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Effects of blood flow on the antibacterial efficacy of chlorhexidine and silver sulfadiazine coated central venous catheter

A simulation-based pilot study

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Abstract

Background: Chlorhexidine and silver sulfadiazine coated central venous catheters (CSS-CVC) may cause loss of antimicrobial efficacy due to friction between the CVC surface and sheer stress caused by the blood flow. Therefore, the aim of this study was to investigate the antibacterial efficacy of CSS-CVC at various flow rates using a bloodstream model.

Methods: Each CVC was subjected to various flow rates (0.5, 1, 2, and 4 L/min) and wear-out times (0, 24, 48, 72, 96, and 120 hours), and the optical density (OD) 600 after a *Staphylococcus aureus* incubation test was used to determine the antibacterial effect of CSS-CVC.

Results: In the 0.5 L/min group, there was no significant change in the OD600 value up to 120 hours compared with the baseline OD600 value for CSS-CVC ($P > .467$). However, the OD600 values of CSS-CVC in the 1 L/min ($P < .001$) and 2 L/min ($P < .001$) groups were significantly reduced up to 72 hours, while that in the 4 L/min ($p < 0.001$) group decreased rapidly up to 48 hours.

Conclusion: This study suggests that there is a doubt whether sufficient antibacterial function can be maintained with prolonged duration of catheter placement.

Abbreviations: CRBI = central venous catheter-related bloodstream infection, CSS = chlorhexidine and silver sulfadiazine, CVC = central venous catheters, LB = lysogeny broth, OD = optimal density, PBS = phosphate buffer solution.

Keywords: antibacterial activity, bloodstream model, catheter-related bloodstream infection, central venous catheters

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YHC and YJC contributed equally to this work.

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The authors declare that they have no conflict of interest.

The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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1. Introduction

Central venous catheters (CVCs) play important roles in the treatment of critical patients by providing intravenous access for resuscitation, emergency and major surgery patients, treatment, and perioperative nutritional support.[1] CVCs are currently used in clinical trials for the rapid rehydration of blood volume deficiency, monitoring of heart failure, cardiovascular surgery, and in clinically ill patients for the administration of vasoactive drugs.

Despite their main benefits, CVCs also have serious complications. Unfortunately, according to previous research, the incidence of side effects from the use of CVCs is 15%, and the prevalence of catheter-related infection is 5% to 26%.[2] Colonization of organisms in the patient's skin or catheter hubs or ports, due to problems such as inflow into the blood vessels during catheter insertion and postcatheter care, can cause catheter-associated infections.[3–5] Colonization of CVC and subsequent bloodstream infection are closely related to the duration of CVC use.[6] Saint et al[7] showed that if standard, especially uncoated, CVC catheters are placed for more than 8 days, 25% of patients will develop catheter colonization, and approximately 5% of these patients will develop bloodstream infection. In addition, the main cause of bloodstream infection in hospitals is CVC-related bloodstream infection (CRBI), which is known to occur during long-term use of CVCs.[8] CRBIs affect the disease severity and in-hospital mortality, increase the economic burden due to increase in the length of hospital stay, and increase the incidence of resistant bacteria due to the increased use of antibiotics.[8,9]

Considerable efforts have been made to reduce the incidence of CRBIs; aside from maximal sterilization and proper skin disinfection, these include the use of antibiotic/disinfectant-coated catheters, suture-free devices, hand hygiene, and the application of central venous bundles. Furthermore, the invention of antibiotic-coated CVCs has significantly reduced catheter-related infections.[3,6,10] Thus, the Centers for Disease Control and Prevention guidelines recommend the use of antibiotic/disinfectant-coated catheters if CRBIs are not reduced despite all other efforts, and if they are expected to last 5 days or more.[11] However, the efficacy of central vein catheters coated with chlorhexidine and silver sulfadiazine (CSS-CVC) remains controversial. One study found that the risk of catheter-related infection with CSS-CVCs was one-fifth lower than that of standard CVC.[12] Similarly, a meta-analysis showed that the incidence of colonization and CVC-related bloodstream infections was reduced in patients with CSS-CVC.[13] However, another study reported that in critical patients, silver-coated CVCs did not reduce colonization compared with standard CVCs.[14]

