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State of the Science Review

Skin antisepsis with chlorhexidine versus iodine for the prevention of surgical site infection: A systematic review and meta-analysis

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Key Words:
Surgical site infections
Preoperative antisepsis
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Chlorhexidine
Iodine

Background: Surgical site infection (SSI) is one of the most frequent health care–associated infections. One of the practices to reduce their incidence is preoperative skin antisepsis. Two of the most commonly active components used are chlorhexidine gluconate and povidone iodine. Of 3 reviews conducted between 2010 and 2012 comparing antiseptics, 2 were in favor of chlorhexidine; however, the latest was unable to draw conclusions.
Purpose: To verify whether recent evidence supports the hypothesis that chlorhexidine in preoperative antisepsis is more efficient than other antiseptics in reducing SSI rates.
Procedures: We conducted a systematic review from 2000-2014 in all languages. The primary end point was SSI incidence and secondary skin bacterial colonization.
Results: Nineteen studies were included. Meta-analysis were conducted for comparable studies for both outcomes. The results of the meta-analysis, including all of the studies in which chlorhexidine was compared with iodophor, were in favor of chlorhexidine for both SSI incidence (risk ratio [RR], 0.70; 95% confidence interval [CI], 0.52-0.92) and bacterial skin colonization (RR, 0.45; 95% CI, 0.36-0.55).
Conclusions: There is moderate-quality evidence supporting the use of chlorhexidine for preoperative skin antisepsis and high-quality evidence that the use of chlorhexidine is associated with fewer positive skin cultures. Further rigorous trials will be welcomed to attain stronger evidence as to the best antiseptic to be used before surgery.

Surgical site infections (SSIs) are one of the most frequent health care–associated infections (HCAIs), accounting for approximately 20% of all HCAIs and approximately 38% of the HCAIs in surgical patients. They have an incidence of up to 19%, depending on the kind of surgery.[1-3]

SSIs may involve the superficial or deep layers of the incision (two-thirds) or the organ or space manipulated or traumatized (one-third).[4]

SSIs can range from a wound discharge to a life-threatening condition, and they are associated with considerable morbidity. SSIs lead to an increase in the length of hospital stay from 3.3-32.5 days, and patients are twice as likely to die, twice as likely to spend time in

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intensive care, and 5 times more likely to be readmitted after discharge.[5-10]

Health care costs increase substantially for patients with SSI. In the United States, approximately 500,000 SSIs occur each year, with 3.7 million excess hospital days and >$1.6 billion in excess hospital costs per year.[11] In the United Kingdom, the excess cost for each infection has been calculated from £959-£6,103.[10] In the European Union, SSIs exact an economic toll of €1.5-€19.1 billion per year.[12]

The main additional costs are related to reoperation, extra nursing care, and drug treatment and litigation.

SSI prevention

Practices to prevent SSI are aimed at minimizing the number of microorganisms introduced into the operative site or enhancing the patient's defenses against infection by, for example, removing microorganisms that normally colonize the skin; preventing the multiplication of microorganisms at the operative site (eg, by using prophylactic antimicrobial therapy); minimizing tissue damage; and preventing access of microorganisms postoperatively using a wound dressing.[13]

The removal of transient bacteria and reduction of the number of commensal organisms with an antiseptic is recommended prior to surgery by several organizations, including the Centers for Disease Control and Prevention (CDC).[4,13-16] The purpose of the preoperative skin antisepsis is to reduce rapidly (within 10 minutes of application) the numbers of microorganisms within the surgical field prior to the wound incision and suppress regrowth for the duration of the surgical procedure and beyond.[17]

Two of the most commonly used active components in preoperative skin antisepsis are chlorhexidine gluconate and povidone iodine (PI). Another iodine-based skin disinfectant, iodine povacrylex in isopropyl alcohol, is commercially available.

It is generally recognized that chlorhexidine gluconate, although comparable with iodophors in terms of spectrum of antimicrobial activity, exhibits superiority in terms of a prolonged activity.[4,18] This confers an obvious advantage, especially for long-lasting surgical procedures.

In contrast with PI, the antimicrobial activity of chlorhexidine is not affected by the presence of body fluids.[19-21]

Rationale

The CDC recommends that 2% chlorhexidine-based preparations be used to cleanse the site of insertion of central venous and arterial catheters[22] but has not issued a recommendation as to which antiseptic should be used to prevent SSIs. On the contrary, chlorhexidine is recommended as skin antiseptic by Health Protection Scotland and the Canadian Patient Safety Institute.[14,15]

In 2010, a meta-analysis of 7 randomized controlled trials (RCTs) [23] (3,437 patients) was published, comparing chlorhexidine (0.5%-4%) with PI or other iodophors (0.7%-10%) for preoperative skin antisepsis. The use of chlorhexidine was associated with fewer SSIs (adjusted risk ratio, 0.64; 95% confidence interval [CI], 0.51-0.80) compared with iodine. In a cost-benefit model, sensitivity analysis documented that switching from iodine to chlorhexidine resulted in a net savings per surgical case of $16-$26.

