlorhexidine-alcohol reduced the risk of surgical-site infection by 41% as compared with the most common practice in the United States of using aqueous povidone-iodine.⁷ This degree of protection

is similar to the 49% reduction in the risk of vascular catheter-related bloodstream infection in a meta-analysis that showed the superiority of skin disinfection with chlorhexidine-based solutions versus 10% povidone-iodine.¹⁶ Although the overall rates of surgical-site infection of 10 to 16% in this study are higher than those reported in some previous studies,^{17,18} they are similar to the pre-study rates at the participating hospitals and those reported in other studies¹³ and are lower than the rates reported in trials that used the CDC definition of infection and had adequate follow-up,^{11,12,19} as we did in this trial. On the basis of our findings, the estimated number of patients who would need to undergo skin preparation with chlorhexidine-alcohol instead of povidone-iodine in order to prevent one case of surgical-site infection is approximately 17.

Although both the antiseptic preparations we studied possess broad-spectrum antimicrobial activity,⁹ the superior clinical protection provided by chlorhexidine-alcohol is probably related to its more rapid action, persistent activity despite exposure to bodily fluids, and residual effect.²⁰ The superior clinical efficacy of chlorhexidine-alcohol in our study correlates well with previous microbiologic studies showing that chlorhexidine-based antiseptic preparations are more effective than iodine-containing solutions in reducing the bacterial concentration in the operative field for vaginal hysterectomy²¹ and foot-and-ankle surgery.^{22,23} Although the use of flammable alcohol-based products in the operating room poses the risk, though small, of fire or chemical skin burn, no such adverse events occurred in this study or the other studies.²¹⁻²³

In this trial we universally enforced standard-of-care preventive measures (e.g., administering systemic prophylactic antibiotics within 1 hour before the first incision was made and, if needed, clipping hair immediately before surgery),^{9,24} but hospitals were allowed to continue their pre-existing practices, which offer potential but not established protective efficacy (e.g., preoperative showering).²⁵ However, we controlled the effect of differences in hospital practices by using hospital-stratified randomization, which ensured close matching of the two study groups as well as trial results that are applicable to a broadly representative population of hospitalized patients.

Because antiseptics act only against organisms

Table 3. Proportion of Patients with Surgical-Site Infection, According to Type of Surgery (Intention-to-Treat Population).

Type of Surgery	Chlorhexidine-Alcohol		Povidone-Iodine	
	Total No. of Patients	Patients with Infection <i>no. (%)</i>	Total No. of Patients	Patients with Infection <i>no. (%)</i>
Abdominal	297	37 (12.5)	308	63 (20.5)
Colorectal	186	28 (15.1)	191	42 (22.0)
Biliary	44	2 (4.6)	54	5 (9.3)
Small intestinal	41	4 (9.8)	34	10 (29.4)
Gastroesophageal	26	3 (11.5)	29	6 (20.7)
Nonabdominal	112	2 (1.8)	132	8 (6.1)
Thoracic	44	2 (4.5)	57	4 (7.0)
Gynecologic	42	0	40	1 (2.5)
Urologic	26	0	35	3 (8.6)

Table 4. Clinical Adverse Events (Intention-to-Treat Population).

Clinical Adverse Event	Chlorhexidine-Alcohol (N = 409)	Povidone-Iodine (N = 440)	Absolute Difference* <i>percentage points (95% CI)</i>	P Value†
	<i>no. (%)</i>	<i>no. (%)</i>		
Adverse events in ≥5% of patients in either group	228 (55.7)	256 (58.2)	-2.4 (-9.1 to 4.2)	0.49
Drug-related adverse events‡	3 (0.7)	3 (0.7)	0.1 (-1.1 to 1.2)	>0.99
Serious adverse events in >1% of patients in either group	72 (17.6)	70 (15.9)	1.7 (-3.3 to 6.7)	0.52
Serious drug-related adverse events	0	0	—	—
Death	4 (1.0)	3 (0.7)	0.3 (-0.9 to 1.5)	0.72

* The absolute difference is shown as the rate in the chlorhexidine-alcohol group minus the rate in the povidone-iodine group.

† P values were calculated with the use of Fisher's exact test.

‡ Drug-related adverse events included pruritus, erythema, or both around the surgical wound and are reported even though the rate was not 5% or higher in either group.

that reside on the patient's integument, the overall superior protection afforded by chlorhexidine-alcohol was attributed primarily to a reduction in the rates of superficial and deep incisional infections that were caused mostly by gram-positive skin flora. Since two thirds of surgical-site infections are confined to the incision,^{9,11} optimizing skin antisepsis before surgery could result in a significant clinical benefit.

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