ORIGINAL ARTICLE

Skin Antisepsis before Surgical Fixation of Extremity Fractures

The PREP-IT Investigators*

ABSTRACT

BACKGROUND

Studies evaluating surgical-site infection have had conflicting results with respect to the use of alcohol solutions containing iodine povacrylex or chlorhexidine gluconate as skin antisepsis before surgery to repair a fractured limb (i.e., an extremity fracture).

METHODS

In a cluster-randomized, crossover trial at 25 hospitals in the United States and Canada, we randomly assigned hospitals to use a solution of 0.7% iodine povacrylex in 74% isopropyl alcohol (iodine group) or 2% chlorhexidine gluconate in 70% isopropyl alcohol (chlorhexidine group) as preoperative antisepsis for surgical procedures to repair extremity fractures. Every 2 months, the hospitals alternated interventions. Separate populations of patients with either open or closed fractures were enrolled and included in the analysis. The primary outcome was surgical-site infection, which included superficial incisional infection within 30 days or deep incisional or organ-space infection within 90 days. The secondary outcome was unplanned reoperation for fracture-healing complications.

RESULTS

A total of 6785 patients with a closed fracture and 1700 patients with an open fracture were included in the trial. In the closed-fracture population, surgical-site infection occurred in 77 patients (2.4%) in the iodine group and in 108 patients (3.3%) in the chlorhexidine group (odds ratio, 0.74; 95% confidence interval [CI], 0.55 to 1.00; P=0.049). In the open-fracture population, surgical-site infection occurred in 54 patients (6.5%) in the iodine group and in 60 patients (7.3%) in the chlorhexidine group (odd ratio, 0.86; 95% CI, 0.58 to 1.27; P=0.45). The frequencies of unplanned reoperation, 1-year outcomes, and serious adverse events were similar in the two groups.

CONCLUSIONS

Among patients with closed extremity fractures, skin antisepsis with iodine povacrylex in alcohol resulted in fewer surgical-site infections than antisepsis with chlorhexidine gluconate in alcohol. In patients with open fractures, the results were similar in the two groups. (Funded by the Patient-Centered Outcomes Research Institute and the Canadian Institutes of Health Research; PREPARE ClinicalTrials.gov number, NCT03523962.)

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Clinical practice guidelines universally recommend the use of antiseptic skin solutions containing alcohol to prevent surgical-site infection.[1-4] Although some guidelines favor antisepsis with chlorhexidine gluconate over an iodophor,[1,2] all recommendations recognize a lack of consensus with respect to the most effective agent.[1-4]

Globally, millions of patients fracture a limb (i.e., have an extremity fracture) each year.[5] Despite the large number of fracture surgeries performed annually, few studies of skin antisepsis have included patients with such fractures.[6] Furthermore, generalized evaluations of antisepsis with iodine as compared with chlorhexidine need to be more nuanced because the active agents of antiseptic products differ in their concentrations, chemical compositions, and types of solution.[6] The lack of directly applicable research and the conflicting results in other surgical populations have contributed to ongoing uncertainty among surgeons with respect to the most appropriate type of antisepsis in such cases.

To determine the most effective skin antisepsis solution for limb-fracture surgery, we designed PREPARE (A Pragmatic Randomized Trial Evaluating Preoperative Alcohol Skin Solutions in Fractured Extremities). In this trial, we compared the two most common skin antiseptics used in the United States and Canada and specifically sought to determine the superiority of either iodine povacrylex in alcohol or chlorhexidine gluconate in alcohol for the prevention of surgical-site infection in a population of patients undergoing fixation of a closed lower-limb or pelvic fracture and a population of patients undergoing fixation of an open fracture.

Methods

Trial Design and Oversight

In this trial, we used a multiple-period, cluster-randomized, crossover design. A total of 25 hospitals in the United States and Canada participated in the trial. Of these hospitals, 20 recruited patients with either open or closed fractures; 3 hospitals recruited patients with closed fractures only, and 2 recruited those with open fractures only. All participating hospitals obtained approval from the local institutional review board before trial initiation. The enrolled patients provided written informed consent to allow trial follow-up and the use of their personal health information. An independent data and safety monitoring committee reviewed the trial. The protocol, which has been published previously,[7] is available with the full text of this article at NEJM.org.

