Chlorhexidine Compared with Povidone-Iodine as Skin Preparation before Blood Culture

A Randomized, Controlled Trial

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Background: Chlorhexidine is better than povidone-iodine for care of catheter sites, but it is not known whether chlorhexidine is superior in reducing blood culture contamination.

Objective: To determine whether alcoholic chlorhexidine is a more effective skin antiseptic for collection of blood cultures than aqueous povidone-iodine.

Design: Randomized, controlled trial.

Setting: Three adult intensive care units in a French university hospital.

Patients: 403 adults who had at least one blood culture drawn through a peripheral vein.

Interventions: Patients were randomly assigned to receive skin preparation with an aqueous solution of 10% povidone-iodine or an alcoholic solution of 0.5% chlorhexidine before phlebotomy.

Measurements: Contamination rates of blood cultures.

Results: Of 2041 blood cultures collected in 403 patients, 124 yielded pathogens. Chlorhexidine reduced the incidence of blood culture contamination more than povidone-iodine (14 of 1019 cultures [1.4%] compared with 34 of 1022 cultures [3.3%]; odds ratio, 0.40 [95% CI, 0.21 to 0.75]; $P = 0.004$).

Conclusion: Skin preparation with alcoholic chlorhexidine is more efficacious than skin preparation with aqueous povidone-iodine in reducing contamination of blood cultures.

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Contamination of blood cultures is common because microflora are usually present on the skin. The misinformation that results from contamination of blood cultures may have deleterious consequences. Therefore, it is important that blood cultures be collected by using a procedure that minimizes contamination (1). In general, preparation of the skin with one or more antiseptic agents should permit satisfactory antisepsis, provided that a suitable period (0.5 to 2 minutes) is allowed for the antiseptic to take effect (2). In many hospitals, however, the personnel collecting blood cultures do not carefully follow the recommended procedures, leading to an excessively high rate of blood culture contamination. This is especially true in the intensive care unit, possibly because of the high workload of nurses (2).

A recent trial comparing povidone-iodine and iodine tincture antiseptics showed a substantially lower rate of blood culture contamination with use of iodine tincture; this finding was related to the fact that iodine tincture acts faster than povidone-iodine (1). However, use of iodine tincture in the intensive care unit is limited because repeated exposure to high concentrations of iodine can be toxic (3). Alternately, chlorhexidine has been found to be superior to povidone-iodine and alcohol when it is used for catheter care (3–5), but its value in preventing blood culture contamination remains unknown.

We assumed that the decreased effectiveness of aqueous 10% povidone-iodine in previous studies could be related to the time required to achieve skin antisepsis with this agent. We examined whether the use of alcoholic chlorhexidine decreased the rate of blood culture contamination in hospitals in which personnel did not consistently allow antiseptics to act for the recommended time period before collection.

Methods

Patients

The study was conducted between 1 December 1997 and 24 April 1998 in three adult intensive care units (medical, surgical, and neurosurgical) at Hôpital Bicêtre, a 1000-bed teaching hospital in France. All adult patients without apparent skin infection

who had blood cultures drawn through a peripheral vein were eligible for the study. Because we compared two well-accepted interventions, institutional review board approval was not sought, in accordance with the policy at our institution.

Study Design

We assigned patients to one of two groups according to type of antiseptic solution used for skin preparation before blood culture. Computerized randomization lists were generated in blocks of four and were stratified by unit of hospitalization. We used an alcoholic solution of 0.5% chlorhexidine gluconate (Hibitane Champ, Zeneca Pharma, Cergy, France) or an aqueous solution of 10% povidone-iodine (Bétadine, Asta Medica, Marignane, France).

Skin antisepsis was done by vigorously applying the assigned antiseptic solution once. Blood was obtained 15 to 30 seconds after the application. The 20-mL blood samples, which the nurses collected according to a previously determined procedure (dictated by the hospital), were inoculated simultaneously into aerobic and anaerobic vials of blood culture media (Vital, bioMérieux, Marçy-l'Etoile, France). Blood cultures were incubated at 37 °C and were monitored for 5 days. Isolated organisms and their susceptibilities to antibiotics were determined by using standard methods and criteria.