Another meta-analysis of 6 RCTs comparing chlorhexidine (0.5%-4%) with PI for preoperative skin antisepsis yielded a pooled odds ratio of 0.68 (0.50-0.94, 95% CI; $P = .019$) for skin preparation with chlorhexidine versus PI.[24]

On the contrary, a review conducted in 2012 by Kamel et al[25] considering 3 skin antiseptics—iodophors, alcohol, or chlorhexidine gluconate, in any preparation—was unable to draw conclusions about which surgical site antiseptic is most effective for reducing SSIs.

Because new articles on the issue from 2012-2014 were published, we conducted an updated review.

Objectives

The aim of this review is to verify whether the most recent evidence supports the hypothesis that chlorhexidine used for perioperative antisepsis is more efficient than iodine compounds and other antiseptics in reducing the rate of SSIs. Furthermore, considering the relationship between cutaneous bacterial flora and SSI, we think it is necessary to evaluate the reduction of both. Therefore, we searched for studies, either RCTs or observational studies, in which the preoperative skin antisepsis with chlorhexidine was compared with antisepsis with other substances regarding the occurrence of SSI, the bacterial colonization, or both, in any kind of surgical procedure with cutaneous access and in any kind of patient.

We considered the primary end point of our review as the SSI incidence and the secondary end point as the skin bacterial colonization.

METHODS

Literature search strategy

The MEDLINE and Web of Science Core Collection databases were searched in July 2014 using the search terms *chlorhexidine AND (povidone iodine OR skin antisepsis OR surgical antisepsis OR preoperative antisepsis OR preoperative care OR preoperative preparation OR surgical infection OR wound infection OR healthcare acquired infection OR nosocomial infection OR hospital infection)*. The time span was from January 2000-July 2014 to reflect current clinical practice. All languages were searched.

Reference lists of retrieved reviews were browsed to identify additional relevant articles.

Selection criteria

Articles selected for inclusion in the review met the following criteria: (1) they were either RCTs or observational studies, both prospective or retrospective; (2) they compared preoperative chlorhexidine versus any other skin antiseptic; (3) they assessed for at least one of the outcomes of interest, SSI or skin bacterial colonization; (4) they assessed patients in whom the skin antisepsis was performed prior to surgery (ie, we retained studies in which skin bacterial colonization was the only outcome, but only if the study was performed in real practice, excluding studies performed on healthy volunteers); and (5) the surgical procedure, of every kind, was performed through cutaneous access. All types of patients were included. Studies evaluating chlorhexidine shower, bath, or foot bath prior to entry into the operating room were excluded for the purposes of this study. Noncomparative studies were excluded. So-called gray literature, such as conference abstracts, unpublished studies, or data obtained from personal communication, was not included.

Data analysis methods

Because of heterogeneity across the studies, results are partly described using a narrative approach; meta-analyses were conducted for comparable studies only, both for the outcome SSI incidence and for the outcome bacterial colonization rate. An appraisal of the quality of the evidence included in the meta-analysis, based on the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria,[26] which includes, for each of the considered outcomes, quality of the study, inconsistency, indirectness, imprecision, and publication bias, was conducted.

RESULTS

Quantity of research available

The electronic literature search yielded 1,134 results in the Web of Science database and 1,324 in the PubMed database. After eliminating the duplicates, 1,758 articles were retained.

After screening titles and abstracts, 1,728 citations were excluded, and 30 potentially relevant articles were retrieved for full-text review. Ten studies did not meet the inclusion criteria; 1 study[27] was excluded, even if respondent to the criteria, because only 2 patients were treated with chlorhexidine. Nineteen RCTs or observational studies[28-46] were judged eligible and were included in this review.

The reference lists of the retrieved reviews were also screened to identify additional articles, but no other relevant articles were identified responding to the criteria of the study because the only potentially relevant articles were issued at the beginning of the 1980s.

Study characteristics

An overview of the studies is provided in Supplementary Tables S1 and S2.

The effectiveness of chlorhexidine versus another or >1 skin antiseptic for reducing bacterial colonization and SSI was reported in 6 observational studies[28-33] and 13 RCTs[34-46] published between 2000 and 2014. Among the observational studies, 4 were retrospective, based on clinical charts review, and 2 were prospective, with follow-up of patients subject to surgery.

One study[38] reported bacterial colonization as a measure of antiseptic effectiveness and did not report SSI. Nine studies[34,36,37,39-43,46] reported both SSI and skin bacterial colonization: 8 studies did not specify which end point was primary or secondary, and 1 study[46] specified that the colonization rate was the primary end point and SSI incidence was the secondary end point. Nine studies reported SSI only.[28-33,35,44,45] The type of surgery performed varied across the studies: 8 studies[34,36,39-44] involved clean procedures, 7 studies regarded clean contaminated procedures,[28-30,32,35,38,46] and 4 studies included >1 class.[31,33,37,45]