The trial was guided by the master protocol of the Program of Randomized Trials to Evaluate Preoperative Antiseptic Skin Solutions in Orthopedic Trauma (PREP-IT). The PREP-IT investigators included all those who contributed to the development of the master protocol and to the conduct of either PREPARE or Aqueous-PREP (A Pragmatic Randomized Trial Evaluating Preoperative Aqueous Antiseptic Skin Solutions in Open Fractures). The trial was funded by the Patient-Centered Outcomes Research Institute and the Canadian Institutes of Health Research. The manufacturers of the solutions did not supply any products that were used in the trial and did not have any role in the conduct of the trial or in the analyses of the data. Trial oversight was provided by numerous committees and core teams that included researchers, clinicians, patient partners, and relevant stakeholders. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol. The trial funders had no role in the design or conduct of the trial; in the collection, analysis, or interpretation of the data; or in the reporting of the results.

Cluster Selection

We selected hospitals for participation in the trial after we had obtained confirmation that their orthopedic surgery practice group had appropriate research personnel infrastructure to implement the protocol, an adequate volume of patients with fractures to meet enrollment targets, a commitment from all surgeons to adhere to the assigned interventions, and the ability to procure both iodine povacrylex (iodine group) and chlorhexidine gluconate (chlorhexidine group). Hospitals completed a 1-month run-in period to confirm their competence and commitment to enrollment and protocol adherence.

Closed-Fracture Population

The closed-fracture population consisted of adults (≥18 years old) who were undergoing surgical fixation of a closed lower-limb or pelvic fracture. We excluded patients who had a concurrent open fracture, had a medical contraindication to re-

ceive either trial intervention, or had a chronic or acute infection at or near the fracture site at the time of the index surgery.

OPEN-FRACTURE POPULATION

The open-fracture population consisted of adults (≥18 years old) who had an open upper-limb or lower-limb fracture warranting surgical fixation. In addition, the patient's open fracture must have received surgical débridement within 72 hours after injury. We excluded patients with open fractures of the hand and those who had received previous surgical débridement at a nonparticipating hospital.

Patients with multiple fractures were eligible for inclusion. Once the patient had been assigned to the open- or closed-fracture population, data were collected on up to three eligible fracture regions. In the open-fracture population, only eligible regions with open fractures were included. Similarly, only patients with closed lower-limb or pelvic fractures were included in the closed-fracture population. In patients with more than three eligible fracture regions, the treating surgeon determined the three regions with the most severe fractures to include in the trial. The full eligibility criteria for the two fracture populations are provided in the protocol and in Section S1.3A and S1.3B of the Supplementary Appendix, available at NEJM.org.

RANDOMIZATION AND INTERVENTIONS

Participating hospitals were randomly assigned to use a solution of 0.7% iodine povacrylex in 74% isopropyl alcohol (3M Duraprep Surgical Prepping Solution) or a solution of 2% chlorhexidine gluconate in 70% isopropyl alcohol (BD ChloraPrep; 3M SoluPrep S Sterile Antiseptic Solution) for all eligible patients. Randomization was performed once per cluster with the use of a 1:1 ratio and random blocks of 2 and 4. Once the initial treatment period was complete, the hospitals crossed over to the alternative intervention every 2 months to mitigate the effects of seasonal pathogens and potential changes in infection-prevention practice[8,9] (Fig. S1A and S1B in the Supplementary Appendix).

For patients with multiple planned fracture surgeries, the initially assigned solution was used for all subsequent surgeries. In order to be considered to have treatment adherence, patients must have received the assigned intervention for the definitive fracture-management surgery of all fractures. All the patients and surgeons were aware of the group assignments. Reviews by outcome adjudicators and data analysts were performed in a blinded manner.

TRIAL OUTCOMES

The primary outcome was surgical-site infection, as defined by the 2017 reporting criteria of the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network.[10] This outcome included superficial incisional infection within 30 days and deep incisional or organ-space infection within 90 days after definitive fracture-management surgery. Superficial incisional infection was defined as an infection that was characterized by localized erythema and purulent drainage from the skin or subcutaneous tissue and specifically did not include cellulitis or stitch abscess. Deep incisional or organ-space infection was defined as an infection that occurred deep in the muscle or fascia or involved a fractured bone or joint. Complete descriptions of the CDC criteria are provided in Section S1.4.

The secondary outcome was an unplanned fracture-related reoperation within 365 days after the fracture. This definition included reoperation to manage infection, wound-healing complications, and fracture-healing complications, such as delayed union or nonunion.

