Evaluation of central venous catheters coated with a noble metal alloy—A randomized clinical pilot study of coating durability, performance and tolerability

Gunilla Björling,[1,2] Dorota Johansson,[3] Linda Bergström,[3] Anton Strekalovsky,[4] Javier Sanchez,[2,3] Claes Frostell,[2] Sigridur Kalman[4,5]

[1]The Swedish Red Cross University College, Stockholm, Sweden
[2]Danderyd Hospital, Division of Anaesthesia and Intensive Care, Department of Clinical Sciences, Karolinska Institutet, Stockholm, Sweden
[3]Bactiguard® AB, Stockholm, Sweden, Sweden
[4]Department Anesthesia and Intensive Care, Karolinska University Hospital Huddinge, Stockholm, Sweden
[5]CLINTEC, Karolinska Institutet, Stockholm, Sweden

Abstract: The use of Central Venous Catheters (CVCs) commonly results in complications. Coatings with silver or metal alloys can reduce the risk associated with the use of CVC. We have evaluated the durability of a noble metal coated CVC (the Bactiguard Infectious Protection, BIP CVC) and compared with an uncoated CVC for clinical tolerability (Adverse Events, AEs) and performance, in order to create a baseline for a large future study. Patients undergoing major surgery, randomised at a 2:1 ratio to BIP CVC (n = 22) or standard CVC (n = 12), were catheterized 9 - 12 days, respectively. Adverse events, microbial colonization and metal release were measured.

Findings: There were no AEs in the BIP CVC-group, but 5 AEs occurred in 4 patients (1 patient had 2 AEs) in the standard CVC-group, p = 0.011 (whereof 3 were catheter related). The BIP CVC showed an initial release of coating metals in blood (gold, silver and palladium), which rapidly decreased and were far below Permitted Paily Exposure (PDE) for chronical use. The levels of silver concentration were far below those needed to develop microbial resistance. The performance was equal, and there was no difference concerning microbial colonization, for the two CVCs.

Conclusion: In this pilot study the BIP CVC had significantly lower AEs and showed a comparable performance to the standard CVC. The coating was durable throughout the study length (up to 16 days) and toxicological evaluation showed good safety margins. Larger studies are needed. © 2017 Wiley Periodicals, Inc. J Biomed Mater Res Part B: Appl Biomater 106B:2337–2344, 2018.

Key Words: central venous catheter, tolerability, performance, colonization, noble metal alloy coating

INTRODUCTION

Catheter related bloodstream infections (CRBSI) are associated with high morbidity and mortality.[1–3] The World Health Organisation (WHO) reported[4] that CRBSI occur in 2.5/1000 catheter days in the USA and even higher, 3.5/1000 catheter days, in high-income countries together. The rates of CRBSI in publications from 1992 to 2005 reviewed by Wassil et al.[5] vary between 2 and 9/1000 catheter days and 2–29%, depending on the patient group and catheterization time. Another common adverse event (AE), related to the use of vascular catheters, is thrombosis, which occurs at rates of approximately 5–10%, also depending on the study population and catheterization time.[6–8]

In the vast majority of patients, the same microorganisms that cause the infection also colonize the surface of the medical device.[9,10] In order to prevent this, a variety of antimicrobial agents, such as antiseptics or antibiotics, coated onto or incorporated into the catheter polymer material, have been developed.[11] The Bactiguard® coating consists of a thin noble metal alloy of gold, silver, and palladium, firmly attached to the surface, which reduces microbial adhesion and colonization[12] and thereby prevents infections. Other common coated central venous catheter (CVCs) on the market have proven effective to reduce infections,[13,14] but in contrast to the Bactiguard coating, they release antimicrobial agents such as antibiotics, chlorhexidine, and/or silver ions, which kill microbes. The released substances, when

Correspondence to: G. Björling; e-mail: gunilla.bjorling@ki.se

present at concentrations over the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), or minimum selective concentration (MSC), will trigger antimicrobial resistance.[15] MSC is the lowest sub-MIC concentration that may result in the selection of a resistant mutant in case of constant/chronical exposure.[16] The released substances will also spread in the human body and may cause harm to human cells, resulting in, for example, hemolysis or inflammatory responses,[17] and in extreme cases even lead to allergic reactions, including anaphylactic schock.[18,19] Thus, a nonreleasing, durable coating has potential advantages over releasing coatings, regarding better safety profile, lower risk to develop resistance, as well as a more long-lasting effect.