Formulation (aqueous or alcoholic), concentration, and application method of antiseptics were not consistent across studies. Chlorhexidine was tested in all studies, but 1 study mixed it with alcohol (generally 70%, but in 2 studies[34,45] the concentration was not indicated); in the remaining study it was tested both in aqueous and in alcoholic solution, but the concentration was not cited.[32] The chlorhexidine concentration, when indicated, ranged from 0.5%-4%; in 1 study[32] it was not reported. The antiseptic more frequently tested against chlorhexidine was PI (16 studies), either in aqueous solution[30,32,35-39,41,46] or in combination with alcohol.[28,29,31,34,42,44,45] Isopropyl alcohol was most frequently combined with chlorhexidine, whereas the kind of alcohol was generally not specified for PI. Five studies tested iodine povacrylex[31,32,39,40,43] combined with isopropyl alcohol. In 1 study,[33] iodine was indicated with no other specifications. The only other antiseptic tested was chloroxylenol[40] (some studies tested >2 antiseptics).

The sample sizes across the studies ranged from 50 to approximately 7,700.

Nine studies[28-31,33-36,44] defined SSI according to CDC criteria: in 4 studies the assessment was based on predefined clinical criteria[32,37,45,46]; in the other ones no explicit criteria were cited. The follow-up period for detection of SSI was 30 days in 8 studies,[30,33-37,44,45] was not stated in 5 studies,[29,31,40-42] was limited to hospital stay in 1 study,[32] and varied between 2 weeks and 10 months in the other studies.

DATA SYNTHESIS

Infections

The incidence of SSI was assessed in 12 out of 13 RCTs and in the 6 observational studies.

Three RCTs[39,41,42] reported no infections in either group.

Two RCTs[35,37] and 2 cohort studies[28,29] reported a statistically significant reduction in SSI rates in chlorhexidine-prepared patients versus PI-prepared patients. The 2 RCTs, comparing chlorhexidine with PI antisepsis, showed an approximate 40% reduction in SSIs with chlorhexidine use, and the cohort studies showed a roughly 3-fold increase in SSIs with PI antisepsis.

Two observational studies[30,33] and 3 RCTs[34,36,44] reported reduced SSI rates in chlorhexidine-prepared patients versus PI-prepared patients, but without statistical significance.

In contrast, 4 RCTs[40,43,45,46] and 1 prospective cohort study[31] suggested that an iodine solution is more effective than chlorhexidine for reducing SSIs, again without statistical significance.

An observational study[33] comparing 2 formulations of chlorhexidine and 2 iodophors found no statistically significant difference between the risk-adjusted event rates for the 4 antiseptics.

Meta-analyses were performed for the RCTs evaluating SSI as an outcome and where SSIs developed. Based on the GRADE criteria,[26] there is moderate-quality evidence assessing the outcome of SSI (a deduction of 1 point was made for study quality).

The first meta-analysis included all of the studies in which chlorhexidine was compared with a iodophor,[34-37,40,43-46] and the results were in favor of chlorhexidine (risk ratio [RR], 0.70; 95% CI, 0.52-0.92) (Fig 1).

A second meta-analysis comprised just the comparisons between chlorhexidine and PI,[34-37,44-46] and the results were again in favor of chlorhexidine (RR, 0.68; 95% CI, 0.51-0.90) (Fig 2).

The third meta-analysis included the studies comparing chlorhexidine with iodine povacrylex[40,43]: the results were in favor of the latter because there were no events in the patients treated with this substance compared with 2 events in the chlorhexidine group, but this lacked statistical significance (RR, 3; 95% CI, 0.32-28.31) (Fig 3).

A fourth meta-analysis comprised the studies in which the iodophor was used with alcohol,[34,40,43-45] and the results were in favor of this antiseptic, but without statistical significance, again given the low number of events (RR, 1.14; 95% CI, 0.55-2.34) (Fig 4).

Bacterial colonization

Skin colonization was reported by 10 RCTs but by none of the observational studies. All of the studies but 1 study[34] evaluated colonization as bacterial counts and the occurrence of defined bacterial genera. Eight studies measured colonization rates (ie, percentage of subjects in which cultures were positive), and 3 studies measured colony counts (2 studies evaluated both).

Five RCTs showed a statistically significant lower presurgical skin colonization in patients prepared with chlorhexidine in alcohol compared with patients prepared with PI,[37-39,41] iodine povacrylex,[39,40] or chloroxylenol.[40]

Five studies[34,36,42,43,46] found no statistically significant difference in skin colonization after treatment with different antiseptics, even if there was a trend toward a reduction in colonization rate[42,43,46] or colony counts[34,36] with the use of chlorhexidine. One of these studies[46] evaluated the colonization rate at 18 hours, and then a statistically significant lower colonization rate in patients treated with chlorhexidine was found.

