TOTALLY IMPLANTABLE VENOUS ACCESS DEVICES IN ONCOLOGY: RETROSPECTIVE ANALYSIS OF 652 PATIENTS

CATÉTERES VENOSOS CENTRAIS TOTALMENTE IMPLANTÁVEIS EM ONCOLOGIA: ANÁLISE RETROSPECTIVA DE 652 DOENTES

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RESUMO

Introdução: A presença de um acesso venoso adequado é essencial para o tratamento de doentes com cancro. A inserção de catéteres venosos centrais totalmente implantáveis (CVCTI) permite uma administração segura de quimioterapia, não sendo no entanto, isenta de complicações. O nosso objetivo é analisar a experiência do nosso centro no que respeita a utilização de CVCTI. **Materiais e Métodos:** Revisão dos registos médicos eletrónicos de todos os doentes com cancro que colocaram um CVCTI no Hospital da Luz, no período entre 1 de Janeiro de 2008 a 31 de Dezembro de 2014. **Resultados:** Analisaram-se retrospetivamente dados de 652 doentes com cancro. A incidência global de complicações foi 14.1% (91), sendo apenas 0.9% (6) complicações precoces (antes da primeira utilização do CVCTI). As complicações trombóticas (30, 4.5%) e infecciosas (cutâneas e associadas ao CVCTI, 24, 3.5%) foram as mais frequentes, seguindo-se a exteriorização (13, 1.9%) e disfunção do catéter (11, 1.6%). Removeram-se 155 CVCTI, a maioria (95, 61.3%) após o fim do tratamento, e os restantes devido a complicações (60; 38.7%). **Discussão:** A taxa global de complicações foi de encontro ao esperado, havendo no entanto um baixo número de complicações precoces e nenhuma complicação potencialmente fatal associada ao procedimento foi identificada. Ao contrário do expectável as complicações trombóticas foram as mais frequentes, seguindo-se as infecciosas. **Conclusões:** A inserção de CVCTI em doentes com cancro é um procedimento seguro, com uma taxa baixa de complicações sem nenhum evento fatal identificado neste estudo.

Palavras-chave: *Neoplasia; Quimioterapia; Cateteres venosos totalmente implantáveis.*

ABSTRACT

Introduction: Adequate venous access is essential for the treatment and management of cancer patients. Insertion of totally implantable venous access devices (TIVADs) provide a safe method for chemotherapy (ChT) administration, but it's not free of complications. We aim to analyze our institution clinical practice experience regarding TIVADs. **Materials and Methods:** Electronic medical records (EMR) review of all cancer patients that required placement of a TIVAD at Hospital da Luz between January 1st 2008 and December 31st 2014. **Results:** Clinical data from 652 cancer patients was retrospectively reviewed. The overall incidence of complications was 14.1% (91), with only 6 (0.9%) being early complications (before the first clinical TIVAD utilization). The most common complications were thrombosis (30, 4.5%) and infections (TIVAD related and cutaneous, 24, 3.5%), followed by exteriorization (13, 1.9%) and catheter dysfunction (11,1.6%). 155 TIVADs were removed, the majority (95, 61.3%)

because of end of treatment and the remainder (60; 38.7%) due to catheter complications. **Discussion:** Global complication rate was as expected, however we observed a low rate of early complications, and we didn't observe any potentially fatal complication related to the procedure. Unlike expected, thrombotic complications were the most frequent, followed by infectious complications. **Conclusions:** TIVADs insertion is a safe procedure in cancer patients with an apparent low rate of complications with no fatal events identified in this study.

Keywords: *Neoplasms; Chemotherapy; Totally implantable catheters.*

INTRODUCTION

Totally implantable venous access devices (TIVADs) of long duration are widely used in cancer patients worldwide. They allow a safer administration of cytotoxic medication and provide an easier and more comfortable venous access for blood samples, transfusions and other needed medications. While placed under local anesthesia and as an outpatient procedure, TIVADs can be associated with complications that need to be recognized and treated. Early complications refer those ones directly related to its insertion and include pneumothorax, hemothorax, air embolism, accidental arterial puncture, cardiac arrhythmia, cardiac tamponade, brachial plexus injury, hematoma, infection of surgical wound and catheter dysfunction. Late complications include bloodstream infection, catheter-site infection, thrombosis, catheter dysfunction, rupture, migration or embolization, exteriorization, port inversion, superior vein cava erosion and perforation. The total complication rate varies between 8 and 38% in recent published retrospective analysis, with infections and thrombosis being the most frequent.[1,2,3,4]

The aim of this study was to evaluate our institutional clinical practice experience regarding TIVADs associated complications in cancer patients.

