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AUTHOR(S)

Firas Ayoub, Michael Quirke, Ronan Conroy, Arnold DK Hill

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Review Article

Chlorhexidine-alcohol versus povidone-iodine for pre-operative skin preparation: A systematic review and meta-analysis

Firas Ayoub [a,*], Michael Quirke [a], Ronan Conroy [b], Arnold Hill [a]

[a] Department of Surgery, Beaumont Hospital, Dublin, Ireland
[b] Department of Epidemiology & Public Health Medicine, Royal College of Surgeons, Dublin, Ireland

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ABSTRACT

Background: Surgical site infection (SSI) is a dreaded postoperative complication. Although preoperative skin cleansing in order to prevent surgical site infection (SSI) is standard surgical practice, there is clinical equipoise concerning whether povidone iodine (PI) or chlorhexidine alcohol (CHA) is the antiseptic agent of choice.
Objectives: To determine whether CHA or PI is the preferred preoperative skin preparation for reducing SSI in clean, clean-contaminated and contaminated surgery.
Search methods: PubMed, Embase, and gray literature sources were searched for randomized controlled trials (RCTs) comparing both CHA and PI between 1980 and 2014. Comparative RCTs of preoperative CHA versus PI studying SSI in clean, clean-contaminated and contaminated surgery were included. Risk of bias was assessed using Cochrane risk of bias.
Main result: We identified six eligible studies with an overall 2484 participants. The overall rate of SSI was 6.8% in the CHA group versus 11.0% in the PI group ($P < 0.0002$). CHA was superior to PI in the prevention of SSI with a pooled RR of 0.62 (95% CI, 0.48–0.81).
Conclusions: Preoperative surgical skin preparation with CHA is more effective than PI in preventing SSI across clean and clean-contaminated surgery. Further studies should evaluate the effectiveness of CHA versus PI in contaminated surgery.
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1. Introduction

Surgical site infection (SSI) is a dreaded postoperative complication that affects approximately 5% of all patients undergoing surgery [1]. It is associated with prolonged length of hospital stay, prolonged postoperative recovery time, higher hospital readmission rates, and higher morbidity and mortality rates than patients without SSI [2]. The majority of SSIs are caused by contamination of a surgical incision with bacteria from the patient's own body [3].

There are several antiseptic skin cleansing agents available to the surgeon to use for patients undergoing clean, clean-contaminated, contaminated, and dirty surgery [3]. The traditional antiseptic cleansing agent of choice is povidone iodine (PI). It is cheap, effective, and the most commonly used agent of choice worldwide [4]. Chlorhexidine-alcohol (CHA) is a newer skin preparation agent, commonly composed of 2% chlorhexidine gluconate and 70% isopropyl alcohol [5]. Although more expensive than PI, it represents an alternative skin antiseptic agent, is reported to have a more rapid onset of action than PI and has persistent activity in the presence of body fluids [6]. In 2002, the CDC recommended the use of CHA prior to central venous and peripheral arterial catheterizations. CHA has recently been shown to be superior to PI in the prevention of SSI for clean surgery [7].

A recently performed Cochrane review did not reach a clear consensus on which antiseptic skin cleansing agent is associated with the lowest risk of SSI [8]. This study was performed in order to evaluate and synthesize existing evidence in the published literature concerning the role of PI and CHA in preventing SSIs in patients undergoing clean surgery.

2. Methods

A systematic review of randomized trials was undertaken according to PRISMA guidelines [9] to compare CHA versus PI in preventing SSI in patients undergoing clean, clean-contaminated, and contaminated surgery.

* Corresponding author. Department of Surgery, Beaumont Hospital, Beaumont Road, Dublin 9, Ireland.
E-mail address: fayoub@rcsi.ie (F. Ayoub).

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Table 1
Characteristics of studies included in the meta-analysis of CHA versus PI in preventing SSI.