Outcomes were assessed at 3 months, 6 months, 9 months, and 12 months after the fracture. Trial outcomes were independently assessed by the members of the central adjudication committee, who were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

Details regarding the sample-size calculation have been reported previously.[7] In the closed-fracture population, a 3.5% baseline risk of infection was estimated on the basis of data from previous studies.[11,12] In the open-fracture population, a 12.5% baseline risk of infection was estimated on the basis of data from the large Fluid Lavage of Open Wounds (FLOW) trial comparing fluid lavage techniques during open-fracture débridement.[13] The anticipated effect size for both populations was derived from a secondary analysis of iodophor effectiveness among the patients in the FLOW trial. We estimated that the enrollment of 6280 patients with a closed fracture would provide the trial with 80% power to detect a relative

between-group difference of 36% in the odds of infection, with a two-sided alpha level of 5%. Similarly, we estimated that the enrollment of 1540 patients with an open fracture would provide the trial with more than 80% power to detect a 38% difference in the odds of infection, with a two-sided alpha level of 5%. Both sample-size calculations allowed for 10% attrition and assumed the establishment of 10 clusters, no between-period variance, and a between-cluster variance of 0.095.[13] We subsequently increased the number of clusters from 10 to 25 to meet the contractual milestones of the funders, a change that conferred a modest gain in statistical power.[8,14] We did not perform an interim analysis.

Our primary analysis was performed in the intention-to-treat population and used multiple imputations according to trial group and accounted for cluster to impute missing outcome data. We evaluated treatment effects on the trial outcomes using mixed-effects regression models with binomial distributions.

As prespecified, the closed-fracture model included fixed effects for trial group, a continuous measure of the chronologic recruitment period (time in days), and indicators for severe soft-tissue injuries and periarticular fractures. We also included a cluster indicator as a random intercept with an exchangeable correlation structure. We confirmed that the random effects were normally distributed and that the results were robust to specifying time as a categorical indicator or nonlinear term. For the primary outcome, the intraclass correlation was 0.03 (Table S1).

In the open-fracture population, we started with a mixed-effects regression model and attempted to fit the model with an exponential decay correlation structure, a nested exchangeable correlation structure, and an exchangeable correlation structure, as prespecified. However, because the random-effects (i.e., cluster) variance was estimated to be very near zero, indicating singularity, we used a simple logistic-regression model that included fixed effects (trial group, open-fracture severity, fracture location, wound contamination, and recruitment period). Consistent with closed-fracture models, the results were robust to other time-period specifications, including a categorical indicator or nonlinear term. In the two populations, we obtained marginal-standardization standard errors using the delta method.[15]

In addition, we assessed treatment effects in the as-treated populations and conducted Bayesian analyses with prespecified prior effects (Section S1.5). We also refit the primary model to expand the CDC surveillance criteria for surgical-site infection to 365 days after injury and the fracture-related infection confirmatory criteria.[16]

We assessed the heterogeneity of treatment effects by adding an interaction term to the primary and secondary outcome models. The prespecified subgroups included binary indicators for severe soft-tissue injuries or periarticular fractures in the closed-fracture population and open-fracture severity (Gustilo–Anderson type III or either type I or type II), fracture location (lower or upper limb), and severity of wound contamination (embedded contamination or no, minimal, or surface contamination) in the open-fracture population. Subgroup hypotheses were prespecified.[7]

We prespecified an alpha of 0.05 to indicate statistical significance for the primary outcome. For the secondary outcome and additional analyses, we did not adjust the widths of the confidence intervals for multiplicity, so the confidence intervals should not be used to infer definitive treatment effects. All hypothesis testing was two-sided. All analyses were performed with R software, version 4.2.2 (R Foundation for Statistical Computing).

RESULTS

CLOSED-FRACTURE POPULATION

A total of 20,937 adult patients were screened for eligibility after presenting to a participating hospital with a closed fracture of a lower limb or pelvis during the trial period. Of the screened patients, 6785 were included in the primary analysis, with 95% completing follow-up for the primary analysis (Fig. S2A, Table S2A, and Table S3A). The mean (±SD) age of the patients in the closed-fracture population was 53.9±20.3 years, and 3469 (51.1%) were women. The trial groups had similar characteristics at baseline (Table 1), with fractures of the proximal femur (approximately 25%) being the most common injury in this population (Table 2 and Table S4A).