Meta-analyses were performed for comparable studies evaluating antiseptic effect with skin colonization rate; only the postpreparation colonization rate was considered. Based on the

Model		Statistics for each study					SSI / Total		Weight (Fixed)			
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Chlorhexidine	Iodophor	Relative weight	Relative weight	Relative weight	Relative weight
	Ostrander	3,000	0,126	71,508	0,679	0,497	1 / 40	0 / 40	0,78		0,78	
	Paocharoen	0,625	0,207	1,884	-0,835	0,404	5 / 250	8 / 250	6,48		6,48	
	Darouiche	0,593	0,411	0,855	-2,803	0,005	39 / 391	71 / 422	59,04		59,04	
	Savage	3,000	0,125	71,923	0,678	0,498	1 / 50	0 / 50	0,78		0,78	
	Veiga	0,111	0,006	2,042	-1,479	0,139	0 / 125	4 / 125	0,93		0,93	
	Sistla	0,737	0,380	1,428	-0,904	0,366	14 / 200	19 / 200	18,01		18,01	
	Perek	0,500	0,096	2,591	-0,826	0,409	2 / 44	4 / 44	2,92		2,92	
	Rodriguez	1,556	0,628	3,855	0,955	0,339	11 / 103	7 / 102	9,59		9,59	
	Kunkle	2,095	0,205	21,423	0,624	0,533	2 / 21	1 / 22	1,46		1,46	
Fixed		0,695	0,524	0,920	-2,542	0,011	75 / 1224	114 / 1255				
Random		0,695	0,524	0,920	-2,542	0,011	75 / 1224	114 / 1255				

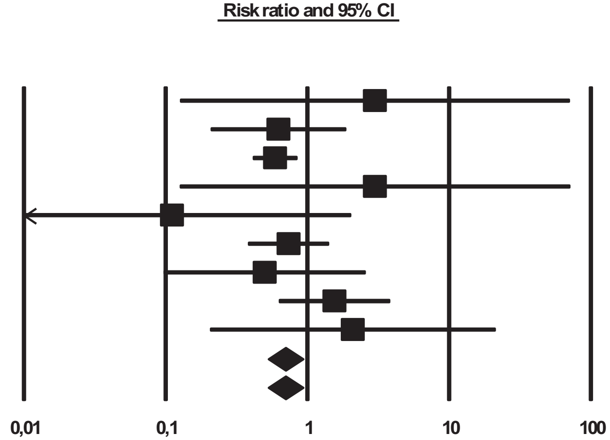

Fig 1. Meta-analysis of studies considering SSIs as outcome: comparison of chlorhexidine with iodophors. On the left side of the forest plot are studies that favor chlorhexidine; right side, studies that favor iodophors. *CI*, confidence interval; *SSI*, surgical site infection.

Model		Statistics for each study					SSI / Total		Weight (Fixed)			
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Chlorhexidine	Povidone Iodine	Relative weight	Relative weight	Relative weight	Relative weight
	Paocharoen	0,625	0,207	1,884	-0,835	0,404	5 / 250	8 / 250	6,58		7,73	
	Darouiche	0,593	0,411	0,855	-2,803	0,005	39 / 391	71 / 422	59,98		54,36	
	Veiga	0,111	0,006	2,042	-1,479	0,139	0 / 125	4 / 125	0,95		1,15	
	Sistla	0,737	0,380	1,428	-0,904	0,366	14 / 200	19 / 200	18,30		20,18	
	Perek	0,500	0,096	2,591	-0,826	0,409	2 / 44	4 / 44	2,96		3,55	
	Rodriguez	1,556	0,628	3,855	0,955	0,339	11 / 103	7 / 102	9,74		11,24	
	Kunkle	2,095	0,205	21,423	0,624	0,533	2 / 21	1 / 22	1,48		1,79	
Fixed		0,679	0,511	0,901	-2,683	0,007	73 / 1134	114 / 1165				
Random		0,691	0,506	0,945	-2,313	0,021	73 / 1134	114 / 1165				

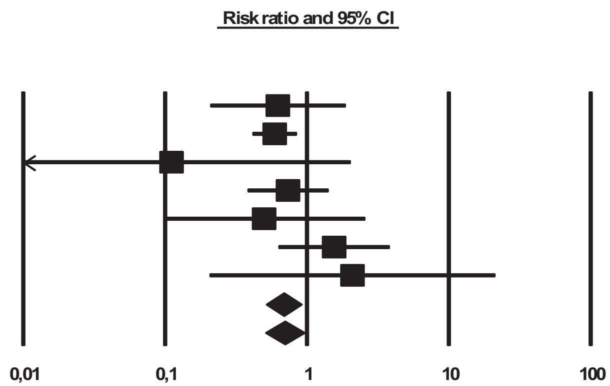

Fig 2. Meta-analysis of studies considering SSIs as outcome: comparison of chlorhexidine with povidone iodine. On the left side of the forest plot are studies that favor chlorhexidine; right side, studies that favor povidone iodine. *CI*, confidence interval; *SSI*, surgical site infection.

