JOURNAL OF CLINICAL MICROBIOLOGY, Jan. 2009, p. 54–58 Vol. 47, No. 1
0095-1137/09/$08.00+0 doi:10.1128/JCM.01425-08

Isopropyl Alcohol Compared with Isopropyl Alcohol plus Povidone-Iodine as Skin Preparation for Prevention of Blood Culture Contamination▽

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Received 24 July 2008/Returned for modification 1 September 2008/Accepted 17 October 2008

Despite a number of studies on the efficacies of antiseptics for the prevention of blood culture contamination, it still remains unclear which antiseptic should be used. Although the combination of povidone-iodine and isopropyl alcohol has been traditionally used in many institutions, the application of povidone-iodine needs extra time, and there is little evidence that this combination could have an additive effect in reducing contamination rates. To elucidate the additive efficacy of povidone-iodine, we compared two antiseptics, 70% isopropyl alcohol only and 70% isopropyl alcohol plus povidone-iodine, in a prospective, nonrandomized, and partially blinded study in a community hospital in Japan between 1 October 2007 and 21 March 2008. All blood samples for culture were drawn by first-year residents who received formal training on collection techniques. Skin antisepsis was performed with 70% isopropyl alcohol plus povidone-iodine on all inpatient wards and with only 70% isopropyl alcohol in the emergency department. For the group of specimens from inpatient wards cultured, 13 (0.46%) of 2,797 cultures were considered contaminated. For the group of specimens from the emergency department cultured, 12 (0.42%) of 2,856 cultures were considered contaminated. There was no significant difference in the contamination rates between the two groups (relative risk, 0.90; 95% confidence interval, 0.41 to 1.98; $P = 0.80$). In conclusion, the use of a single application of 70% isopropyl alcohol is a sufficient and a more cost- and time-effective method of obtaining blood samples for culture than the use of a combination of isopropyl alcohol and povidone-iodine. The extremely low contamination rates in both groups suggest that the type of antiseptic used may not be as important as the use of proper technique.

The collection of blood samples for culture is essential for the diagnosis and management of patients with suspected bacteremia, and the importance of this practice has recently been reconfirmed in the Clinical and Laboratory Standards Institute's guideline *Principles and Procedure for Blood Cultures* in 2007 (5). However, the problem of false-positive results due to contamination has remained since the beginning of the use of modern techniques over 70 years ago. Contamination most commonly occurs when exogenous bacteria are inoculated into the culture medium from the patient's skin, the phlebotomist's hands, or phlebotomy kits. Contamination rates below 3% are generally considered acceptable (5, 9). Nevertheless, the reported rates of contamination vary from 0.8% to over 8% among institutions. Almost half of all positive results were reported to be contaminants at some institutions (1, 4, 15, 18, 20, 23, 24, 26, 31). With such a high contamination rate, it is not easy to interpret the results properly for clinicians. Consequently, contaminated blood cultures lead to extra costs because of the unnecessary use of antibiotics, prolonged hospitalization, and the subsequent possible development of antimicrobial resistance (3, 15, 23, 25).

In an effort to reduce contamination, several studies have investigated the efficacies of prevention methods. Those studies have examined such factors as the following: the choice of skin antiseptics and venipuncture site, the need for needle exchange, culture bottle preparation, and the use of a dedicated phlebotomy team (4, 7–9, 16, 20, 31). Among those studies, a number of studies have been conducted on the antiseptics used to cleanse the skin at the venipuncture site because the most common source of contamination is often considered to be the patient's skin. However, it remains unclear which antiseptic should be used to effectively minimize contamination. Some studies had conflicting results, and others were not ideally designed to answer the research question (4, 9, 15, 16).

Traditionally, the combination of an alcohol and an iodine-containing disinfectant has been employed at many hospitals, but there is no firm evidence that this combination provides an additive effect in reducing contamination rates. The application of povidone-iodine (PI) requires extra time, thereby making the procedure more complicated. To elucidate the optimal method to be used to obtain blood samples for culture with a minimum contamination rate and also with improved cost-effectiveness and feasibility, we investigated the additive efficacy of PI on contamination rates by comparing two antiseptic methods. The omission of PI use may be desirable in clinical practice if it would not cause a higher contamination rate.