We previously reported a prospective laboratory-and-clinical pilot study that aimed to investigate the antimicrobial effects of CSS-CVCs compared with standard polyurethane CVCs and antibiotic (minocycline/rifampin)-impregnated CVCs over time.[15] We demonstrated that the efficacy of CSS-CVCs decreased over time, and that the antibacterial capacity can be lost within 48 hours of simulated wear-out. We concluded that CSS-CVCs may be safely and continuously used in veins for up to 48 hours, but that antibiotic-impregnated CVCs may be a better option when longer (> 48 hours) indwelling is needed.

Nonetheless, our previous study had limitations. We choose the flow rate in the circuit as 5.6 L/min to reflect the cardiac output[16]; however, considering that less than half of the cardiac output returns via the SVC, where most CVCs are placed, it would be safe to assume that the laboratory setting of flow and velocity was more than twice than that of normal human conditions, which may have exaggerated the results. We hypothesized that the coating on the CVC would peel off due to friction between the saline and catheter even at low cardiac output status. Thus, the purpose of this study was to determine whether the antimicrobial effect of CSS-CVC decreases over time under various cardiac outputs using a bloodstream model.

2. Materials and methods

2.1. Central venous catheters

An overview of the experimental study design is shown in Fig. 1. A total of 5 standard CVCs (ARROW; Arrow International, Inc) and 105 CSS-CVCs (ARROWg+ard Blue; Arrow International, Inc) that is the first generation of the chlorhexidine-based antiseptic catheter (impregnated only outside) were used in this study. Among them, 100 CSS-CVCs were exposed to saline using a bloodstream model as the experimental group, and 5 CSS-CVCs and 5 standard CVCs were removed immediately after insertion into the bloodstream model in order to prevent exposure to flowing saline.