The effectiveness of the Bactiguard coating has been evaluated for indwelling urinary tract catheters, endotracheal tubes, and CVCs in clinical use. The coating has indicated a reduction of device-related bacteriuria and infections by 32–73%, without an increased risk for the patient.[20–22] The use of Bactiguard coated catheters could result in decreased antibiotic usage and decreased costs for healthcare associated infections.[23–25] An early version of Bactiguard coated CVC has been previously studied in a randomized trial in the 1990s and showed reduction of catheter related infections by 52% ($p = 0.011$).[12]

In the present study, we aimed to evaluate the durability of the noble metal coating in blood (which has never been described before) and to evaluate tolerability and performance of the new version of Bactiguard infectious protection coated CVC, BIP CVC (see Figure 1) and compare it to a standard uncoated CVC to create a baseline for the large future study. The coating in the BIP CVC is identical to the coating in the early version of Bactiguard coated CVC mentioned above, but the underlying catheters come from different manufacturers (both made of polyurethane). We also aimed to describe the microbial catheter colonization of the devices, as a potential surrogate endpoint for clinical outcome. No sample size calculation was performed.

METHODS
Study design
This was a single-center, randomized, single-blinded, controlled, first in man, post European Certification, and Conformité Européenne (CE) marking study of tolerability and performance of the BIP CVC. The study was conducted at a tertiary university hospital in Sweden, and was approved by the Independent Ethics Committee in Stockholm, Sweden (permit no. 2013/622–31/4) and filed as National Clinical Trials (NCT)02811380 in clinicaltrials.gov. Informed consent was obtained from all patients.

Investigational device
The BIP CVC is a polyurethane catheter with very low amounts of the noble metals gold, silver, and palladium on the outside of the catheter. In the study, 7 Fr, 2 lumen, and 20 cm long CVCs were used. The BIP CVC, is an EC certified/CE marked device, which is intended for use in adults and children for up to 30 days.
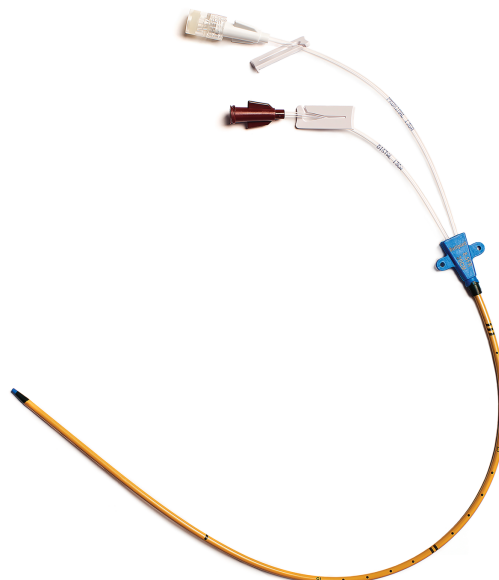
FIGURE 1. A picture of the Bactiguard CVC, BIP-CVC two lumen.

Standard device
A corresponding standard, uncoated CVC (Biosensors International CVC, Biosensors International Group Ltd., Netherlands) of the same size was used as a reference device. The standard CVC devices were 7 Fr, 2 lumen, 20 cm long and were made of polyurethane.

Study population
The following inclusion criteria were applied for participation in the present study: Adult men and women ≥18 years of age; requiring a CVC device for venous access, preferably through right or otherwise left jugular or subclavian veins, during and after elective abdominal surgery such as pancreas resection planned for at least 3 days, and had signed the informed consent. Exclusion criteria were: known transmissive blood disease, known multiresistant microbial colonization, ongoing infection, thromboembolism, anticoagulation treatment excluding prophylaxis, a CVC placed during the last 2 months, history of problems with a CVC, or pregnancy.

Objectives and endpoints
Our primary objective was to determine the tolerability of the medical device BIP CVC compared to the corresponding standard uncoated CVC. Primary endpoints were AEs and serious adverse events (SAEs), which were further divided into adverse device effects (ADEs) and serious ADEs (SADEs). Examples of AEs are sepsis and local infections, thrombotic events, such as pulmonary embolism or local thrombotic phlebitis as well as any other problems occurring during the postoperative course. Visual inspection of CVC insertion site was performed every day from the day of surgery until the day of removal of the CVC. Any findings from the inspections, for example, signs of infection, were noted as comments.

