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Cutaneous bacterial colonization, modalities of chemotherapeutic infusion, and catheter-related bloodstream infection in totally implanted venous access devices

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Abstract *Goals of work:* Prospective clinical study to evaluate patients suffering from solid tumor using a totally implanted venous access device (TIVAD) to determine: (1) if there is a relationship between cutaneous contamination at port insertion site and catheter-related bloodstream infection (CRBI); (2) development modalities of CRBI; (3) if there is a relationship between chemotherapy administration modalities by push/bolus versus continuous infusion and CRBI. *Patients and methods:* We studied 41 consecutive patients who needed a TIVAD positioned for chemotherapy administration by bolus/push or continuous infusion. In every patient, we performed blood cultures from blood samples from port catheters and cutaneous cultures from cutaneous tampons of the skin surrounding the implant area on the first (T0) and eight day (T1) postoperatively, after 1 month (T2), and after 3 months (T3) from insertion. *Main results:* The study was completed on 40 patients; in one case, the port was removed at T2 for septic complications. We obtained four positive blood cultures (two, 5%), two in the same patient, all caused by staphylo-

coccus. Positive cutaneous tampons were 21 (13%) in 11 patients (27%); the four CRBI occurred in this group of patients with none in the remaining 30 patients (73%) for a total number of 120 tampons ($p<0.01$). In two cases, the same germ was isolated from both the skin and blood. None of the patients presented a local infection of the subcutaneous pocket. Positive cutaneous cultures decrease over time: T0–T2, 24–5%; T1–T3, 20–5% ($p<0.04$). There were no differences in CRBI incidence and positive cutaneous tampons between the two chemotherapy administration modalities. *Conclusions:* Cutaneous microbial flora has a primary role in CRBI development within TIVADs; there is a relationship between cutaneous colonization and CRBI; colonization reaches its maximum during the first days after catheterization in which the use of the system is at high risk; colonization occurs both via extraluminal and endoluminal routes; there is no difference in CRBI incidence between bolus and continuous infusion administration.

Keywords TIVAD · CRBI · Cutaneous bacterial colonization

Introduction

Totally implanted venous access devices (TIVAD) allow easy and effective treatment for chemotherapy and pain control in cancer patients [1]. However, local and sys-

temic infections still remain the major cause of morbidity and catheter failure [2, 3]. The patient's cutaneous microbial flora has a fundamental role in the etiology of catheter-related bloodstream infection (CRBI) [4, 5]. These germs initially colonize the external catheter in-

sersion site and later migrate along the catheter's external surface until reaching the blood (extraluminal route) [6, 7], or they may be directly inserted in the catheter lumen (endoluminal route) [8, 9]. More rare is the contamination of the catheter via the bloodstream from bacteria that originate from a distant focus or the contamination of the fluids or solutions [10, 11].

The highest incidence of extraluminal CRBI occurs during the first week of catheterization, while the endoluminal CRBI occur, generally, later and are associated with the manipulation of the system and the modalities of its use [12].

Compared to indwelling catheters, TIVAD present a smaller incidence of infective complications regardless of the patient's disease or immunocompetence status and the aggressiveness of the chemotherapeutic treatment [13, 14]. This may depend on the fact that TIVADs are completely imbedded in the subcutaneous layer and, unlike indwelling catheters, do not create continuity between the catheter and patient's cutaneous microbial flora.

The aim of this study was to evaluate: (1) if there is any relationship between cutaneous bacterial colonization over the skin surrounding the port and development of CRBI; (2) how this develops; (3) if there is any relationship between administration modalities of chemotherapeutic treatment (push versus continuous infusion) and CRBI development.

Patients and methods

We performed a 5-month prospective study on 41 consecutive patients suffering from solid cancer who needed placement of a TIVAD for chemotherapy administration. Each patient was followed for 3 months, from the placement of the device until the last survey. The TIVAD we used were Port-a-Cath (Deltec, USA).

All patients were ambulatory and the surgical procedure, done under strict asepsis, took place in an operating room at a day hospital. The same physician inserted all TIVADs using local anesthetic for a field block and under radiosopic visualization. The catheters were inserted in a central vein using a J guide wire and a peel-away introducing system. At end of the surgical procedure, we flushed the system with 500 U of heparin in 5 ml of solution (100 U/ml) and applied a sterile dressing. In all patients, the system was not used until cutaneous suture removal on the eighth postoperative day.

