

# Use of silver-impregnated umbilical venous catheters for prevention of catheter associated bloodstream infection in neonates

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## Abstract

**Aim:** Neonates hospitalized in neonatal intensive care units (NICU)s often require a venous access. Umbilical venous catheter (UVC) is the commonly used one. UVCs are known to cause life-threatening complications such as catheter-associated bloodstream infections (CABSI). To the best of our knowledge, our unit is the first and only NICU in Turkey that used silver-impregnated UVCs. This study aims to evaluate the impact of silver-impregnated UVC insertion on the incidence of CABSI.

**Materials and Methods:** A total of 108 patients were included in this retrospective study. After the application of exclusion criteria, the control group was composed of neonates (n=58) who had polyurethane (PU) UVCs inserted and the study group consisted of infants (n=41) who had silver-impregnated UVCs inserted. Demographic and clinical data of the mothers and neonates including duration of UVC insertion and sepsis incidence were collected and compared statistically.

**Results:** There was no statistically significant difference between the groups except for intubation period and mortality. One neonate in each group had CABSI (p=1). Four neonates, two in each group, were diagnosed with clinical sepsis. Total CABSI incidence in our whole population was 2% and 3.3 per 1000 catheter days.

**Conclusion:** Strict precautions should be taken to prevent infection in every unit. In NICUs with low incidence of sepsis, silver-impregnated UVCs may have no further effect in the reduction of CABSI.

**Keywords:** Catheter-associated bloodstream infection; neonate; silver; umbilical venous catheter

## INTRODUCTION

Central venous catheters (CVCs) are essential in the care of critically ill infants and very low birth weight (VLBW) infants in neonatal intensive care units (NICU) to administer total parenteral nutrition (TPN), fluids and medications (1-3). CVCs are recommended for the neonates who need an intravenous access for more than 5 days (4). Moreover, it has been reported that preterm neonates who receive nutrition via a CVC have significantly higher weight gain, lower rates of infection and shorter hospital stay compared with the ones with multiple peripheral venous access (5,6).

In the first days of life, umbilical venous catheters (UVC) are preferred to be used as the umbilical vessels are easy to identify compared to other vascular access (2,7). UVCs can cause multiple complications including vessel injury and perforation, catheter-associated bloodstream infection (CABSI), thrombosis, liver abscess and ischemia

(8-10). It has been reported that the mean CABSI rates ranges from 2.1 to 17 per 1000 catheter days or 6 to 36.8%, depending on the birth weight (BW) of the infant. As the BW decreases, the rate of CABSI increases (2,11-13). To prevent CABSI, sterile catheter insertion, proper catheter position, minimized catheter use by promoting early enteral feeding and regular catheter care are recommended (13,14). Apart from these, to reduce the risk of CABSI, different types of antimicrobial impregnated catheters such as antiseptics, antimetabolites, antimicrobials and silver ions impregnated catheters are recommended for patients at high risk for infection. Silver-impregnated catheters which is the combination of plastic with a special silver compound, namely the patented silver compound AgIONTM, releases antimicrobially active silver ions from the inner and outer surfaces of the catheter when they interact with body fluids and intravenous solutions. Antimicrobially active silver ions may help to prevent CABSI (15,16). In adult population,

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several studies were done using CVCs impregnated with silver compounds, chlorhexidine plus silver compounds or minocycline-rifampicin and were found to be associated with lower rates of catheter colonization and CABSIs (17-21). A multicenter randomized controlled trial reported that the use of antimicrobial-impregnated CVCs versus non-impregnated (standard) CVCs reduced CABSIs also in children (22). To the best of our knowledge, in newborn population, few studies have been done comparing standard and antimicrobial-impregnated CVCs to reduce CABSIs. Moreover, our NICU is the first and only one used silver-impregnated UVC in Turkey.

This study was designed to evaluate the impact of silver-impregnated UVC insertion on CABSIs in neonates which is the first report about the usage of silver-impregnated UVCs in Turkey.