Our secondary objective was to assess the overall performance related to the medical device, based on CVC-related problems experienced by the physician/healthcare personnel.

The exploratory endpoints were coating metal analysis results from blood samples and on the CVC surface after clinical use. The microbial exploratory endpoint was colonization of the catheter, assessed by microbial culture on the CVC (quantification and typing), and blood culture with typing of a blood sample, drawn through the CVC just before its withdrawal.

Data collection

Patient's demographics, physical examination, medical history, and smoking habits were collected. Patients were electronically randomized to BIP CVC or to uncoated standard CVC at a 2:1 ratio. We aimed at randomizing 36 patients: 24 to BIP CVC and 12 to uncoated CVC.

Assessment of tolerability: AEs/ADEs (primary endpoint). Monitoring of the patients followed standard hospital routines. In addition, AEs/ADEs, including any problems in the postoperative course, judged by the physician or nurse, were recorded and inspections of the CVC insertion site were performed from the day of surgery until the day of removal of the CVC. If medically indicated, blood sampling for microbiological assessments (peripherally and via CVC) and X-ray or CT scan were performed.

All AEs were graded for severity, seriousness and relatedness to the medical device or to use of the device. The AEs graded by the investigator as related to the medical device were considered to be ADEs. For all AEs, the start and end dates, actions taken with the device, and outcome were recorded, as well as any medications or treatments given as a result of the AE. Examples of events that could be related to the use of CVC were phlebitis/local infection, symptomatic catheter related infections (including sepsis and septic shock) with positive blood culture (peripheral and via CVC), and clinical thrombosis (local or embolism).[26,27]

Any other problems during the postoperative course, for example, whether there were any CVC-related problems experienced by the physician/healthcare personnel, were documented. Inspections of the CVC and insertion site were performed and any findings from the inspections, that is, signs of infection, or issues related to the use of the CVC that were observed during the inspection, were documented.

Performance of the CVC (secondary endpoint). Performance of the CVC was assessed by documenting any CVC-related problems experienced by the physician/healthcare personnel (e.g., catheter occlusion, catheter dysfunction, catheter breakage, difficulties during insertion or removal, etc.).

Coating metal analysis in blood and on BIP CVC after clinical use (exploratory endpoint). Blood samples for analysis of traces of CVC-coating metals (gold, silver, and palladium) were taken immediately through the main lumen after CVC insertion, as well as 2 h, 20–26 h and 3 days after insertion. Whole blood (3 mL) was drawn in heparin tubes and sent to an accredited laboratory (ALS Scandinavia, Luleå, Sweden) for analysis using Inductively Couples Plasma Mass Spectrometry (ICP-MS). To assess coating

durability, analyses of BIP CVC coating metals (gold, silver, and palladium) were performed on catheters after patient use. Pieces of BIP CVCs were sent to ALS Scandinavia after use for determination of remaining surface concentration of coating metals using ICP-MS.[28] Unused BIP CVC of the same batch was analyzed as a control. The total surface area is approximately 15.1 cm^2. The results were compared to toxicological safety limits for chronical use for all metals and silver concentrations, which can cause microbial resistance.

Catheter and blood microbial colonization (exploratory endpoint). Microbial colonization of the CVCs was analyzed at the final visit based on cultures of blood samples, taken through the CVC (from either one of the two lumen) immediately before removal from the patient and cultures of samples taken from the CVC shortly after its removal on the CVC tip and on the subcutaneous insertion part, (approximately 3 cm) by sonication. The limit of detection (cut-off) for the surface colonization method has been estimated to 10 CFU/mL, corresponding to approximately 50 CFU/cm^2 on the surface. Any results important for the patient's health and well-being (e.g., the presence of pathogenic bacteria on the CVC after catheter removal) were documented.

Statistics

No sample size calculation was performed due to the exploratory nature of this study. The sample size of 30–40 was judged as suitable from a descriptive statistic point of view. The patient ratio 2:1 of BIP CVC to standard CVC was chosen in order to obtain more data on the coating durability.