OPEN-FRACTURE POPULATION

Of the 4513 adult patients who presented to a participating center with an open fracture, 1700

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Closed-Fracture Population		Open-Fracture Population	
	Iodine Povacrylex (N=3360)	Chlorhexidine Gluconate (N=3425)	Iodine Povacrylex (N=854)	Chlorhexidine Gluconate (N=846)
Age — yr	54.3±20.2	53.6±20.4	45.0±18.3	44.2±18.1
Sex — no. (%)				
Female	1730 (51.5)	1739 (50.8)	312 (36.5)	309 (36.5)
Male	1629 (48.5)	1686 (49.2)	542 (63.5)	537 (63.5)
Missing data	1 (<0.1)	0	0	0
Race or ethnic group — no. (%)†				
White	2652 (78.9)	2706 (79.0)	584 (68.4)	589 (69.6)
Black	501 (14.9)	480 (14.0)	227 (26.6)	214 (25.3)
Asian	140 (4.2)	147 (4.3)	22 (2.6)	17 (2.0)
Indigenous	27 (0.8)	33 (1.0)	9 (1.1)	12 (1.4)
Central or South American	4 (0.1)	7 (0.2)	2 (0.2)	1 (0.1)
Multiracial	3 (0.1)	4 (0.1)	2 (0.2)	4 (0.5)
Native Hawaiian or Pacific Islander	3 (0.1)	5 (0.1)	1 (0.1)	1 (0.1)
Missing data	30 (0.9)	43 (1.3)	7 (0.8)	8 (0.9)
Hispanic ethnic group — no. (%)†	170 (5.1)	181 (5.3)	65 (7.6)	47 (5.6)
Body-mass index — no. (%)‡				
<18.5: underweight	99 (2.9)	80 (2.3)	12 (1.4)	13 (1.5)
18.5–24.9: normal weight	1068 (31.8)	1106 (32.3)	252 (29.5)	250 (29.6)
25.0–29.9: overweight	1082 (32.2)	1024 (29.9)	279 (32.7)	294 (34.8)
≥30: obese	1111 (33.1)	1215 (35.5)	311 (36.4)	289 (34.2)
Diabetes of any type — no. (%)	470 (14.0)	445 (13.0)	80 (9.4)	64 (7.6)
Current smoker — no. (%)	753 (22.4)	722 (21.1)	289 (33.8)	282 (33.3)
Injury severity score§	9.0±6.2	8.9±6.2	13.4±8.5	12.9±8.0
Score on the ASA physical-status classification — no. (%)¶				
Class I or II	1760 (52.4)	1752 (51.2)	440 (51.5)	463 (54.7)
Class III or higher	1600 (47.6)	1673 (48.8)	414 (48.5)	383 (45.3)
No. of included closed fractures per patient — no. (%)				
One	3169 (94.3)	3240 (94.6)	782 (91.6)	771 (91.1)
Two	166 (4.9)	162 (4.7)	62 (7.3)	68 (8.0)
Three	25 (0.7)	23 (0.7)	10 (1.2)	7 (0.8)

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding. ASA denotes American Society of Anesthesiologists.
† Race or ethnic group was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The injury severity score standardizes the severity of traumatic injuries on the basis of the worst injuries present across a maximum of three different body regions; total scores range from 1 to 75, with higher scores indicating more severe injury.
¶ Scoring on the ASA physical-status classification is as follows: I, good health; II, mild systemic disease; III, severe systemic disease that is not incapacitating; IV, severe life-threatening systemic disease; and V, moribund and not expected to survive without operation.

Table 2. Treatment Characteristics of Closed-Fracture Injuries.*

Characteristic	Iodine Povacrylex (N=3576 fractures)	Chlorhexidine Gluconate (N=3633 fractures)
Location of fracture — no. (%)		
Proximal femur	865 (24.2)	772 (21.2)
Foot or ankle	778 (21.8)	830 (22.8)
Proximal tibia or fibula	430 (12.0)	443 (12.2)
Pelvis or acetabulum	369 (10.3)	415 (11.4)
Femoral shaft	358 (10.0)	382 (10.5)
Distal tibia or fibula	288 (8.1)	275 (7.6)
Tibia or fibula shaft	241 (6.7)	264 (7.3)
Distal femur	183 (5.1)	183 (5.0)
Patella	64 (1.8)	69 (1.9)
Periarticular fracture — no. (%)†	1122 (31.4)	1155 (31.8)
Severe soft-tissue injury — no. (%)‡	149 (4.2)	149 (4.1)
Temporary fracture stabilization — no. (%)	294 (8.2)	301 (8.3)
No. of planned surgeries — no. (%)		
1	3264 (91.3)	3307 (91.0)
2	284 (7.9)	303 (8.3)
≥3	28 (0.8)	23 (0.6)
Median no. of days of antibiotic administration (IQR)§	1.0 (1.0–2.0)	1.0 (1.0–2.0)