Reference	Year	Country	Sample size	Inclusion criteria	Exclusion criteria	Intervention	Control
Bibbo et al. [10]	2005	US	127	Clean surgery (elective foot and ankle surgery)	Open wounds, skin ulcers, active or chronic infection, antimicrobial therapy	4% Chlorhexidine in 70% isopropyl alcohol scrub for 7 minutes	7.5% Povidone iodine scrub for 7 minutes followed by 10% povidone-iodine paint
Paocharoen et al. [11]	2009	Thailand	500	Clean, clean-contaminated and contaminated wound	Dirty wound, uncontrolled diabetes, on immunosuppressive drugs, serum albumin less than 3.0 mg/dl	4% Chlorhexidine in 70% isopropyl alcohol followed by Hibitane scrub and paint	10% Povidone-iodine scrub followed by iodine solution
Saltzman et al. [12]	2009	US	100	Clean surgery (shoulder surgery)	Open wound, recurrent infection, or chronically immunosuppressed	2% Chlorhexidine in 70% isopropyl alcohol (ChloraPrep)	0.75% Povidone-iodine scrub followed by 1.0% iodine paint
Sistla et al. [13]	2010	India	400	Clean surgery (inguinal hernia repair)	Recurrent or complicated inguinal hernia	2.5% Chlorhexidine in 70% ethanol	10% Povidone-iodine
Darouiche et al. [7]	2010	US	849	Clean-contaminated surgery	Evidence of infection or adjacent to the operation site	2% Chlorhexidine gluconate in 70% isopropyl alcohol	10% Povidone iodine
Patil et al. [14]	2013	India	508	Clean and clean-contaminated surgery	Contaminated and dirty wounds, evidence of infection adjacent to operative site	2.5% Chlorhexidine gluconate in 63% isopropyl alcohol	5% Povidone-iodine

2.1. Literature search

An electronic literature search was conducted in July 2014 using the following three databases of scientific literature: EMBASE, PubMed and the Cochrane. The search strategy was developed by an experienced librarian in conjunction with a clinical researcher. The search strategy used the following medical subject heading (MeSH) terms: chlorhexidine-alcohol OR chlorhexidine-isopropyl OR chloraprep OR iodine OR povidone-iodine OR betadine OR iodophor AND surgical site infection OR SSI OR wound infection.

No restrictions were applied on language, the type of risk factor, age, or gender of the subject. All abstracts that met our search strategy were examined. To limit publication bias, the references of all primary studies were also hand searched for studies potentially missed in the electronic search. In addition we searched gray literature sources, including OpenGray and the NLM gateway. We personally communicated with authors where necessary. For studies not published in English we used Google Translate to translate relevant journals to English. All shortlisted titles and abstracts were downloaded to a reference manager (EndNote) for detection of duplicates. In addition, a researcher manually checked this list for duplicates.

2.2. Study selection

This review was planned, conducted and reported in adherence to the PRISMA guidelines. Our inclusion criteria included all RCTs that reported the rate of postoperative SSI in patients who have undergone clean, clean contaminated, and contaminated surgery to any part of the body. We excluded non-randomized trials, studies with incomplete method selection, studies that did not compare CHA with PI, studies that did not measure SSI, duplicate publications and narrative reviews. Two reviewers performed eligibility assessment independently by assessing titles and abstracts of citations identified by the search databases results. Any differences between the reviewers were resolved by discussion and mutual agreement.

2.3. Data extraction

Information of the included studies was extracted for analysis using piloted data forms. The extracted information includes study ID, year, country, design, number of participants, intervention, comparison, and primary and secondary outcomes. The primary outcome was postoperative SSI. The secondary outcome was bacterial decolonization.

See Table 1 for characteristics of studies included in the meta-analysis of CHA versus PI in preventing SSI, and Table 2 for primary and secondary outcomes.

2.4. Quality assessment

Risk of bias was assessed by considering randomization procedure, allocation concealment, blinding, and data completion using the Cochrane Collaboration's tool for assessing risk of bias [15]. These items were classified as low, unclear, or high according to risk (see Table 3 for risk of bias).

2.5. Data analysis

Data were entered into Microsoft Office Excel sheets for analysis. Statistical analysis was performed using Stata Version 13.1. Relative risk was calculated (95% CI) for primary outcomes using a random effect model. Standard Chi-square and I^2 test were used to assess for heterogeneity.

3. Results

3.1. Literature search

The search identified fifty-three relevant studies. After applying exclusion criteria, six studies were eligible for meta-analysis (Fig. 1). Details of the included trials are summarized in Table 1.