All statistical analyses were performed, using SAS® version 9.3 (SAS Institute Inc., Cary, NC) and R (version 3.1.2). The tolerability analysis and performance analysis were performed on all patients who received a CVC using Fisher's exact test. Analysis of exploratory endpoints was performed on all patients who had a CVC for at least 3 days. In analyses, where a patient had more than one event, we assumed that the number of events a patient experienced came from a Poisson distribution. The hypothesis test was accordingly a test of the difference between two rates. The microbiological evaluations and metal analysis in whole blood were blinded, whereas the type of CVC was open for the patient, investigator, and study nurses. Time to removal of the catheter was analyzed by the Kaplan–Meier method and the Log-Rank test. A p values of <0.05 was considered significant.

RESULTS

Demographics, baseline conditions, concomitant medications, and CVC parameters

In total, 36 patients were randomized to BIP CVC ($n = 24$) or standard (uncoated) CVC ($n = 12$); 34 were included in the analysis and 33 completed the entire study. Demographics for the study groups did not differ, see Table I.

Physical examination and clinical signs. The baseline vital signs values were comparable between the treatment groups.

TABLE I. Demographics and Baseline Characteristics

		BIP CVC ($N = 22$)	Standard CVC ($N = 12$)	Total ($N = 34$)
Age	n/n_{miss}[a]	22/0	12/0	34/0
	Median (Min, Max)	67.5 (29, 80)	69.5 (34, 81)	68.0 (29, 81)
Sex	Female	9 (41%)	8 (67%)	17 (50%)
	Male	13 (59%)	4 (33%)	17 (50%)
Weight (kg)	n/n_{miss}	22/0	12/0	34/0
	Median (Min, Max)	70.5 (51, 101)	71.7 (54, 93)	70.5 (51, 101)
Height (cm)	n/n_{miss}	22/0	12/0	34/0
	Median (Min, Max)	173.3 (161, 203)	164.5 (152, 181)	171.0 (152, 203)
Smoking status	Current	4 (18%)	1 (8%)	5 (15%)
	Former	7 (32%)	3 (25%)	10 (29%)
	Never	11 (50%)	8 (67%)	19 (56%)

[a] Max, maximum; min, minimum; n_{miss}, number of missing values; percentages are based on the number of patients within each treatment group.

Insertion site of the CVC and number of catheter days. Ninety-four percent of the patients had the CVC inserted into the right jugular vein. The length of the CVC inserted beneath the skin ranged between 9.5 and 18.5 cm in the BIP CVC group and between 12.5 and 18.5 cm in the standard CVC group. The CVCs were extracted where they were no longer needed. None of CVCs were extracted due to safety or performance reasons. The average number of catheter days was approximately 3 days longer in the standard CVC group (mean 12.4 days, range 6 to 21) compared to the BIP CVC group (mean 9.2 days, range 4 to 16), which can influence the interpretation of some study data. The percentage of patients with a CVC as a function of time is shown in Figure 2 as Kaplan–Meier plot. The long-rank test revealed a significant difference ($p = 0.02$).

Concomitant medication. All patients received antithrombotics as prophylaxis and 21 of 22 patients in the BIP CVC group and 11 of 12 patients in the standard CVC group received antibacterials for systemic use as prophylaxis. Drugs for acid related disorders were used by 7/34 patients and corticosteroids for systemic use by 3/34 patients. All other types of medications were administered to two patients or fewer. Four patients in the standard CVC group received medications that were given due to AEs, which were Antithrombotics (two patients), Antibacterials for systemic use (three patients), and Antivirals for systemic use (one patient).

A summary of medications, given for nonprophylactic use, showed that antibacterials for systemic use were used by 9 of 22 patients (41%) in the BIP CVC group and by 8 of 12 patients (68%) in the standard CVC group. Antithrombotics for nonprophylactic use were used by 2 of 22 patients (9%) in the BIP CVC group and by 2 of 12 patients (17%) in the standard CVC group.

Tolerability evaluation—Primary endpoint
Adverse events. AEs occurred in four patients in the standard CVC group and there were no AEs in the BIP CVC group ($p = 0.011$). The total number of AEs was 5 (one sepsis, two pulmonary embolism, one pneumonia, and one acute respiratory distress syndrome), of which three were classified as serious (SAEs, including SADES) and three events were judged as possibly related or related to the study device (ADEs or SADEs, no statistical significance), see Table II and Figures 3 and 4.