* Data are listed according to the number of fractures rather than the number of patients. IQR denotes interquartile range
† Periarticular fractures are fractures of the distal femur, proximal tibia, distal tibia, or ankle.
‡ Severe soft-tissue injury is defined as having one of the following: extensive skin contusion or crush injury, severe damage to the underlying muscle, compartment syndrome, or internal degloving.
§ The duration was based on the receipt of at least one antibiotic dose in a calendar day.

were included in the primary analysis (Fig. S2B and Tables S2B and S3B). The mean age of the patients in the open-fracture population was 44.6±18.2 years, and 63.5% were men. The trial groups had similar characteristics at baseline (Tables 1 and 3 and Table S4A). Primary outcome data were available for 1651 of 1700 patients (97.1%).

REPRESENTATIVENESS OF TRIAL POPULATIONS

The trial populations were representative of patients undergoing surgery for fractures of the limbs or pelvis in the general population. The distributions of age, sex, and race or ethnic group were similar to those observed in population-based research (Table S5A and S5B).

ADHERENCE TO TREATMENT

In the closed-fracture population, the assigned skin antisepsis was used during fracture-management surgery in 3254 of 3360 patients (96.8%) in the iodine group and in 3411 of 3425 patients (99.6%) in the chlorhexidine group. Similarly, in the open-fracture population, the assigned skin antisepsis was used in 816 of 854 patients (95.6%) in the iodine group and in 827 of 846 patients (97.8%) in the chlorhexidine group.

PRIMARY OUTCOME

In the closed-fracture population, surgical-site infection occurred in 77 of 3205 patients (2.4%) in the iodine group and in 108 of 3272 patients (3.3%) in the chlorhexidine group (odds ratio, 0.74; 95% confidence interval [CI], 0.55 to 1.00; P=0.049) (Table 4). The absolute difference in the risk of surgical-site infection between the iodine group and the chlorhexidine group was −0.8 percentage points (95% CI, −1.6 to 0.0). The results in the as-treated population, analyses with alternative definitions of infection, and Bayesian

Table 3. Treatment Characteristics of Open-Fracture Injuries.

Characteristic	Iodine Povacrylex (N=936 fractures)	Chlorhexidine Gluconate (N=928 fractures)
Gustilo–Anderson severity grade — no. (%)*		
Grade I	219 (23.4)	213 (23.0)
Grade II	316 (33.8)	317 (34.2)
Grade IIIA	361 (38.6)	361 (38.9)
Grade IIIB or IIIC	40 (4.3)	37 (4.0)
Location of fracture — no. (%)		
Lower limb or pelvis	687 (73.4)	672 (72.4)
Upper limb	249 (26.6)	256 (27.6)
Wound contamination — no. (%)		
None or minimal	573 (61.2)	576 (62.1)
Surface only	282 (30.1)	266 (28.7)
Contaminant embedded in bone or deep soft tissue	81 (8.7)	86 (9.3)
Temporary fracture stabilization — no. (%)	184 (19.7)	165 (17.8)
No. of planned surgeries — no. (%)		
1	678 (72.4)	673 (72.5)
2	184 (19.7)	190 (20.5)
3	38 (4.1)	42 (4.5)
4	12 (1.3)	10 (1.1)
≥5	24 (2.6)	13 (1.4)
Median no. of days of antibiotic administration (IQR)†	3.0 (2.0–4.0)	3.0 (2.0–3.3)
Closure method — no. (%)‡		
Primary wound closure	855 (91.3)	859 (92.6)
No closure attempted or secondary wound healing	17 (1.8)	14 (1.5)
Skin graft	35 (3.7)	20 (2.2)
Local flap	12 (1.3)	20 (2.2)
Free flap	17 (1.8)	15 (1.6)

* The Gustilo–Anderson open-fracture classification system is as follows: grade I, clean wound measuring less than 1 cm in length; grade II, wound measuring 1 cm or more without extensive soft-tissue damage, flaps, or avulsions; grade IIIA, wound of any length with adequate soft-tissue coverage of a fractured bone despite extensive soft-tissue laceration or flaps or high-energy trauma; grade IIIB, extensive soft-tissue loss and periosteal stripping and bone damage, usually associated with massive contamination or need for soft-tissue flap; and grade IIIC, wound associated with an arterial injury requiring repair regardless of the degree of soft-tissue injury.
† The duration was based on the receipt of at least one antibiotic dose in a calendar day.
‡ More than one type of closure method may have been performed during surgery, but only the most complex method of closure is listed here according to the following hierarchy: 1, free flap; 2, local flap; 3, skin graft; 4, no closure attempted or secondary wound healing; and 5, primary wound closure.

analyses are provided in Tables S6A, S7A, S8A, S9A, and S10A).