3.2. Characteristics of studies included in the final analysis

All six studies compared CHA versus PI in preventing SSI. CHA concentration was similar across all studies and ranged from 2% to 4% of chlorhexidine, and 63% to 70% of alcohol. PI concentration ranged from 5% to 10%. The method in which these skin preparing agents were applied on the skin was different; three studies by Bibbo et al. [10], Saltzman et al. [12] and Sistla et al. [13] used simple painting, two studies by Paocharoen et al. [11] and Darouiche et al. [7] used scrubbing and painting, and one study by Patil et al. [14] did not mention an application method. All studies reported that preoperative skin preparation with CHA is more efficient than PI in preventing SSI (Table 2: primary and secondary outcomes).

Table 2
Primary and secondary outcomes.

Study ID	Wound classification	Primary outcome				Secondary outcome
		CH + IPA	No. SSI (%)	PI	No. SSI (%)	*Positive bacterial culture:* CHA (n = 60) 23/60 (38%) PI (n = 67) 53/67 (79%)
Bibbo et al. [10]	Clean	60	0 (0%)	67	0 (0%)	*Post-op colonization > 103 CFU/ml:* CHA (n = 250): 36 (14.4%) PVI (n = 250): 78 (31.2%)
Paocharoen et al. [11]	Clean and clean-contaminated and contaminated	250	5 (2%)	250	8 (3.2%)	*Overall rate of positive bacterial culture:* CHA (n = 50): 7% PI (n = 50): 31% PIA (n = 50): 19%
Saltzman et al. [12]	Clean	50	0 (0%)	50	0 (0%)	*Bacterial count reduction:* CHA (n = 50): 82% PI (n = 50): 59.14%
Sistla et al. [13]	Clean	200	14 (7%)	200	19 (9.5%)	*Positive bacterial culture:* CHA (n = 60) 23/60 (38%) PI (n = 67) 53/67 (79%)
Darouiche et al. [7]	Clean-contaminated	409	39 (9.5%)	440	71 (16.1%)	
Patil et al. [14]	Clean and clean-contaminated	251	25 (9.96%)	257	41 (15.95%)	
Total		1220	83	1264	139	

Values in parentheses are percentages. CH, chlorhexidine; CHA, chlorhexidine-alcohol; PI, povidone-iodine; IPA, isopropyl-alcohol; SSI, surgical site infection, CFU colony-forming units.

3.3. Meta-analysis

The total number of postoperative SSIs across all included studies was 222 (8.9%) out of 2484 patients. In the CHA group, there was 83 SSIs out of 1220 (6.8%) and in the PI group 139 out of 1264 (11.0%). Risk of bias across studies is illustrated in Table 3, and this shows that the overall the risk of bias in the included studies was unclear.

On meta-analysis CHA was associated with a reduced risk of SSI when compared to PI (relative risk [RR], 0.62; 95% confident interval [CI], 0.48 to 0.81; $I^2 = 0\%$) $p = 0.000$ (Fig. 2).

Given that the primary search evaluated patients undergoing clean, clean-contaminated and contaminated surgery, a sensitivity analysis was performed. After excluding studies that included contaminated surgery, CHA was still associated with lower rate of SSI than PI (RR, 0.62; 95% CI, 0.48 to 0.81, $I^2 = 0$) $p = 0.000$ (Fig. 3).

4. Discussion

Despite increasing evidence for newer skin antiseptic cleansing agents, there is still clinical equipoise concerning which agent is associated with a lower risk of postoperative SSI. This study was performed in order to analyze existing RCTs for evidence concerning the relative effectiveness of CHA versus PI in preventing SSIs. Using our search criteria, we found that CHA was associated with lower rates of postoperative SSIs in patients undergoing clean and clean-contaminated surgery.

The primary meta-analysis included six prospective randomized trials that studied the rate of SSI in clean, clean-contaminated, and contaminated surgery. The pooled analysis showed that CHA was superior to PI in the prevention of postoperative SSI in clean, clean-contaminated and contaminated surgery. Although the primary meta-analysis included one study [11] of patients undergoing contaminated surgery, a sensitivity analysis also found CHA to be associated with a lower risk of SSI.

