

TITLE: Pre-Operative Skin Preparation Solutions: A Review of the Evidence on Safety

DATE: 31 May 2011

CONTEXT AND POLICY ISSUES:

Prevention of surgical site infection involves a suite of tools including antibiotic and antiseptic prophylaxis, hair removal, perioperative glucose control, and perioperative normothermia.¹ Topical antiseptics applied to the patient preoperatively to reduce the risk of infection are primarily alcohol, iodine, or chlorhexidine gluconate (CHG) (in aqueous or alcohol base).² However, there are some safety concerns surrounding these antiseptic agents: improper use of chlorhexidine and povidone iodine (PI) can cause allergic reaction or chemical burns,³⁻⁵ and alcohol, used either alone or as a base for CHG or PI, introduces the risk of surgical fire.⁶

Safer Healthcare Now!,¹ which helps inform Canadian practice, recommends the use of alcohol-based CHG solution for pre-surgical skin preparation followed by sufficient time to allow the solution to dry prior to making the first incision. Similar guidance from NICE⁷ recommends ensuring antiseptic skin preparations are dried and that pooling of alcohol-based preparations is avoided to reduce fire risk. The purpose of this review is to examine the clinical evidence regarding the safety of pre-operative skin preparation products in the surgical setting.

RESEARCH QUESTIONS:

1. What is the evidence on the clinical safety of iodophor, alcohol, and chlorhexidine gluconate (aqueous or alcoholic) products for pre-operative skin preparation in the surgical setting?

KEY MESSAGE:

Safety issues surrounding pre-operative skin antiseptic products are rare and are captured mainly in case reports.

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METHODS:**Literature search strategy**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2011, Issue 5), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2001 and May 10, 2011.

Selection criteria and method

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult and pediatric patients undergoing surgery
Intervention	Iodophor, alcohol and chlorhexidine gluconate (aqueous or alcoholic) based solutions
Comparator	Not specified
Outcomes	Clinical harms: safety issues, advisories, warnings
Study designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and observational studies.

Exclusion criteria

Studies were excluded if they did not meet the selection criteria, were duplicate publications or included in a selected systematic review, or were published prior to 2001.

Critical appraisal of individual studies

The quality of included systematic reviews was assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool.⁸ Randomized and non-randomized study quality was assessed using the Downs and Black instrument.⁹ A numeric score was not calculated for each study. Instead, strengths and weakness of each study were summarized and described.

A formal quality assessment of case reports was not conducted since these study designs are considered to be inferior quality. The quality of these studies will be discussed with other limitations.

SUMMARY OF EVIDENCE:

Quantity of research available

The literature search yielded 277 citations. Upon screening titles and abstracts, 258 citations were excluded and 18 potentially relevant articles were retrieved for full-text review. An additional three potentially relevant reports were identified by hand searching. Of the 21 potentially relevant reports, ten did not meet the inclusion criteria. Eleven publications were included in this review. The study selection process is outlined in a PRISMA flowchart (Appendix 1).¹⁰ One systematic review,¹¹ two RCTs,^{12,13} one retrospective chart review,¹⁴ and seven case reports,^{5,15-20} describing a total of 14 patients, met inclusion criteria. Study characteristics and findings are summarized in Appendix 2.

Summary of study characteristics

Country of origin

One systematic review, prepared by Australian authors, included RCTs from different countries.¹¹ One RCT¹² came from the USA and one RCT¹³ was performed in Thailand. One retrospective observational study reported cases from three centres in Germany.¹⁴ Of the 14 cases described in seven publications, six occurred in Denmark,^{17,19} three in Israel,⁵ two in New Zealand,²⁰ two in the USA,^{15,18} and one in Taiwan.¹⁶

Interventions and comparators

The systematic review compared pre-operative bathing with chlorhexidine to placebo.¹¹ Two RCTs compared alcoholic chlorhexidine solutions to povidone-iodine.^{12,13} The retrospective analysis reviewed charts based on outcome, not intervention, and included outcomes based on PI use.¹⁴ Among the case reports, four involved chlorhexidine in alcohol^{17,19,20} and three involved chlorhexidine but did not specify the base.^{17,19} Four cases were the result of PI in alcohol,^{5,16,18,20} one involved aqueous PI,¹⁵ and two used PI in an unspecified base.⁵

Outcomes measured

The systematic review,¹¹ one RCT,¹³ and six cases^{17,19} reported allergic reactions. One RCT,¹² the observational study,¹⁴ and five cases^{5,15,16} reported chemical burns. The same RCT¹² and three cases^{18,20} involved operating room fires.