Related/possibly device related AEs (ADEs/SADEs). There was one ADE in the study: device related sepsis. Its overall frequency was 3/1000 catheter days (0/1000 for BIP CVC; 7/1000 for the standard CVC group). The sepsis started on catheter day 15 and was judged to be related to the study device. The ADE led to immediate treatment with antibacterials for systemic use and CVC removal on catheter day 17. The same patient was, together with another patient, diagnosed with pulmonary embolism. Both were considered SAEs and possibly related to the study device (SADE). For the second patient the pulmonary embolism was diagnosed on catheter day 4, while the other was diagnosed at the same time as of the device-related sepsis. Concomitant treatment with an antithrombotic agent (Dalteparin) was given to both patients. No actions were taken with the study device due to the pulmonary embolisms. Analysis of the number of device-related events per days of exposure gave no significant difference between the two groups ($p = 0.35$ for ADE and $p = 0.12$ for SADEs) using the Fisher's exact test, significance level $p \leq 0.05$.
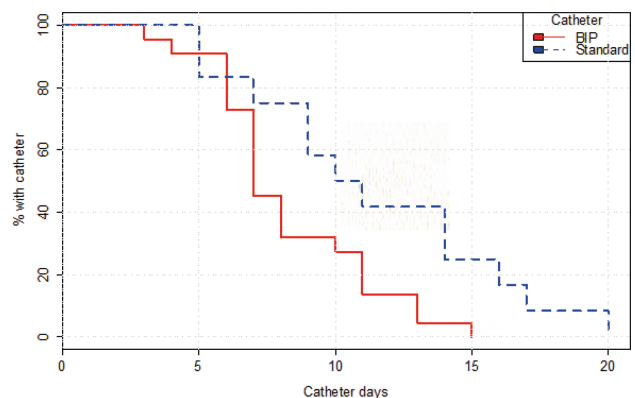
FIGURE 2. Percentage of patients with catheter as a function of time (Kaplan–Meier plot). Log-Rank test ($p = 0.02$).

TABLE II. Overview of AEs

	BIP CVC (N = 22)		Standard CVC (N = 12)		Total (N = 34)		
	n (%)[a]	Events	n (%)	Events	n (%)	Events	p value[b]
AE[c]	**0**	**0**	**4 (33)**	**5**	**4 (12)**	**5**	**0.01**
SAE[d]	0	0	3 (25)	3	3 (9)	3	–
ADE (sepsis)[e]	0	0	1 (8)	1	1 (3)	1	0.35
SADE (pulmonary embolism)[f]	0	0	2 (17)	2	2 (6)	2	0.12

[a] n = number of patients. Percentages are based on the number of patients within each treatment group.
[b] Fisher exact test, ($p < 0.05$ significant).
[c] AEs including all AEs whether or not related to study device, or whether or not a serious AE.
[d] SAEs include all serious events whether or not considered related to study device.
[e] ADEs are defined as nonserious AEs possibly related or related to the study device.
[f] SADEs are defined as serious AEs possibly related or related to the study device.

Performance—Secondary endpoint

Performance was evaluated based on CVC-related problems (device malfunctions, and problems during the daily inspections of the CVC). Overall, the performance of the BIP CVC was comparable to the standard CVC in the study.

Device malfunctions, problems with the clamp fastener at surgery, and problems with the guidewire, were reported for 22.7% of patients in the BIP CVC group and 8.3% of patients in the standard CVC group ($p = 0.38$), using the Fisher's exact test.

CVC-related problems/issues collected during daily CVC inspections, all classified as "occlusion during use," were reported for 41% of patients in the BIP CVC group and for 58% of patients in the standard CVC group ($p = 0.48$), Fisher's exact test.