MATERIALS AND METHODS

This study is a retrospective review of the EMR of all cancer patients in which a TIVAD was inserted for chemotherapy administration, at Hospital da Luz, Lisbon, between January 1st, 2008 and December 31st, 2014. The study was performed according to the principles of the Declaration of Helsinki. The study was reviewed and approved by the Ethics Committee of the Institution. Waiver of Informed Consent was requested by the investigators and approved by the Ethics Committee due to the retrospective noninterventional nature of the study. The study population was identified by cross-referencing the list of patients who placed TIVAD with the list of patients with a diagnosis of cancer. We reviewed the medical records and collected data regarding gender, age, cancer diagnosis and stage (locoregional *versus* metastatic), anatomic site of venous access placement of TIVAD, duration of TIVADs, causes of replacement/removal and other complications. The complications were assessed until April 2015. We also reviewed the reports of all upper extremity venous Doppler ultrasounds, thoracic and neck computed tomography (CT) angiographies and pulmonary ventilation/perfusion scans of those patients in order to evaluate the incidence of catheter related thrombosis and pulmonary thromboembolism in the study population.

All TIVADs were inserted by a general surgeon of Hospital da Luz, the majority under local anesthesia as an outpatient regimen. No TIVAD was inserted in the presence of fever, known systemic infection or inflammatory signs at the site of insertion. Two types of TIVADs were used, both from B.Braun manufacturer: Celsite implantofix standard F8.5 and F10. Prior to placement, a complete blood count with platelets and coagulation tests (PT and aPTT) were performed to ensure the safety of the procedure. Right

subclavian vein was the preferred venous access site, due to surgeon´s preference, to greater ease of insertion and shorter distance to the superior vena cava and right atrium. However, left subclavian vein or jugular veins were chosen in patients who underwent right-sided mastectomy, radiotherapy or in whom the right sided approach was unsuccessfully attempted. After insertion, the correct location and potential early complications were ascertained by chest x-ray. The catheter was ready to be used 24-48h after insertion and maintained with routine flushing with saline and heparin after each manipulation with a maximum interval of 6 to 8 weeks.

For this study, TIVAD *infection* was defined as the presence of inflammatory signs on the site of the TIVAD placement with positive blood cultures drawn from the TIVAD. In the presence of inflammatory signs on the site of the TIVAD, with negative or absent blood cultures it was classified as *cutaneous infection of the TIVAD site. Systemic infection* was defined as absence of local signs of TIVAD infection, positive peripheral blood cultures, with or without positive blood culture drawn from the TIVAD, with an identified source of infection other than the TIVAD. *Febrile syndrome* was referred as persistent fever with no clinical source identified and negative blood cultures after appropriate etiological investigation. *Catheter associated thrombosis* was defined as thrombotic occlusion of the catheter with involvement of the vein where the catheter was placed, as documented by Doppler ultrasound or CT angiography. *Catheter obstruction* was related to intraluminal obstruction without extension to the vein, reservoir rotation, misplacement, pinch-off syndrome or disconnection. *Catheter disfunction* was considered if there was persistent inability to inject fluid and/or aspirate blood through the TIVAD without an identified cause. Venous thromboembolism was defined as a ventilation-perfusion mismatch in lung scintigraphy or a filling defect within the pulmonary vasculature in CT angiography. No routine examinations were performed to identify thrombosis, unless there was clinical suspicion.

Complications were subdivided in *early complications* (associated with the procedure or occurring up to the first catheter utilization) and *late complications* (after first catheter use).

Statistical analysis was performed using both Microsoft Excel and SPSS 23.0 software. Continuous data are expressed as medians and ranges, while categorical variables are expressed in frequencies and percentages. Categorical data were compared by Fisher's exact test.

RESULTS

Between January 1st 2008 and December 31st 2014, 681 TIVADs were inserted in 652 cancer patients, with a median age of 60 years-old (minimum 17, maximum 89), 431 (66%) in women. The most frequent anatomic site for venous access was right subclavian vein (601, 88.3%) followed by left subclavian vein (56, 8.2%) and right jugular vein (17, 2.5%) (Table I).

Table I – **Characteristics of the study population**

Total Patients / TIVADs	652/681
Gender (Male:Female)	221:431
Age (median, range)	60 (17-89)
Anatomic site of venous access	681
Right subclavian vein	601 (88.3%)
Left subclavian vein	56 (8.2%)
Right jugular vein	17 (2.5%)
Left jugular vein	4 (0.6%)
Right cephalic vein	2 (0.3%)
Left femoral vein	1 (0.1%)

The majority of patients had solid tumors, only 14 (2.9%) had hematologic malignancies. The most common cancer diagnoses were colorectal (30.4%), breast (24.5%), pancreas (8.3%), lung (7.4%) and stomach (6.4%). Among patients with solid tumors 394 (60%) patients had locoregional disease *versus* 244 (37%) who had metastasis.

