Research Article

Pamukkale Medical Journal
doi:https://dx.doi.org/10.31362/patd.1343916

Evaluation of risk factors for central venous line-associated bloodstream infections (CLABSIs) and the benefits of central line bundle application in reducing CLABSIs

Santral venöz kateter ilişkili kan dolaşımı enfeksiyonları için risk faktörlerinin ve santral venöz kateter paket uygulamasının yararlarının değerlendirilmesi

Suna Seçil Öztürk Deniz, İrem Akın Şen, Kevser Özdemir, Nurefsan Aydeniz, Ayşe Kıvrak, Simay Karaduman, Hülya Sungurtekin, Hüseyin Turgut

Received:15.08.2023 Accepted:26.09.2023

Abstract

Purpose: We aimed to identify the risk factors for central line-associated bloodstream infections (CLABSIs) and the efficacy of bundle application to prevent CLABSIs. **Materials and methods:** This study was performed in the anesthesia-intensive care unit (AICU) of a tertiary hospital. A structured survey form including patients' characteristics and a central line bundle checklist was used for following of patients. Adult patients who had undergone recent central venous catheter (CVC) insertion at the AICU, those who had been transferred to ICU with the previous catheter insertion in other departments and who had received a diagnosis of CLABSI fourty-eight hours after remaining in the ICU were included in the study. The data obtained were evaluated with respect to the risk factors for CLABSIs. **Result:** The current study included 156 patients with the mean age 67.97±17.20 years (median 71.00 years), 66 were women (42.3%). Fourty-seven patients developed CLABSIs. Evaluating the results of univariate analysis, the rate of infection was lowest when catheters were inserted with the aim hemodialysis (p<0.01). The subclavian vein (p<0.01) and three-lumen catheters (p<0.01), receiving CVCs under emergency conditions (p=0.04), having been intubated (p=0.01), undergoing surgery (p=0.04) and receiving antibiotics before catheterization (p<0.01), receiving blood products through CVCs (p=0.01), repeat catheter insertions (p<0.01) were found to be associated with the development of CLABSI. **Conclusion:** In summary, multivariate analyses showed that repeat catheter insertions (p<0.01) and prolonged ICU stay (p<0.01) could raise the risk of CLABSIs. However, the risk of infection was lower (p<0.01) in patients with bundle application.

Keywords: Bundle, central line, blood stream infection, intensive care.

Ozturk Deniz SS, Akin Sen I, Ozdemir K, Aydeniz N, Kivrak A, Karaduman S, Sungurtekin H, Turgut H. Evaluation of risk factors for central venous line-associated bloodstream infections (CLABSIs) and the benefits of central line bundle application in reducing CLABSIs. Pam Med J 2023;16:716-725.

Öz

Amaç: Bu çalışmada santral venöz kateter-ilişkili kan dolaşımı enfeksiyonlarının (SKİ-KDE) risk faktörlerini ve SKİ-KDE'larını önlemek için paket uygulamasının etkinliğini belirlemeyi amaçladık. **Gereç ve yöntem:** Bu çalışma üçüncü basamak bir hastanenin anestezi yoğun bakım ünitesinde (AYBÜ) yapıldı. Hastaların takibi için hasta özelliklerini içeren yapılandırılmış anket formu ve santral venöz kateter paketi kontrol listesi kullanıldı. Yakın zamanda AYBÜ'de santral venöz kateter (SVK) takılmış olan, daha önce diğer bölümlerde kateter takılarak YBÜ'ne nakledilmiş olan ve YBÜ'de 48 saat kaldıktan sonra SKİ-KDE tanısı alan erişkin hastalar çalışmaya dahil edildi. Elde edilen veriler SKİ-KDE için risk faktörleri açısından değerlendirildi.

Suna Seçil Öztürk Deniz, Asst. Prof. Pamukkale University, School of Medicine, Department of Infectious Diseases, Denizli, Türkiye, e-mail: susede20@yahoo.com (https://orcid.org/0000-0002-5440-5383) (Corresponding Author)

İrem Akın Şen, Asst. Prof. Mersin University, School of Medicine, Department of Internal Medicine Intensive Care Unit, Mersin, Türkiye, e-mail: driremakinsen@hotmail.com (https://orcid.org/0000-0002-5402-4636)

Kevser Özdemir, Asst. Prof. Pamukkale University, School of Medicine, Department of Infectious Diseases, Denizli, Türkiye, e-mail: drkevser@gmail.com (https://orcid.org/0000-0002-9942-6487)