A performed Cochrane review did not reach a clear consensus on which antiseptic skin cleansing agent is associated with the lowest risk of SSI [8]. This study focused mainly on the role of PI and CHA in preventing SSIs in patients undergoing clean surgery only. It showed that there is evidence that preoperative skin preparation with chlorhexidine alcohol was associated with lower rate of SSI, but this was based on one study only that met their selection criteria. They concluded that practitioners should consider the cost and potential side effects when choosing their preoperative skin preparation.

This research included antiseptic agents used in clean, clean-contaminated and contaminated surgery. However, our result showed that CHA is associated with a lower rate of SSI in clean and clean-contaminated surgery only [8]. We also found a similar review to ours done by Maiwald and Chan in 2012 [16]. However, this study focused on investigating the role of alcohol in combination with chlorhexidine across blood culture collection, vascular catheter insertion and surgical skin preparation without accounting for specific surgical wound type. Our review is different in terms of selection criteria, design and overall result.

To our knowledge, this is the first study to include clean, clean-contaminated, and contaminated surgery. Despite excluding studies with contaminated surgery, our sensitivity analysis proved that CHA was associated with reduced rate SSI in the clean and clean-contaminated surgery. Skin bacterial colonization was reported in four trials [10–13]. Although all studies reported lower rates of

Table 3
Summary of Cochrane risk of bias in included trials.

Reference	Randomization	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete data
Bibbo et al. [10]	Unclear	Unclear	Unclear	Unclear	Unclear
Paocharoen et al. [11]	Random number table	Sealed envelopes	Unclear	Unclear	Complete
Saltzman et al. [12]	Randomly assigned	Sealed envelopes	Unclear	Unclear	Complete
Sistla et al. [13]	Unclear	Sealed envelopes	Unclear	Unclear	Complete
Darouiche et al. [7]	Computer generated	Sealed envelopes	Unclear	Blinder SSI assessors	Complete
Patil et al. [14]	Unclear	Unclear	Unclear	Unclear	Complete