MATERIALS AND METHODS

Study design and patients. We conducted a prospective, nonrandomized, and partially blinded study in a community teaching hospital in Okinawa, Japan. This institution has 550 inpatient beds and an emergency department (ED) and provides primary to tertiary care for a community with a population of approximately 200,000 in the central area of mainland Okinawa. All patients in our

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▽ Published ahead of print on 29 October 2008.

hospital who were over 15 years of age and who were suspected of having bacteremia were enrolled between 1 October 2007 and 21 March 2008. We considered the period suitable for the study because first-year (PGY-1) residents perform all phlebotomy procedures for the collection of blood samples for culture. Residents start their training in April and finish at the end of March. Their procedural techniques were thought to be the most reliable and consistent in the latter half of their year of training. The presence of bacteremia was suspected on the basis of each patient's clinical findings, such as hyper- or hypothermia, shaking chills, acute distress, as well as other physical examination and laboratory findings (19, 27).

We assigned patients who visited the ED into a group for which we did not use PI but used only 70% isopropyl alcohol (IPA) for skin antisepsis before blood samples for cultures were obtained; the patients in inpatient wards were assigned to a group in which we used both PI and IPA for skin antisepsis. The contamination rates between the study sites over the previous year (from July 2006 to June 2007) showed no significant difference (33/5,830 [0.57%] in the ED versus 46/6,665 [0.69%] in the wards; relative risk [RR], 0.82; 95% confidence interval [CI], 0.52 to 1.28; $P = 0.39$). The difference in positive culture rates between the two sites also was not significant (417/5,830 [7.2%] in the ED versus 508/6,665 [7.6%] in the wards; $P = 0.09$). In the previous year, the blood samples for culture were obtained after the use of both PI and IPA. On the basis of these data and under the condition that the members of the same group of physicians performed all phlebotomies for the collection of blood samples for culture in these two locations, a nonrandomized comparison between the groups was considered acceptable.

The hospital's ethical committee approved the study and determined that the collection of informed consent could be waived because both procedures for skin disinfection are in common use and are considered acceptable. The study was preregistered on the Clinical Trial Registration System on the UMIN website (www.umin.ac.jp) in September 2007 (clinical trial registration no. UMIN000000833).

Phlebotomist and phlebotomy technique. Traditionally, at the hospital, residents are required to obtain blood samples for culture for themselves after participating in an education session organized by the Infectious Diseases Division. When probable contamination is identified, the resident who obtained the blood sample is notified of this result as feedback for the resident. The phlebotomy protocol for obtaining blood samples for culture used in the study is described in Table 1. Most swabs soaked with PI and all related instruments were removed from the ED. When a blood sample for culture was taken by using PI in the ED, a yellow label was placed on each bottle before it was submitted to the laboratory, and these samples were excluded from the analysis.

Data collection. Blood was inoculated into an aerobic bottle and an anaerobic bottle as a set of blood cultures by using Bactec Plus resin medium (Becton, Dickinson and Company; Franklin Lakes, NJ). Then, a total of two sets of blood samples for culture from different venipuncture sites were transported to the hospital laboratory. Laboratory technicians were available at all hours; and when they received the blood samples, they incubated the samples with the Bactec 9240 system, an automated blood culture system, until the culture media were flagged as positive or for 7 days, unless the physicians ordered them to be incubated longer. Broth from positive bottles was Gram stained and subcultured by the use of standard laboratory techniques. All data for the specimens, including positive culture results, were recorded in a database for further analysis.