Nurefsan Aydeniz, Research Asst. Pamukkale University, School of Medicine, Department of Infectious Diseases, Denizli, Türkiye, e-mail: nurefsan.ay@gmail.com (https://orcid.org/0009-0002-1477-1351)

Ayşe Kıvrak, Attending Nurse, Pamukkale University, School of Medicine Hospital Infection Control Committee, Denizli, Türkiye, e-mail: aysekivrak_20@hotmail.com (https://orcid.org/0009-0008-4231-2180)

Simay Karaduman, Prof. Dr. Pamukkale University, School of Medicine, Department of Anesthesiology and Reanimation, Denizli, Türkiye, e-mail: siserin@yahoo.com (https://orcid.org/0000-0001-9401-7812)

Hülya Sungurtekin, Prof. Pamukkale University, School of Medicine, Department of Anesthesiology and Reanimation, Denizli, Türkiye, e-mail: hsungurtekin@yahoo.com (https://orcid.org/0000-0002-9453-5625)

Hüseyin Turgut, Prof. Pamukkale University, School of Medicine, Department of Infectious Diseases, Denizli, Türkiye, e-mail: huturgut@yahoo.com (https://orcid.org/0000-0003-4270-3997)

Bulgular: Bu çalışmaya yaş ortalaması 67,97±17,20 (medyan 71.00 yıl) olan 156 hasta alındı, hastaların 66'sı kadındı (%42,3%). Kırk yedi hastada SKİ-KDE gelişti. Tek değişkenli analizlerin sonuçları değerlendirildiğinde, hemodiyaliz amacıyla kateter takıldığında enfeksiyon oranı en düşüktü (p<0,01). Subklavian ven (p<0,01) ve üç lümenli kateterler (p<0,01), SVK'nın acil şartlarda takılması (p=0,04), entübe olmuş olmak (p=0,01), kateterizasyon öncesi operasyon geçirilmesi (p=0,04) ve antibiyotik kullanımı (p<0,01), SVK'ler yoluyla kan ürünü alınması (p=0,01), tekrarlı kateter takılması (p<0.01) SKİ-KDE gelişimi ile ilişkili bulunmuştur. **Sonuç:** Özetle, çok değişkenli analizler, tekrarlı kateter takılmasının (p<0,01) ve YBÜ'de uzun süre kalmanın (p<0,01) SKİ-KDE riskini artırabileceğini gösterdi. Ancak, paket uygulaması olan hastalarda enfeksiyon riskinin daha az olduğu (p<0,01) görüldü.

Anahtar kelimeler: Bundle, santral kateter, kan dolaşım enfeksiyonu, yoğun bakım.

Öztürk Deniz SS, Akın Şen İ, Özdemir K, Aydeniz N, Kıvrak A, Karaduman S, Sungurtekin H, Turgut H. Santral venöz kateter ilişkili kan dolaşımı enfeksiyonları için risk faktörlerinin ve santral venöz kateter paket uygulamasının yararlarının değerlendirilmesi. Pam Tıp Derg 2023;16:716-725.

Introduction

At present, insertion of central venous catheters is an essential procedure to administer solutions that are unlikely to be given via a peripheral route, and to perform cardiovascular measurements especially in the follow-up of patients in the intensive care unit (ICU) and to perform hemodialysis [1, 2]. However, central venous catheterization may be associated with a variety of complications as well as benefits. Apart from mechanical complications, bloodstream infections (BSIs) are main crucial complications of catheterization [3] caused by microbial invasion at the time of catheter insertion or care [4]. Central-line-associated blodsteram infections (CLABSI) could lead to thousands of deaths each year and could increase mortality, hospital stay and health care costs, espacially among ICU patients [5, 6].

The National Healthcare Safety Network (NHSN) data between 2009 and 2018 from the USA reported CLABSIs decreased from 1.6 per 1000 central line-days to 0.9, except for an incraese in 2015 [7]. In contrast, the International Nosocomial Infection Control Consortium (INICC) surveillance data in 45 countries including Turkey reported a remerkably increased CLABSI rate (5.30/1,000 (CL-days) between 2013 and 2018 [8]. Since the use of central line (CL) bundles including proper antiseptic solution and adherence to protective barrier measures have been reported to prevent CLABSIs [9-11], the Centers for Disease Control and Prevention (CDC) updated the guidelines in 2011 to reduce CLABSIs and emphasized the use of chlorhexidine, taking maximal sterile barrier precautions (MBPs) [9, 10].