Exploratory evaluations

Metal analysis in blood. Analysis of traces of BIP CVC coating metals (gold, silver, and palladium) in blood was performed immediately after CVC insertion, and at 2 h, 20–26 h, and approximately 3 days (Table III). The mean silver concentration was 0.879 ($\pm$0.632) µg/L in the BIP CVC group, but decreased to 0.113 µg/L 2 h after insertion. The first value was above the reference range for metal levels in the general population, while the 2-h value was within the reference range ($<$0.045–0.272 µg/L). The mean gold concentration was 0.07 ($\pm$0.04) µg/L directly after insertion and

remained similar after 2 h. Both these values were within the reference range for the general population (0.007–0.217 µg/L).[29] The mean palladium concentration was 0.075 ($\pm$0.066) µg/L directly after insertion and decreased to 0.031 ($\pm$0.024) µg/L after 2 h. Both these values were also within reference range for the general population (0.009–0.125 µg/L).[29] All measured metal concentrations in blood for the BIP CVC group were far below the toxicological safety limits for chronic use (Permitted Daily Exposure [PDE]); day 3-values were between 0.2 and 1.4% of the PDE and the highest transient values for each metal was below 50% of the PDE (approximately 2–47%).

Metal analysis of the BIP CVC surface after clinical use. Analysis of BIP CVC coating metals (gold, silver and palladium) was performed on a majority of catheter surfaces after use. Analysis of unused BIP CVC of the same batch as used in the study was performed as controls. The results are presented in the Table III. There was no additional metal leakage for insertion times 5–16 days in this study. Calculation of the released amounts of metals based on the surface concentrations revealed that they correspond to 0–3.85% of accepted PDEs limits for chronical use see Table IV.

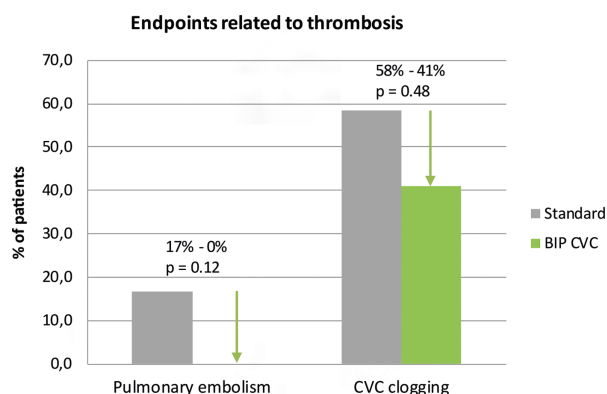*Total metal amounts on a BIP CVC.* For environmental assessment, the total amount of metals on a BIP CVC has

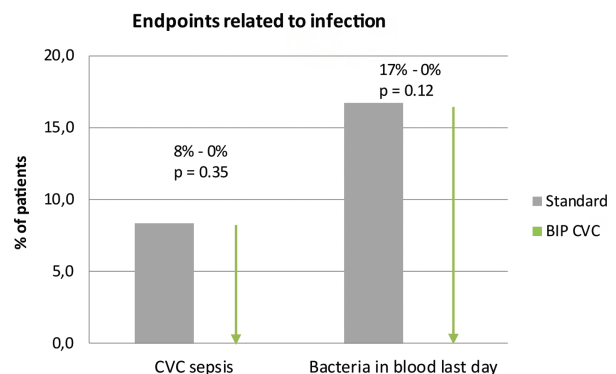**FIGURE 3.** Tolerability findings—frequency of events possibly related to thrombosis in the study groups.

FIGURE 4. Efficacy findings—frequency of events related to infections for the study groups.

TABLE III. Coating Metal Concentration in Blood After CVC Insertion in µg/L

Time After Insertion	Gold (Au)	Silver (Ag)	Palladium (Pd)
Directly (approximately few minutes)	0.07 (±0.04)	0.879 (±0.632)[a]	0.075 (±0.066)
2 h	0.08 (±0.06)	0.113 (±0.108)	0.031 (±0.024)
20–26 h	0.07 (±0.04)	0.095 (±0.101)	0.029 (±0.014)
Approximately 3 days	0.14 (±0.09)	0.130 (±0.129)	0.030 (±0.016)
Reference range in normal population	0.007–0.217 µg/L	<0.045–0.272 µg/L	0.009–0.125 µg/L

[a] Outside the reference range in normal population.

been calculated using the highest amounts of metals on the unused CVCs (Table V) and surface area of entire CVC of 20 cm length (15.1 cm^2): 2.3 µg gold, 18.7 µg silver, and 2.0 µg palladium.