Chemotherapy administration

According to the different cancer subtypes, patients were treated with two different protocols of chemotherapy administration. All patients were ambulatory; some received repeated bolus administration, others a continuous infusion administered at home by external pump. Patients' characteristics were evenly distributed between the two groups. For intermittent administration, the port access was carried out with a Huber needle, which was removed after every treatment. In the continuous infusion group, the duration of administration was variable accordingly with the chemotherapeutic protocol in use: 2 days for the de Gramont [15], 5 days in the

chronomodulated therapy of colorectal cancer [16], and protracted infusion with low doses of fluorouracil and cisplatin for head and neck cancer and in some other tumor subtypes [17]. In these patients, the port was accessed with a Huber needle, which was removed at the end of every infusion cycle with a maximum duration of 14 days for protracted infusions. In all cases, prior to Huber needle insertion, the skin was disinfected with 10% povidone-iodine solution and, after needle insertion, covered with a sterile and semipermeable dressing.

Microbiology methods

Blood cultures were carried out with the ISOLATOR 10 OXOID method [18]. The ISOLATOR test tube contained some leukocyte and erythrocyte lytic factors. Factors we used were: purified saponin, polypropylene glycol and sodium polyanethol sulfonate. A blood sample (~10 ml) was inoculated in the ISOLATOR 10 test tubes and centrifuged at 3,000 rpm for 30 min. The supernatant was then removed and the pellets seeded on the following culture media: blood agar (anaerobe 35–73°C); chocolate agar (5–10% CO₂ 35–37°C); Sabouraud's agar (anaerobe 22–30°C). We checked for bacterial growth every 24 h and eliminated plates at 4, 6, and 8 days respectively.

After incubation, we proceeded with isolation and identification of microorganisms with the VITEK 32 BIOMERIEUX automatic system, and bacteria count was determined with the following formula:

$$\text{CFU/ml} = \frac{\text{Total no. of CFUs of all plates} \times \text{no. of inoculated plates}}{\text{no. of plates on which growth of microorganism was expected} \times \text{Blood volume}}$$

Cutaneous cultures were obtained by passing a swab over the skin surrounding the port, and the cutaneous swabs were then seeded with the "three zone" technique on CAN blood agar, mannitol, MacConkey agar, Sabouraud's agar, and chocolate agar and incubated for 48 h at 35–37°C. The automatic system VITEK 32 BIOMERIEUX was used for identification of microorganisms.

We considered CRBI positive when cultures of blood samples aspirated from the port developed a count of 100 CFUs or more in absence of any clinical sign related to an infection related to a different focus rather than the central venous catheter (CVC).

Data collection

For every patient, we recorded age, diagnosis, platelet and leukocyte count at time of the surgical procedure, the date of catheter insertion, removal due to any complication, insertion site, use of catheter (intermittent chemotherapy or continuous infusion by external pump), eventual local infections at the site of insertion, results of cultures of blood samples obtained from the TIVAD, and cutaneous cultures from the skin surrounding the device's area. Both blood and cutaneous cultures were carried out on the first day postoperatively (T0), the eighth day (after cutaneous suture removal and the beginning of chemotherapeutic treatment) (T1), after 1 month (T2), and after 3 months (T3) from implant.

Statistics and data analysis

Different percentages of positive cultures among recorded factors were evaluated with the Fisher exact test.

Results

During the study period, we evaluated 41 implanted TIVADs on 41 patients. The study was completed on 40 patients since in one patient, the device was removed at T2 because of septic consequences. In total, we carried out 163 blood cultures and 163 cutaneous cultures. During catheter placement, none of the patients were affected by fever and/or granulocytopenia.

In 20 patients, the catheter was placed in the right subclavian vein, in 20 in the left subclavian vein, and in one in the right internal jugular. In 22 patients, chemotherapy was carried out by bolus; in the other 19, it was carried out by continuous infusion. Three patients developed four positive blood cultures, which represented 2.5% out of the 163 samples analyzed. In all cases, detected germs were *Staphylococcus simulans*, *capitis*, and *aureus*. *S. aureus* was isolated at T1 in one patient after he had received antibiotic treatment (teicoplanin 400 mg×2 IV). Afterward, the patient developed septicemia associated with the use of the device, and the same bacterium was isolated from a blood culture at T2. The port was then removed (Table 1), and culture of the catheter tip revealed the presence of *S. aureus* with the same antibiotic sensitivity test of the germ detected in the blood culture.