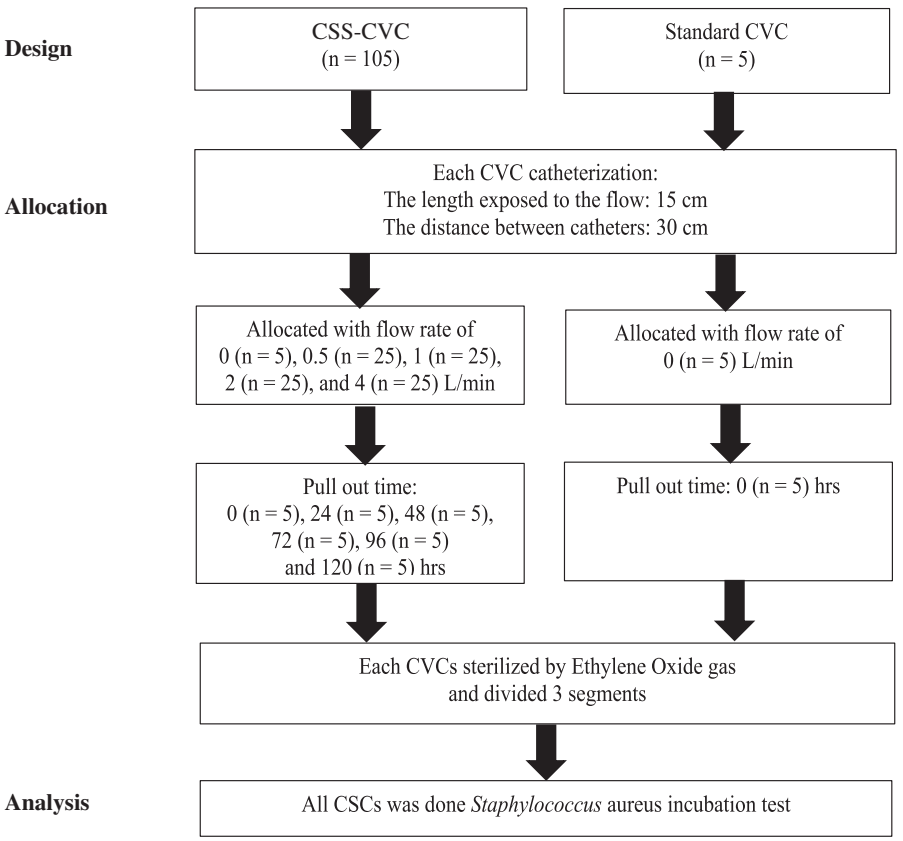

Figure 1. Study flow diagram for the evaluation of the antiseptic activity of CSS-CVC. CSS-CVC = central vein catheter coated with chlorhexidine and silver sulfadiazine.

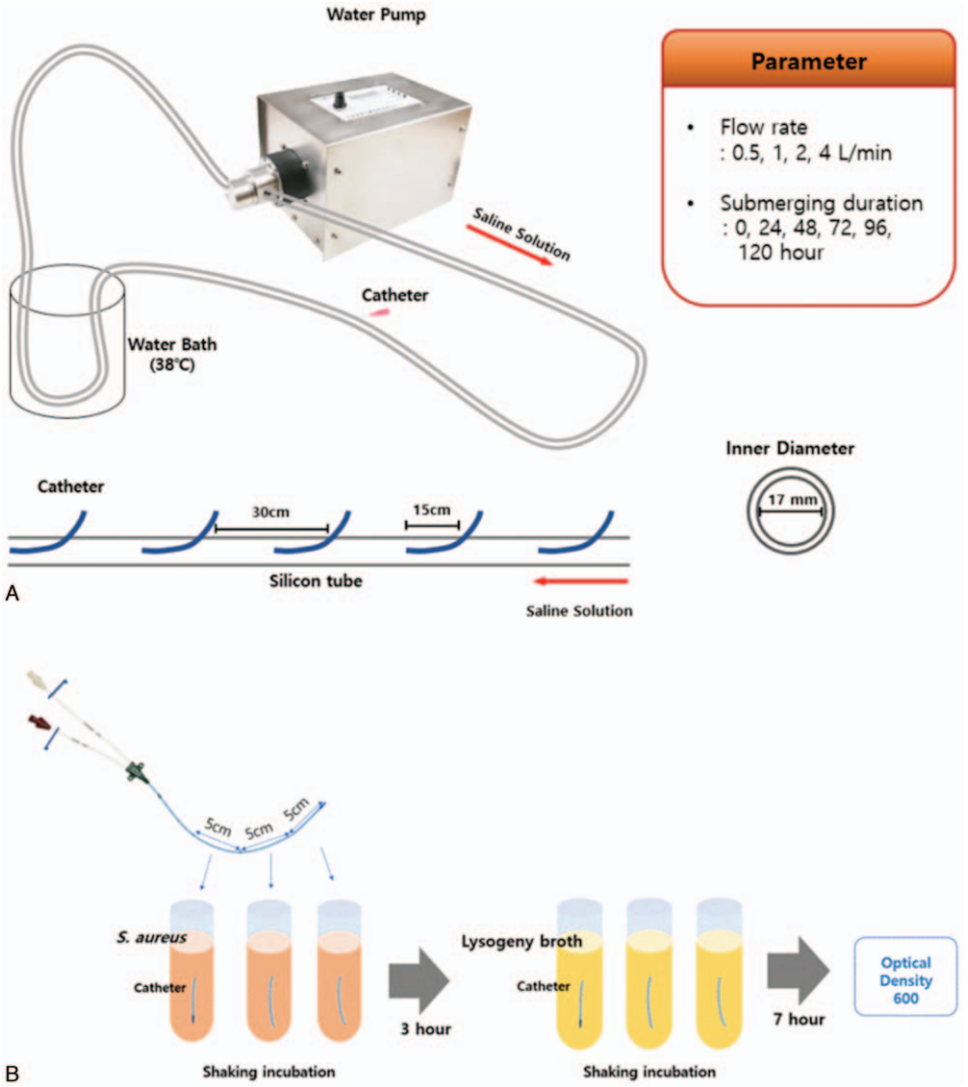

Figure 2. Study design. (A) Bloodstream model. The bloodstream model involved a water pump, silicon tube, and water bath. (B) *Staphylococcus aureus* incubation test. The portion of the catheter exposed to saline was divided into 3 parts, and each part was incubated for 3 h in *Staphylococcus aureus* colloid. After physical washing, the catheters were incubated for 7 h in lysogeny broth and the OD600 value was measured.