Summary of critical appraisal

The included systematic review¹¹ was based on a comprehensive literature search, with study selection and data extraction performed in duplicate, and characteristics and quality of included studies were described in detail. However, it was unclear whether grey literature was included in the search strategy, and there was no assessment of the risk of publication bias. Both RCTs^{12,13} clearly reported objectives, outcomes, and potential confounders, but failed to report the characteristics of patients lost to follow-up and participation rates. Statistical methods were described, but neither study was designed to assess safety and may not have been large enough to detect rare events. The retrospective chart review¹⁴ had clearly stated objectives and outcomes, and patient characteristics and study findings were clearly described. Because of study design, there was no randomization or blinding. Statistical analyses were not performed in

this study.¹⁴ Formal appraisal of case reports was not performed due to the inferior quality of this type of evidence. A summary of strengths and limitations of the appraised studies can be found in Table 1.

Table 2: Summary of Critical Appraisal

Author, Year, Country	Study design	Strengths	Limitations
Webster, ¹¹ 2011, Australia	Systematic Review; 2 RCTs (3,589 patients) reporting on safety	<ul style="list-style-type: none"> Comprehensive literature search based on pre-defined criteria 	<ul style="list-style-type: none"> Unclear whether grey literature was searched No assessment of publication bias
Darouiche, ¹² 2010, USA	RCT (n = 849)	<ul style="list-style-type: none"> Randomization method described Clear reporting of objectives and outcomes Description of statistical methods 	<ul style="list-style-type: none"> Sampling method and participation rate not reported Study not designed for safety outcomes
Paocharoen, ¹³ 2009, Thailand	RCT (n = 500)	<ul style="list-style-type: none"> Clear reporting of objectives and outcomes Patients randomized to each intervention Description of statistical methods 	<ul style="list-style-type: none"> Characteristics of interventions not completely described No blinding of patients or outcome assessors Study not designed for safety outcomes
Demir, ¹⁴ 2006, Germany	Retrospective chart review (n = 19 surgical burn accidents)	<ul style="list-style-type: none"> Clear description of objectives, participants and findings 	<ul style="list-style-type: none"> Lack of randomization or blinding Lack of statistical analysis

Summary of findings

Allergic reaction

One systematic review¹¹ identified two RCTs that included allergic reaction as an outcome and found no statistically significant difference in allergy rate between chlorhexidine and placebo (0.5% versus 0.6%, RR 0.89, 95% CI 0.36 to 2.19). One RCT¹² identified three patients (0.7%) treated with chlorhexidine and three (0.7%) treated with PI who experienced pruritus, erythema, or both. One RCT¹³ identified two cases of skin irritation (0.8%) among 250 patients whose skin was prepared with PI scrub, and detected no allergic reaction in patients treated with chlorhexidine in alcohol (n = 250). Six cases of allergic reaction to chlorhexidine preparations were identified.^{17,19} Four of these cases¹⁷ were anaphylactic reactions to chlorhexidine and two¹⁹ were cases of eczema caused by curcumin used to give CHG a yellow colour.

Chemical burns

One RCT¹² identified no cases of chemical skin burn in a total of 849 subjects receiving either chlorhexidine-alcohol (n = 409) or aqueous PI (n = 440). One retrospective chart review¹⁴ identified 19 patients with burn accidents during surgery. Of these, five (26%) were chemical burns after receiving PI as a pre-operative antiseptic agent. Case reports^{5,15,16} identified an additional five cases of chemical burns related to PI use in surgery.

