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Major Article

Maximal sterile barrier precautions independently contribute to decreased central line–associated bloodstream infection in very low birth weight infants: A prospective multicenter observational study

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Key Words:
Neonatal intensive care unit
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Background: The use of peripherally inserted central catheters (PICCs) in neonates differs among various institutions and countries because there are no random controlled trials or large observational studies regarding maximal sterile barrier (MSB) precautions in neonatal intensive care units. Our objective was to investigate the association of MSB implementation with central line–associated bloodstream infection (CLABSI) in very low birth weight infants.

Methods: This was a prospective multicenter observational study in Japan of infants with birth weight less than 1501 grams and in whom a PICC was placed for the first time between October 2014 and March 2017. Risk factors for CLABSI, both related and unrelated to MSB, were assessed by the mixed-effects Cox proportional hazards model, with the neonatal center variable as the random effect.

Results: In total, 33,713 catheter-days among 2383 infants were included. We observed 70 cases of CLABSI. MSB precautions were implemented in 13.9% of insertions and were associated with a lower CLABSI risk (adjusted hazard ratio, 0.20; 95% confidence interval, 0.05-0.84).

Conclusions: We found that MSB implementation during PICC insertion in infants with birth weight less than 1501 grams independently contributed to a decrease in CLABSI risk.

BACKGROUND

The use of a bundle strategy to prevent central line–associated bloodstream infection (CLABSI) reportedly contributes to decreased morbidity, mortality, length of hospitalization, and health care costs in modern intensive care settings.[1-6] Current bundle strategies consist primarily of (1) evidence-based sterile central line insertion, and (2) daily maintenance techniques. The important elements of central line insertion are hand hygiene, skin antisepsis, and maximal sterile barrier (MSB) precautions, such as the use of a cap, mask, sterile body gown, sterile gloves, and large sterile drape.[4,7–11]

Peripherally inserted central catheters (PICCs) are frequently required for very low birth weight infants (VLBWIs)—those weighing less than 1501 grams.[12] Insertion and maintenance bundle strategies to prevent CLABSI in a neonatal intensive care unit (NICU) should particularly be considered, as various aspects of neonatal patients differ significantly from those of adult patients, including their gestational age, the need for a closed incubator to maintain a stable temperature, and the increased permeability of their immature skin, in addition to the difficulty of confirming CLABSI (eg, nonspecific symptoms of sepsis).[7,13-15] Because there are no random controlled trials or large observational studies regarding MSB implementation in the NICU population, the use of PICCs in neonates varies among institutions and countries.[6,16,17]

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The present study is a large prospective observational study that aimed to investigate the association of MSB implementation with CLABSI in VLBWIs.

METHODS

Study design

This prospective multicenter observational study included all infants with a birth weight (BW) of less than 1501 grams who were admitted to the 26 participating NICUs (see Supplementary Appendix) and in whom a PICC was placed in one of the great vessels for the first time. The study was performed between October 1, 2014, and March 31, 2017. Placement of the PICC was performed according to the policy of each unit and caregiver. For patients with multiple PICC lines, only the first PICC was included in the analysis. Patients who were admitted with a PICC already in place, those who died within 24 hours of birth, those for whom information regarding PICC placement was missing, and those for whom informed consent was not obtained were excluded.

Data collection

All data were collected by research collaborators and included information on PICC placement and maintenance. In this study, MSB precautions included strict adherence to wearing a cap, mask, sterile gown, sterile gloves, and large sterile drape, regardless of whether or not a closed incubator was used. Adequate waiting time between skin preparation and catheter insertion was considered to be 60 to 120 minutes for the use of 10% povidone iodine, 60 to 120 minutes for chlorhexidine gluconate (CHG) without ethanol, 30 to 60 minutes for CHG with ethanol, and 15 to 30 minutes for ethanol only. We collected a list of antibiotics prescribed during placement, as well as the symptoms and blood culture results of patients with suspected sepsis. Common commensal organisms identified in a single blood culture of 2 or more sets of blood cultures were considered to be blood culture contaminants.

