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SCIENTIFIC REVIEW

A Meta-analysis of Prophylaxis of Surgical Site Infections with Topical Application of Povidone Iodine Before Primary Closure

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Abstract

Background Povidone iodine (PVI) is a widely used antiseptic solution among surgeons. A meta-analysis based on randomized controlled trials (RCTs) was conducted to establish whether application of PVI before wound closure could reduce surgical site infection (SSI) rates.

Methods Systematic review of MEDLINE/PubMed, Scopus, CINAHL, and Web of Science databases from inception to September 2017, with no language restrictions. Only RCTs were retrieved. The primary outcome was the SSI rate. Meta-analysis was complemented with trial sequential analysis (TSA).

Results A total of 7601 patients collected from 16 RCTs were analyzed. A reduction in overall SSI rate was found (RR 0.64, 95% CI 0.48–0.85, $P = 0.002$, $I^2 = 65\%$), which was attributed to patients undergoing elective operations ($n = 2358$) and mixed elective/urgent operations ($n = 2019$). When RCTs of uncertain quality ($n = 9$) were excluded, the use of PVI before wound closure ($n = 4322$ patients) was not associated with a significant reduction of SSI (RR 0.81, 95% CI 0.55–1.20, $P = 0.29$, $I^2 = 51\%$) and was only significant in clean wounds (RR 0.25, 95% CI 0.09–0.70, $P = 0.008$, $I^2 = 0\%$). For the primary outcome, the TSA calculation using a relative risk reduction of 19% and an 11% proportion of control event rate (CER) with 51% of I^2, the accrued information size ($n = 4322$) was 32.8% of the estimated optimal information size ($n = 13{,}148$).

Conclusions There is no conclusive evidence for a strong recommendation of topical PVI before wound closure to prevent SSI.

Manuel López-Cano and Miquel Kraft have contributed equally to this work.

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Introduction

Surgical site infection (SSI) remains an important cause of morbidity, prolonged hospitalization, and mortality, as well as resource consumption. [1]. Three types of SSI have been recognized including superficial incisional, deep incisional, and organ/space infection [2]. However, at the level of the wound [3], a general consensus on the definition of SSI has not been reached, but it is frequently accepted as one that develops during the first 30 days postoperatively and includes the superficial and deep incisional SSI types [2, 3]. Strategies for the prevention of SSI are complex and include actions at minimizing preoperative, intraoperative, and postoperative risk factors. Recently, updated recommendations on measures for SSI prevention have been proposed by international bodies, including the World Health Organization (WHO) [4, 5], the Centers for Disease Control (CDC) [6], and the National Institute for Health and Care Excellence (NICE) [7]. One of these measures is topical application of antiseptics.

Antiseptics can be used for preventing SSI at the level of the wound as an adjunct just before wound closure, when the rest of surgery is performed [8]. However, clinical guidelines are heterogeneous regarding both the application of topical povidone iodine (PVI) and topical antiseptics in general before wound closure. Recommendations range from suggesting irrigation with aqueous PVI especially in clean or clean-contaminated wounds [5], to consider that the use of antimicrobials in this area remains unanswered [6], or to recommend further research on the effects of antiseptics in clean elective surgical contexts without insertion of prosthetic mesh materials [7]. This lack of uniformity of different guidelines may potentially confuse clinicians about the hypothesis that aqueous PVI in the prevention of SSI before wound closure would be useful.

Therefore, to provide an answer to the question of whether topical application of PVI before primary wound closure could reduce SSI rates, we performed a meta-analysis in which only randomized controlled trials (RCTs) were selected. Evidence provided by this meta-analysis is important to clarify whether systematic implementation of this strategy in surgical patients is justified.

Materials and methods

This meta-analysis was performed following recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) report [9]. This review was registered in the international database PROSPERO for prospectively registered systematic reviews (registration number CRD42017072243; http://www.crd.york.ac.uk/PROSPERO).