Comparing patients receiving intermittent versus continuous infusion chemotherapy, blood cultures were positive at T1 and T2 in 4.5 versus 0% (NS) and in 4.8 versus 5.3% at T3 (NS). Considering both groups of patients, blood cultures appeared to be positive for 2.5% at T1 and

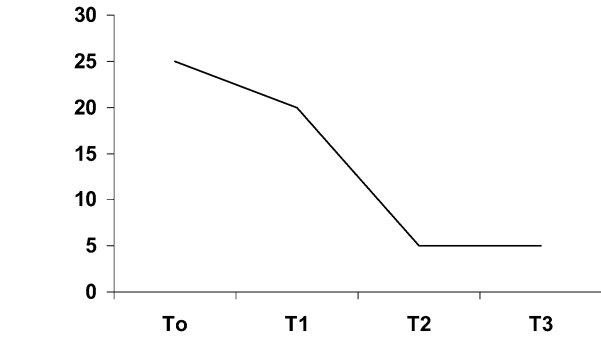


Fig. 1 Positive skin cultures in time T0–T2 (first day to one month following catheter insertion) $p<0.01$; T1–T3 $p<0.04$

T2 and for 5% at T3. Positive cutaneous swabs were 21 (13%) out of 163 on 11 patients (27%); the four positive blood cultures were in this group of patients. The other 30 patients (73%) with 120 negative cutaneous swabs ($p<0.01$) showed no positive blood culture. No patient, either with positive or negative cutaneous swabs, reported local infection in the subcutaneous pocket where the device had been placed. In positive skin cultures, we detected *Staphylococcus* in almost all cases, in particular *S. aureus*, *S. epidermidis*, and *S. simulans*; in two out of three patients with CRBI, we detected the same germ at the same time both from skin and blood samples obtained via the TIVAD (Table 1). In positive cutaneous cultures, the difference between continuous infusion chemotherapy and push/bolus chemotherapy reached its maximum value

Table 1 Patients with positive blood and skin cultures (T0 first day postoperatively, T1 eighth day postoperatively, T2 1 month after implant, T3 3 months after implant)

Pa-tient	Age	Pathology	Subcla-vian vein	Chemo-therapy	Blood cultures (BC), skin cultures (SC)	T0	T1	T2	T3
2	61	Breast	Right	Bolus	BC	Negative	Negative	Negative	Negative
					SC	<i>S. epidermidis</i>	Negative	Negative	Negative
8	63	Colon	Right	Infusion	BC	Negative	Negative	Negative	Negative
					SC	<i>S. epidermidis</i>	<i>S. epidermidis</i>	<i>S. epidermidis</i>	<i>S. epidermidis</i>
11	52	Lung	Right	Bolus	BC	Negative	Negative	Negative	<i>S. simulans</i>
					SC	<i>S. epidermidis</i>	Negative	<i>S. simulans</i>	<i>S. simulans</i>
							<i>S. haemolyticus</i>		
14	57	Breast	Right	Infusion	BC	Negative	<i>S. aureus</i>	<i>S. aureus</i>	Removed
					SC	Negative	<i>S. aureus</i>	Negative	
20	58	Breast	Left	Bolus	BC	Negative	Negative	Negative	Negative
					SC	<i>S. epidermidis</i>	<i>S. epidermidis</i>	Negative	Negative
26	63	Esophagus	Left	Infusion	BC	Negative	Negative	Negative	Negative
					SC	<i>S. auricularis</i>	<i>S. epidermidis</i>	Negative	Negative
								<i>S. haemolyticus</i>	
28	41	Colon	Right	Infusion	BC	Negative	Negative	Negative	Negative
					SC	<i>S. capitis</i>	Negative	Negative	Negative
30	58	Pharynges	Left	Infusion	BC	Negative	Negative	Negative	Negative
					SC	Negative	<i>Micrococcus</i>	Negative	Negative
33	66	Colon	Left	Infusion	BC	Negative	Negative	Negative	Negative
					SC	<i>S. epidermidis</i>	<i>S. epidermidis</i>	Negative	Negative
38	71	Breast	Left	Bolus	BC	Negative	Negative	Negative	Negative
					SC	<i>S. epidermidis</i>	<i>S. epidermidis</i>	Negative	Negative
39	70	Colon	Left	Infusion	BC	Negative	Negative	Negative	<i>S. capitis</i>
					SC	<i>S. epidermidis</i>	<i>S. epidermidis</i>	Negative	Negative

at T1 with respectively 26.3% and 13.6% (NS). The number of positive cutaneous cultures, considering both groups of patients, decreased in time from 24% to 5% ($p < 0.01$) T0- T2 and from 20% to 5% ($p < 0.04$) T1-T3 (Fig. 1).