Outcome

Our primary endpoint was CLABSI, including both laboratory-confirmed bloodstream infection (LCBI) and clinical sepsis (CSEP). LCBI was defined based on the description provided by the Centers for Disease Control and Prevention's National Healthcare Safety Networks,[18] and CSEP was defined based on their 2008 surveillance definitions.[19] In this study, we collected CLABSI cases that occurred from 48 hours up to 28 days after PICC placement or 2 days after PICC removal. Diagnostic data for the LCBI and CSEP cases were examined by authors D.K., Y.O., S.H., and M.N. If there were any doubts regarding the diagnosis, more precise medical information on the suspected sepsis episode was presented so the research collaborators could reach a consensus on the diagnosis.

Statistical analysis

The cumulative incidence of CLABSI was estimated by the Kaplan-Meier method and compared by the log-rank test. The

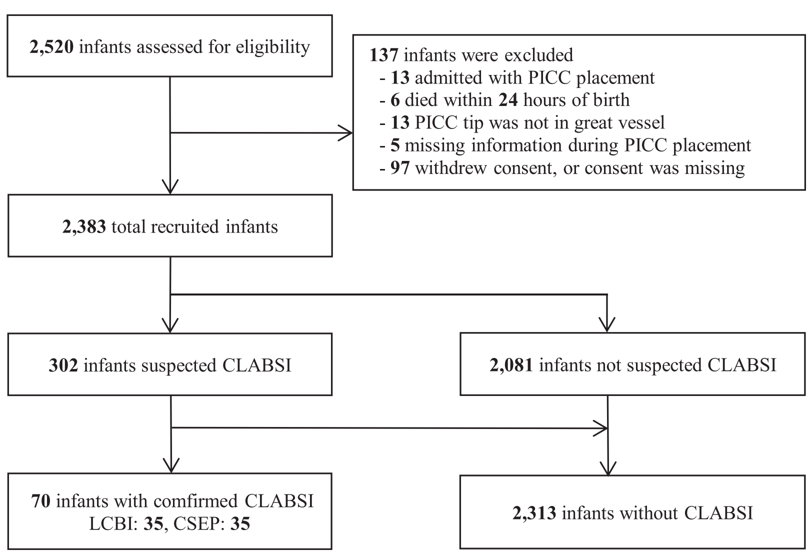

Fig 1. Flow diagram. *CLABSI*, central line−associated bloodstream infection; *LCBI*, laboratory-confirmed bloodstream infection; *PICC*, peripherally inserted central catheter.

Table 1
Infant demographics

Demographics	Total (N = 2383)	With MSB precautions (n = 332)	Without MSB precautions (n = 2051)	*P* value
Gestational age (wk), mean ± SD	28.5 ± 3.3	28.2 ± 3.2	28.6 ± 3.3	<.001
Birth weight (g), mean ± SD	1024 ± 301	1007 ± 319	1027 ± 298	.29
Female, n (%)	1126 (47)	149 (45)	977 (48)	.35
5-min APGAR score, mean ± SD	7.2 ± 2.0	6.6 ± 2.3	7.3 ± 2.0	<.001
Cesarean delivery, n (%)	1874 (79)	261 (79)	1613 (79)	.99
Postnatal day for PICC insertion (d), mean ± SD	1.7 ± 2.7	1.1 ± 3.3	0.6 ± 2.6	.024

NOTE: Either the *t*-test or chi-square test was used for comparison, as appropriate.
APGAR, Appearance, Pulse, Grimace, Activity, and Respiration test; *MSB*, maximal sterile barrier; *PICC*, peripherally inserted central catheter; *SD*, standard deviation.

effects of MSB implementation and other factors were assessed by the mixed-effects Cox proportional hazards model, with the neonatal center variable as the random effect; results were expressed as the hazard ratio (HR) with 95% confidence interval (CI). Proportional hazard assumptions were assessed on the plots of log(time) versus log(−log(survival)), and the assumptions were verified. Data were analyzed with SAS 9.4 (SAS Institute; Cary, NC).