Systematic literature search

We conducted a systematic literature search of MEDLINE (PubMed), SCOPUS, CINAHL, and Web of Science databases from inception until September, 2017. Combinations of key words and free text for each database were used as search strategies. In the case of MEDLINE, the following terms were used: (“anti-bacterial agents”[Pharmacological Action] OR “anti-bacterial agents”[MeSH Terms] OR (“anti-bacterial”[All Fields] AND “agents”[All Fields]) OR “anti-bacterial agents”[All Fields] OR “antiseptics”[All Fields]) OR (“anti-infective agents”[Pharmacological Action] OR “anti-infective agents”[MeSH Terms] OR (“anti-infective”[All Fields] AND “agents”[All Fields]) OR “anti-infective agents”[All Fields] OR “antimicrobial”[All Fields]) OR topical[All Fields] AND (“surgical wound infection”[MeSH Terms] OR (“surgical”[All Fields] AND “wound”[All Fields] AND “infection”[All Fields]) OR “surgical wound infection”[All Fields]) OR (“wound infection”[MeSH Terms] OR (“wound”[All Fields] AND “infection”[All Fields]) OR “wound infection”[All Fields]) AND Randomized Controlled Trial[ptyp]. Only human studies (as species) and RCT (as article type) were included in the search, with no limits regarding languages. In order to select eligible studies, the abstracts of all documents retrieved were assessed independently by three investigators (ML-C, AC, and MK). Additional studies were identified by cross-checking the reference lists of all retrieved articles.

Selection of studies and extraction of data

The PICO approach was used for the selection of studies. PICO represents an acronym for patient (P), intervention (I), comparison (C), and outcome (O). It has been recommended to apply these four PICO elements to properly establish a research question and accordingly to perform a reliable search of the literature. [10]. The patient population (P) consisted of patients undergoing abdominal, hernia, cardiovascular, trauma, and orthopedic surgeries. The intervention (I) was the use of topical PVI before primary closure of the surgical wound by means of irrigation solution, aerosol spray, or other forms of antiseptic application. SSI prevention was the outcome (O). Exclusion criteria were as follows: previous infection in the site of surgical wound, application of PVI at other sites more than the surgical wound, application of other antimicrobials than PVI and surgical procedures different from those already mentioned. Patients with surgical wounds in which PVI was not applied before primary wound closure were

included in the comparator group (i.e., placebo). For the purpose of this meta-analysis, the rate of SSI ((superficial and/or deep incisional) was the primary outcome. Secondary outcomes were SSI rates according to the following variables: (a) type of surgery, defined as specific when a single surgical procedure was performed or miscellaneous when different surgical techniques were combined; (b) urgent or elective surgery (or mixed when it was not possible to differentiate patients undergoing urgent or elective operations in the same study); (c) mode of PVI administration and concentration; (d) presence or absence of associated use of systemic antibiotics; (e) grade of contamination of the surgical field defined as clean, clean-contaminated, contaminated, and dirty following the 1999 CDC classification [2]; and (f) definition of SSI [2].

Data extraction was performed by two investigators (ML-C and MK) independently. The opinion of a third researcher (JMGA) was requested to reach consensus in doubtful cases during data extraction.

Assessment

The internal validity of trials was evaluated using the checklist of the Scottish Intercollegiate Guidelines Network (SIGN) (https://www.sign.ac.uk/checklists-and-notes.html). Factors influencing the quality of evidence across studies for different outcomes (i.e., external validity) were also assessed following recommendations of the Cochrane Collaboration [11] in the following aspects: method of randomization; allocation concealment; use of masked outcome assessments; intention-to-treat (ITT) analysis; definition of SSI; and time of assessment of infection. Definition and time of assessment infection was included in quality of evidence evaluation because the most widely accepted definition of SSI should develop during the first 30 days after the surgical operation [2, 3]. Depending on whether information on these aspects was present (at least four aspects and 30 days of follow-up), partially present (at least three aspects and 30 days of follow-up) or absent (less than three aspects independently of follow-up or a follow-up <30 days) the quality of the studies was considered high, low, or uncertain, respectively.

Statistical analysis

A meta-analysis of all RCTs eligible for the primary outcome was planned. To evaluate the impact of topical application of PVI on the overall effect according to the quality of trials, a sensitivity analysis was performed. Also, separated meta-analyses were planned for secondary outcomes in the different predefined subgroups for all studies and according to the quality of them. This type of meta-analysis was performed when more than two RCTs were eligible for a given outcome. We used a random-effects model. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for all outcomes. Heterogeneity in the included studies evaluated using I^2 statistic was used to quantify heterogeneity of selected studies, with small heterogeneity for I^2 values of 25%, moderate heterogeneity for I^2 values between 25 and 50%, and high heterogeneity for I^2 values >50% [12]. P values were also calculated. Funnel plots were constructed to assess publication bias. The present meta-analysis was carried out using the Review Manager 5.3, which is the software used for preparing and maintaining Cochrane Reviews (Review Manager (RevMan) [Computer program] version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). In addition, a trial sequential analysis (TAS) (http://ctu.dk/tsa/index.html) was carried out to control the risk of type I error related to sparse data and sequential multiplicity [13, 14].