The insidences of CLABSIs in the ICU of the Hospital of Medical School of Pamukkale University were 7.14/1000 CL-days and 8.3/1000 CL-days in 2017 and 2018, respectively. In order to reduce the rates of CLABSIs, the use of CL bundles, including chlorhexidine as well as MBPs and hand hygiene before and after the procedure was put into practice in 2019 in the ICU. The current study sought to identify the risk factors for CLABSIs and the efficacy of bundle application to prevent CLABSIs.

Materials and methods

Study setting and population

This prospective observational study was performed in the anesthesia-intensive care unit (AICU) of a tertiary hospital with 900 beds from February 2019 to February, 2020. This study was performed in accordance with the Declaration of Helsinki, and the Pamukkale University, Non-Invasive Clinical Research Ethics Committee approved the study with the number of 60116787/020/8888 on 06/02/2019.

Study design and procedures

In line with the recommendations of the national and international guidelines, a CL bundle checklist was prepared that included the precautions (i.e., hand hygiene before and after the procedure, chlorhexidine use; which had not been used previously for cleaning the skin, and maximal sterile barrier precautions containing a cap, mask, gown, sterile gloves and drape for covering up patients and was begun to implement routinely after several months of experience. The site of cathether insertion was left to the discrition of attending physicians.

Health care workers involved in catheter insertion were informed about the procedures. Therefore, the team involved in procedures was asked to prepare the required equipment earlier, to fill out the checklist, and to adhere to the recommendations of the guidelines.

Adult patients between the ages of 18 years and older, who had undergone recent central venous catheter (CVC) insertion at the ICU, and those who had been transferred to ICU with the previous catheter insertion in departments other than ICU and who had received a diagnosis of CLABSI fourty-eight hours after remaining in the ICU were included in the study. Patients who had been transferred to the ICU having been infected were not included in the study.

Patients who were inserted CVC accompanied by bundle application in the ICU were followed up pending the development of catheter-related bloodstream infection or removal of catheters or discharge from the ICU. After catheter insertion, the procedures of catheter care were left at the discretion of ICU staff, but unlike the previous practice in which batticon had been used, clorhexidine use was required for cleaning of skin during catheter care. After insertion, catheter care was performed 72 hours apart, but when dressings had become contaminated or deformed, they were changed regardless of the time interval of care.

Data collection

Data were collected via structured survey forms. An AICU physician and a nurse from the infection control committee were assigned to collect data on patients' characteristics (age, sex, comorbidities, intubation status and APACHE-II scores, use of total parenteral nutrition via CVC at the time of catheterization, a history of surgery and use of antibiotics, etc.), as well as on the care of the catheter. During each catheterization, the physicians in charge filled out the checklist forms as to whether they adhered to the items on the checklist form. Failure to comply with even one item on the checklist was considered a total incompliance and accepted as non-compliance with CL bundle checklist.

Patients with central catheters were followed on a daily basis to identify whether any infections occurred. An infectious diseases specialist made the diagnosis of CLABSIs on the basis of the results of blood culture and the CDC criteria, which define CLABSIs as laboratory-confirmed bloodstream infection that develops in a patient who has had a central catheter for more than two days (>2 calendar days) at the date of the event in line with surveillance data [5]. The day when the catheter is placed is accepted as the first day, and the catheter that is replaced after the first two days is accepted as the new catheter. In addition, an infection developing within the first fourteen days after catheter insertion is considered to be the first episode. Furthermore, once a new infection occurs with the same catheter after the first 14 days, it is considered to be a second episode [5]. Consistent with these definitions, the study included only one procedure of catheter insertion, and one episode of each patient. Recurrent infections of the same patient were not included in the study.

During the study period, rates of infections were controlled monthly; in case of any increase in the numbers, the reasons for increases were sought, adherence to hand hygiene in the ICU was observed accordingly, training in this context was planned. All patients who met the study criteria over a 13-month period were evaluated in terms of the risk factors for infection. Furthermore, the rates of CLABSIs were compared in patients with bundle adherence and those without. The rate of CLABSI was estimated by dividing the number of CLABSIs into the number of central line-days x1000 [12, 13].

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics version 22 (Nyc, USA). Shapiro-Wilks test was used for normal distribution of data. Continuous data without normal distribution were presented as median with inter quartile range (25-75 percentiles) and nonparametric Mann Whitney U test was used for between-group comparisions. Categorical variables were presented as frequency and number and compared using the chi-square test. Together with Bonferoni correction, *p* values were corrected for multiple tests. A *p* value of <0.05 was considered as significant and confidence interval (CI) was set 95.0%.