## MATERIALS and METHODS

### Study Design

This retrospective study was conducted in two level III NICUs of the same institution, between May 2015 and September 2020. Both hospitals are tertiary hospitals with a total of 24 incubators and approximately 350-400 annual admissions.

The present study was executed in accordance with the Declaration of Helsinki, and approved by the same university hospital (approval number 2020.490.IRB1.180). Written informed consents were obtained from parents of all patients included in this study. There was no funding source relevant to the study.

### Study Population

According to the medical reports, 108 patients were included in the study. The infants who died in the first 72 hours of life (n=2), had congenital malformations (n=2), and metabolic disorders (n=1) were excluded. In addition, four more patients were excluded as the catheter was removed on the same day of insertion due to the inappropriate UVC tip position (n=3), and after the exchange transfusion (n=1). A total of 99 infants were enrolled in the study.

Until May 2018, PU catheters (with double-lumen umbilical catheters, 3.5-5.0 F, Vygon, Ecouen, France) were routinely used in both NICUs of two hospitals. After this date, AgION-impregnated UVCs (with double-lumen umbilical catheters, 3.0-5.0 F, Agion Vygon, Aachen, Germany) were used for umbilical venous catheterization. Therefore, the infants were divided into two groups according to the type of the UVC that was inserted; the control group consisted of infants who had polyurethane (PU) catheters (n=58) inserted before May 2018 and the infants who had AgION catheters (n=41) inserted after May 2018 constituted the study group. Demographic and clinical data about mothers and neonates were collected in terms of BW, gestational age (GA), gender, mode of delivery, prolonged premature rupture of membranes (PROM), presence of chorioamnionitis, respiratory distress syndrome (RDS), mechanical ventilation duration, retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), necrotizing

enterocolitis (NEC), bronchopulmonary dysplasia (BPD), duration of UVCs, the postnatal day when the infant was diagnosed with sepsis, the day of reaching to full enteral feeding and length of hospital stay.

The GA of the neonates was based on the date of the last menstrual period of the mother and dating ultrasound performed in the first trimester of pregnancy. RDS was defined as having respiratory distress accompanied by the characteristic radiological findings (23). Infants receiving oxygen therapy or assisted ventilation at postnatal 28th day were defined as having BPD (24). IVH was diagnosed by cranial ultrasound and classified according to Papile grading system (25). NEC was diagnosed and managed with respect to Bell's staging criteria (26).

### UVC Insertion, Care and Removal

All UVCs were inserted under sterile conditions according to the recommendations of Centers for Disease Control and Prevention (CDC) guidelines for the prevention of intravascular catheter-related infections (27). UVC tip position was simultaneously checked by an anteroposterior abdominal graph, and if the UVC tip was at the level of the diaphragm, the catheter was secured through the umbilical stump with a suture. Furthermore, the catheter was secured using 'H-Tapes' affixed to the skin of the abdominal area. The umbilicus was left uncovered and lifted, inspected at least every 3 hours during the nursery care and venous lines were changed daily. Heparin 0.5 IU/mL was added to all intravenous fluids infused through the venous line.

The infants who had risk for sepsis received ampicillin (100 mg/kg/d) and gentamicin (4.5-5 mg/kg/24-48 h). Moreover, the infants weighing less than 1250 gr had received fluconazole prophylaxis (3 mg/kg per dose twice weekly). If the infant's clinical symptoms and laboratory tests did not suggest an infection and the cultures remain sterile, the antibiotic treatment was stopped at 2-3 days. If sepsis was suspected, UVC was removed after obtaining blood culture from the peripheral vein.

Our unit policy is to remove UVCs at about one week of life other than exceptional circumstances, to promote early enteral feeding and to reach full-enteral feeding in a short time. After UVC removal, a tip culture is not routinely performed. A peripherally inserted central catheter (PICC) is inserted if the infant needs a venous access after the UVC is removed.