Surgical Fires

One RCT¹² reported that there were no cases of operating room fires in 849 surgeries with either chlorhexidine-alcohol (n = 409) or aqueous PI (n = 440). Case reports of two fires in surgeries using PI-alcohol skin preparations^{18,20} and one in surgery using chlorhexidine-alcohol as a skin preparation²⁰ were identified.

Limitations

This report is limited by the lack of high-quality evidence on rates of allergic reaction, chemical burn, or operating room fires associated with each skin antiseptic. Case reports are considered inferior evidence and while they are useful for describing individual rare events, they give no indication of the frequency of these events. While one systematic review¹¹ and two RCTs^{12,13} that reported safety outcomes were identified, these studies focused on effectiveness of treatment and were not designed to capture potentially rare safety issues. One retrospective analysis¹⁴ reviewed cases of accidental burns during surgery and their causes but gave no indication of the frequency of these kinds of events

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Two RCTs^{12,13} indicated low rates of allergic reaction to either CHG in alcohol or PI, and one systematic review¹¹ found no statistically significant difference in allergic reaction rates when comparing CHG to placebo. One retrospective analysis¹⁴ found PI-related chemical burns to be responsible for 26% of patients with surgical burn accidents.

While safety issues with PI, CHG, and alcohol-base pre-surgical skin antiseptic agents appear rare, adverse safety outcomes do exist as demonstrated by six allergic reactions, five chemical burns, and three operating room fires identified in case reports.^{5,15-20} Larger, safety-oriented studies are necessary to determine the risk of these events.

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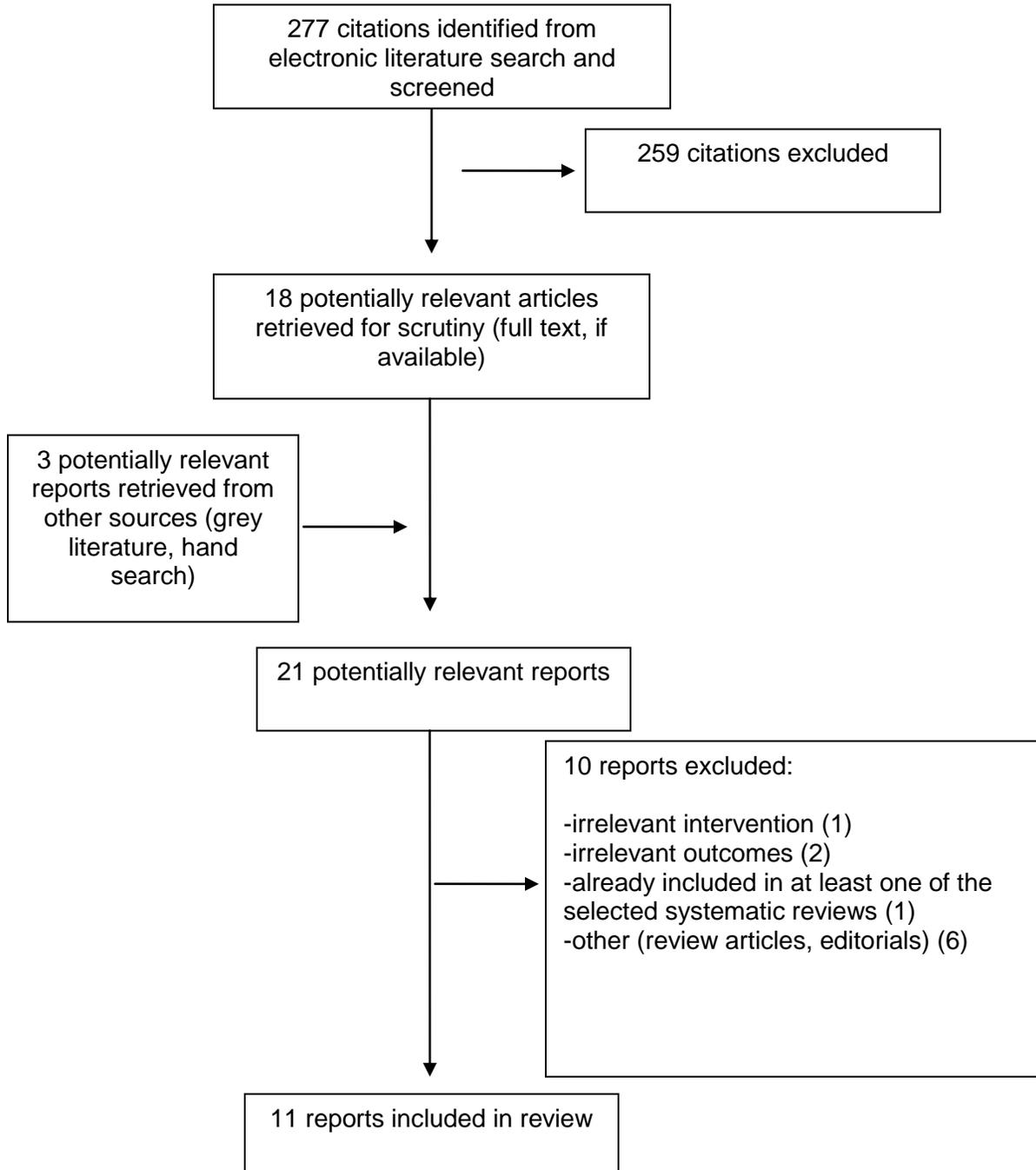
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APPENDICES:

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Summary of Included Studies

Author, Year, Country	Study Design	Interventions and comparators	Findings
Webster, ¹¹ 2011, Australia	Systematic Review, including 2 RCTs (3,589 patients) reporting on safety	4% CHG, base not described (n = 1,804); Placebo (n = 1785)	Allergic reaction CHG: 9 events (0.5%) Placebo: 10 events (0.6%) RR 0.89, 95% CI 0.36 to 2.19
Darouiche, ¹² 2010, USA	RCT (n = 849)	2% CHG in 70% isopropyl alcohol (IPA) (n = 409); 10% aqueous PI (n = 440)	Allergic reaction CHG: 3 events (0.7%) PI: 3 events (0.7%) No cases of chemical or operating room fire reported.
Paocharoen, ¹³ 2009, Thailand	RCT (n = 500)	4% CHG in 70% IPA (n = 250); PI (solution not described) (n = 250)	Allergic reaction CHG: 0 events PI: 2 events (0.8%)
Demir, ¹⁴ 2006, Germany	Retrospective chart review	Patients with surgical burn accidents (n = 19)	Chemical burn in five patients (26%) after receiving aqueous PI skin preparation
Rees, ¹⁵ 2011, USA	Case report (1 case)	10% aqueous PI	Chemical burn
Meltzer, ¹⁸ 2005, USA	Case report (1 case)	5% PI in 62% ethanol	Operating room fire
Fischer, ¹⁹ 2004, Denmark	Case report (2 cases)	0.5% CHG in 83% ethanol (n = 1); CHG (solution not described, n = 1)	Both patients experienced an allergic reaction caused by curcumin used to colour CHG solutions.
Tooher, ²⁰ 2004, New Zealand	Case report (2 cases)	PI in 70% alcohol, concentration not described (n = 1); 0.5% CHG in 70% alcohol (n = 1)	Two cases of operating room fire.
Liu, ¹⁶ 2003, Taiwan	Case report (1 case)	10% PI in 70% alcohol	Chemical burn
Garvey, ¹⁷ 2001, Denmark	Case report (4 cases)	0.5% CHG in ethanol (n = 2); CHG, solution not described (n = 2)	Four cases of anaphylactic reaction due to CHG allergy
Nahlieli, ⁵ 2001, Israel	Case report (3 cases)	10% PI in 70% alcohol (n = 1); PI, solution not described (n = 2)	Three cases of chemical burn