Model	Study name	Statistics for each study					SSI / Total		Weight (Fixed)			
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Chlorhexidine	Povacrylex Iodine	Relative weight	Relative weight	Relative weight	Relative weight
	Ostrander	3,000	0,126	71,508	0,679	0,497	1 / 40	0 / 40	50,09		50,09	
	Savage	3,000	0,125	71,923	0,678	0,498	1 / 50	0 / 50	49,91		49,91	
Fixed		3,000	0,318	28,305	0,959	0,337	2 / 90	0 / 90				
Random		3,000	0,318	28,305	0,959	0,337	2 / 90	0 / 90				

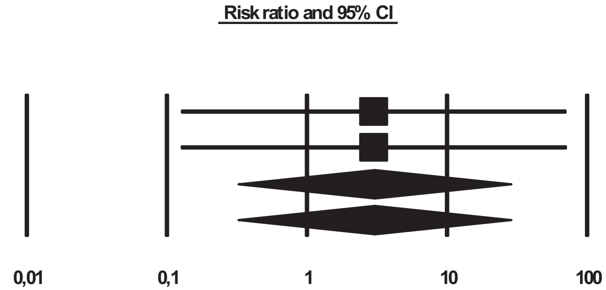

Fig 3. Meta-analysis of studies considering SSIs as outcome: comparison of chlorhexidine with iodine povacrylex. On the left side of the forest plot are studies that favor chlorhexidine; right side, studies that favor iodine povacrylex. *CI*, confidence interval; *SSI*, surgical site infection.

Model	Study name	Statistics for each study					SSI / Total		Weight (Fixed)			
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Chlorhexidine	Iodophor-alcohol	Relative weight	Relative weight	Relative weight	Relative weight
	Ostrander	3,000	0,126	71,508	0,679	0,497	1 / 40	0 / 40	5,23		7,11	
	Savage	3,000	0,125	71,923	0,678	0,498	1 / 50	0 / 50	5,21		7,09	
	Veiga	0,111	0,006	2,042	-1,479	0,139	0 / 125	4 / 125	6,21		8,36	
	Perek	0,500	0,096	2,591	-0,826	0,409	2 / 44	4 / 44	19,44		23,08	
	Rodriguez	1,556	0,628	3,855	0,955	0,339	11 / 103	7 / 102	63,91		54,36	
Fixed		1,135	0,549	2,343	0,341	0,733	15 / 362	15 / 361				
Random		1,054	0,442	2,514	0,119	0,905	15 / 362	15 / 361				

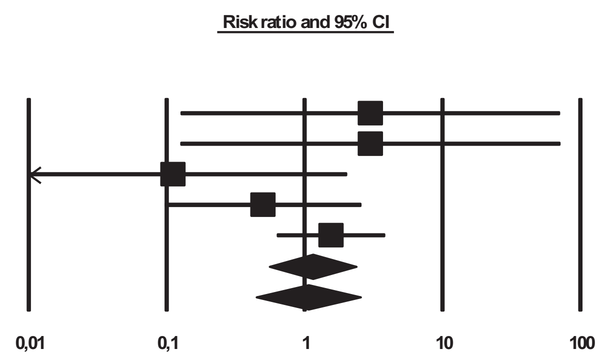

Fig 4. Meta-analysis of studies considering SSIs as outcome: comparison of chlorhexidine and alcohol with iodophor and alcohol. On the left side of the forest plot are studies that favor chlorhexidine and alcohol; right side, studies that favor iodophor and alcohol. *CI*, confidence interval; *SSI*, surgical site infection.

GRADE criteria,[26] there is high-quality evidence available for the outcome of skin culture positive result (1 point was deducted for study quality, and 1 point was added for large effect size).

A first meta-analysis was performed comprising all of the RCTs in which the use of chlorhexidine was compared with the use of iodophor.[37-43,46] It found that the use of chlorhexidine significantly decreased the risk for a positive skin culture after application, compared with iodophors (RR, 0.45; 95% CI, 0.36-0.55) (Fig 5).

A second meta-analysis included only the 5 studies comparing chlorhexidine with PI[37-39,41,42,46]: again the results were clearly in favor of chlorhexidine (RR, 0.44; 95% CI, 0.35-0.56) (Fig 6).

A third meta-analysis was done for the 3 studies opposing chlorhexidine to iodine povacrylex,[39,40,43] and the results were similar (RR, 0.43; 95% CI, 0.24-0.76) (Fig 7).

A fourth meta-analysis comprised the studies in which iodophor was used with alcohol,[39,40,42,43] and the results were again in favor of chlorhexidine (RR, 0.45; 95% CI, 0.26-0.78) (Fig 8).

Adverse events

Three RCTs comparing chlorhexidine with PI[35,37,38] assessed adverse events related to skin antisepsis. In the Darouiche et al study[35] the incidence of events as pruritus and/or erythema was the same in both groups (0.7%), in the Paocharoen et al study[37] there were 2 cases (0.8%; 2/250) of hypersensitivity in the PI group, and in Yeung et al study[38] no events occurred.

No fire or chemical skin burns occurred in the operating room. In the other studies adverse events were not cited.

DISCUSSION

Our results are consistent with those of the reviews of Lee et al[23] and Noorani et al.[24]

We report that there is moderate-quality evidence supporting the use of chlorhexidine over iodine for preoperative skin antisepsis to prevent SSI. Additionally, there is high-quality evidence that the use of chlorhexidine is associated with fewer skin culture positive results after application.