### Definition of Infection

For the purpose of the present study, CABSIs was defined as the infants who had clinical manifestation of infection and laboratory (leukocytosis, leukopenia, immature to total neutrophil ratio, C-reactive protein, procalcitonin) abnormalities suggesting any new onset or worsening sepsis till 48 hours after the removal of a UVC with a positive blood culture like in the study of Shalabi et al.(5) The clinical symptoms included hypothermia

(rectal <36 °C), fever (>38 °C), heart rate <100 beats/min or >180 beats/min, hypotension, new-onset crisis of apnea, respiratory distress, hypotonia, lethargy, feeding intolerance, coagulopathy and unstable vital signs.

### Statistical Analysis

Statistical analysis was performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The variables were investigated using visual (histograms, probability plots) and analytical methods (Shapiro-Wilk test) to determine if they are normally distributed. Descriptive analyses were presented using means±SD for normally distributed variables, as medians (range, 25–75%) for the nonparametric variables and as percentages for categorical variables. Normally distributed variables were compared by Student t-test, nonparametric variables by Mann–Whitney U test, and categorical variables by chi-square test. Incidence rate comparisons using two-sided mid-P exact test have been performed with Stata/MP 13.1. Poisson exact confidence intervals are presented for incidence rates.  $P < 0.05$  was considered to indicate a significant difference.

## RESULTS

A total of 99 infants were eligible for the study. Fifty-eight infants had PU UVC inserted (control group) and

41 had AgION UVC inserted (study group). There was no statistically significant difference between the groups in terms of clinical characteristics except for intubation period and mortality rate (Table 1). In the control group, twenty-six infants were intubated, and the median intubation duration was 1 (1-3) day, whereas in the study group, twenty-three infants were intubated, and the median intubation duration was 7 (2-16) days ( $p=0.001$ ). The mortality rate was 1.7% and 12.2% in the control and the study groups, respectively ( $p=0.04$ ). One infant in the control group and three infants in the study group died before reaching to full-enteral feeding, therefore analyzes for these infants were not done in terms of reaching to full-enteral feeding day. One neonate in each group had CABSIs. Blood culture of the neonate in the control group grew candida, whereas E. coli was isolated in the blood culture of the neonate in the study group. Four neonates, two in each group, were diagnosed with clinical sepsis and their catheters were removed; however, no bacteria or fungi grew in their blood culture. Total CABSIs incidence in our whole population was 2% and 3.3 per 1000 catheter days. The CABSIs incidence rate in the study and control groups are 4.2 (95%CI: 0.1-23.5) and 2.8 (95%CI: 0.1-15.3) per thousand, respectively. This corresponds to a non-significant ( $p=0.79$ ) incidence rate ratio of 1.53 (95%CI:0.02-119.9).

**Table 1. Characteristics of the study groups**

Parameters	Control group (n= 58)	Study group (n= 41)	p-Value
GA (weeks), (mean±SD)	30.7±3.9	30±4.5	0.50
BW (g), (mean±SD)	1411±811	1337±815	0.65
Gender (male), n (%)	23 (39.7)	18 (43.9)	0.66
Mode of delivery (c/s), n (%)	54 (93.1)	39 (95.1)	1
PROM >18 h, n (%)	12 (20.7)	5 (12.2)	0.30
Presence of chorioamnionitis, n (%)	6 (10.3)	2 (4.9)	0.30
Entubation duration (day), median (25-75 p)	1 (1-3)	7 (2-16)	0.001
RDS, n (%)	35 (60.3)	27 (65.9)	0.70
BPD, n (%)	19 (32.8)	20 (48.8)	0.14
IVH (stage 1-2), n (%)	7 (12.1)	4 (9.8)	0.10
IVH (stage 3-4), n (%)	0	3 (7.3)	0.10
NEC, n (%)	7 (12.1)	4 (9.8)	0.46
ROP, n (%)	1 (1.7)	4 (10.3)	0.15
Reaching to full-enteral feeding (day), median (25-75 p)	7 (6-9.5)	9.5 (5.75-16)	0.10
Sepsis day, median (25-75 p)	3 (3-9)	3 (1-7)	0.60
Duration of hospitalization (day), median (25-75 p)	56 (27.5-72.25)	58 (28-110)	0.20
Antibiotic prophylaxis, n (%)	39 (67.2)	27 (65.9)	1
Total UVC days, (n)	362	237	
Duration of UVCs (day), median (25-75 p)	6 (4-8)	5 (3-8)	0.20
CABSIs, n (%)	1 (1.7)	1 (2.4)	1
CABSIs rate (/1000 catheter days)	2.8	4.2	0.79
Mortality, n (%)	1 (1.7)	5 (12.2)	0.04