To examine the results for positive blood cultures, we held monthly meetings with the study's principal investigator (T.K.), a microbiology laboratory technician coinvestigator (T.H.), and two physician coinvestigators who were blinded to the results (S.S. and K.E.; Japanese board-certified infectious diseases physicians). We defined coagulase-negative staphylococci, *Bacillus* species, *Propionibacterium* species, *Micrococcus* species, *Clostridium* species, and α-streptococci as potential contaminants. They were classified as a true pathogen, a contaminant, or an indeterminate isolate by the physician investigators (S.S. and K.E.) on the basis of the following information obtained in a blinded manner: the patients' sex, age, and underlying comorbidities; the number of blood cultures positive for each organism; the presence of intravascular devices or invasive procedures; the length of incubation; and the antibiotic used against the organism. The principal investigator (T.K.) routinely collected these data from the patients' electronic medical records and presented them in such a manner that the group assignment for each patient was concealed. If any of the potential contaminants described above except α-streptococci was isolated from only one of two or more blood samples collected from different sites, it was strongly considered a contaminant. Otherwise, they used the information mentioned above to assess the clinical significance of each positive blood culture result.

Statistical analysis. We had set the first 2-week period (between 1 October and 14 October) as a washout period, and all samples obtained during this period were excluded from the analysis. The sample size necessary to detect a twofold increase in the incidence of contaminated blood cultures was estimated to be approximately 2,500 blood cultures for each group (80% statistical power and 5% type 1 error). This estimation was based on a chi-square test with Yates' continuity correction, along with the assumption that the expected incidence of contaminated blood cultures in inpatient wards would be 1% on the basis of data collected in the study hospital in 2006. The test was one sided because the additional application of PI was not considered to increase the risk of contamination. In addition, the contamination rates between the previous year and the study period were compared to find the possible effect of the phlebotomists' increased awareness of complying with the appropriate procedures for the collection of blood samples for culture. *P* values of less than 0.05 were considered statistically significant. We also calculated an estimate of the cost savings associated with the omission of PI.

TABLE 1. Protocol of phlebotomy technique for obtaining blood cultures

1. Set up two sets of venipuncture devices with butterfly needles, adapter needles and holders.
2. Prepare two sets of venipuncture devices, four blood culture bottles, a tourniquet, a pair of gloves, two packs of swabs soaked in 70% isopropyl alcohol. Additionally, in the ward, a cup of sterile swabs soaked in povidone-iodine and a set of forceps are required.
3. Determine the site of venipuncture. If the patient condition permits, forearms are preferred, considering local cleanliness of the site. When the venipuncture site appears unclean, wipe the area with a swab soaked in 70% isopropyl alcohol only once before skin disinfection.
4. Scrub the venipuncture site firmly with a 70% isopropyl alcohol swab beginning in the center and continuing outwardly in a concentric fashion.
5. Repeat the antisepsis with a 70% isopropyl alcohol swab once more. In the ward, two swabs of povidone-iodine are additionally applied on the puncture site.
6. Wait until the area dries completely or for at least 30 s if povidone-iodine is used.
7. Open the cap of blood culture bottles and wipe the top with an alcohol pad.
8. Put on a tourniquet, puncture the vein by using the venipuncture device, and carefully avoid touching the vein. If the vein needs to be touched for localizing it, phlebotomists must wear sterile gloves.
9. Insert the top part of blood culture bottles into the holder so that the adapter needle can puncture the top, inoculating 5ml or more of blood into an aerobic bottle and an anaerobic bottle.
10. Repeat the same procedure on a different site to obtain another set of blood cultures.

RESULTS

During the study period, 6,175 blood samples for culture were obtained in the hospital. Of these, 522 blood samples obtained during the washout period were excluded from the analysis. In the ED, protocol violations were identified for six samples during this washout period. No additional protocol violations were noted during the study period.

A total of 5,653 blood samples for culture met the inclusion criteria for analysis; these were collected from 1,768 patients (mean age, 62 years; 47% of the patients were women). Of these 5,653 blood samples, 437 yielded pathogens that were subsequently classified as true pathogens ($n = 411$; 7.3%), contaminants ($n = 25$; 0.44%), and an indeterminate isolate ($n = 1$). The indeterminate isolate was an anaerobe that could not be further identified in the laboratory.