A total of 155 (22.8%) TIVADs were removed after a median duration of 375 days (minimum 6, maximum 2763). The main reason for catheter removal was the end of cancer treatment (95, 14%) followed by catheter associated complications in 60 (8.8%) patients, including, exteriorization (13, 1.9%), disfunction (11, 1.6%), thrombosis (9, 1.3%), infection (8, 1.2%), obstruction (7, 4.5%), febrile syndrome (6, 3.9%), cutaneous infection (3, 1.9%), systemic infection (2, 1%), brachial plexus injury (1, 0.15%).

There were 96 (14.1%) complications documented in the study population, of which 6 (0.9%) were early complications and 90 (13.2%) late complications (Table II). None resulted in death of a patient.

Table II – **TIVAD Complications**

Complications	N (%)
Total	96 (14.1%)
Early complications	6 (0.9%)
TIVAD infection	2 (0.3%)
Hematoma	2 (0.3%)
Brachial plexus injury	1 (0.1%)
Dysfunction	1 (0.1%)
Late complications	90 (13.2%)
TIVAD thrombosis	30 (4.5%)
Cutaneous infection	15 (2.2%)
Exteriorization	13 (1.9%)
Dysfunction	10 (1.5%)
Obstruction	7 (1.0%)
TIVAD infection	7 (1.0%)
Febrile syndrome	6 (0.9%)
Sepsis	2 (0.3%)

The incidence of catheter related thrombosis was 4.4% (30 patients). This subgroup had a median age of 59 years-old (minimum 29, maximum 82), most of them women (21, 70%) with all TIVADs implanted on the subclavian vein (77% on the right side, 23% on the left side); 58% had metastatic disease and the most frequent cancer diagnosis were colorectal (9 out of 198), breast (6 out of 166), stomach (3 out of 42), pancreas (3 out of 54), lung (2 out of 48), ovary (2 out of 35) and occult primary (2 out of 14). Thrombosis was diagnosed a median of 75 days after TIVAD insertion (minimum 7 days, maximum 1600 days). In 3 cases (10%) thrombosis was an isolated imaging finding (detected on a procedure requested for non-TIVAD related reasons), thus the incidence of symptomatic thrombosis was 4% (27). The most common clinical presentation was upper limb edema (18 patients, 60%) followed by pain (11, 36,7%), neck edema (6, 20%), collateral venous circulation (5, 16.7%), difficulty with injection/aspiration of fluids (2, 6.7%) and superior vena cava syndrome (2, 6.7%). None of these patients was under prophylactic anticoagulation and all of them were treated with therapeutic doses of low molecular weight heparin (LMWH) after confirming the diagnosis on an imaging exam. However, it was deemed necessary to remove the catheter in 9 cases (30%).

We identified 13 cases of pulmonary embolism (PE) in 652 patients with TIVADs (incidence of 2%), 3 had concomitant catheter related thrombosis (3 out of 30 (10%) patients with catheter related thrombosis; p=0,0184, Fisher's exact test). All 3 patients had metastatic disease, 2 from colon cancer (none on Chemotherapy (ChT) or within 6 months of surgery), and 1 with a recent diagnosis of lung cancer (< 6 months) on ChT.

TIVAD infection was observed in 9 cases (incidence of 1.3%) with the following isolated microorganisms: *Pseudomonas aeruginosa* (3), Methicillin-resistant *Staphylococcus aureus* (3), *Enterococcus faecalis* (1), *Staphylococcus epidermidis* (1), *Klebsiella pneumonia* (1).

There were 7 cases of non-thrombotic TIVAD obstruction due to misplacement (3 cases), reservoir rotation (2 cases), catheter disconnection from the reservoir (1 case) and pinch-off syndrome (1 case) were documented. TIVAD dysfunction was reported in 11 cases (1.6%).

DISCUSSION

Since the first report on TIVADs insertion in 1982 by Niederhuber et al. many studies have demonstrated their safety and clinical benefit in patients with cancer.[5] TIVADs became a fundamental part in the treatment of these patients as they reduced the number of complications related to chemotherapy administration and allowed a better quality of life. Despite its undeniable advantages, the use of TIVADs is associated with potentially serious complications. In this series we report a total of 96 (14.1%) complications, with infections and catheter related thrombosis accounting for 56.3% of the total (24 infections and 30 catheter related thrombosis). Our results are comparable to most recent publications, which report complication rates between 8 and 38%.[1,2,3,4] However, it should be noted that the number of early complications was less than expected (6, 0.9%), since previous studies report rates between 1.8% and 26.8%.[6] This can be explained, at least in part, by the fact that insertion of TIVADs is a standardized procedure performed by a specialized team, but we must acknowledge this is a retrospective analysis subject to potential limitations in data documentation. Nevertheless, it's important to point out that we didn't observe any potentially fatal complication related to the procedure such as pneumothorax, hemothorax, air embolism or cardiac tamponade.