In the open-fracture population, surgical-site infection occurred in 54 of 825 patients (6.5%) in the iodine group and in 60 of 826 patients (7.3%) in the chlorhexidine group (odds ratio, 0.86; 95% CI, 0.58 to 1.27; P=0.45) (Table 4). The results in the as-treated population, analyses with alternative definitions of infection, and Bayesian analyses are reported in Tables S6B, S7B, S8B, S9B, and S10B.

SECONDARY OUTCOME

In the closed-fracture population, unplanned reoperation within 365 days after fracture occurred in 5.5% of the patients in the iodine

Table 4. Primary and Secondary Outcomes.*

Outcome	Iodine Povacrylex	Chlorhexidine Gluconate	Odds Ratio (95% CI)†	P Value	Risk Difference (95% CI)†‡
	no./total no. (%)				*percentage points*
Closed-fracture population					
Surgical-site infection: primary outcome§	77/3205 (2.4)	108/3272 (3.3)	0.74 (0.55 to 1.00)	0.049	–0.8 (–1.6 to 0.0)
Superficial infection in ≤30 days	20/3205 (0.6)	27/3272 (0.8)			
Deep infection in ≤90 days	29/3205 (0.9)	54/3272 (1.7)			
Organ-space infection in ≤90 days	28/3205 (0.9)	27/3272 (0.8)			
Unplanned reoperation: secondary outcome¶	164/2982 (5.5)	179/3047 (5.9)	0.96 (0.77 to 1.20)	NA	–0.3 (–1.6 to 1.1)
For infection	98/2982 (3.3)	117/3047 (3.8)			
For wound-healing problem	57/2982 (1.9)	65/3047 (2.1)			
For delayed union or nonunion	66/2982 (2.2)	66/3047 (2.2)			
Open-fracture population					
Surgical-site infection: primary outcome§	54/825 (6.5)	60/826 (7.3)	0.86 (0.58 to 1.27)	0.45	–0.9 (–3.4 to 1.5)
Superficial infection in ≤30 days	6/825 (0.7)	9/826 (1.1)			
Deep infection in ≤90 days	21/825 (2.5)	20/826 (2.4)			
Organ-space infection in ≤90 days	27/825 (3.3)	31/826 (3.8)			
Unplanned reoperation: secondary outcome¶	126/784 (16.1)	114/785 (14.5)	1.16 (0.87 to 1.54)	NA	1.8 (–1.7 to 5.3)
For infection	70/784 (8.9)	70/785 (8.9)			
For wound-healing problem	49/784 (6.2)	42/785 (5.4)			
For delayed union or nonunion	61/784 (7.8)	50/785 (6.4)			

* NA indicates not applicable because P values were not calculated for secondary outcomes.
† For the secondary outcomes, the widths of the confidence intervals have not been adjusted for multiple comparisons.
‡ The risk difference is the average marginal effect obtained from the mixed-effects regression model in the closed-fracture population and from the logistic-regression model in the open-fracture population.
§ Outcome data for surgical-site infection were missing for 4.5% of the patients in the closed-fracture population and for 2.8% of those in the open-fracture population.
¶ Patients who underwent multiple reoperations within 365 days after fracture may have more than one indication reported. Outcome data for reoperation were missing for 11.1% of the patients in the closed-fracture population and for 7.7% of those in the open-fracture population.

group and in 5.9% of those in the chlorhexidine group (odds ratio, 0.96; 95% CI, 0.77 to 1.20) (Table 4).

In the open-fracture population, unplanned reoperation within 365 days after fracture occurred in 16.1% of the patients in the iodine group and 14.5% of those in the chlorhexidine group (odds ratio, 1.16; 95% CI, 0.87 to 1.54) (Table 4). Unplanned reoperation to treat infection or wound-healing complications or to promote fracture healing each had a similar incidence in the two groups and in the two populations.

SERIOUS ADVERSE EVENTS

The incidence of serious adverse events was similar in the two groups (Table S11A and S11B). There were no chemical burns or surgical fires reported in either trial group.