Microbiological findings

The proportion of patients with microbial colonization of the CVCs tended to be somewhat larger in the BIP CVC group than in the standard CVC group (27 vs. 17%, on CVC-tip, $p = 0.68$; 27 vs. 8%, on subcutaneous part of CVC, $p = 0.38$). Positive blood culture results (based on scheduled and non-scheduled blood sampling) were obtained from two patients in each treatment group. Positive blood culture results at CVC removal were only obtained in two patients (17%) in the standard CVC group, $p = 0.118$. The patient, having device-related sepsis, had bacteremia with *Staphylococcus epidermidis* from catheter day 15 to 17. The same bacterial species was found on the CVC-tip but no microorganisms were detected on the subcutaneous part of the CVC.

DISCUSSION

This study showed that the BIP CVC has comparable tolerability and performance to the standard uncoated CVC, when used in patients undergoing elective large abdominal surgery. As the present study was designed to be an explorative pilot study prior to planning of a larger study, we choose to randomly allocate the study participants to a BIP CVC or a standard CVC at a ratio of 2:1. With this explorative design and small sample size any results should be regarded as indicative. No power calculation was performed as it was a pilot study. Note that tolerability and performance evaluations were performed unblinded. One of the important outcomes from the study is the durability of the coating in the bloodstream and evaluation of safety of the traces of released metals, which cannot be performed in very large studies.

Tolerability

The primary objective of the study was to evaluate tolerability based on AEs. Five AEs occurred, all in the standard CVC group ($p = 0.01$). Since only three AEs were catheter related, no conclusions could be drawn regarding differences between treatment groups. Differences between catheterization time between the groups is another reason why the results should be interpreted with caution. Device-related events comprised one sepsis and two pulmonary embolisms (possibly related to catheter thrombosis); both common complications of CVCs.[26,27] The low frequency of all AEs indicated a good tolerability and performance of both CVCs used in the study. The overall frequency of catheter-related infections in the entire study, 3/1000 catheter days (0/1000 for BIP CVC; 7/1000 for the standard CVC group) is at the same level as those reported by the WHO,[4] that is, 2.5/1000 for USA, 3.5/1000 in high-income countries.

The results from this pilot study support prior data on Bactiguard coated CVCs from a study on 266 oncology patients receiving chemotherapy, that has shown a reduced incidence of catheter-related infections in the Bactiguard CVC group (10% of patients vs. 21% in the control group using an uncoated standard CVC).[12] Superior blood compatibility of BIP CVC compared to standard CVC has been reported in *ex-vivo* experiments,[17,18] which possibly correlates with decreased embolism cases in this study.

Performance

Overall, the performance of the BIP CVC was comparable to the standard CVC. The most common problem, "occlusion during use," was somewhat more common in the standard CVC group (58%) than in the BIP CVC group (41%) and the longer catheterization time for the patients with standard CVC could be a contributing factor to this difference.

Coating durability; no selection pressure for microbial resistance. The study included an evaluation of CVC coating durability in blood by studying the amounts of the metals (gold, silver, and palladium) in blood and on catheters after use. The results showed higher mean blood concentrations of all coating metals in the BIP CVC compared to standard CVC. However, the increases in the BIP CVC group were modest and only a few individual patients had concentrations above

TABLE IV. Coating Metals on BIP CVC Surface After Clinical Use

Days of Use	n	Gold Au (µg/cm^2) Mean (Std)	Silver Ag (µg/cm^2) Mean (Std)	Palladium Pd (µg/cm^2) Mean (Std)
0 (unused)	13	0.08 (0.07)	1.04 (0.20)	0.10 (0.03)
5–8	11	0.06 (0.01)	0.77 (0.11)	0.14 (0.02)
9–12	5	0.06 (0.02)	0.57 (0.28)	0.13 (0.01)
13–16	3	0.05 (0.02)	0.65 (0.04)	0.14 (0.01)

TABLE V. Total Coating Metal Release, Release per Day, Safe Daily Limits and Safety Margins[a]

	Gold (Au)	Silver (Ag)	Palladium (Pd)
Total release (mean for 18 patients, μg)	0.23	3.26	0
Release per day (mean for 18 patients, μg/day)	0.03	0.38	0
PDE limit for chronic use in μg/day[a]	100	10	10
Release in % of safe chronic limit[a]	0.03	3.85	0
Safety margin	4700	33	Infinite

[a] On average, 14 cm BIP CVC is in contact with blood. The coating is applied only on the outer surface. Surface area of 7 Fr, 2 lumen CVC in contact blood has been calculated to 10.6 cm^2.