Results

General characteristics of patients and CVC insertion

The current study included 156 patients with the mean age 67.97±17.21 years (19 to 98 days; median 71.00; IQR 62.25-80.00), 66 women (42.3%), 90 men (57.7%), all of whom had CVCs and had been followed in the ICU.

The duration of catheter stays varied from zero to 163 days with a mean of 20.85±24.47 days (median 14.50; IQR 4.25-28.00), total catheter days were calculated as 3252 catheter days. Over the study period, 47 patients (30.1%) developed CLABSIs, on hospital days from three to 137 days with a mean of 24.17±24.54 days (median 17.00; IQR 9.00-27.00). The mean ICU stay was 59.11±129.11 days with a minimum zero to maximum 1007 (median: 26.00, IQR: 8.00-58.75).

Of 156 catheters, 146 (93.6%) were placed electively; the remaining 10 catheters were placed under emergency condiditions. Furthermore, 97 patients (62.2%) had new catheters for venous access, four patients (2.6%) for obtaining hemodynamic data, 49 (31.4%) recieved new catheters for hemodialysis and six (3.8%) underwent catheter reinsertion because of dysfunction of their former catheters. 136 catheters (87.2%) were inserted by residents and 20 (12.8%) by specialists with expertise in the field. The internal jugular vein (74 CVCs; 47.4%) was the site where catheters were most frequently inserted, followed by femoral vein (52 CVCs; 33.3%) and then the subclavian vein (30 CVCs; 19.2%). Of patients, 106 (67.9%) had 3-lumen CVCs and 50 (32.1%) had 2-lumen CVCs. Of 156 patients, 132 had bundle implementation accompanied by catheterization, of whom 128 (82.1%) had bundle compliance.

Time to catheter insertion from ICU admission ranged from 24 days before ICU admission to 802 days after ICU admission, with a mean of 17.51±69.31 days (median 3.00 days, IQR 0.00-15.00). Most patients received catheters within 28 hospital days, however, the maximum time was as long as 802 days because of prolonged hospital stay as well as repeat catheter insertions in one patient.

A total of 119 patients (76.3%) had been intubated at the time of CVC placement, with the APACHE II scores of 1 to 45 with a mean of 19.60±8.18 (median: 19.60, IQR 5.13-25.00). Of patients, 49.4% (n=77), 26.3% (n=41) and 0.6% (n=1) had had endotracheal, tracheal and nasotracheal intubations, respectively.

Analyzing the diseases at baseline, one patient (0.6%) had cholangitis, one (0.6%) had sepsis, one (0.6%) had liver diseases, one (0.6%) had malignant neuroleptic sendrome, three (1.9%) had benign prostatic hyperplasia, three (1.9%) had deep venous thrombosis, three (1.9%) had rheumatic diseases, three (1.9%) had mental health disorders, four (2.6%) had hypothyroidism, five (3.2%) had pulmonary diseases other than asthma and chronic obstructive pulmonary diseases (COPD), eight (5.1%) had asthma, eight (5.1%) had hematologic diseases, 13 (8.3%) had nephrological diseases, 20 (12.8%) had COPD, 25 (16.0%) had solid organ malignancies, 31 (19.9%) had cardiac diseases, 32 (20.5%) had neurologic diseases, 39 (25.0%) had diabetes mellitus, 46 (29.5%) had hypertension.

Of patients, 49 patients (38.3%) were A-Rh positive, five (3.9%) were A-Rh negative, 14 (10.9%) were B-Rh positive, four (2.3%) were B-Rh negative, 12 (9.4%) were AB-Rh positive, two (1.6%) were AB-Rh negative, 39 (30.5%) were 0-Rh positive and four (3.1%) were 0-Rh negative. Prior to catheterization, 57 patients (36.5%) had undergone surgery and 85 (54.5%) had received antibiotics over the last 10 days. After catheterization, 57 patients (36.5%) received enhanced usual care and 8 had (5.1%) excessive catheter manipulation. During the catheter stay, 72 patients (46.2%) received blood products and 24 (15.4%) received total parentheral nutrition (TPN) via CVCs. Thirty days after catheter removal, 99 patients (63.5%) had died.

Risk factors

As shown in Table 1, evaluating the results of univariate analysis, there was no significant association between the development of CLABSIs and sex ($p>0.05$), also age ($p>0.05$). However, there was a significant association between the reason for CVC insertion and the development of CLABSIs.