The meta-analysis of the RCTs showed a 30% reduction in the incidence of SSI among patients treated with chlorhexidine, compared with those who received iodine.

It is not surprising that our meta-analysis gave results similar to those conducted by Noorani et al and Lee et al because most studies are the same in the 3 reviews.

A criticism moved toward both the 2 previously published reviews was that in their meta-analyses, the authors made no distinction between solutions containing alcohol and those that did not when they drew the conclusion that chlorhexidine is superior to iodophor.[47-50] As Walsh et al[51] answered that, given the better efficacy of chlorhexidine-alcohol respect a widely used antiseptic as aqueous PI, the composition of the antiseptic is an academic matter. Lee et al did a subgroup meta-analysis including just the studies in which PI was used in combination with alcohol, and the results were in favor of chlorhexidine.[52] We too did a subgroup meta-analysis including just the studies in which PI was used in combination with alcohol, and the results were in favor of chlorhexidine (RR, 0.45; 95% CI, 0.26-0.78) (Fig 8) regarding the outcome colonization rate, whereas considering SSI were not statistically significant, given the low number of SSIs (RR, 1.14; 95% CI, 0.55-2.34) (Fig 4).

The colonization rate is a good outcome indicator and therefore should not be considered a surrogate one because the aim of a skin antiseptic is to reduce skin flora. Obviously, being that the ultimate aim is the reduction of SSI occurrence, this practice affects only one SSI risk factor and not others, such as the environment and those related to patients.

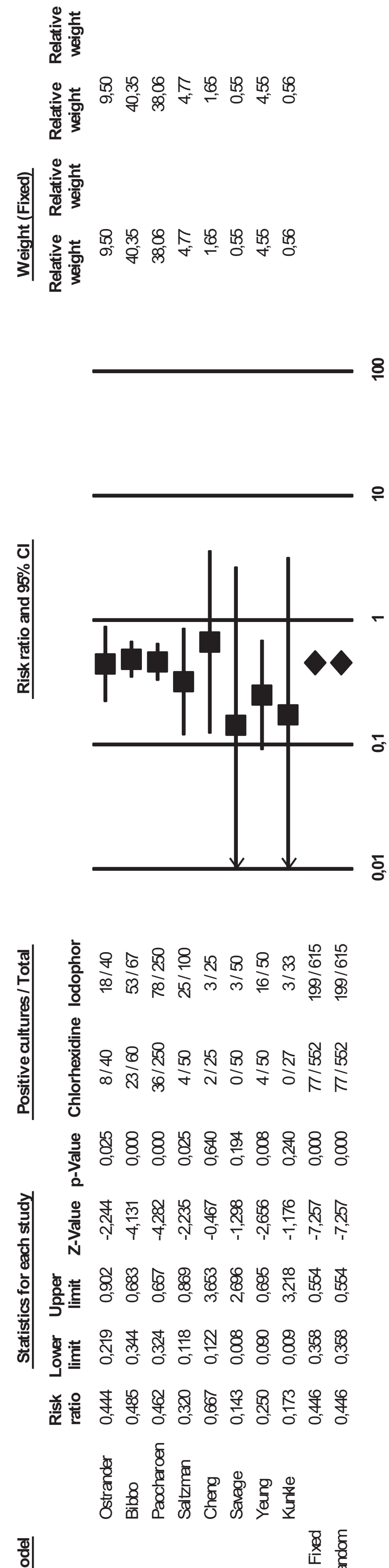

Fig 5. Meta-analysis of studies considering colonization rate as outcome: comparison of chlorhexidine with iodophors. On the left side of the forest plot are studies that favor chlorhexidine; right side, studies that favor iodophors. *CI*, confidence interval.

Model		Statistics for each study					Positive cultures / Total		Weight (Fixed)			
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Chlorhexidine	Povidone Iodine	Relative weight	Relative weight	Relative weight	Relative weight
	Bibbo	0,485	0,344	0,683	-4,131	0,000	23 / 60	53 / 67	44,97		44,97	
	Paocharoen	0,462	0,324	0,657	-4,282	0,000	36 / 250	78 / 250	42,42		42,42	
	Saltzman	0,250	0,090	0,695	-2,656	0,008	4 / 50	16 / 50	5,08		5,08	
	Cheng	0,667	0,122	3,653	-0,467	0,640	2 / 25	3 / 25	1,84		1,84	
	Kunkle	0,173	0,009	3,218	-1,176	0,240	0 / 27	3 / 33	0,62		0,62	
	Yeung	0,250	0,090	0,695	-2,656	0,008	4 / 50	16 / 50	5,08		5,08	
Fixed		0,444	0,352	0,559	-6,912	0,000	69 / 462	169 / 475				
Random		0,444	0,352	0,559	-6,912	0,000	69 / 462	169 / 475				

Risk ratio and 95% CI

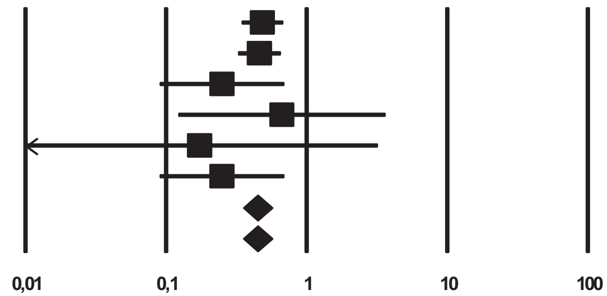

Fig 6. Meta-analysis of studies considering colonization rate as outcome: comparison of chlorhexidine with povidone iodine. On the left side of the forest plot are studies that favor chlorhexidine; right side, studies that favor povidone iodine. *CI*, confidence interval.