Results

A total of 3730 records were initially identified by the literature search, but 3701 were considered non-eligible and were excluded. Therefore, 29 RCTs were tentatively included in the meta-analysis. However, 13 RCTs were finally excluded for the following reasons: use of antiseptics other than PVI (n = 5) [15–19], use of a comparator other than placebo (n = 2) [20, 21], lack of proper application of PVI in the surgical wound (n = 3) [22–24], combination of intraabdominal and surgical wound irrigation (n = 2) [25, 26], and duplicate data (n = 1) [27]. The study sample included 16 RCTs, with a total final number of patients of 7601 [28–43]. The strategy followed for the selection of studies is shown in Fig. 1.

Elective operations were performed in 5 RCTs [33, 38–41], urgent operations in 5 [30, 31, 36, 37, 43], and mixed elective and urgent procedures in 6 [28, 29, 32, 34, 35, 42]. PVI was administered as an irrigation solution in 9 studies [29, 34, 35, 37–40, 42, 43], aerosol spray in 6 [28, 30–33, 36], and using a soaked gauze in 1 [41]. The most frequently used concentrations of PVI were 10% [34, 35, 38, 41, 42] and 1% [29, 34, 37, 43]. The surgical field was clean in 4 studies [38–41], contaminated in 5 [30, 31, 35, 36, 42] a combination of clean, clean-contaminated, contaminated, and dirty in 6 [28, 29, 32, 34, 35, 42], and was not clearly stated in 1 [33]. Seven studies reported the administration of systemic antibiotics [35–40, 42].

Table 1 summarizes the characteristics of the 16 RCTs selected for the meta-analysis. The quality of RCTs was high in 1 RCT [42], low in 6 [28, 32, 36, 37, 39, 41], and