Among the group for which the IPA disinfectant only was used, 189 of 2,856 cultures (6.6%) yielded potential pathogens;

TABLE 2. Positive rates and contamination rates according to the study site

	Previous year (July 2006 to June 2007)			Study period (October 2007 to March 2008)		
	ED (IPA[a] + PI[b])	Inpatient wards (IPA + PI)	Total	ED (IPA only)	Inpatient wards (IPA + PI)	Total
No. of cultures	5,830	6,665	12,495	2,856	2,797	5,653
No. of positive cultures (%)	417 (7.2)	508 (7.6)	925 (7.4)	189 (6.6)	248 (8.9)	437 (7.7)
No. of contaminants (%)	33 (0.57)	46 (0.69)	79 (0.63)	12 (0.42)	13 (0.46)	25 (0.44)

[a] IPA, isopropyl alcohol.
[b] PI, povidone-iodine.

12 (0.42%) of these 2,856 cultures were considered to contain contaminants. In the group for which IPA plus PI was used, 248 of 2,797 cultures (8.9%) yielded potential pathogens, and 13 (0.46%) of these 2,797 cultures were considered to contain contaminants (Table 2). There was no significant difference in the contamination rates between the two groups (RR, 0.90; 95% CI, 0.41 to 1.98; $P = 0.80$). The absolute risk difference in contamination rates was 0.045% (95% CI, −0.039% to 0.0305%). There was a significant difference ($P = 0.0015$) in the positive culture rate between the group for which IPA was used (6.6%) and the group for which IPA plus PI was used (8.9%).

Compared to data from the preceding year within each group, the contamination rates during the study period showed no significant difference in either group: for the ED, 12/2,856 during the study period versus 33/5,830 in the preceding year (RR, 0.74; 95% CI, 0.38 to 1.44; $P = 0.37$); for the inpatient wards, 13/2,797 during the study period versus 46/6,665 in the preceding year (RR, 0.67; 95% CI, 0.36 to 1.24; $P = 0.20$).

Of the 27 PGY-1 residents, there were 18 residents who performed the phlebotomies for the contaminated blood cultures: 11 residents obtained the contaminated blood cultures in the ED and 9 residents obtained them in the wards. There were two residents who were twice notified of contaminated blood cultures.

For the 25 patients with contaminated blood cultures, the mean age was 73.4 years, and 44% of the patients were women. The principal clinical diagnoses for these patients included pneumonia ($n = 6$), urinary tract infection ($n = 3$), spontaneous bacterial peritonitis ($n = 2$), congestive heart failure ($n = 2$), and viral infection or an unknown focus ($n = 2$). The other diagnoses included one case each of intracranial hemorrhage, upper gastrointestinal tract bleeding, alcoholic ketoacidosis, acute myocardial infarction, unstable angina, cellulitis, electrolyte disturbance, surgical site infection, femoral neck fracture, and status after aortic valve replacement.

At the monthly meetings, the results for 48 isolates that were potential contaminants (Table 3) were reviewed by the physician coinvestigators who were blinded to the results. Among these isolates, all eight isolates of α-streptococci were considered true pathogens. One case had two sets of positive cultures, and the others each had a single set of positive cultures. Four of these patients had liver cirrhosis, one had agranulocytosis, and one had an advanced stage of rectal carcinoma. There was only one case of a solitary blood culture that grew coagulase-negative staphylococci. This result was considered true positive because it was preceded by three sets of cultures of blood collected on the previous day that were positive for coagulase-negative staphylococci.

An estimate of the savings associated with the omission of PI was calculated. A cup of swabs soaked with PI for the collection of blood for two sets of cultures costs \$0.97 (US\$1 = ¥105.5 as of 5 June 2008). If we assume that about 12,500 sets of blood samples for culture are taken per year and that it takes an additional 1 to 2 minutes to obtain a set of blood samples for culture, the savings would amount to \$6,060 and 208 to 416 h of residents' time per year in the study setting.