SUBGROUPS ANALYSES

In the closed-fracture population, the presence of a severe soft-tissue injury or periarticular fracture did not substantially modify the effect of iodine povacrylex as compared with chlorhexidine gluconate on the primary or secondary outcome (Fig. 1 and Table S12A). Similarly, in the

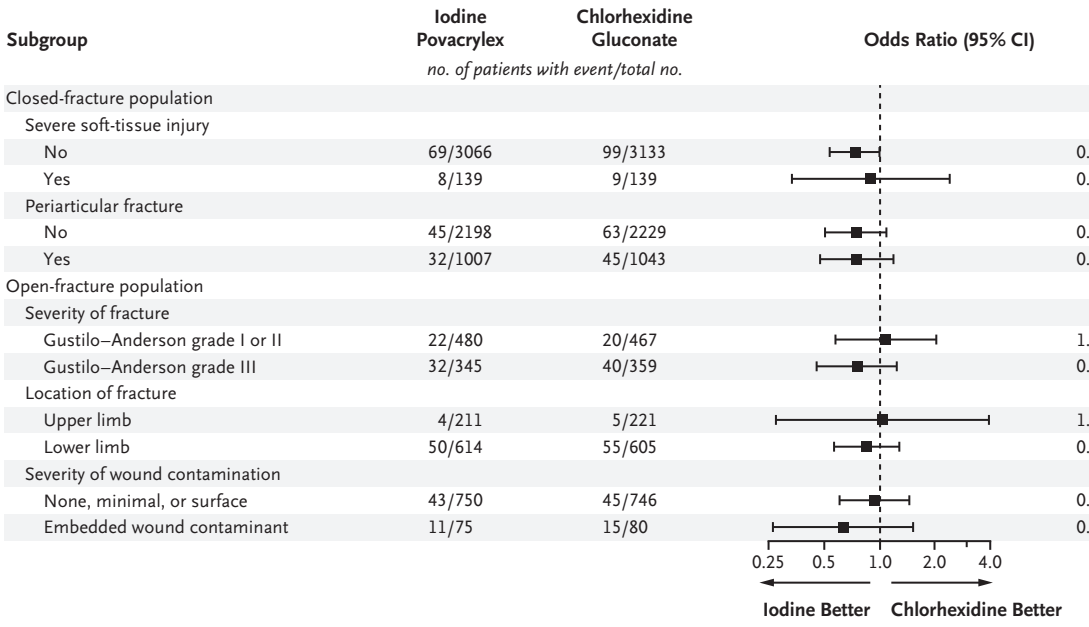

Figure 1. Subgroup Analyses of Surgical-Site Infection.

The presence of a severe soft-tissue injury or periarticular fracture did not substantially modify the effect of iodine povacrylex as compared with chlorhexidine gluconate in the closed-fracture population. Similarly, in the open-fracture population, there was no major differential treatment effect associated with the severity or location of the fracture or with the presence of wound contamination.

open-fracture population, the severity or location of the open fracture or the presence of wound contamination did not result in a differential treatment effect (Fig. 1 and Table S12B).

DISCUSSION

In patients who were undergoing surgical fixation of a closed fracture of a lower limb or the pelvis, we found that the risk of surgical-site infection (the primary outcome) was lower with skin antisepsis provided by iodine povacrylex in alcohol than with antisepsis provided by chlorhexidine gluconate in alcohol. In contrast, the risk of surgical-site infection did not differ significantly between the two trial groups in the open-fracture population. The treatment estimates for surgical-site infection were similar among additional prespecified analyses in the two populations. The treatment effect did not differ across any subgroup in either population, and the incidence of serious adverse events was similar in the two groups.

The findings of previous trials of preoperative skin antisepsis have been inconsistent.[6] Unless contraindicated, clinical practice guidelines support the use of alcohol-based solutions,[1-4] and some recommend chlorhexidine plus alcohol as the preferred agent.[1,2] However, the support for chlorhexidine skin antisepsis has been based primarily on the results of trials that evaluated chlorhexidine gluconate as compared with povidone iodine in patients undergoing abdominal, obstetrical, or gynecologic surgeries.[17,18]

Two previous studies have directly compared chlorhexidine gluconate in alcohol with iodine povacrylex in alcohol to reduce surgical-site infection.[19,20] The results of one randomized, controlled trial involving 788 patients who underwent elective colorectal surgery under clean-contaminated conditions (i.e., in which the surgical area is entered under controlled conditions with a low probability of contamination)[10] was inconclusive (between-group difference, 2.8 percentage points; 95% CI, –3.2 to 8.9).[19] Conversely, a prospective study involving 3209 general surgery patients favored iodine povacrylex for the prevention of surgical-site infection (3.9% vs. 7.1%).[20]