GA: Gestational age, BW: Birth weight, PROM: prolonged premature rupture of membranes, RDS: Respiratory distress syndrome, BPD: Bronchopulmonary dysplasia, IVH: Intraventricular hemorrhage, NEC: Necrotizing enterocolitis, ROP: Retinopathy of prematurity, UVC: Umbilical venous catheters, CABSIs: Catheter-associated bloodstream infection

## DISCUSSION

In the last decades, the survival rates of preterm infants increased with the use of exogenous surfactant, medical treatments, mechanical ventilation and invasive procedures performed in NICUs. This vulnerable group of infants have high risk for infections due to their immature immune system, invasive procedures, need for central catheters and long hospital stay. High rate of catheter insertion in these neonates makes them vulnerable to CABSIs which is associated with a higher risk of mortality and long-term neurodevelopmental impairment. This retrospective study is the second study in the literature performed on silver impregnated UVC and did not reveal any difference between the use of PU or AgION UVCs in terms of CABSIs in neonates. There is only one previous study reported in the literature with AgION UVCs, which is prospective and reported significant reduction in CABSIs, and the Cochrane review on antimicrobial-impregnated CVCs for the prevention of CABSIs in neonates enrolled only this study in their metaanalysis and concluded the data to be insufficient to guide clinical practice (15,28).

CABSIs are defined as the presence of a bacteria or a fungus in one or more blood cultures obtained from a symptomatic neonate after two days of insertion of a central catheter or within a 48-hour period after the removal of the catheter (11,29). However, the sepsis evaluations that are done due to the relevant clinical signs may reveal negative blood culture results in some neonates and this entity is referred as 'clinical sepsis'. False negative blood culture results are often acquired due to the small blood volumes obtained from the neonates. In the present study we defined CABSIs as clinical, hematological and infective marker abnormalities suggesting any new onset or worsening sepsis 48 hours after removal of a UVC with a positive blood culture. In addition, we defined clinical sepsis as the infant manifesting signs consistent with infection together with laboratory findings however, without a positive blood culture. Though the incidence of CABSIs varies between units, no unit is CABSIs free. CABSIs can occur in 13-20% of catheterized neonates varying according to the duration of UVC days; in shorter kept ones the incidence is lower (27). Turkish Neonatal Society Nosocomial Infections Study Group reported CABSIs incidence ranging between 0 to 15.7% in 6 different centers in Turkey (30). In our study, UVC related sepsis rate was 2% which was less than the average reported figures in the literature.

In VLBW infants, UVCs are commonly first choice for vascular access. However, after a median period of 5 days, the rate of late onset sepsis increases which results in the removal of UVC (5,14,31). In this study, the median duration of UVC day was 6 and 5 days in the control and the study groups, respectively. As secure venous access is crucial for the preterm infants after the removal of UVC, frequently used alternative venous access is PICC which have a longer dwelling time, considered cost effective and equally safe (5,32-34). Therefore, we preferred to insert UVC followed by PICC. Moreover, we believe that the low infection rates in our unit is due to the removal UVCs early,

the replacement of UVCs with PICCs when necessary, the regular UVC care, the early enteral feeding protocol with short term use of TPN and rapid access to full-enteral feeding.