2.2. Study design

This study did not require approval from an ethics committee or institutional review board and also did not require patient consent because it was not about humans, animals, or human derivatives. The design of the bloodstream model is shown in Fig. 2A and was developed using a circulating water pump (MG317XKWBS; Nanjing Oerlik Pump & Valve Co., Ltd., China), silicon tubing (Korea Ace Scientific, Korea), and normal saline [isotonic sodium chloride (IR) injection; JW Pharmaceutical, Korea]. The magnetic drive gear pump was connected to a silicone tube filled with sterile saline solution, and part of the tube was placed in a hot water tank (CW-05G; Lab Companion, South Korea) and heated to 38°C to create an environment similar to human body temperature (Fig. 3A). The pump flow rates for each experimental group were set at 0.5, 1, 2, and 4 L/min (N = 25 for each flow rate). The saline solution was changed 10 times, once every 12 hours, in order to reduce the risk of contamination; the saline solution was exchanged through the machine without affecting the saline flow rate.

The length of the silicone tube was 5 m with an inner diameter of 17 mm. The inside and outside of the silicone tube was sterilized before the experiment; the outside of the silicone tube was sterilized with HEXANE Solution (chlorhexidine gluconate 2% and isopropanol 70%) and the inside was sterilized with 70% alcohol. After sterilization, saline was irrigated through the inside and outside of the silicone tube and the CVCs were inserted into the silicone tube (Fig. 3B). The length of the CVC inserted into the silicone tube in the blood flow model was 15 cm, and the distance between the CVCs was 30 cm, which was twice the length of the insertion. The saline solution was advanced through the silicon tube for 120 hours using a water pump. The inserted CVCs had 24, 48, 72, 96, and 120 hours of exposure time in flowing saline (n = 5), and were sterilized with ethylene oxide gas. The sterile CVC exposed to normal saline was divided into 3 parts (5 cm each).