Table 1. Univariate analysis of the risk factors of CLABSI*

	CLABSI (+) (n=47) n (%) or median (IQR)	CLABSI (-) (n=109) n (%) or median (IQR)	*p* value
Age (years)	70 (53-78)	71 (64-81)	*p*=0.24
Time to catheter insertion from ICU admission	1 ((-1) to 26)	3 (1 to10)	*p*=0.16
Catheter day (CD)**	27 (17-40)	7 (2-20)	*p*<0.01
ICU* stay (day)**	59 (34-114)	16 (5-36)	*p*<0.01
APACHE-2	21 (16-25)	19 (14-24)	*p*=0.11
Urea (mg/dl)	45 (32-70)	94 (53-131)	*p*<0.01
Creatinine (mg/dl)	0.7 (05-1.7)	1.4 (0.8-2.8)	*p*<0.01
Procalcitonin (ng/mL)	0.3 (0.2-0.4)	0.2 (0.1-0.3)	*p*<0.01
Female	19 (29%)	47 (71%)	*p*=0.45
Reason for CVC** insertion**			
Hemodialysis	4 (8%)	45 (92%)	
Dysfonction	4 (67%)	2 (33%)	*p*<0.01
Hemodynamic data	4 (100%)	0 (0%)	
Venous acsess	35 (36%)	62 (64%)	
Site of cathether insertion			
Subclavian vein	16 (53%)	14 (47%)	*p*<0.01
Femoral vein	6 (12%)	46 (88%)	
Internal juguler vein	25 (34%)	49 (66%)	
Number of CVC lumen			
3-lumen catheter	43 (41%)	63 (59%)	*p*<0.01
2-lumen catheter	4 (8%)	46 (92%)	
Catheter insertion			
by residents	43 (32%)	93 (68%)	*p*=0.29
by specialists	4 (20%)	16 (80%)	
Emergency	6 (60%)	4 (40%)	*p*=0.04
Elective	41 (28%)	105 (72%)	
Intubation	42 (35%)	77 (65%)	*p*=0.01
Bundle adherence	24 (19%)	104 (81%)	*p*<0.01
Surgery	23 (40%)	34 (60%)	*p*=0.04
Receiving antibiotics	35 (41%)	50 (59%)	*p*<0.01
Blood transfusion	29 (40%)	43 (60%)	*p*=0.01
TPN ***	10 (42%)	14 (58%)	*p*=0.18
Unusual catheter care	14 (25%)	43 (%75)	*p*=0.24
Repeat catheter insertions	14 (70%)	6 (30%)	*p*<0.01
Mortality	24 (24%)	75 (76%)	*p*=0.04

* CLABSI: Central line-associated bloodstream infections, ** Note: Patients who had CLABSIs without bundle adherence had significantly higher catheter day then those who had CLABSIs with bundle adherence, *** ICU: Intensive care unit, **** CVC: Central venous catheter
***** TPN: Total parenteral nutrition

The rate of CLABSIs was lowest when catheters were inserted with the aim of performing hemodialysis (8.2%) (p<0.01). While the rates of infections were found to be significanlty higher when catheters were inserted due to dysfonction (66.7%) or for obtaining hemodynamic data (100%), the rates of infections were lower when catheters were inserted for hemodialysis and for obtaining venous acsess (62.2%) (p<0.01). Given the sites of catheter insertion, surprisingly, the subclavian vein was found to have the highest rate of CLABSIs (16/30 CVCs; 53.3%), but the femoral vein was observed to have the lowest infection rate (6/52 CVCs; 11.5%), which are statistically significant (p<0.01). Patients with 3-lumen catheters had statistically higher rates of CLABSIs (40.6%) as compared with those with two-lumen cathathers (8.0%) (p<0.01) (Table 1).

Considering development of CLABSIs, patients receiving CVCs under emergency condition developed significantly higher rate of CLABSIs (60.0%, p=0.04). Furthermore, patients who had been intubated prior to catheterization developed statistically higher rate of infection (35.3%, p=0.01) of whom, there was a lower rate of infection with tracheal intubation which is statistically significant (43.9%, p=0.03). Patients undergoing surgery (40.4% p=0.04) before catheterization as well as those receiving antibiotics for the last 10 days prior to catheter insertion (41.2%, p<0.01) developed significantly higher rate of CLABSIs. Given the comorbidities, only three patients with the diagnosis of mental health disorders were noted to developed infection (100% p=0.03). There was no significant association between blood type and CLABSIs (p>0.05 p=0.32). However, a higher rate of CLABSIs was found in patients receiving blood products through CVCs (40.3%, p=0.01). Repeat catheter insertions were also associated with development of CLABSI (p<0.01) (Table 1).