Discussion

The highest incidence of extraluminal CRBI occurs during the first week after placement of the CVC [12]. An early contamination can occur when viable microorganisms are impacted, during insertion, onto the distal tip of the CVC. Cutaneous microorganisms were detected from skin and from catheter tip samples 90 min after insertion despite rigorous skin disinfection and a strict aseptic technique [19]. An early CRBI can also occur during the days immediately following due to bacterial contamination and growth in the subcutaneous pocket and, subsequently, migration of bacteria along the catheter's external surface to the bloodstream [6]. Even though TIVADs are completely inserted in the subcutaneous layer, this second mechanism may occur due to the colonization of skin microorganisms that may move by capillary action via the surgical incision into the pocket and then along the dermal tunnel surrounding the catheter. With indwelling catheters, it has been widely proven that cutaneous colonization is strongly predictive for CRBI [20, 21], and also, cutaneous microorganisms surrounding the insertion site are strongly related to germs detected on catheter tip cultures [22, 23].

Given the evidence of the importance of cutaneous microorganisms in the pathogenesis of CRBI, we decided to evaluate if there is any relationship between cutaneous bacterial colonization of the device's insertion area and CRBI and how this develops. Our results highlight all CRBI in patients with positive cutaneous cultures, and no detectable infection occurred in the group of patients with negative cutaneous cultures. Therefore, TIVADs, as indwelling catheters, present a strong correlation between bacterial colonization surrounding the device's insertion site and CRBI. This evidence is furthermore confirmed by the fact that in two CRBIs, we detected the same germ at same times in cutaneous tampons and in one case on the catheter tip as well.

Relating to the time of detection, we presume the catheter colonization modalities by cutaneous microbial flora are different in the CRBIs we observed. In early CRBI, observed at T1, when the device had not yet been used and therefore no percutaneous communication with the port had occurred, except for the flushing of the device with heparin after insertion, the catheter colonization took place via extraluminal route probably due to the colonization of the cutaneous wound site of implant and migration to the pocket and along the catheter. We detected the same germ at T1 from both skin surrounding

the device's insertion wound and blood samples obtained via the TIVAD. This was reversed in the two CRBIs that developed at T3 and therefore lengthy use, and the catheter colonization appeared to be via the endoluminal route. The cutaneous microorganisms could have been introduced during the in-use manipulation of the IV line, with the needle during percutaneous puncture of the port, or, in protracted infusions, germs may have colonized the percutaneous needle implanted in the port and successively the catheter. These pathogenic mechanisms can also be responsible for endoluminal CRBIs in TIVADs.

We found no difference in the incidence of CRBI between administration by push/bolus, where manipulation of the system and percutaneous punctures for access to the port are numerous, and the administration by continuous infusion in which the longer transdermal duration of the needle is likely to facilitate germ migration into the port. Similar results have been reported in another study where comparison between chemotherapy administration by push/bolus or by continuous infusion does not highlight any statistically significant difference in the incidence of infections or other complications [24].

We observed colonization of the area surrounding the device's insertion wound in 11 patients (27%) without any of these presenting a superficial infection of the pocket. Bacterial colonization of a cutaneous, noninfected surgical wound is a relatively common event. In a large study of women undergoing cesarean section, colonization of noninfected wounds occurred in 17% of cases [25] and, in another study of patients undergoing cardiac surgery, colonization of the wound until 6 days post operatively appeared to be related to the antibiotic prophylaxis in use and occurred in 52–78% of cases [26].

It has been demonstrated that there is a wide bacteria colonization of sutures of noninfected wounds, mostly staphylococcus coagulase-negative, which tends to develop in adhesive glyco-calix that protects it from the host's defense mechanisms until suture removal [27]. Microbial colonization of the cutaneous area surrounding the implant's wound, observed in our study, presents the highest incidence until suture removal (T2) and then significantly decreases with time. This appears to be clinically significant because the density of microbial cutaneous flora is one of the major risk factors for CRBI development, and the system should not be used immediately after the implant. In our institute, we have therefore recommended, as a guideline of good clinical practice, that TIVAD use should follow suture removal from the cutaneous pocket.

In conclusion, our study results have demonstrated: (a) the host's cutaneous microbial flora, staphylococcus coagulase-negative and *S. aureus* in particular, have a primary role in CRBI etiology of TIVADs; (b) bacterial cutaneous colonization surrounding the device's implant area and CRBI development are related; (c) cutaneous colonization occurs in more than one fourth of patients

without necessarily presenting a superficial infection of the pocket; (d) cutaneous colonization reaches its maximum, as does the risk of infection, during the days immediately following catheterization and decreases in time; (e) pathogenic mechanisms of catheter colonization for TIVADs, as for indwelling catheters, are the endoluminal route prevalent in CRBIs that arise later and are due to in-use of the IV system; (f) the endoluminal route is

more frequent than the extraluminal route (two patients versus one). In the end, we confirmed that there is no difference in CRBI incidence between chemotherapy administrations in bolus versus continuous infusion.

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