[b] European Medicine Agency, (25 July 2016). "ICH guideline Q3D on elemental impurities."
Retrieved from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180284.pdf[22]

the reference values in the normal population. The exception was silver concentrations immediately after CVC insertion, which were above the reference range, but decreased below the reference values 2 h after catheter insertion. Altogether, the data suggest some initial leakage of small amounts of silver into blood from the BIP CVC, which quickly decreased. Even the highest transient values of silver, (0.879 [±0.632] μg/L), represents <50% of the accepted[28,29] PDE limit for chronical use and is at least 10 000 times lower than MIC, 8–32 mg/L, MBC, >512 mg/L, and MSC for silver to inhibit or kill microbes.[27] To address a potential risk for microbial resistance in a rare case of chronical use of CVCs, we compared the highest transient values of silver, 0.879 (±0.632) μg/L, with the MSC for silver (250 μg/L) and found it approximately 300 times lower. Hence, no selection pressure is created to build microbial resistance, even in a rare case of prolonged use[16,30] (Personal communication: Professor Dan Andersson and MD Lisa Albrecht, Dept. of Medical Biochemistry and Microbiology (IMBIM), Uppsala University, Sweden; Dan.Andersson@imbim.uu.se). For the gold and palladium, even the highest values in the blood correspond to a fraction of the PDE limit[29] for chronical use. The findings from the analysis of remaining coating metals on removed catheters after clinical use confirm the conclusion from the blood analysis; low initial release, well below PDE limits, and stable coating up to 16 days of use (study length). The study confirmed a nonreleasing mechanism of action of the Bactiguard coating in blood, in contrary to the other widespread CVC coatings on the market. The fact that the noble metal coating remained relatively intact for the study period, supports the idea that the biochemical mode of action can be assumed to have been relevant for this period and not just initially after CVC insertion.

The environmental perspective. The total amount of coating metal per one BIP CVC used in this study (which is a representative sample) is 2.3 μg gold, 18.7 μg of silver, and 2.0 μg of palladium (23 μg in total). An amount of metal of 10 g (a jewellery ring) corresponds to approximately 435 000 BIP CVCs, which is the total amount of CVCs consumed in a medium sized Swedish hospital in approximately 40 years. In comparison, a mobile phone contains approximately 250 mg of silver, 24 mg of gold, and 9 mg palladium (283 mg in total), which corresponds to approximately 12 300 BIP CVCs.[15] Thus, the amount of noble metals in BIP CVCs is neglible from an environmental perspective.

When BIP CVCs are to be disposed of in accordance with normal hospital procedures for medical wastes (burned), the noble metals are not destroyed during incineration but are trapped in the filters as part of the purification of flue gases from the combustion plant. The metals will end up in the ashes from where they can be extruded or deposited in a closed system in accordance with the rules that apply to this type of waste and will not reach the storm water.[31,32]

Colonization. The evaluation of colonization of catheters found to be comparable in the two groups (numerically slightly higher for BIP CVC, nonsignificant). However, no catheter-related infections were found in the BIP CVC group. We hypothesize that decreased infections in this and our previous study may be due to a reduced amplification of microorganisms on the catheter surface (which cannot be quantified by standard microbiological methods), which previously has been seen *in vitro*.[33] Therefore, microbial colonization (% of colonized catheters), which is sometimes used as surrogate endpoint for releasing coatings,[13,14] may not be a suitable surrogate endpoint to study the effect of nonreleasing coatings on the infection rates.

CONCLUSION

In summary, in this study the BIP CVC has shown significantly less AEs and a comparable performance to the standard uncoated CVC, when used in patients undergoing elective large abdominal surgery. The results should be taken with caution, due to the small study size and different catheterization length in the study groups. Overall, few cases of sepsis and thrombotic events were seen, with an uneven distribution toward the standard CVC group. Microbial colonization was similar for BIP CVC and standard CVC and is probably not suitable as a surrogate endpoint for clinical infections. The Bactiguard coating is durable in blood and does not create selective pressure for microbial resistance. Toxicological evaluations show a good safety margin toward permitted daily exposures for chronical use for all coating metals and the same levels in blood as for normal population shortly after the catheter insertion. Larger studies are needed, in which the incidence of colonization and infection, including bacterial resistance pattern, is studied.

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