Model	Studyname	Statistics for each study					Positive cultures / Total		Weight (Fixed)			
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Chlorhexidine	Povacrylex Iodine	Relative weight	Relative weight	Relative weight	Relative weight
	Ostrander	0,444	0,219	0,902	-2,244	0,025	8 / 40	18 / 40	68,27		68,27	
	Saltzman	0,444	0,146	1,349	-1,431	0,152	4 / 50	9 / 50	27,76		27,76	
	Savage	0,143	0,008	2,696	-1,298	0,194	0 / 50	3 / 50	3,97		3,97	
Fixed		0,425	0,237	0,763	-2,867	0,004	12 / 140	30 / 140				
Random		0,425	0,237	0,763	-2,867	0,004	12 / 140	30 / 140				

Risk ratio and 95% CI

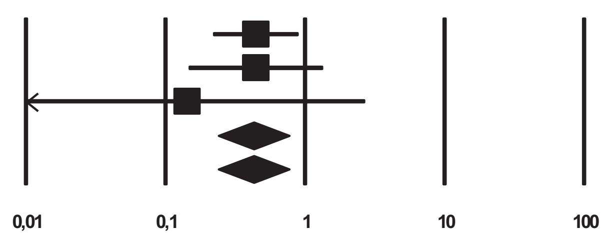

Fig 7. Meta-analysis of studies considering colonization rate as outcome: comparison of chlorhexidine with iodine povacrylex. On the left side of the forest plot, studies that favor chlorhexidine; right side, studies that favor iodine povacrylex. *CI*, confidence interval.

Model	Study name	Statistics for each study					Positive cultures / Total		Weight (Fixed)			
		Risk ratio	Lower limit	Upper limit	Z-Value	p-Value	Chlorhexidine	Iodophor-alcohol	Relative weight	Relative weight	Relative weight	Relative weight
	Ostrander	0,444	0,219	0,902	-2,244	0,025	8 / 40	18 / 40	61,05		61,05	
	Saltzman	0,444	0,146	1,349	-1,431	0,152	4 / 50	9 / 50	24,82		24,82	
	Cheng	0,667	0,122	3,653	-0,467	0,640	2 / 25	3 / 25	10,58		10,58	
	Savage	0,143	0,008	2,696	-1,298	0,194	0 / 50	3 / 50	3,55		3,55	
Fixed		0,446	0,256	0,775	-2,863	0,004	14 / 165	33 / 165				
Random		0,446	0,256	0,775	-2,863	0,004	14 / 165	33 / 165				

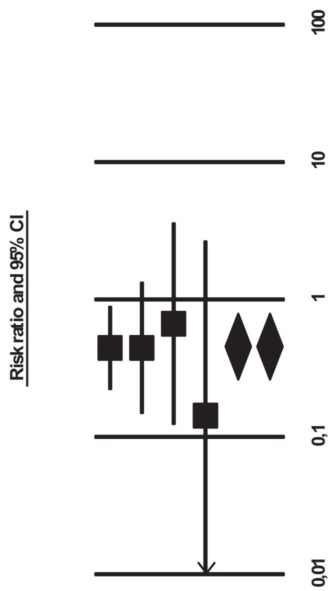

Fig 8. Meta-analysis of studies considering colonization rate as outcome: comparison of chlorhexidine and alcohol with iodophor and alcohol. On the left side of the forest plot are studies that favor chlorhexidine and alcohol; right side, studies that favor iodophor and alcohol.

We did not include the Berry et al study[53] because it was published in 1982, and this could have had an influence on the resulting differences between our review and the Lee et al review,[23] because in that study a consistent number of SSIs occurred and the results of the comparison between chlorhexidine/spirit and povidone-isopropyl alcohol were in favor of the former. Another study found in the Lee et al[23] and Noorani et al[24] reviews, but not in our study (because the antiseptic was used on a mucous membrane), was conducted by Culligan et al,[54] in which the comparison was between aqueous chlorhexidine and aqueous PI and the effect on vaginal contamination; the results were still in favor of the former. On the other hand, the efficacy of aqueous chlorhexidine compared with that of alcoholic chlorhexidine was tested in a study conducted by Hibbard et al[55] on healthy subjects; they did not find any statistically significant differences in microbial count reduction among the 2 treatments at 10 minutes or 6 hours after antiseptic application.