Evaluation of Efficacy

The primary end point was the number of blood cultures considered to be contaminated. Two independent reviewers who were blinded to the patients' study group assignment classified each blood culture isolate as a contaminant or a true pathogen. Contaminant isolates were defined as isolates of several organisms—coagulase-negative staphylococci, *Propionibacterium acnes*, *Streptococcus viridans*, *Corynebacterium* species (excluding group JK), *Micrococcus* species, or *Bacillus* species—that were obtained from one set of blood cultures and an identical organism (that is, an organism of the same species with the same antibiotic susceptibility and the same pulsed-field gel electrophoresis pattern [6]) that was not obtained from another potentially infected site (for example, blood culture, catheter tip, or urine) 5 days before or 5 days after blood culture collection. In all other cases, blood culture isolates were considered to be true pathogens.

We defined positive blood culture as a positive bacterial culture obtained from any aerobic or anaerobic vials; such a culture was considered to be contaminated when it yielded a contaminant and was considered to be truly positive when it yielded a true pathogen. In cases of polymicrobic cultures, the positive blood culture was considered to be a single contaminated or truly bacteremic culture when all bacteria were interpreted as contaminants or true pathogens. A positive blood culture was considered to be a single concomitantly contaminated and truly bacteremic culture when some isolates were interpreted as contaminants and others were interpreted as true pathogens.

Table 1. Distribution of Patients and Blood Cultures among the Three Intensive Care Units*

Intensive Care Unit	Povidone-Iodine Group		Chlorhexidine Group	
	Patients	Blood Cultures	Patients	Blood Cultures
	← n →			
Medical	102	307	101	310
Surgical	138	473	133	470
Neurosurgical	78	242	76	239

*Some patients were included in the povidone-iodine group and in the chlorhexidine group.

Statistical Analysis

Our study was designed to determine whether skin preparation with alcoholic chlorhexidine reduced the risk for blood culture contamination. We computed the sample size necessary to detect a twofold decrease in the incidence of contaminated blood cultures. We assumed that the incidence of contaminated blood cultures in the povidone-iodine group would be 5%; therefore, 1900 blood cultures would be required to detect a difference of this magnitude (power, 0.8; type I error, 5%).

Statistical analysis (odds ratio estimation) was performed by using generalized estimating equations that took into account a possible clustering effect of multiple cultures by patient (PROC GENMOD, SAS software, version 6.12, SAS Institute, Inc., Cary, North Carolina). All tests were two-tailed. A P value of 0.05 or less was considered statistically significant.

Role of the Funding Source

The funding agencies (Zeneca Pharma and Université Paris XI [UPRES JE 2227]) were not involved in the design, conduct, or reporting of this study or in the decision to submit the manuscript for publication.

Results

A total of 2041 blood cultures were collected in 403 patients. The two study groups were similar with regard to distribution among the three intensive care units (**Table 1**). Of these 2041 cultures, 124 yielded pathogens and were interpreted as contaminated (45 cultures), truly positive (76 cultures), or concomitantly contaminated and truly positive (3

cultures). Chlorhexidine significantly reduced the rate of blood culture contamination compared with povidone-iodine (14 of 1019 cultures [1.4%] compared with 34 of 1022 cultures [3.3%]; odds ratio, 0.40 [95% CI, 0.21 to 0.75]; $P = 0.004$). The chlorhexidine group and the povidone-iodine group were similar with regard to incidence of true bacteremias (43 of 1019 cultures [4.2%] compared with 36 of 1022 cultures [3.5%]; odds ratio, 1.09 [CI, 0.79 to 1.51]; $P > 0.2$) and sterile blood cultures (963 of 1019 cultures [94.5%] compared with 954 of 1022 cultures [93.3%]; odds ratio, 1.28 [CI, 0.93 to 1.75]; $P = 0.13$). Coagulase-negative staphylococci were the main organisms recovered, accounting for about 98% of contaminants and 22% of true pathogens (**Table 2**).