DISCUSSION

The use of a single application of 70% IPA is sufficient and more clinically feasible to reduce contamination rates. In the current study, we have shown that the additional application of PI to 70% IPA has little effect on the reduction of contamination rates. Since many institutions employ the traditional method, the sequential use of 70% IPA and PI, the cost savings of \$6,060 and the time savings of 208 to 416 h of phlebotomists' time in a hospital with 550 beds can have a big impact. In addition, after the application of PI to the patients' skin, the need to wait for at least 30 s or more beside a patient in distress might occasionally be stressful for caring physicians, especially in acute-care settings, even if they know the necessity of the waiting time. Indeed, Qamruddin et al. reported a rate of compliance with the protocol of as low as 30% among the

TABLE 3. Potential contaminants detected during the study period

Microorganism	Isopropyl alcohol group		Isopropyl alcohol + povidone-iodine group	
	Contaminants (no. of Tx[a])	True pathogens (no. of Tx)	Contaminants (no. of Tx)	True pathogens (no. of Tx)
Coagulase-negative staphylococcus	12 (1)	2 (2)	11 (2)	8 (8)
Bacillus species	0	0	1 (0)	0
Micrococcus species	0	0	1 (0)	0
α-Streptococcus	0	4 (3)	0	4 (2)
Corynebacterium jeikeium	0	0	0	1 (1)
Brevibacterium species	0	0	0	1 (0)
Gemella haemolysans	0	0	0	1 (0)
Clostridium species				1 (1)
Capnocytophaga species				1 (1)

[a] Number of cases in which antibiotics were used against the detected microorganism.

phlebotomists in their study (20). Simple and easy procedural protocols will likely increase the rate of compliance with the protocol.

The results of the current study support those from the study reported by Calfee and Farr in 2002 (4). They compared the efficacies of four skin antiseptics, including 10% PI, 70% IPA, tincture of iodine, and PI with 70% ethyl alcohol, to prevent blood culture contamination. They suggested that IPA was the optimal antiseptic because there were no significant differences in the blood culture contamination rates when these four antiseptics were used. To the best of our knowledge, no other study that has compared IPA and IPA plus PI has been reported previously.

Alcohol provides a rapid bactericidal effect against most gram-positive and gram-negative bacteria, *Mycobacterium tuberculosis*, and certain enveloped viruses as a result of protein coagulation and denaturation. The effect is not persistent, however (4, 9, 12, 13, 16, 22). The use of PI results in the slow and continuous release of free iodine that is effective against almost the same spectrum of microorganisms as alcohol, but it can be neutralized by proteins on the skin surface (9, 12, 16). Venipuncture of a patient's arm does not need such a persistent antimicrobial effect, and no data about the different depths to which the antiseptics permeate can a patient's skin are available. If alcohol permeates the skin surface as well as PI does, the application of PI theoretically cannot have an additional antiseptic effect.

The reason for the significantly lower positive culture rate for the group of patients for whom the IPA disinfectant was used is not clear. The volume of blood cultured is a known determinant of the sensitivity for the detection of microorganisms (6, 10, 14, 17), and the volume of blood drawn in the ED might have been smaller than that drawn in inpatient wards when the increased time pressure in examining each patient in the ED is considered. Furthermore, in an attempt not to miss a case of bacteremia in a high-risk patient in the ED, the threshold for obtaining blood cultures might possibly have been lower, and thus, the diagnostic yield of blood cultures obtained in the ED might have decreased. However, the relationship between positive culture rates and contamination rates also remains unclear, further studies are needed to clarify whether the difference in positive culture rates affects contamination rates in some way.

Unlike other studies which showed increased rates of contamination for cultures of blood drawn by resident physicians (21, 28, 29), the residents in the current study achieved a considerably lower contamination rate than that determined from other published data. Although trends of reductions in contamination rates for both groups were noted during the study period compared to those achieved in the year before the study period, the differences were not significant. We believe that the extremely low contamination rates were due to the traditional educational system for residents at the Okinawa Chubu Hospital. The hospital has a postgraduate medical education program affiliated with the University of Hawaii which began in 1966. Since then, traditional American infectious disease practices, such as obtaining blood cultures and Gram staining, have been well developed (2, 11). In addition, a Japanese physician who was board certified in infectious diseases in the United States in 1976 has consistently continued to educate the residents in the principles of clinical infectious diseases for the past 30 years. For these reasons, residents are well educated in the importance of the blood culture test and the procedural protocol for the collection of blood for culture. In addition, the monthly feedback to the residents who collected blood samples that were contaminated may have contributed to the residents' awareness of the appropriate procedural technique over years. Several published studies have consistently shown significantly decreased contamination rates following educational interventions for phlebotomists or dedicated phlebotomy teams (7, 8). This may help explain the low contamination rates achieved in the current study. Although in the past more studies have focused on the efficacies of various antiseptics than how they are applied to patients, our results suggest that the type of antiseptic used on a patient's skin may not be as important as the use of proper technique and compliance with the blood collection protocol. Like the hospital in this study, we consider it necessary to establish the culture of "culture" among all personnel involved in patient care in each hospital to reduce contamination rates.