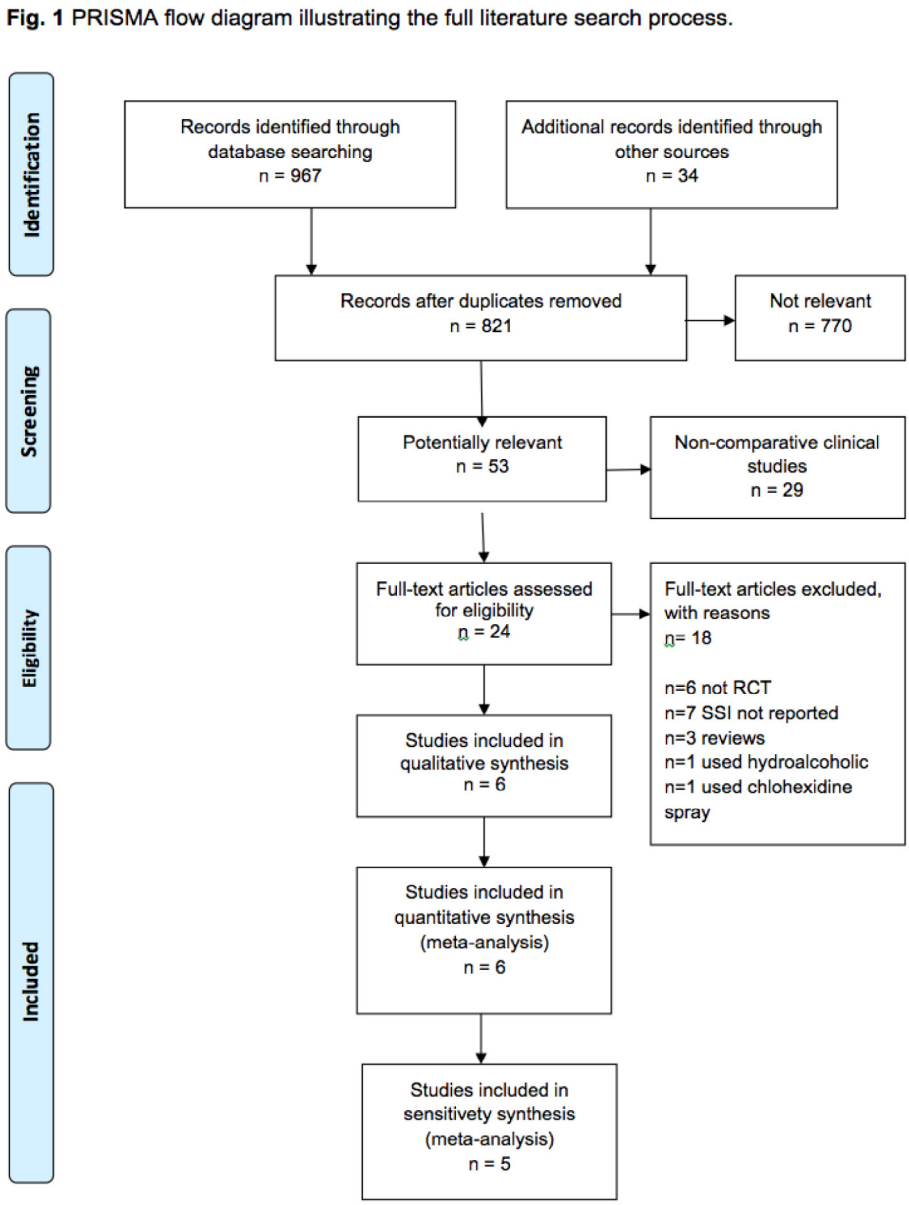

Fig. 1. PRISMA flow diagram illustrating the full literature search process.

bacterial colonization when CHA was used instead of PI, each had a different method of measuring bacterial reduction or decolonization, thus preventing further analysis.

There were some limitations. First, we have found that studies differ in the method and duration in which these skin preparing agents were applied on the skin. While some used scrubbing followed by painting, others used painting alone. Several studies aimed to compare painting versus scrubbing technique. A meta-analysis conducted by Ellenhorn et al. [17] showed no difference between scrubbing before painting versus painting alone in terms of SSI or bacterial decolonization rate. Second, the CHA and PI concentrations varied across most studies, so we retained the variability of the antiseptic concentration taking into consideration that there is no evidence to suggest that varying the concentration of CHA or PI could improve the efficacy of the antiseptic agents. Third, some studies did not define SSI. Instead terms such as cellulitis and wound infection were used. Where this occurred the author inferred the presence of SSI from the study results. Fourth, none of the included studies were double blinded, increasing the risk of bias. The overall risk of bias across all studies was unclear. Our review focuses on CHA versus PI only, without accounting for agents combining PI and alcohol (PIA), such as DuraPrep. Recent evidence suggests the superiority of PIA to CHA [18]. Future studies should assess CHA with PIA in preventing SSI.

5. Conclusion

In our review, CHA was associated with reduced risk of postoperative SSI in clean and clean-contaminated surgery when compared to PI. Further studies should evaluate the effectiveness of CHA versus PI in reducing SSI across contaminated surgery.