PU catheters are widely used biomedical materials as they are less prone to microbial colonization and they have smooth hydrophilic surface that reduces the adherence of bacteria. However, they do not have antimicrobial properties and cannot actively prevent CABSIs (15,35). The antimicrobial properties of silver-impregnated catheters occur via silver zeolites and are used as an ion exchanging matrix. They slowly release silver ions in exchange for sodium ions from the blood. The silver ions diffuse the outer and inner surface of the catheter providing protection against bacteria and fungus for the whole duration of catheterization (15,16). Silver-impregnated catheter insertion was reported to lead to a significant reduction in CABSIs in adult kidney transplant patients (35). Additionally, there are studies showing that CVC containing silver reduces the incidence of colonization and the risk of CABSIs in adult patients (36,37). However, there is also a study demonstrating no significant effect of the use of silver-impregnated CVCs among adult patients on CABSIs, colonization or mortality (16). In pediatric patients, the studies also yielded controversial results. Carbon and colleagues conducted a prospective, randomized comparative study of silver-impregnated versus silicon CVCs in 41 pediatric patients and reported that the rate of catheter infections can be fundamentally reduced by using a silver-impregnated CVCs (38). In 2008, Gilbert et al (39) reviewed 37 randomized controlled trials involving 11586 patients. Among these studies, seven of them compared silver-impregnated and standard CVCs and they concluded that there is no evidence that silver impregnation reduces colonization. Whereas reduction in the CABSIs incidence was reported in three studies including heparin-coated CVCs and seven studies including antibiotic-impregnated CVCs. In the literature there is a paucity of data regarding the use of antimicrobial-impregnated UVCs in neonates. There is a multicenter randomized controlled trial enrolling 861 neonates which reported no evidence or harm due to the insertion of miconazole and rifampicin impregnated PICCs when compared with standard PICCs (40). To the best of our knowledge, there is only one clinical trial regarding the use of silver-impregnated UVCs in neonates which is a randomized controlled trial performed by Bertini and colleagues. They conducted a study with 86 infants, 41 of whom received the AgION UVC and 45 PU UVC. They showed that 2% of infants in the AgION UVC group developed CABSIs in comparison with 22% of infants in the PU UVC group and the incidence density were 2.1 vs 25.8/1000 catheter days ( $p < 0.001$ ).<sup>15</sup> The incidence of CABSIs observed in PU UVC group (22%) was much higher than the incidence observed in both groups of our study (1.7% and 2.8/1000 catheter days vs 2.4% and 4.2/1000 catheter days in the control and study groups respectively). The CABSIs rate of AgION UVC group in that study was similar to our whole group. In the present study, there was no statistically significant difference between

the study and the control groups as only 2 infants, one in each group, had CABSİ. In addition, the present study is the first and only one which was conducted in Turkey.

In the present study, only two parameters differed significantly between the two groups. The first one was the intubation duration day ( $P=0.001$ ) and the second one was the mortality rate ( $P=0.04$ ). However, we believe that these differences had no impact on the results of this study and none of the patients died due to the complications of the UVC. Our primary output measurement was to determine CABSİ however due to the low rates of sepsis, we did not find statistically significant difference between study and control groups.

## LIMITATIONS

The major limitation of this study was its retrospective design including neonates in two different time periods without any randomization. However, as the policy and the quality of patient care in our institution was the same in both periods of time, we believe that having control and study groups from different time periods did not influence our results. Another limitation is the small sample size and low sepsis incidence in our unit. As only two neonates had culture proven sepsis, we cannot make any strict conclusion about the impact of silver-impregnated UVC on the incidence of sepsis in our study.

## CONCLUSION

In conclusion, if all the precautions to prevent CABSİ due to UVC are taken in a unit, the incidence of CABSİ will be low regardless of the content of the catheter. In a unit with low incidence of sepsis, antimicrobial-impregnated catheters may have no effect in further reduction of CABSİ. Therefore, routine use of these catheters cannot be recommended in every NICU. However, they can be beneficial in units where CABSİ incidences are higher. We recommend conducting randomized controlled large sample sized multicenter studies for the further evaluation of the impact of different types of the UVCs on CABSİ in newborn patient population where cost effectiveness of these catheters is also evaluated.

*Competing Interests: The authors declare that they have no competing interest.*

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*Ethical Approval: The study was approved by Koc University School of Medicine Clinical Research Ethics Committee (Ref. Number: 2020.490. IRB1.180).*

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