Infections are the most frequently reported catheter related complications, yet, in this series, thrombosis was the most common. Even if we consider TIVAD related infection and cutaneous infection together the incidence is still lower than thrombosis (24, 3.5% versus 30, 4.5%). In the literature, the rate of symptomatic thrombosis ranges from 2 to 8%, however, if routine screening is performed with Doppler ultrasound in asymptomatic individuals the incidence increases to 27-66%.[4,6,7,8,9] Accordingly, our results fit into the expected with a symptomatic thrombosis rate of 4.1%. If we consider Virchow's triad it's easy to understand the high risk of thrombosis in these patients, considering the hypercoagulability state related with cancer and the endothelial lesion promoted either by ChT and the TIVAD. There is an association between catheter related thrombosis and PE. Given that catheter related thrombosis is one of the commonest complications of TIVADs, prophylaxis with anticoagulants has been studied with inconclusive results and is not recommended. Treatment guidelines for catheter related thrombosis recommend at least three months of LMWH or LMWH followed by warfarin (INR, 2.0 to 3.0), with total duration depending on clinical characteristics of individual patients. Although it is appropriate to try treat thrombosis without catheter removal, if there are contraindications to anticoagulant medication, persistent or worsening symptoms, infection or TIVAD dysfunction, catheter removal must be considered. In this series only the 2 patients presenting with superior vena cava syndrome had their catheter immediately removed. The remainder were treated with LMWH, with 7 patients with persistence or worsening symptoms had their catheter removed. Concerning routine catheter management only saline flushing is indicated by guidelines, with insufficient data supporting routine use of anticoagulants to prevent catheter occlusion. [6] However in our institution TIVADs have been managed with heparin infusion.

Infectious complications were the second most frequent complication. They are a matter of concern as cancer patients are immunocompromised by the disease and its treatment, therefore more susceptible to develop sepsis. Reported rates of catheter associated infections can be as high as 31%, with lower rates in recent series (around 2%). These data are difficult to compare due to great variability between studies in the diagnostic criteria used to define catheter related infection. Coagulase-negative staphylococci are usually the most frequent identified microorganisms in patients with cancer and a catheter and initial empiric selection of antimicrobial agent should include a third-generation cephalosporin or vancomycin.[2,10] However in our series, *Pseudomonas*

aeruginosa and Methicillin-resistant *Staphylococcus aureus* accounted for more than half of the microorganisms isolated. Infection is considered an indication for TIVAD removal except if there aren't any local signs of infection, blood cultures are negative after 48-72hours of antimicrobial treatment, patients are hemodynamically stable and there is no infection relapse with the same agent after the first course of antimicrobials.[6] In this series 15 cutaneous infections were identified, the majority managed with oral antimicrobial therapy, with only 3 TIVADs removed due to lack of response or relapse of infection.

Regarding non-thrombotic causes of TIVAD obstruction it is important to identify possible causes for the malfunction, namely, the pinch off syndrome in catheters placed in the subclavian vein, where changing the arm and shoulder position can sometimes overcome the catheter dysfuncion. If there is difficult in aspiration of blood but maintained infusion capacity, changing the patient's position can also help if the catheter tip is positioned against the vein wall. Even if this malfunction cannot be overcome, in most cases TIVAD is maintained for ChT administration, collecting blood samples from a peripheral vein.

CONCLUSION

TIVADs are safe and provide benefits for patients with cancer undergoing systemic iv treatment, with a low risk of associated complications. As others, we also report a low rate of complications with no fatal events. A multidisciplinary effort must be made to minimize these complications by the promotion of a correct insertion technique, TIVAD aseptic management and optimized patient follow up.

However, since this is a retrospective study, we have to acknowledge potential limitations, including, under-reporting of complications, lack of optimal documentation of clinical information and empiric treatment with antimicrobials without previous blood cultures.

ABBREVIATIONS LIST

TIVAD: Totally implantable venous access devices
CT: Computed tomography
EMR: Electronic medical records
LMWH: low molecular weight heparin
PE: pulmonary embolism
ChT: Chemotherapy
IV: intravenous

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