Some of the critics of the Lee et al review were the authors of the prospective cohort study comparing 10% PI/70% alcohol, 2% chlorhexidine/70% alcohol, and iodine povacrylex/alcohol,[31] which they cite as a demonstration of iodine superiority. Actually, the study was unable to demonstrate a significant reduction of SSIs in the multivariate analysis (odds ratio, 1.35; 95% CI, 0.97-1.87; $P = .073$), despite the inclusion of 3,209 patients.

Interestingly, 2 other cohort studies (retrospective studies)[27,28] included in our review, comparing alcoholic solutions of PI and chlorhexidine, gave statistically significant results in favor of chlorhexidine.

A recent Cochrane review[56] stated in its conclusion that "a comprehensive review of current evidence found evidence from a single study that preoperative skin preparation with 0.5% chlorhexidine solution in methylated spirits was more effective in preventing SSIs following clean surgery than alcohol-based povidone iodine paint" and that "no other comparisons yielded statistically significant differences." The cited study[53] is not included in our review because it dates to 1982. The Cochrane review yields different results from ours because it considers clean surgery only, and most studies had no events in both groups, whereas it excluded studies with a consistent number of events which we included.[35,37]

In the same Cochrane review,[56] the 2 comparisons between aqueous and alcoholic solutions of iodophors found no statistically significant differences in efficacy for the 2 formulations.

In our review, no adverse events were related specifically to the use of chlorhexidine. Actually, chlorhexidine is recognized as well tolerated, with a low rate of episodes of hypersensitivity and skin irritation, and rare cases of severe allergic reactions, including anaphylaxis, have been reported. Caution should nevertheless be exercised to avoid direct contact with the eyes and the insides of the ears (to avoid vestibular and ototoxicity).[57]

As for other alcohol-based antiseptics, the risk exists that chlorhexidine-alcohol combined with the oxygen-rich environment of an anesthetizing location could ignite when exposed to a heat-producing device.

The risk of fire can be significantly reduced using skin preparation solutions packaged to ensure controlled delivery in unit dose applicators and providing clear and explicit instructions. Dripping or pooling of the solution must be avoided on sheets, padding, positioning equipment, adhesive tape, and on or under the patient (umbilicus and groin), and the solution must be completely dry prior to draping.[58]

Clinicians should be aware of the risk of surgical fires or burns associated with the use of alcohol-based preparation solutions, but there is a need to balance this risk with the significant risk posed to patients by SSIs.[59]

An additional risk of infection identified by the Food and Drug Administration is contaminated topical antiseptic agents.

Governing bodies, such as the Medicines and Healthcare products Regulatory Agency and Food and Drug Administration, are encouraging companies to adopt single-use packaging and to label their product as sterile or nonsterile (http://www.fda.gov/Drugs/DrugSafety/ucm374838.htm).

The use of 2% chlorhexidine gluconate in 70% isopropyl alcohol skin preparation before surgery is recommended by Health Protection Scotland,[14] the Canadian Patient Safety Institute,[15] and the Joint Royal College of Surgeons in Ireland/Royal College of Physicians of Ireland Working Group on Prevention of Surgical Site Infection,[60] which bases its recommendations on the literature review performed by Health Protection Scotland. The Health Protection Scotland and the Joint Royal College of Surgeons in Ireland/Royal College of Physicians of Ireland Working Group on Prevention of Surgical Site Infection grade the recommendation as 1A "strong recommendation based on high to moderate quality evidence," according to the Healthcare Infection Control Practices Advisory Committee categories.

CONCLUSIONS

Chlorhexidine gluconate, PI, and iodine povacrylex in isopropyl alcohol are the most commonly used active components in preoperative skin antisepsis. Chlorhexidine gluconate, whereas it is comparable with iodophors for spectrum of activity, shows a prolonged activity and is not affected by the presence of body fluid, with a significant advantage in several surgical procedures.

We conducted this review, updated up to 2014, to verify whether chlorhexidine used for perioperative antisepsis is more efficient than iodine compounds in reducing SSIs and bacterial colonization, respectively, as primary and secondary end points.

Even if the available studies are heterogeneous (different kinds of surgery, formulation and method of application of the antiseptic, duration of follow-up, and primary and secondary end points), making it difficult to attain strong conclusions, there is evidence of moderate-quality studies in favor of chlorhexidine gluconate compared with iodine in the prevention of SSI and evidence of high-quality studies in favor of chlorhexidine gluconate compared with iodine in reducing the bacterial colonization of the skin, which should not be considered as a surrogate marker because it is the primary objective of skin antisepsis.

In addition, it must be taken into account that alcoholic solutions have the advantage of drying faster than aqueous solutions on the skin, reducing the time of surgical site preparation.

Finally, no adverse events were found to be specifically related to the use of chlorhexidine gluconate. The risk of fire can be reduced using solutions packaged to ensure controlled delivery. These unit dose applicators also keep the antiseptic sterile, eliminating the risk of bacterial contamination of the product and therefore of the skin to be treated.

Further rigorous RCTs will be welcomed to attain stronger evidence as to the best antiseptic to be used prior to surgery given the current burden of SSIs.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ajic.2016.09.017.

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