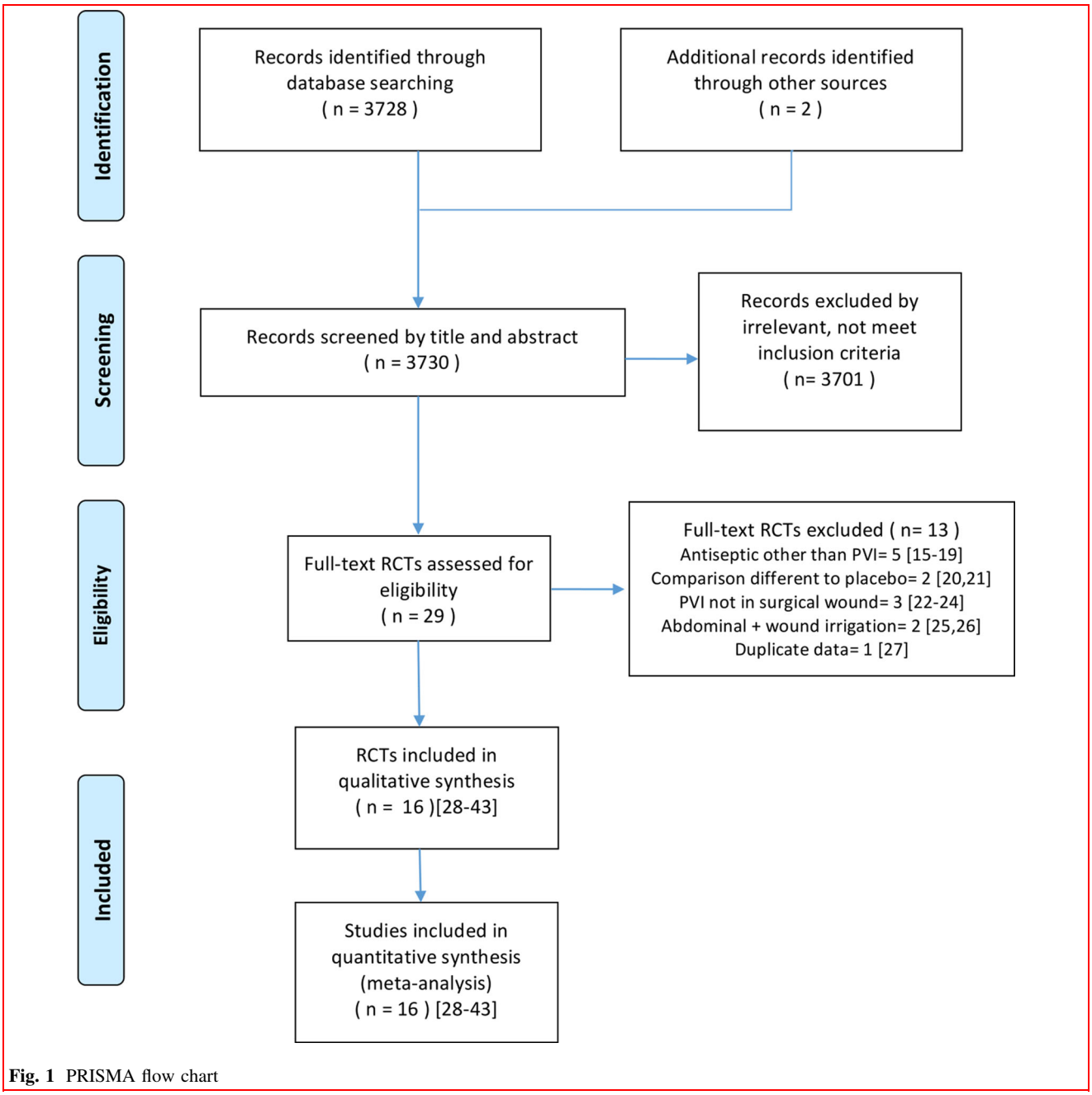

Fig. 1 PRISMA flow chart

uncertain in the remaining 9 [29–31, 33–35, 38, 40, 43]. Risk of bias assessments is presented in Table 2.

Primary outcome

The meta-analysis for the primary outcome (SSI rate) included all 16 RCTs (7601 patients) [28–43] and showed a reduction of the incidence of SSI with the application of PVI before primary surgical wound closure, which was statistically significant (RR 0.64, 95% CI 0.48–0.85, $P = 0.002$), $I^2 = 65\%$). This significant reduction in the overall SSI rate was attributed to patients undergoing elective operations ($n = 2358$) (RR 0.4, 95% CI 0.17–0.97, $P = 0.04$, $I^2 = 58\%$) and mixed elective and urgent operations ($n = 2019$) (RR 0.56, 95% CI 0.33–0.96, $P = 0.03$, $I^2 = 72\%$). Among patients undergoing urgent surgical procedures ($n = 3187$), a reduction in the incidence of SSI was not found (RR 0.79, 95% CI 0.50–1.27, $P = 0.34$, $I^2 = 69\%$). When RCTs of uncertain quality were excluded, a significant reduction in SSI with the use of PVI before primary wound closure ($n = 4322$ patients) was not

Table 1 Characteristics of included studies

Author [Ref]	Year of publication	No of patients	Global SSI rate Exp Cont (*n*) (*n*)	Povidone iodine concentration	Elective/urgent	Type of surgery	Grade of surgery SSI rate Exp (*n*); Cont (*n*)	Type of admon	Comparator	Systemic ab (yes/no)
Gilmore [28]	1975	133	6/63 18/70	Povidone iodine (Disadine DP)	Mixed (elective and urgent)	Abd surg	Cl 1/33; 6/35 C 5/30; 12/35	Spray aerosol	Propellant alone	No
Sindelar [29]	1977	500	7/242 39/258	Povidone iodine 1%	Mixed (elective and urgent)	Abd surg/Misc	Cl 0/113; 7/121 C-C 1/49; 7/49 C 3/44; 12/46 D 3/36; 13/42	Irrigation solution	Saline solution	Surgeon criteria
Morgan [30]	1978	320	10/166 22/154	Povidone iodine	Urgent	ASW	C 10/166;22/154	Spray aerosol	Nothing	No
Naunton Morgan [31]	1980	572	14/263 45/309	Povidone iodine (Disadine DP)	Urgent	ASW	C 14/263;45/309	Spray aerosol	Nothing	Not uniform
Walsh [32]	1981	627	28/308 40/319	Povidone iodine (Betadine 5% + 0.5% iodine)	Mixed (elective and urgent)	Abd surg	Cl 2/59; 6/63 C-C 21/232; 25/232 D 5/17; 9/24	Spray aerosol	Nothing	Surgeon criteria
Gray [33]	1981	153	7/71 20/82	Povidone iodine (Disadine DP, 0.5% available iodine)	Elective	Abd surg	Not clearly defined	Spray aerosol	Nothing	No defined
de Jong [34]	1982	582	17/154 21/142	Povidone iodine 1% (Phase 1)	Mixed (elective and urgent)	Abd sg/Misc	Cl 8/89; 3/83 C-C 6/29; 9/33 C 2/21; 3/17 D 1/15; 6/9	Irrigation solution	Nothing	No
			22/149 15/137	Povidone iodine 10% (Phase 2)			Cl 7/84; 3/79 C-C 9/31; 6/31 C 1/22; 3/15 D 5/12; 3/12			
Rogers [35]	1983	187	4/86 11/101	Povidone iodine 10%	Mixed (elective and Urgent)	Abd Sg/Misc	Cl 2/56; 5/68 C-C 1/24; 5/27 D 1/6; 1/6	Irrigation solution	Saline solution	Yes
Galland [36]	1983	200	13/95 14/105	Povidone iodine	Urgent	Colorectal (Appe)	C 13/95; 14/105	Spray aerosol	Nothing	Yes
Lau [37]	1986	315	9/159 3/156	Povidone iodine 1%	Urgent	Colorectal (Appe)	C 9/159; 3/156	Irrigation solution	Nothing	Yes
Cheng [38]	2005	414	0/208 7/206	Povidone iodine 3,5%	Elective	Spinal surgery	Cl 0/208; 7/206	Irrigation solution	Saline solution	Yes
Chang [39]	2006	244	0/120 6/124	Povidone iodine 3,5%	Elective	Spinal surgery	Cl 0/120; 6/124	Irrigation solution	Saline solution	Yes
Kokavec [40]	2008	162	0/89 2/73	Povidone iodine 3,5%	Elective	Orthopedic surgery	Cl 0/89; 2/73	Irrigation solution	Saline solution	Yes
Walker [41]	2013	67	1/31 3/36	Povidone iodine 10%	Elective	Vascular surgery	Cl 1/31; 3/36	Soaked gauze in the groin wound	Saline-soaked gauze	No