Table 2
Hazard ratios for central line–associated bloodstream infection

	Cox proportional hazards model analysis		Mixed-effects Cox proportional hazards model analysis*	
Variables	Hazard ratio (95% CI)	*P* value	Adjusted hazard ratio (95% CI)	*P* value
Baseline characteristics				
Infant sex, male	0.66 (0.41-1.06)	.086	0.74 (0.42-1.29)	.29
Gestational age, per each week	0.85 (0.78-0.93)	<.001	—	—
Birth weight, per each 10 g	0.98 (0.97-0.99)	<.001	0.998 (0.997-0.999)	.006
1-min APGAR score, per each point	0.83 (0.75-0.93)	<.001	—	—
5-min APGAR score, per each point	0.88 (0.80-0.97)	.01	0.93 (0.81-1.06)	.26
Number of conceptuses, multiple	0.41 (0.20-0.83)	.01	0.49 (0.20-1.19)	.116
Cesarean delivery	0.56 (0.34-0.92)	.023	0.63 (0.33-1.20)	.161
Location of PICC insertion				
Delivery room	1 (Ref)	—	1 (Ref)	—
Operation room	0.36 (0.02-5.71)	.47	0.72 (0.04-12.51)	.83
NICU	1.10 (0.15-7.98)	.92	1.49 (0.17-12.96)	.72
Environment during PICC insertion				
Through access port doors of infant incubator	1 (Ref)	—	—	—
Open front panel of a closed infant incubator	0.17 (0.02-1.24)	.08	—	—
On opened infant incubator	0.32 (0.16-0.68)	.003	—	—
Experience of PICC insertion physician				
More than 8 y	1 (Ref)	—	1 (Ref)	—
Less than 8 y	1.21 (0.76-1.94)	.43	1.68 (0.93-3.04)	.086
Implementation of MSB during PICC insertion	0.19 (0.06-0.61)	.005	0.20 (0.05-0.84)	.027
Cap	0.32 (0.18-0.57)	<.001	—	—
Mask	0.50 (0.30-0.83)	.007	—	—
Sterile gloves	0.44 (0.27-0.72)	.001	—	—
Full body drape	0.44 (0.26-0.76)	.003	—	—
Sterile gown	0.34 (0.15-0.79)	.012	—	—
MSB implementation by assistant	0.50 (0.26-0.98)	.042	—	—
Hand hygiene before PICC insertion				
No	1 (Ref)		—	—
Yes	0.75 (0.10-5.41)	.78	—	—
Skin preparation				
10% povidone iodine	1 (Ref)	—	1 (Ref)	—
More than 1% CHG/ethanol	1.60 (0.81-3.17)	.177	1.96 (0.77-4.94)	.156
Less than 1% CHG/ethanol	5.75 (2.86-11.57)	<.001	4.95 (1.33-18.40)	.017
Other	2.55 (1.40-4.67)	.002	1.43 (0.60-3.43)	.42
Enough waiting time after skin preparation				
Yes	1 (Ref)	—	—	—
No	1.06 (0.51-2.22)	.88	—	—
Unknown	0 (0-0)	.98	—	—
Site of insertion				
Upper extremity	1 (Ref)	—	1 (Ref)	—
Lower extremity	0.55 (0.34-0.88)	.013	0.73 (0.40-1.32)	.29
Others	0 (0-0)	.99	—	—
More than a second attempt at PICC insertion	1.39 (0.85-2.28)	.192	—	—
PICC lumen type				
Single	1 (Ref)	—	1 (Ref)	—
Double	0.30 (0.16-0.58)	<.001	0.39 (0.13-1.16)	.09
Postnatal day of PICC insertion, per each day	1.07 (1.02-1.12)	.003	1.05 (1.00-1.11)	.049
Frequency of dressing change, per each change	1.25 (1.01-1.54)	.039	0.80 (0.56-1.15)	.23
Surgical operation during PICC placement	0.58 (0.31-1.06)	.077	—	—
Administration of antibiotics during PICC placement	2.13 (0.92-4.96)	.078	—	—
Administration of immunoglobulin product	1.79 (1.10-2.89)	.018	1.78 (0.93-3.40)	.08
Medication through PICC				
None	1 (Ref)		—	—
Packed red blood cells	1.66 (0.98-2.81)	.061	—	—
Platelets	4.00 (1.98-8.09)	<.001	2.28 (0.87-5.96)	.093
Fresh frozen plasma	1.93 (1.09-3.43)	.025	1.70 (0.74-3.93)	.21
Blood product (albumin, antithrombin)	0.78 (0.42-1.42)	.41	—	—
Lipid product	1.11 (0.70-1.78)	.66	—	—
Amino acid product	1.84 (0.45-7.52)	.39	—	—
Total days of systemic steroid therapy during PICC placement	1.03 (1.00-1.05)	.068	—	—

APGAR, Appearance, Pulse, Grimace, Activity, and Respiration test; *CHG*, chlorhexidine gluconate; *CI*, confidence interval; *MSB*, maximal sterile barrier; *NICU*, neonatal intensive care unit; *PICC*, peripherally inserted central catheter; *Ref*, reference.