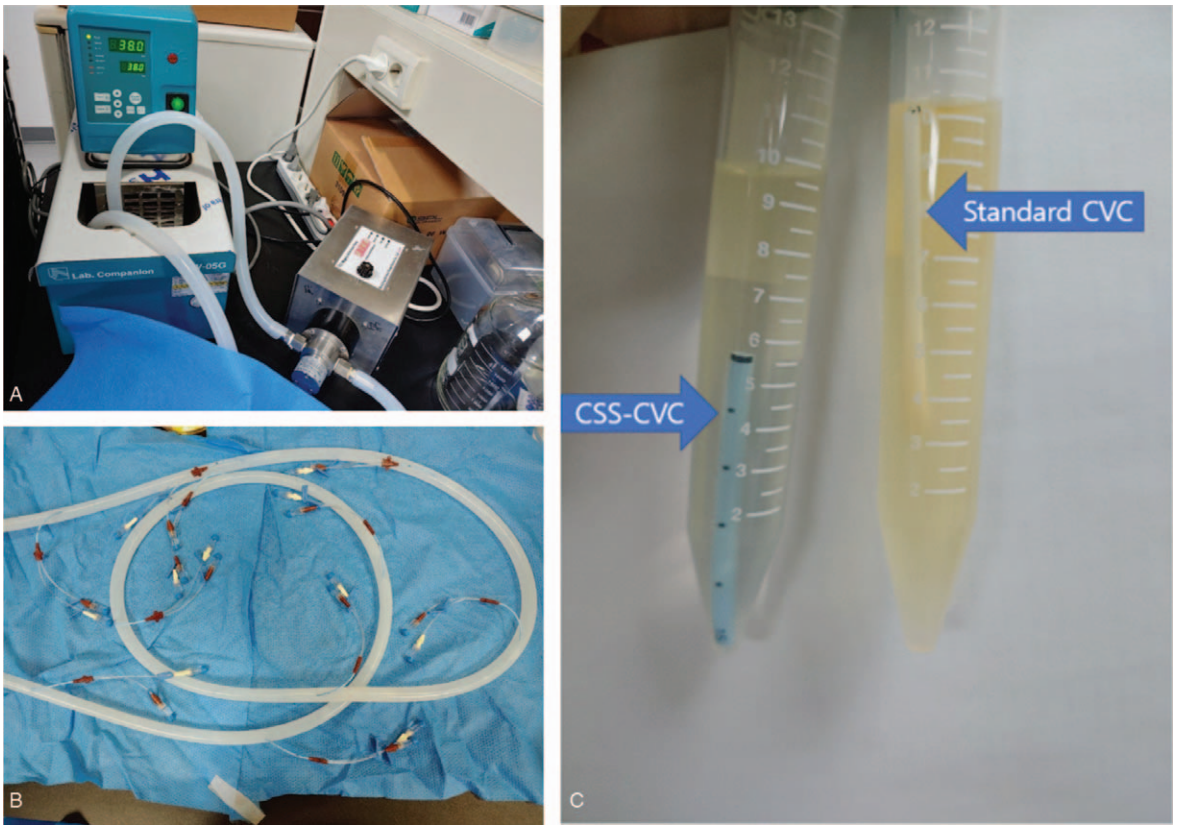

Figure 3. Experimental settings and instruments. (A) Water pump (MG317XKWBS; Nanjing Oerlik Pump & Valve Co., Ltd., China) and water bath (CW-05G; Lab Companion, South Korea). (B) The central venous catheter placed in a silicone tube. (C) CVC catheters in pure lysogeny broth. CSS-CVC = central vein catheter coated with chlorhexidine and silver sulfadiazine.

2.3. Design of the in vitro culture test for evaluating antimicrobial activity

The *S. aureus* colloid incubation test was performed in the following 3 steps (Fig. 2B):

(1) First culture: Culturing the worn CVC in *S. aureus* colloid for 3 hours.
(2) Physical cleaning: Washing the cultured CVC in phosphate buffer solution (PBS) 3 times.
(3) Second culture: Culturing the washed CVC in pure lysogeny broth (LB).

Each portion of the CVC was incubated with 10 mL of *S. aureus* colloid in a 15 mL conical tube for 3 hours. Subsequently, each part of the CVC was physically washed with PBS. Before the third step, conical tubes were sterilized and filled with 15 mL sterilized LB. Each PBS-cleaned segment was immersed in one of the prepared LB aliquots and incubated for a further 7 hours on a shaking incubator. During the incubation, the optical density of samples (1 mL) from each tube was measured at 4 different time points. The samples were removed by pipetting after 4, 5, 6, and 7 hours, and the optical density was measured by OD600 (optimal density) using a microscopic spectrophotometer (Nanodrop One. Thermo Fisher Scientific) (Fig. 3C).

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, New York), and all results were expressed as mean ± standard deviation.

The differences in the OD values of CVCs exposed to normal saline over time in the bloodstream model at the same flow rate were analyzed using the Kruskal–Wallis Test. The P value was $< .05$ for each flow rate, and the OD value was statistically significant according to the time exposed to the saline flowing at the same flow rate. Therefore, Mann–Whitney U test was conducted. The false discovery rate method was applied to the 21 pairs of multiple comparisons and the results were considered statistically significant when $P < .05$.

The differences in the OD values of CVCs exposed to normal saline according to the flow rate at the same time were analyzed using the Kruskal–Wallis Test. The P value was $< .05$ for each timepoint, and the OD value was statistically significant according to the flow rate of saline in the bloodstream model at the same time. Therefore, Mann–Whitney U test was conducted. The false discovery rate method was applied to the 6 pairs of multiple comparisons and the results were considered statistically significant when $P < .05$.