Table 1 continued

Author [Ref]	Year of publication	No of patients	Global SSI rate Exp Cont (*n*) (*n*)	Povidone iodine concentration	Elective/urgent	Type of surgery	Grade of surgery SSI rate Exp (*n*); Cont (*n*)	Type of admon	Comparator	Systemic ab (yes/no)
Mahomed [42]	2016	2736	144/1376 147/1360	Povidone iodine 10%	Elective	Cesarean section	C-C 81/676; 82/669	Irrigation solution	Nothing	Yes
					Urgent		C 63/700; 65/691			
Ghafouri [43]	2016	389	15/196 14/193	Povidone iodine 1%,	Urgent	ASW	C 15/196; 14/193	Irrigation solution	Saline solution	No

Cl, Clean; C-C, Clean-contaminated; C, Contaminated; D, Dirty; Abd Surg, abdominal surgery; Misc, miscellaneous; ASW, Accidental superficial wounds; Exp, experimental; Cont, control

found (RR 0.81, 95% CI 0.55–1.20, $P = 0.29$, $I^2 = 51\%$) (Fig. 2).

Secondary outcomes

Findings for secondary outcomes for all RCTs and after excluding RCTs of uncertain quality are detailed in Table 3. There were statistically significant differences in favor of using PVI before primary wound closure for contaminated surgical fields (RR 0.66, 95% CI 0.44–0.98, $P = 0.04$, $I^2 = 59\%$), when diluted at 3.5% concentration (RR 0.09, 95% CI 0.02–0.50, $P = 0.006$, $I^2 = 0\%$), use of aerosol spray (RR 0.53, 95% CI 0.37–0.75, $P = 0.0003$, $I^2 = 40\%$), and when definition of SSI was based on purulent discharge only (RR 0.62, 95% CI 0.42–0.91, $P = 0.02$, $I^2 = 64\%$). When RTCs of uncertain quality were excluded, the use of PVI before primary would closure was only associated with a statistically significant decrease in SSI in clean surgical fields (RR 0.25, 95% CI 0.09–0.70, $P = 0.008$, $I^2 = 0\%$).

A slightly asymmetrical funnel plot of all 16 RCTs, suggested a publication bias of studies that favored PVI prophylaxis (Supplementary Fig. S1).

Also, TSA estimation for the primary outcome (SSI rate) included all 7 RCTs with best quality [28, 32, 36, 37, 39, 41, 42] using a 19% relative risk reduction (RRR) and a proportion of 11% for a control event rate (CER) with 51% for I^2, the accrued information size ($n = 4322$) was 32.8% of the estimated optimal information size (OIS) ($n = 13{,}148$) (Supplementary Fig. S2).

Discussion

This meta-analysis showed that topical application of PVI before primary closure of the surgical incision appears to be effective to reduce the rate of SSI, with an overall decrease in the incidence of SSI of 36%. However, this favorable effect was mainly attributed to patients undergoing elective surgical procedures (59% reduction) and mixed (elective and/or urgent) procedures (44% reduction). In relation to secondary outcomes, an overall favorable effect of PVI was also found in the subgroups of contaminated surgical field, PVI concentration of 3.5%, use of aerosol spray, and when SSI definition was exclusively based on purulent drainage.