*Analyzed by the mixed-effects Cox proportional hazards model, with the neonatal center variable as the random effect. Included in the model were infant sex; birth weight; 5-minute APGAR score; number of conceptuses; mode of delivery; skin preparation; site of insertion; experience of physician; MSB; frequency of dressing change; PICC lumen type; administration of immunoglobulin product, platelets, or fresh frozen plasma; and postnatal day of PICC insertion.

Ethics

This study was approved by the Internal Review Board of the Japanese Red Cross Kyoto Daiichi Hospital and each participating hospital.

RESULTS

Clinical demographics of the study population

Initially, a total of 2520 infants with BW less than 1501 grams were enrolled in this study across 26 NICUs. Of these, 137 infants were excluded, leaving 2383 infants with 33,713 catheter-days were eligible for analysis. Out of 302 suspected cases of CLABSI, we confirmed 70 cases, 35 as LCBI and 35 as CSEP (Fig 1). Table 1 presents the demographics of all study infants, as well as for the groups with and without MSB precautions. Overall, the mean ± standard deviation for gestational age was 28.5 ± 3.3 weeks; for BW, 1024 ± 301 grams.

Risk factor of CLABSI

Table 2 shows univariate and multivariate analyses for the groups with and without MSB precautions. The univariate analysis found that gestational age; BW; Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) test score; rate of cesarean delivery; insertion of the catheter into the lower extremity; use of a double-lumen PICC; use of <1% CHG; dressing changes; history of administration of immunoglobulin G, platelets, or fresh frozen plasma; and postnatal days for insertion of the catheter were significantly associated with CLABSI. MSB implementation for placement of the PICC was associated with a lower risk of CLABSI (HR, 0.19; 95% CI, 0.06-0.61). In multivariate analysis, using the mixed-effects Cox proportional hazards model, with the neonatal center variable as the random effect, MSB implementation was associated with a lower CLABSI risk (adjusted HR, 0.20; 95% CI, 0.05-0.84); whereas, the use of <1% CHG and lower BW were associated with a higher CLABSI risk. As presented in Figure 2, the Kaplan-Meier curve and the results of the log-rank test showed that MSB implementation was associated with a lower cumulative incidence of CLABSI.

CLABSI rate and isolated pathogen

The overall rate of CLABSI was 2.1 per 1000 catheter-days. The rates of CLABSI in infants with BW ≤ 750 grams, 751 to 1000 grams, and 1001 to 1500 grams were 3.6, 2.0, and 1.1 per 1000 catheter-days, respectively. Among the 70 CLABSI cases, the predominant pathogens isolated were coagulase-negative staphylococci (n = 21, 30%), methicillin-sensitive *Staphylococcus aureus* (n = 10, 20%), and methicillin-resistant *S aureus* (n = 9, 13%), followed by *Streptococcus viridans*, *Klebsiella* spp, *Escherichia coli*, and *Bacillus* spp with 3 cases each and by *Pseudomonas* spp, *Candida* spp, *Enterobacter* spp, and *Burkholderia cepacia* with 1 case each. Fourteen (20%) CLABSI patients had negative blood culture results. Among the 35 CSEP cases, 27 (77%) had single blood culture sampling and 2 (6%) cases did not have any.

DISCUSSION

To the best of our knowledge, this was the first large prospective multicenter study that clarified the association between CLABSI and MSB implementation in NICUs during PICC placement. Except for 2 studies in adult patients,[20,21] we could not find any previously reported random controlled trials or prospective observational studies regarding MSB implementation in the NICU population.