Patients with CLABSs had a longer period of catheter stay with a mean of 35.40±29.42 days (6 to163 days; median: 27.00; IQR 17.00-40.00; p<0.01) and also prolonged ICU stay with a mean of 114.51±169.52 days (11 to 890 days; median 59.00; IQR 34.00-113.00; p<0.01), which was statistically significant.

Patients with no CLABSIs had higher levels of urea with a mean of 99.22±54.94 mg/dl (17-288 mg/dl; median 94.00, IQR 53.00-131.00 p<0.01, normal range; 16.6-48.5 mg/dl,) and creatinine with a mean of 3.29±7.14 mg/dl (0.06-57.00 mg/dl; median 1.39; IQR 0.80-2.82 p<0.01 normal range; 0.50-0.95 mg/dl). However, patients with CLABSIs had higher levels of procalcitonin with a mean of 2.12±7.70 ng/mL (0.06-47.00 ng/mL; median 0.25; IQR 0.19-0.40; normal range 0.5<p<0.01), as was expected.

CL Bundle adherence

In our study, the group undergoing catheterization with bundle adherence had statistically a lower rate of infection (18.8%) than the group undergoing catheterization without bundle adherence (82.1%), findings consistent with the goal of the current study (p<0.00). However, when the rate of CLABSI was estimated in line with the CDC criteria by using surveillance data from our hospital, we found that rate of CLABSI was 10.09 per 1000 central line-days during the 13-month period. When the groups were evaluated seperately, the group with bundle adherence had a rate of CLABSIs of 11.36 per 1000 central line-days, but the group with no bundle adherence had a rate of CLABSIs of 9.3 per 1000 central line-days, which was not an expected rate. This might be attributed to the way in which the rate of infection is estimated (the rate of CLABSI is calculated by dividing the number of CLABSIs by the number of central line-days x1000), that is, the longer days in the denominator, the lower the rate of infection. This is consistent with the result of the group with no bundle adherence.

Multivariable logistic regression analysis was performed to identify the effect of independent factors on CLABSIs, which was found statistically significant (X^2=108.59, p<0.001). Independent variables in the model could explain 76.7% of the total variance in developing CLABSIs (p<0.01). ICU days (β=1.00, p<0.01) and repeated catheter insertions (β=0.03, p<0.01) were independent risk factors for CLABSIs, but bundle adherence (β=24.03, p<0.01) was found to be an independent protective factor.

Of 47 patients with CALBSIs, 24 had a mortality rate of 51.1% as compared with those with no CLABSIs, 75 had a mortality rate of 68.8% (p=0.04).

Causative agents of CLABSIs

Candida spp. grew in blood cultures of 16 patients [(10.25%) (*C. albicans* in four patients, *C. parapsilosis* in eleven, *C. glabrata* in one)], *Enterococcus* spp. in eleven patients (7.05%) [*E. avium* in one (0.6%); *E. faecalis* in ten patients (6.4%)], Coagulase-negative staphylococci (CoNS) in eight patients (5.13%), *K. pneumonia* in five patients (3.20%), *Acinetobacter* spp. in four (2.56%) (*A. baumannii* in three*, A. iwoffii* in one patient), *Pseudomonas* spp. in four patients (2.56%) (*P.* spp. in one patient, *P. aeruginosa* in three patients), *E. coli* in three patients (1.9%), *Aeromonas* spp. in two patients (1.28%), *Serratia marcescens* in one patient (0.6%), *Morganella morgannii* in one patient (0.6%) and *Streptococcus* spp. in one patient (0.6%).

Of the blood cultures of 8 patients growing CoNS, which are part of normal skin flora, six were without bundle applications; there was a statistically significant difference between the groups with or without bundle application ($p<0.01$). This emphasizes the importance of appropriate skin cleaning that decreases the risk for contamination when bundle applications are performed.

Discussion

The aim of this study is to determine the risk factors for CLABSIs, define the measures to be taken, and evaluate the outcome of bundle application during central catheter insertion as well as catheter care.