These findings are consistent, at least in part, with suggestions for the use of topical aqueous PVI solution in some clinical guidelines [5] or the conclusion of a recent meta-analysis in which prophylactic intraoperative wound irrigation was analyzed [44]. However, a reliable meta-analysis should be based on an adequate sample size (as

Table 2 Quality of studies

Author, year	Randomization type	Concealment	Blinded evaluation	Definition SSI	Intention to treat	Time assessment	Quality
Gilmore [28]	Random numbers	Undescribed	Yes	Ljungqvist criteria[a]	Undescribed	6 weeks	Low
Sindelar [29]	Undescribed	Undescribed	Undescribed	Pus developed at any time	Undescribed	3 months	Uncertain
Morgan [30]	Undescribed	Undescribed	Undescribed	Definite discharge from the wound, from which a swab could be taken	Undescribed	6 days	Uncertain
Naunton Morgan [31]	Undescribed	Undescribed	Yes	Pink and painful or purulent.	Undescribed	Unreported	Uncertain
Walsh [32]	Computer random number	Undescribed	Yes	Pus discharged in 1 months or serosanguinolent drenaje with positive culture	Undescribed	1 month	Low
Gray [33]	Numbered randomization card	Undescribed	Unclear	Purulent discharge major or minor plus culture	Undescribed	2 weeks	Uncertain
De Jong [34]	Undescribed	Undescribed	Undescribed	Purulent discharge or culture of fluid from the wound result +	Undescribed	4 weeks	Uncertain
Rogers [35]	Odd or even nature of the last number of hospital number	Undescribed	Undescribed	Purulent discharge independent of culture result	Undescribed	1 month	Uncertain
Galland [36]	Sealed envelopes	Undescribed	Yes	Pus within or discharged from the wound	Undescribed	1 month	Low
Lau [37]	Sealed envelopes	Undescribed	Yes	Ljungqvist criteria* combined with the results of culture	Undescribed	6 weeks	Low
Cheng [38]	Sealed envelopes	Undescribed	Undescribed	Unusual pain, tenderness, erythema, induration, fever, or wound drainage was noted, +_ cultures	Undescribed	2 months	Uncertain
Chang [39]	Sealed envelopes	Yes	Yes	Undescribed	Undescribed	19 months	Low
Kokavec [40]	Undescribed	Undescribed	Undescribed	Tenderness, erythema, induration, fever, or wound drainage	Undescribed	1,5 months	Uncertain
Walker [41]	Sealed envelope (computer-generated random instruction)	Undescribed	Yes	Discharge of pus from wound, Wound dehiscence with infection, presence of pus and necrotic tissue	Undescribed	6 weeks	Low
Mahomed [42]	Sealed envelope (computer-generated random instruction)	Yes	Yes	Wound abscess or the wound was draining pus or serosanguineous fluid, if there was redness, induration, warmth and tenderness or if the woman's general practitioner (GP) had seen her and prescribed antibiotics for presumed infection	Undescribed	2 years	High
Ghafouri [43]	Computer-generated randomization blocks of 4	Undescribed	Undescribed	Signs (cellulitis >1 cm, lymphangitis, presence of discharge, presence of necrotic tissue and abscess) and symptoms (pain, dryness and itching) of wound infection and presence/absence of wound dehiscence	Undescribed	10 days, at 1 month telephone call	Uncertain

[a]Ljungqvist criteria (clear collection of pus, which empties itself spontaneously or after incision) were defined in 1964 in the paper: Ljungqvist U. Wound sepsis after clean operations. Lancet 1964;1(7342):1095–1097