Discussion

Contamination of blood cultures considerably increases the cost of patient care, particularly laboratory and pharmacy expenses, and prolongs hospital stay (7–9). Lack of good skin preparation is the most common cause of contaminants in blood cultures (7). Povidone-iodine solutions have greater in vitro microbicidal activity than chlorhexidine solutions (10). However, in a randomized trial comparing 10% povidone-iodine, 2% aqueous chlorhexidine, and 70% isopropyl alcohol applied once for the prevention of infection associated with central venous and arterial catheters, substantially fewer infections occurred with chlorhexidine (3). The superiority of chlorhexidine over povidone-iodine for skin antisepsis in preventing catheter infection, even when the antiseptics were applied serially, was confirmed (4, 5). Chlorhexidine is a potent, broad-spectrum germicide that is effective against all nosocomial pathogens (3). Primary bacterial resistance to chlorhexidine is rare (11), and acquired resistance is detected only when diluted aqueous solutions are used (12). In addition, although blood, fat, and other protein-rich biomaterials of the skin surface neutralize the germicidal activity of iodine-containing disinfectants, proteinaceous solutions have little effect on the antibacterial activity of chlorhexidine (13). Finally, the in vivo bactericidal effect of chlorhexidine on gram-positive cocci is dramatically improved by the addition of alcohol and is superior to that of aqueous povidone-iodine (14–16).

Coagulase-negative staphylococci are the organisms most frequently found in normal skin flora and are also predominant among contaminants (17). Such gram-positive organisms tend to be resistant to multiple drugs and often remain susceptible only to glycopeptides. In critically ill patients who are predisposed to nosocomial infections, reflexive use of vancomycin after reports of gram-positive cocci in blood cultures is common, even when contamination is recognized (17). In an era of emerging vancomycin-resistant enterococci (18) and, more recently, vancomycin-intermediate *Staphylococcus aureus* (19), prudent use of vancomycin is necessary to limit the spread of vancomycin-resistant gram-positive cocci (20).

Our trial has several limitations. The two antiseptics were different colors; this lack of blinding may have introduced bias. However, because these antiseptics were widely used in the three intensive care units before our study began, we do not believe that the nurses who obtained the cultures knew that one solution was more effective than the other. The relatively short period between application of the antiseptic and performance of the venipuncture may have been another source of bias. Although this practice is common in many institutions, it could have biased the results in favor of alcoholic chlorhexidine because it takes several minutes for aqueous povidone-iodine to provide its maximum antiseptic effect. Finally, the judgment of which isolates were considered to be contaminants may have bi-

Table 2. Microorganisms That Were Recovered and Classified as Contaminants or as True Pathogens

Microorganism	Povidone-Iodine Group		Chlorhexidine Group	
	Contaminants (Patients)	True Pathogens (Patients)	Contaminants (Patients)	True Pathogens (Patients)
	← *n (n)* →			
Coagulase-negative staphylococci	36 (33)	10 (6)	16 (14)	6 (4)
Staphylococcus aureus	0	7 (4)	0	9 (5)
Streptococcus species	0	7 (4)	1 (1)	6 (3)
Enterococcus faecalis	0	1 (1)	0	1 (1)
Escherichia coli	0	3 (2)	0	6 (4)
Klebsiella pneumoniae	0	1 (1)	0	4 (2)
Pseudomonas aeruginosa	0	3 (2)	0	3 (2)
Acinetobacter baumannii	0	1 (1)	0	1 (1)
Anaerobic organisms	0	0	0	1 (1)
Actinobacillus species	0	2 (1)	0	4 (1)
Candida species	0	2 (2)	0	2 (1)

ased our results, but our explicit definition of contaminant reduced this risk substantially.

Our data suggest that alcoholic chlorhexidine as skin antisepsis is more effective than aqueous povidone-iodine in reducing the incidence of blood culture contamination. Further study will probably show that the resulting lower contamination rates lead to cost savings.

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