The iodophor that we used in our trial differs from povidone iodine. Iodine povacrylex is a novel iodophor that is available in alcohol and distinguished by its copolymer, povacrylex. The structure of the iodine povacrylex copolymer may provide important benefits beyond those of traditional povidone iodine for the prevention of surgical-site infection. Although iodine is inactivated by organic matter, povacrylex is a water-insoluble deliverer of free iodine that is resistant to fluids and blood, thereby potentially offering longer protection than povidone iodine or other agents.[21] In addition, the iodine povacrylex copolymer was designed for improved adhesion to a surgical drape, which could potentially reduce the migration of skin flora into the incision during surgery.[22] In the closed-fracture population, the lower risk of surgical-site infection in the iodine group may have resulted more from the sustained protection of iodine by the povacrylex copolymer than from the potential superiority of iodine over chlorhexidine gluconate.

In contrast, we did not observe the same benefit of iodine povacrylex in the open-fracture population. There are several potential reasons for the contrasting results in the two populations. First, open-fracture wounds are promptly irrigated with 3 to 9 liters of saline early in the débridement phase of surgery. This procedure could attenuate the protective effect of povacrylex. Second, open-fracture wounds are exposed to heterogeneous environmental contamination and prolonged bacterial exposure before surgery. At the time of injury, bacteria can reach the deep tissues and begin early biofilm formation several hours before skin antisepsis is performed in the operating room. For surgical fixation of open fractures, it is plausible that the choice of antiseptic solution does not have a strong enough effect to measurably alter the risk of infection, whereas antiseptic reduction of skin flora immediately before fixation of a closed fracture can significantly reduce infection.

Our trial has several strengths. The large sample size, high adherence to trial interventions, and low attrition provided adequate statistical power to detect meaningful differences in patient outcomes. The recruitment was designed to independently assess closed- and open-fracture populations because of their widely contrasting demographic characteristics, treatment principles, and baseline risk. The cluster-crossover design allowed for the immediate application of the trial interventions, increased the enrollment rate, and subsequently minimized selection bias among more severely injured patients. The enrollment of patients from 25 geographically diverse hospitals in the United States and Canada improved the generalizability of the results. Fifth, this pragmatic trial compared the two alcohol antiseptic solutions that are most commonly used in the two countries for orthopedic trauma surgery.[23] Thus, the findings are relevant to current clinical practice.

The trial also has some limitations. First, the baseline infection risk in the open-fracture population was lower than anticipated, which reduced the statistical power for the primary comparison. This lower event rate occurred because data from patients with surgical-site infections who presented outside the 30-day and 90-day CDC surveillance periods were censored from the primary outcome. Extending the surveillance period to 1 year mirrored the initially hypothesized risk of infection in the open-fracture population. However, the treatment effect at 1 year was similar to the primary result and was not significant. Second, the patients and their surgeons were aware of the trial-group assignments. However, the members of the central adjudication committee were unaware of all assignments, which mitigated potential assessment biases. Third, even though overall treatment adherence exceeded 95% in the two populations, the percentages differed slightly between the trial groups, with better adherence among the patients in the chlorhexidine group. As such, the as-treated analysis suggests that the intention-to-treat analysis may underrepresent the true treatment effect. Fourth, the size of the clusters varied tremendously, which could have led to prognostic imbalance.[24] Despite this variability, our intracluster correlation coefficient was low in the closed-fracture population and the cluster variance was near zero in the open-fracture population, which suggests that cluster imbalance had a negligible effect on our estimates. Finally, the trial was limited to patients who were undergoing surgery for a fracture, so the generalizability of these findings to other surgical populations is unknown. In addition, changes in surgical practice and antimicrobial resistance may also influence efficacy over time.

Worldwide, approximately 178 million persons

fracture a limb each year, including more than 1 million who are treated surgically in the United States.[5,25] In all these procedures, the treating surgeon selects a skin antiseptic. The interventions that we compared in this trial are similar in price, availability, and directions for use. Our findings suggest that the use of iodine povacrylex in alcohol as preoperative skin antisepsis could prevent surgical-site infection in thousands of patients with closed fractures, but such use is unlikely to improve the outcomes in patients with open fractures. Nevertheless, the possibility that patients will have an allergic reaction to an ingredient in either solution means that hospitals will need to continue to stock both interventions.

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APPENDIX

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