SSI, Surgical site infection

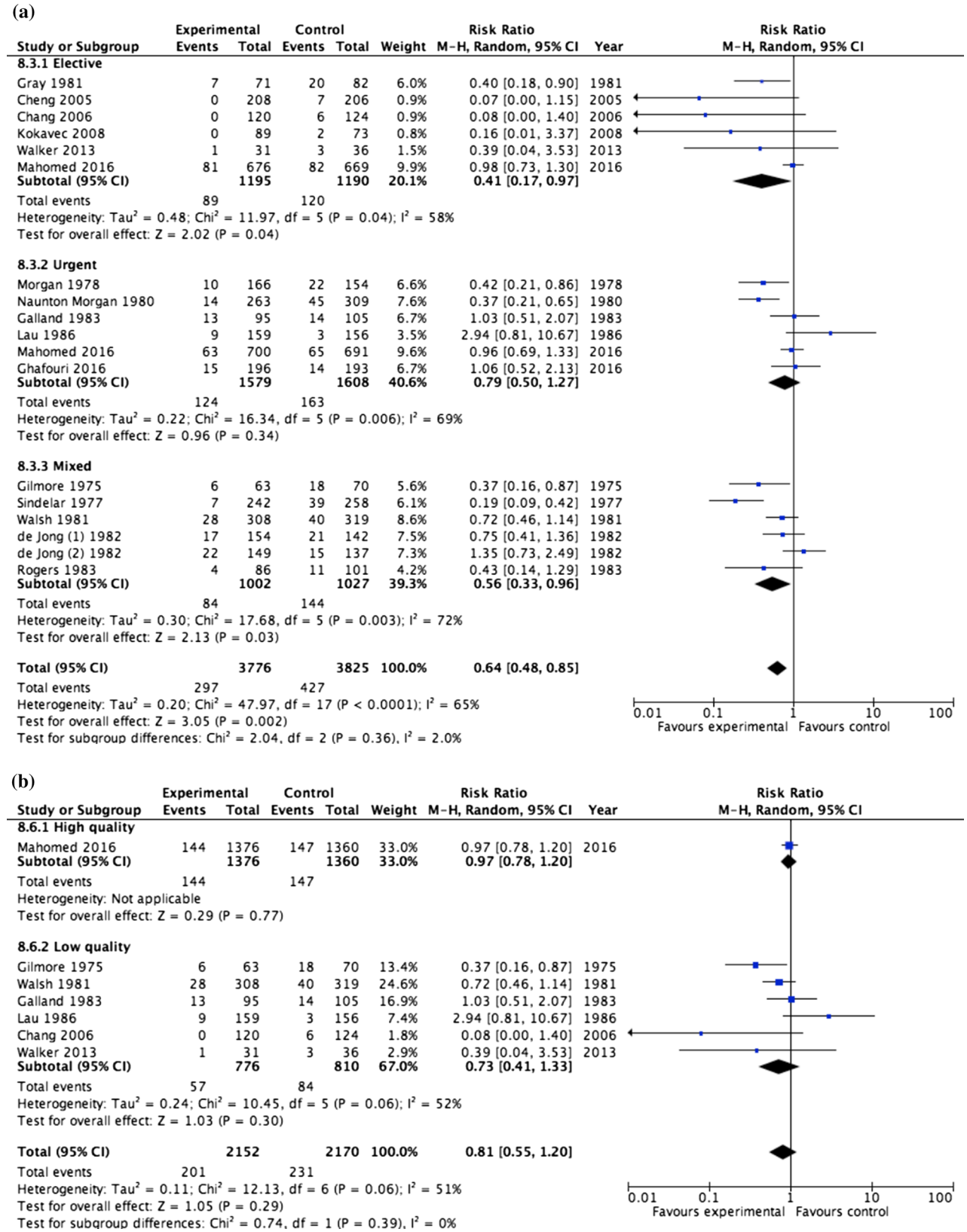

Fig. 2 **a** SSI rate including all 16 RCTs and divided by type of surgery **b** SSI rate with only high- and low-quality studies (excluding uncertain quality studies)

Table 3 Secondary outcomes meta-analysis with all studies included and excluding uncertain quality studies

Meta-analysis with high-, low-, and uncertain quality studies							Meta-analysis excluding uncertain quality studies					
Outcome	No of studies	No of patients	RR	95% CI	I^2	*P*	No of studies	No of patients	RR	95% CI	I^2	*P*
Clean wound	9	1770	0.42	0.17–1.02	50	0.05	**4**	**501**	**0.25**	**0.09–0.70**	**0**	**0.008**
Clean-contaminated wound	6	2235	1	0.57–1.75	79	1	#					
Contaminated wound	**9**	**3417**	**0.66**	**0.44–0.98**	**59**	**0.04**	4	1971	0.97	0.62–1.54	41	0.90
Dirty wound	4	179	0.56	0.22–1.39	54	0.21	#					
Definition of SSI as only pus discharge	**10**	**3084**	**0.62**	**0.42–0.91**	**64**	**0.02**	5	1342	0.80	0.46–1.39	50	0.42
Definition of SSI as not only pus discharge	5	4273	0.61	0.32–1.18	72	0.14	#					
PVI Irrigation solution 1%	4	1500	0.76	0.30–1.93	82	0.56	#					
PVI Irrigation solution 10%	3	3209	0.97	0.65–1.43	38	0.87	#					
PVI Irrigation solution 3.5%	**3**	**820**	**0.09**	**0.02–0.50**	**0**	**0.006**	#					
PVI spray	**6**	**2005**	**0.53**	**0.37–0.75**	**40**	**0.0003**	3	960	0.69	0.43–1.12	39	0.13
Systemic antibiotic association (elective surgery)	4	2165	0.25	0.04–1.43	62	0.12	#					
Systemic antibiotic association (emergency surgery)	3	1906	1.09	0.71–1.66	27	0.69	3	1906	1.09	0.71–1.66	27	0.69