3. Results

The baseline OD600 values were 0.05 ± 0.02 (CSS-CVC, not exposed to saline flow) and 0.81 ± 0.13 (standard CVC). Figure 4 shows the changes in OD values across various flow rates of the bloodstream model over time. Figure 4A demonstrates the results from comparison with the baseline and previous timepoint. Initially, each group (0.5, 1, 2, and 4 L/min of the bloodstream

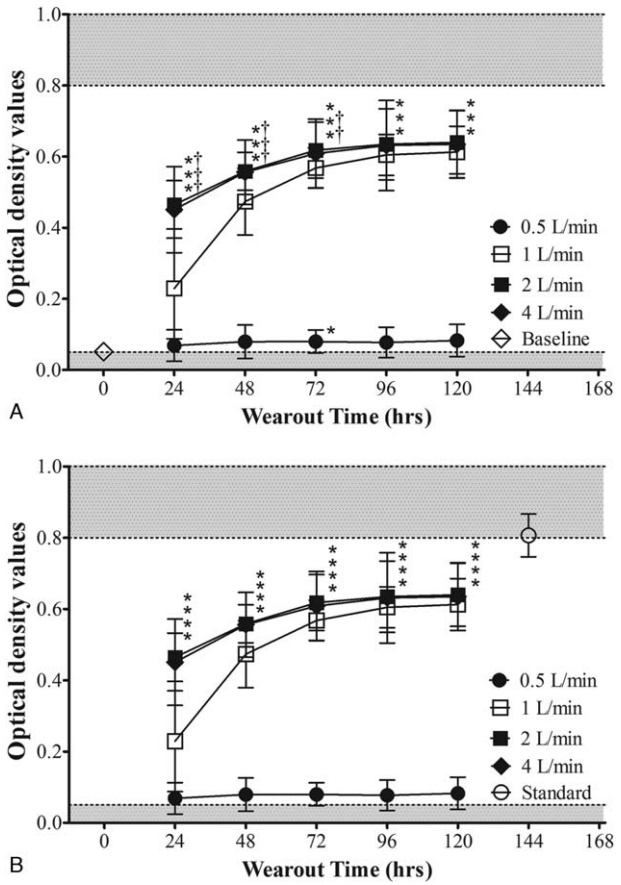

Figure 4. Optical density (OD) of standard CVC or CSS-CVC in the lysogeny broth over time. A. OD600 of CVC at baseline and at flow rates of 0.5, 1, 2, and 4 L/min. $^{*}P > .05$ vs baseline, $^{\dagger}P > .05$ vs previous time. (B) OD600 of CVC at a flow rate of 0.5, 1, 2, and 4 L/min and standard CVCs. $^{*}P > .05$ vs standard CVC. CSS-CVC = central vein catheter coated with chlorhexidine and silver sulfadiazine.