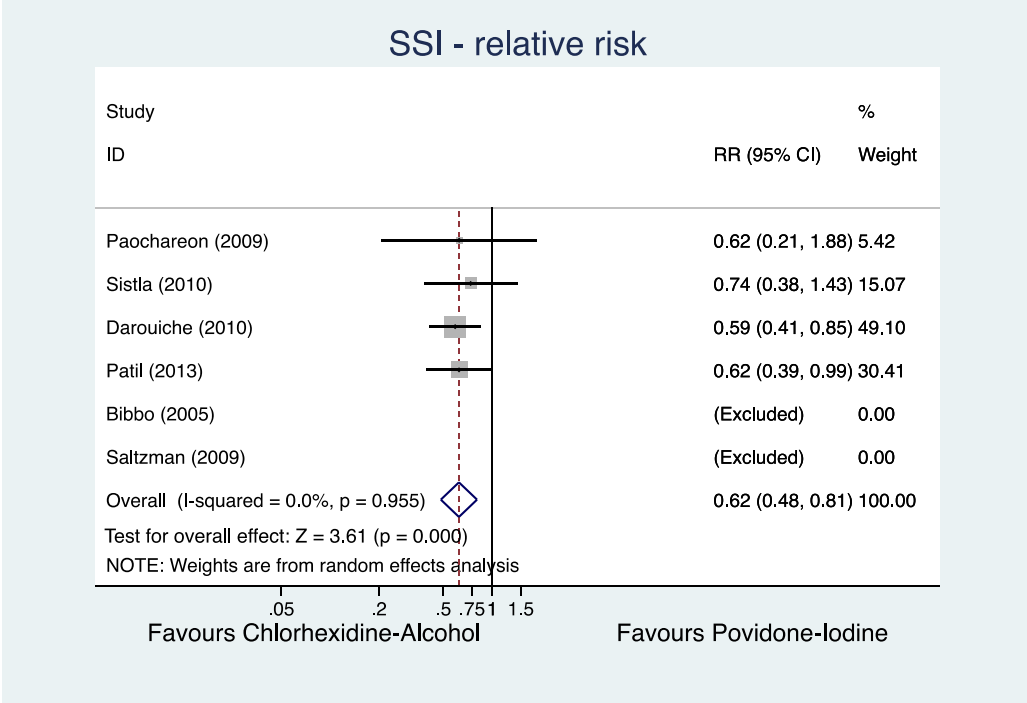

Fig. 2. Meta-analysis of CHA vs. PI in the prevention of SSI across all studies.

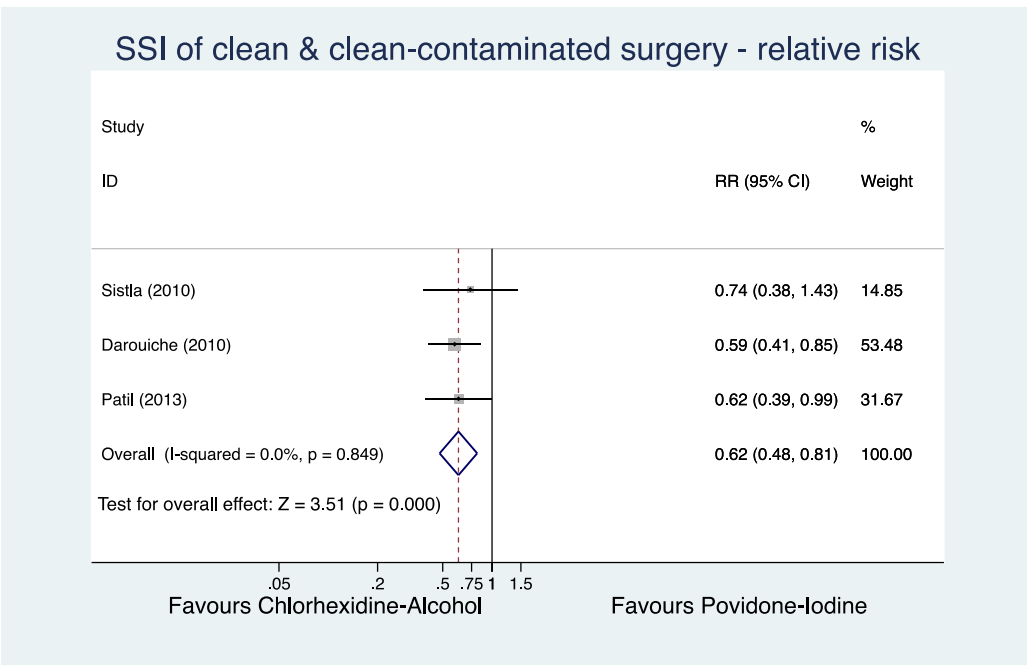

Fig. 3. Sensitivity meta-analysis of CHA vs. PI in the prevention of SSI across clean and clean-contaminated procedures.

Ethical approval

Ethical approval was not needed for this systematic review.

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Author contribution

Firas Ayoub designed the study, extracted data, performed analysis, interpreted data, wrote manuscript and acted as corresponding author. Michael Quirke extracted data and helped in editing the manuscript. Arnold Hill and Ronan and Ronan Conroy acted as clinical and methodological supervisors and helped in writing and evaluating the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.ijso.2016.02.002.

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