The CDC has reported that, while CLABSIs can be prevented, they cause thousands of deaths every year around the world, and they are associated with a heavy economic burden and workload on healthcare systems [2]. Multiple strategies may be necessary to prevent CLABSIs, including training health care personnel (HCP), maximum adherence to hand hygiene (HH), the use of maximum barrier precautions, and chlorhexidine for catheter and skin care. In addition, preventive strategies may also be required, including chlorhexidine patches for catheter care and antiseptic/antibiotic-impregnated catheters, an appropriate catheter site, and refining indications for the insertion and removal of catheters. Strict adherence to bundle application seems to be an advisable alternative in this context [1].

There are studies reporting reduced CLABSIs rates with bundle application and the guidelines by the CDC recommend using chlohexidine for the prevention of CALBSIs [12, 14]. Since we identified increased rates of CLABSIs at our hospital during the period between 2017 and 2018, we made a decision to reduce CLABSIs, using chlohexidine and bundle application in one pilot ICU from February, 2019 to February, 2020.

It was shown that the rate of CLABSIs was reduced with bundle implementation [15]. A study reported that the rates of CLABSI in both medical and surgical ICUs were noted to decrease by 39% and 44.4%, respectively, during periods of bundle applications [12]. In another study using the data from the hospital infection control committee, it was observed that, despite not being significant, the number of CLABSIs decreased from 23 to 13 as compared with the previous years, with a significant decrease in the rate of catheter use [16]. Similarly, another study reported that the more the compliance with CL bundle, the lower the incidence of CLABSIs, although the decreased rates of infection seemed to be statistically insignificant, which means that using bundle application alone may not yield the expected results. Additional preventive measures, including isolation, identifying indications for the insertion and removal of catheters, an appropriate catheter site, and regular and careful catheter care, should also be taken [17]. Furuya et al. [18] also stated that the incidence of CLABSIs decreased from 4.7 to 1.8 episodes per 1.000 CVC-days over a period of bundle application, despite not being statistically significant, consistent with the findings in a study by Waltz et al. [19].

Unlike aforementioned studies, an observational study examined the association between bundle application and the rates of CLABSIs in general ICU over a period of five years and identified that the rates of CLABSIs varied every three moths, without statistically significant reduction in the rates of infection [2]. In this study, the group with bundle adherence had a statistically lower rate of infection as compared to the whole group without bundle, findings consistent with the goal of the current study ($p<0.01$). However, when we estimated the rate of CLABSIs according to CDC criteria with the use of hospital surveillence data (which

included reinfections and patients with no bundle application who had no infection being out of the study scope), the group with bundle adherence seemed to have a higher rate of CLABSIs (11.36 per 1000 central line-days) compared to the group without bundle adherence, which can be attributed to the way in which the rate of infection was estimated: the rate of CLABSIs is calculated by dividing the number of CLABSIs into the number of central line-days x1000), the group with no bundle adherence had higher number of catheter days.

We evaluated the rates of CVC use, CLABSIs and HH adherence monthly and every three months during the study period. We noted that the rates of CLABSIs varied unexpectedly for some reasons, irrespective of the rates of HH adherence. The reason for the increased rates of CLABSIs could be attributed to the change of attending physicians among inexperienced residents. Noting that the infection rates increased, we repeated HH education and reminded new residents of the rules of bundle application, and warned them in this respect. Accordingly, the rates of infection were noted to decrease. Even if the application of CL bundle remains the key to prevent CLABSIs, other preventive interventions, including regularly checking overall adherence to the rules of HH and supporting HCP with reminder strategies, especially at the point-of-care should also be implemented.

This study also analyzed the risk factors related to the development of CLABSIs and found that they were not linked to the demographic data, including age and sex, a finding consistent with the literature [16].

Primarily, catheter placement sites should be carefully evaluated because they may be associated with the risk of infection due to the increased regional floral load of the skin and thrombophlebitis. Guidelines have emphasized that placement site and the type of catheters are important and that use of femoral catheters should be avoided, but subclavian catheters should be preferred [5]. However, in clinical practice, femoral catheters are more preferred for their easy placement and lower rate of complications. In contrast, the placement of subclavian catheters is demanding in that they require USG guidance and may lead to life-threatening complications such as pneumothorax. Regarding risk factors associated with CLABSIs, as opposed to what is usually accepted, a study found that the insertion site was not associated with an increased incidence of CLABSIs [2]. Our study surprisingly found that the femoral vein had the lowest infection rate, as did other studies [17, 20].

The reason for CVC insertion is likely to be associated with infection rates. Periodic change of CVCs is not a preferred method [5], but catheter dysfunction may occasionally occur due to causes such as thrombosis, which prompts catheter change. In a study conducted by Karapanou et al. [21], catheter placement, whether due to dysfunction or emergency, was found to increase the rate of infection.