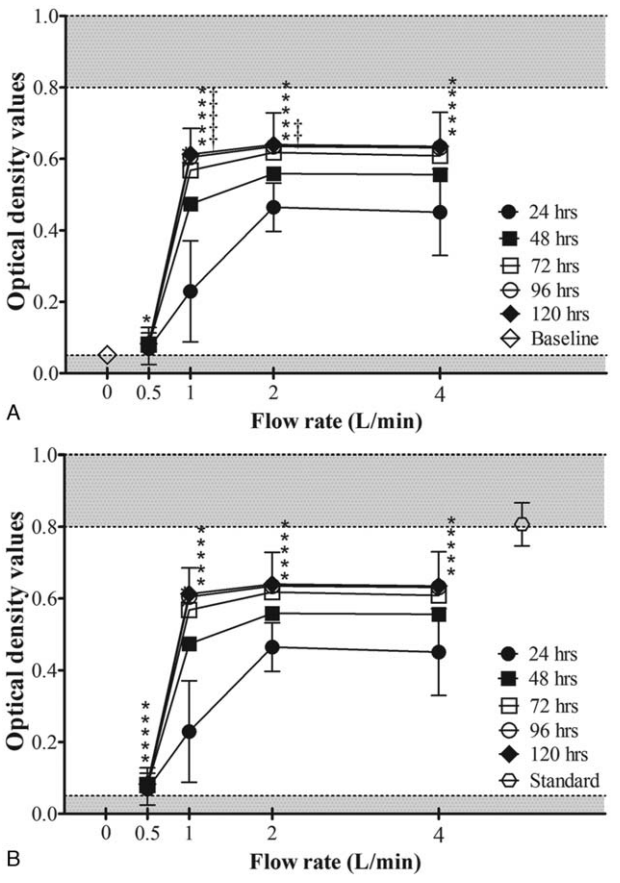

Figure 5. Optical density (OD) of standard CVC or CSS-CVC in the lysogeny broth according to flow rate. (A) OD600 of CVC at baseline and at 24, 48, 72, 96, and 120 h. $^{*}P > .05$ vs baseline, $^{\dagger}P > .05$ vs previous time. (B) OD600 of CVC at 24, 48, 72, 96, and 120 h, and standard CVC. $^{*}P > .05$ vs standard CVC. CSS-CVC = Central vein catheter coated with chlorhexidine and silver sulfadiazine.

model) was compared with the OD value of the baseline. In the 0.5 L/min group, the OD values at each time point (up to 120 hours) were not statistically different from the baseline OD value ($P > .467$), with the exception of the OD value at 72 hours ($P = .012$). The OD values of the 1 and 2 L/min groups were statistically higher than the baseline OD value at every time point up to 120 hours ($P < .001$). The OD value of the 1 and 2 L/min groups up to 72 hours was different from the previous time points ($P < .038$), but there were no significant differences in the OD values of the 1 and 2 L/min groups at 72, 96, and 120 hours ($P > .050$). The OD values of the 4 L/min group were statistically higher than the baseline OD value at every time point (up to 120 hours, $P < .001$). Although the OD value of the 4 L/min group up to 48 hours was different from the previous time points ($P < .023$), there were no significant differences in the OD values of the 4 L/min group at 48, 72, 96, and 120 hours ($P > .173$). Figure 4B shows the results of comparison with the standard CVC; at all flow rates (0.5, 1, 2, and 4 L/min groups), the OD values over time were lower than those of the standard CVC ($P < .001$).

Figure 5 shows the changes in OD values at various timepoints depending on the flow rates of the bloodstream model. Figure 5A demonstrates the results from comparison with the baseline and previous time point. Each group (24, 48, 72, 96, and 120 hours) was compared with the OD value at baseline. In the 1, 2, and 4 L/min bloodstream model groups, the OD values over time were higher than those of baseline ($P < .001$). However, in the 0.5 L/min group, the OD value at every timepoint up to 120 hours was not statistically different from the baseline OD value ($P > .060$), with the exception of the OD value of 72 hours ($P = .012$). The OD values of the 1 L/min group at each time point were statistically higher than those of 0.5 L/min group. The OD values of the 2 L/min group at 24 and 48 hours were statistically higher than those of the 1 L/min of the bloodstream model at 24 and 48 hours ($P < .014$). However, there were no significant differences in the OD values at all timepoints measured in the 2 L/min and 4 L/min groups ($P > .653$). Figure 5B shows the results from comparison with the standard CVC; at all flows (0.5, 1, 2, and 4 L/min groups), the OD values over time were lower than those of the standard CVC ($P < .001$).

4. Discussion

We demonstrated the changes in antimicrobial effects of CSS-CVC according to the exposure time in a bloodstream model simulating various cardiac output status. Our results showed that

the antimicrobial effect of CSS-CVCs in low cardiac output status (0.5 L/min group) was maintained for up to 120 hours. However, the antimicrobial effect of CSS-CVCs in normal or higher cardiac output status (1, 2, and 4 L/min groups) significantly decreased within 72 hours.