Regarding the medical decision making for patients with contaminated blood cultures, most treating physicians successfully recognized the contamination and did not use antibiotics on the basis of these spurious results. The physician investigators who were blinded to the results determined that all isolates of α-streptococci were true pathogens because all patients infected with these isolates had an immunocompromised status to some extent and some patients with liver cirrhosis had also experienced bleeding episodes or invasive procedures that could have been a cause of transient bacteremia. In contrast to previously published data which showed that 45% (38/84) of α-streptococci were considered contaminants (30), our data showed that α-streptococci from blood cultures can be highly clinically significant and that the detection of α-streptococci requires careful consideration on the basis of clinical information.

The contamination rate that we observed in the control group (IPA plus PI) was much lower than we expected to calculate on the basis of the sample size described in the Materials and Methods section (0.44% versus 1%). If a 0.44% risk of contamination in the control group was used to calculate the sample size necessary to detect a 1% increase in the absolute risk, the sample size is estimated to be approximately 1,650 sets of blood cultures for each group (80% of statistical power and 5% type 1 error). As far as we know, no studies have set an absolute reduction or increase in risk as strict as 1% for calculation of their sample sizes (4, 7, 15, 18). On the contrary, the absolute increase in risk that the current study would be able to detect with approximately 2,800 samples in each arm was 0.7%, which would be considered an acceptably small risk in clinical settings.

The current study has several limitations. First, the two places that we used as study settings were not identical; thus, differences in practice patterns and patients' clinical status could have influenced the results (30). Although we confirmed that the contamination rates between the two wards were similar in the previous year and the group of phlebotomists and the phlebotomy kits used were completely the same for both groups, we cannot completely eliminate possible bias. The use of a study design such as a crossover trial, in which the group

assignment was reversed between the inpatient wards and the ED in half of the study period, would have been better to minimize this kind of bias. Second, we did not measure the phlebotomists' compliance with the study protocols, including the waiting time before venipuncture. Noncompliance with the use of PI in the IPA plus PI group or a shorter waiting time when PI was applied might have resulted in a bias toward a lack of a difference between the two groups. However, we repeatedly conducted briefing sessions at the monthly residents' meetings and requested senior residents to observe whether the phlebotomists, mostly PGY-1 residents, complied with the protocol. No protocol violation was reported by anyone involved in the study. In regard to the waiting time before venipuncture, we set the minimal time as 30 s in the study protocol, considering its feasibility, although PI is widely known to provide its maximal antiseptic effect after 1.5 to 2 min. Therefore, PI might not have been maximally effective in the procedures used in our protocol in this study. However, the contamination rate in the intervention group (IPA only) was so low that a contamination rate of less than 0.42% would be hard to achieve and would not make a significant difference even if PI had been maximally effective. Besides, to the best of our knowledge, there is little evidence on the appropriate waiting time for PI to affect contamination rates.

In conclusion, our study results suggest that a single application of 70% IPA is the optimal antiseptic method to be used for the collection of blood samples for culture. A very low contamination rate was also noted when well-educated resident physicians performed phlebotomy, regardless of the antiseptic chosen. Regarding the potential contaminants detected, every isolate of α-streptococci needed careful consideration to determine its clinical significance.

ACKNOWLEDGMENTS

We thank all residents, physicians, and patients involved in the study for their cooperation. We also thank Joshua Jacobs of the Department of Medicine, John A. Burns School of Medicine, University of Hawaii, for reviewing the manuscript.

No financial support for this study is declared.

There is no potential conflict of interest for any of the authors.

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