Examining the indications for catheter placement, we found that catheterization for venous access and hemodialysis were the most common reasons and had the lowest rate of infection when catheter insertion was performed for hemodialysis.

Furthermore, the number of catheter lumens may be significantly involved in the increased rates of infection reported by several studies [5, 15]. Although a meta-analysis reported that there was no significant difference between the rate of infection and the number of catheter's lumens, the guidelines recommend using as few as possible lumens [5]. We also noted a higher rate of infection with the 3-lumen catheters than with the 2-lumen catheters.

Given all these findings, we could speculate that the reason for the unexpectedly low infection rate of femoral catheters may be related to the preference of femoral sites and 2-lumen catheters for hemodialysis, which was found to be associated with the lowest infection rate. Furthermore, difficulty in fixing dressings in subclavian and juguler regions may explain the increased rate of infection in such regions. However, as for the femoral site, dressings can be easily fixed to that region, and dressings may be covered by the diaper as well as the upper sheet of patients.

Furthermore, patients with a history of surgery, and those who received antibiotic therapy for the last 10 days, as well as those who were intubated as compared with those with no intubation had higher rate of infection.

Patients who had repeat catheter insertions also had a higher rate of infection. These invasive procedures and the use of antibiotics might make patients who have already weakened immunity more predisposed to infections. We also found that the need for emergency catheter placement elevated the rate of CLABSIs, which was considered to be probably related to inadequate preventive measures. Although there is a study showing that erythrocyte transfusion is protective in terms of infection development [20], consistent with the study by Polat et al. [16], the current study found that catheters through which blood and blood product transfusions were performed had higher rates of infection.

There are studies identifying that prolonged ICU stay as well as prolonged catheter duration are the factors associated with development of CLABSIs [16, 21]. Furthermore, such studies have also found that while APACHE II scores are associated with development of CLABSIs [2], other studies reported no association between APCHE III/IV scores and CLABSIs [12, 21]. In accordance with the literature, we also found that dwell time and prolonged ICU stay were the factors associated with infection, which could be attributed to more frequent bacterial colonization because of longer periods [2, 16].

In the current study, despite having lower rates of procalcitonin, we found that patients with no CLABSIs had higher levels of urea and creatinine. The reasons for higher levels of urine and creatinine could be that those patients had catheters with the aim of dialysis, which was performed with a two-lumen catheter. Accordingly, it can be concluded that patients with catheters for dialysis have a lower rate of CLABSIs.

When the causative agents were roughly evaluated, of the blood cultures of eight patients growing CoNS, which are part of normal skin flora, six were without bundle applications. This emphasizes the importance of appropriate skin cleaning that decreases the risk of contamination when bundle applications are performed. *Enterococcus* spp. and *Candida* spp., caused by antibiotic overdose, were also mostly isolated agents. Given *Enterococcus* spp., we could infer the importance of adherence to bundle application as well as hand hygiene, irrespective of the patient's own intestinal flora.

Of patients with CALBSIs, 51.1% developed mortality, and of those without CLABSIs, 68.8% died. The unexpectedly higher number of patients without CLABSIs who died may suggest that mortality might occur due to reasons other than infection.

In conclusion, considering risk factors in terms of CLABSIs, repeat catheterization is likely to raise the risk of infection. Patients with CLABSIs had prolonged ICU stay, which means that a longer ICU stay can raise the cost of care as well as the workload of healthcare personnel and the likelihood of developing other infections. In this context, meticulous adherence to bundle application and/or reducing the use of catheters is of vital importance to prevent CLABSIs.

Limitations

This study has several limitations. The study was carried out in only one of the ICUs of the hospital. All patients undergoing catheterization without bundle application were not included in the study. More comprehensive studies with a larger sample size may yield further data on risk factors for CLABSIs.

Conflict of interest: No conflict of interest was declared by the authors.

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Ethics committee approval: This study was approved by the Pamukkale University, Non-Interventional Clinical Research Ethics Committee with the decision numbered 60116787/020/8888 on 06/02/2019.

Authors' contributions to the article

S.D. constructed the main idea and hypothesis of the study. S.D. developed the theory and arranged/edited the material and method section.S.D., I.A.S., A.K., S.K., H.S., K.O., N.A. and H.T. have done the evaluation of the data in the Results section. Discussion section of the article written by S.D., I.A.S., A.K., S.K., H.S., K.O., N.A. and H.T. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.