Statistical significance in bold

SSI, surgical wound infection; PVI, povidone iodine; CI, confidence interval; I^2 heterogeneity, RR, risk ratio

No more than two studies for the meta-analysis

considered in any trial with a sufficient statistical power to detect differences between groups). This requires a more exhaustive exploration of data by calculating the optimal information size (OIS) with tools such as TSA. Also, the exclusion of trials of low or uncertain quality is another factor that may be essential, since the inclusion of these studies may overestimate the magnitude of the effect. These two considerations are necessary when doing a meta-analysis fit for purpose [45]. Apparently, none of the recently published clinical practice guidelines for SSI prevention [4–7] or meta-analysis [44] performed an estimation of TSA or excluded studies of low or uncertain quality from the analysis.

In the present meta-analysis after exclusion of RCTs of low or uncertain quality, the application of PVI before primary wound closure was not associated with a significant decrease of SSI. Moreover, TSA estimations based on RCTs of better quality revealed an estimated OIS of 13,148, which was markedly higher than all 4322 patients included in the analysis, with an accrued information size of only 32.8% of the optimal reliable information required to draw consistent conclusions. Therefore, the present data do not provide evidence to support a conclusive recommendation for the topical use of PVI aqueous solution before primary wound closure to reduce the rate of SSI. Other aspects limiting a clear recommendation of the use of PVI include some considerations. Firstly, after exclusion of RCTs of uncertain quality, 7 studies remained [28, 32, 36, 37, 39, 41, 42] for the analysis, 6 of which [28, 32, 36, 37, 39, 41] were of low quality, and only 1 RCT of high quality [42] was the largest regarding the study population, the authors of which considered that PVI was not beneficial at least in women undergoing a cesarean section. Secondly, RCTs of the better quality included heterogeneous definitions of SSI, with variability in the follow-up. Thus, 4 of these studies [28, 32, 36, 37] were published before introduction of the currently accepted definition of SSI [2, 3] more than 30 years ago. Thirdly, the acceptable SSI rate in clean surgical fields is less than 5% [46, 47]; in the sensitivity analysis for secondary outcomes after exclusion of RCTs of uncertain quality it was found that PVI was only effective in clean surgical wounds; however, the baseline SSI rate observed in the control arm was greater than what is considered acceptable, so the effect of PVI in clean wounds could have been overestimated. Also, after exclusion of RCTs of uncertain quality the favorable effect of PVI in contaminated fields disappears. Fourthly, the slightly asymmetric funnel plot revealed a possible publication bias toward studies in favor of topical PVI. This finding may be explained by selective publication of studies, leading to overestimation of the effectiveness of the intervention.

Summarizing, PVI as an irrigation solution is frequently applied by surgeons to prevent SSI as shown by different

cross-sectional surveys [48, 49]. This frequent use may be justified arguing that it is a measure of "high" yield and "low" healthcare cost because PVI has a broad antimicrobial spectrum, weak allergenic activity, and limited cytotoxicity [8]. However, in some occasions, healthcare procedures with apparently high performance and low cost become widely used with inadequate proof of benefit [50], which may be a low-value practice and susceptible for medical reversal when better powered and design studies contradict the current practice [51].

We conclude that on the basis of the available evidence, topical application of PVI aqueous solution in the surgical wound before primary closure to prevent SSI cannot be recommended, at least in the context of the patient population included in our meta-analysis. We do not seek to issue a final determination regarding any particular practice, and recommendation against the use of this antiseptic does not mean that topical PVI is useless, only that there no conclusive evidence for a generalized recommendation of this measure and for any type of surgery. More well-designed RCTs and with clear consensuated definitions of SSI as well as SSI registries and measures used for SSI prevention are needed to establish a firm conclusion on this elusive matter.

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Compliance with ethical standards

Conflict of interest The Authors declare that they have no conflict of interest.

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