A previously reported study discussed the association between MSB implementation and CLABSI in NICU populations; participating infection prevention and control directors or managers retrospectively reported the frequency of MSB implementation and CLABSI in their NICU patients but did not provide information about gestational age.[6] They reported that >95% compliance with an insertion checklist

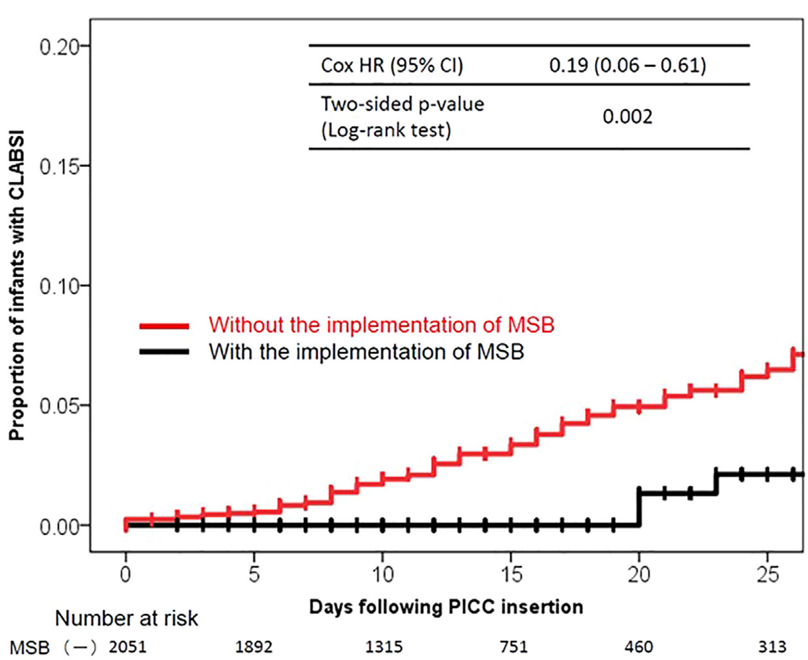

Fig 2. Kaplan-Meier curve for the cumulative incidence of CLABSI infants who were classified according to the implementation of MSB precautions during PICC placement. Comparison was made by the log-rank test. *CLABSI*, central line–associated bloodstream infection; *HR*, hazard ratio; *MSB*, maximal sterile barrier; *PICC*, peripherally inserted central catheter.

and assessment of daily line necessity were significantly associated with lower overall CLABSI rates; however, the effect of MSB implementation alone was not associated with a decrease in CLABSI. Thus, our study is the first prospective observational study to assess the association between MSB implementation and CLABSI in all cases of VLBWIs.

The practice of PICC placement in neonates varies among institutions and countries. Three previous studies reported that the percentage of institutions that routinely used MSB implementation during PICC placement was 26.5% in 19 NICUs in Australia/New Zealand, 62.7% in 190 NICUs in the United States, and 90.4% in 110 NICUs in the United States and Canada combined.[6,16,17] In this study, we found that NICU caregivers in Japan adopted various kinds of sterile precautions and that adherence to MSB implementation was very low at 13.9%. The current recommendations regarding MSB implementation for neonates have been extrapolated from results obtained from random controlled trials and observational studies in adult patients,[4,20,21] but MSB implementation has been reported as being a key factor in the prevention of CLABSI in the neonatal and pediatric populations.[4,7-10,21] The reasons for such diverse implementation of MSB remain unknown. It is possible that some NICU caregivers believe that in complicated cases, especially for VLBWIs, MSB implementation is of less importance than efficient management of temperature instability using closed incubators and meticulous monitoring for respiratory and cardiovascular instability.[22] This study could encourage NICU caregivers to reconsider the importance of MSB implementation in their NICUs.

Several limitations should be considered when interpreting our study results. First, this was an observational study. Although we adjusted the effect of each variable by using the mixed-effects Cox proportional hazards model, the diverse PICC care methods adopted by the participating NICUs potentially limited full exploration of the risk factors for CLABSI and added selection bias. Second, we adopted a definition of CLABSI as LCBI or CSEP. CSEP may only be used to report primary bloodstream infections in neonates and not in adults and children, but in the clinical settings, CSEP is well known to account for a definite proportion of late-onset neonatal infections.[5,12,13] Therefore, it might be better to include CSEP as CLABSI to assess the effect of CLABSI prevention strategies. Third, we had only 70 CLABSI cases, including 35 LCBI cases. Although our regression model converged without a problem, the number of independent variables included in our multivariate analysis might have resulted in overfitting of the data.

CONCLUSIONS

The implementation of maximal sterile barriers during PICC placement in very low birth weight infants appeared to be an independent factor that contributed to a decrease in CLABSI risk. The inclusion of MSB implementation in bundle strategies for PICC placement might be appropriate for VLBWIs in NICUs.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at https://doi.org/10.1016/j.ajic.2019.05.006.

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