Coating the CVC with CSS represents one approach for the prevention of catheter-related infections. Chlorhexidine on the outer surface of CSS-CVC is an antibacterial agent commonly used for wound irrigation or skin disinfection, while silver sulfadiazine is commonly used as an effective bactericide and fungicide.[15] Moreover, Ag nanoparticle coatings slowly release Ag ions with specific antimicrobial activity against gram-positive, gram-negative, and Candida bacteria.[17,18] Ag ions exert antimicrobial activity by preventing bacterial surface adhesion, proliferation, and biofilm formation.[19] In our study, chlorhexidine and silver sulfadiazine-coated CVC, which did not lead to wear on the bloodstream model, had antimicrobial activity. However, the antimicrobial effect of CSS-CVC was found to decrease according to the saline flow exposure time.

We evaluated the antimicrobial activity of CVC using the OD600 value. A standard spectrophotometer to measure the OD that is directly related to biomass is a low-cost, rapid, and nondestructive method for assessing microbial growth and the cell or biomass concentration.[15,20] The OD600 application is used to monitor the growth rate of bacterial or other microbial cell cultures by measuring the optical density (absorbance) of the culture in growth media at 600 nm. *S. aureus* was selected as a study microorganism because it is one of the most frequently found microorganism in infection sites in clinical settings.[3,4,21] Furthermore, it forms a colloid when it is cultured in LB, a nutritionally rich medium, as a badge for *S. aureus*. Because the number of particles in colloidal solution is linearly proportional to the optical absorption density, the OD value can be regarded as a method of expressing the number of bacteria at any time after incubation compared with the initial value.[15]

Our previous simulation-based study showed that the antibacterial function of CSS-CVCs decreased with the duration of catheter placement. However, the previous study had a limitation in that it involved an excessive cardiac output set at 5.6 L/min. Therefore, in the present study, various cardiac outputs were used to confirm the maintenance of antimicrobial activity, and at flow rates above 1 L/min, the antimicrobial activity decreased significantly after 24 hours. In particular, the antimicrobial activity decrease appeared to occur in proportion to the flow rate up to 24 hours, and similar decreases in antimicrobial activity were observed at flow rates of 1 L/min and above for 48 hours. In this study, the OD600 value of CSS-CVCs that were not exposed to the saline flow of the bloodstream model, was 0.05 ± 0.02, and also demonstrated antimicrobial activity. However, the antimicrobial action of CSS-CVCs decreased rapidly in the bloodstream model with a flow rate over 1 L/min. The higher the flow rate, the faster the antimicrobial action was lost. Up to 24 hours, the antimicrobial activity decreased in proportion to the flow rate of the bloodstream model, and over 48 hours, a similar decrease in antimicrobial activity was observed at flow rates above 1 L/min. The ultimate purpose of an impregnated CVC must be to lower the incidence of CRBI, rather than only reducing the catheter colonization rate. This study did not demonstrate a beneficial effect of the dip catheter on the CRBI rate, only the reduced colonization rate associated with the dip catheter.

This study has a number of limitations. We simulated the blood flow model with saline, and although osmotic pressure in human blood is similar to that of normal saline, the viscosity is about 4 cP at 37°C, which is 4 times that of water/physiological saline.[22] If fluids with high viscosities circulated in the circuit, the antimicrobial activity may disappear faster, even at low cardiac output. Furthermore, the composition of a human's blood is more complex than saline. Although the osmotic pressures of saline and blood are similar, but there is a big difference in viscosity of the 2 solutions, future studies should consider creating a model with a blood mimicking solution. In addition, future animal studies should be considered to confirm the clinical implications of these findings as to how the coating is achieved over the catheter surface and what is the average thickness of the coating material per square mm of the catheter surface.

In conclusion, our findings suggest that there is doubt as to whether the antimicrobial activity of CSS-CVC persists after 24 hours under normal cardiac output. The clinical implications of our results should be considered in subsequent clinical trials.

Author contributions

All authors contributed equally to the preparation of the manuscript, tables, and figures.

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Writing – review & editing: Yong Huan Cui, Yoon Ji Choi, Joon Ho Yu, Sung-uk Choi, Seung Zhoo Yoon.

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