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Maintaining patency in totally implantable venous access devices (TIVAD): A time-to-event analysis of different lock irrigation intervals

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A B S T R A C T

Purpose: To evaluate the effectiveness of irrigating totally implantable venous access devices (TIVADs) every eight weeks instead of every four in maintaining the patency of the device.
Methods: An explorative, pragmatic, prospective study design was conducted in two day hospital centres located in the northeast of Italy, from January 2011 to September 2012. Twenty patients who had skipped an appointment and were thus washing their TIVAD every eight weeks (exposed) were included, as were 17 patients following the typical wash regimen of every four weeks (controls). TIVAD occlusion—defined as the inability of the device to aspirate blood and/or the inability to properly irrigate the device—was the principal study end-point.
Results: A total of six occlusions were documented in six patients. Four cases were observed among the exposed group (4/20; 20.0%), while two were observed among the control group (2/17; 11.7%). No statistically significant differences were observed in the occurrence of occlusion between the groups (RR: 1.29, 95%CI: 0.67–2.50, $p = 0.49$). No statistically significant differences emerged between groups in the time that elapsed from study inclusion to occlusion occurrence according to the time-to-event analysis performed using the Kaplan–Meier estimation model (Log Rank [Mantel–Cox] = χ^2 0.284, df 1, $p = 0.594$).
Conclusions: Within the limitations of the study which should be addressed with further research based on double-blinded randomised clinical trials, postponing the irrigation regimen of TIVADs to eight weeks seems to be sufficient to maintain device patency.

Introduction

The totally implantable venous access device (TIVAD) is designed for long-term use when there is a need to access the device frequently, particularly in patients being treated with intermittent chemotherapy (Gallieni et al., 2008). The TIVAD may improve the patient's quality of life given that it allows ease of administration of medication and can be left in place for an extended period, including when the patient is not receiving therapy (Johansson et al., 2009; Nagel et al., 2012). When not in use, the TIVAD is kept patent by periodic irrigation with heparinised saline or normal saline solution (Bertoglio et al., 2012; Goossens et al., 2013). Some TIVAD manufacturers have recommended irrigation the device every four weeks; few studies however, have evaluated the effectiveness of different irrigation frequency in assuring device patency.

In a retrospective cohort study conducted by Ignatov et al. (2010), 349 patients with gynaecological cancer were enrolled after the end of the chemotherapy treatment and were followed until removal of the device or death. The TIVAD irrigation was performed using 500 IU/ml of heparin diluted in a 20 ml solution for injection. The 349 patients were divided into five groups according to the interval of their TIVAD irrigation schedule: 1) 140 patients received a wash every 1–4 weeks; 2) 87 patients every 5–8 weeks; 3) 30 patients every 9–12 weeks; 4) 26 patients every 13 weeks or more; and 5) 66 patients had their TIVAD washed every 1–2 weeks at the beginning and then every 12 weeks or less frequently. At the overall level, eight infections and thromboses were observed, seven having occurred in groups 1 and 2, those with shorter wash intervals. In the fifth group, infection occurred only during the initial period, when the TIVADs were washed once a month. In the fourth group, two thromboses occurred only in

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patients who had not adhered to their wash appointments. In the third group, no complications were observed. Based on the findings, an optimum range of 16 weeks has been suggested, but further multi-centre, randomised control studies were recommended.

In the same year, a prospective, multi-centre, observational study by Dal Molin and colleagues (2011), enrolled a total of 1076 patients (498 males and 578 females) from 26 Italian oncological care centres. The study evaluated the occurrence of late-stage complications—e.g., skins infections, TIVAD infections, occlusions and inability to draw blood from the device. Patients were divided into two groups: 1) 515 undergoing chemotherapy treatments (32,695 days of observation), and 2) 561 patients receiving follow-up care that required them to access the department only for TIVAD irrigation (106,173 days of observation). In the group of patients receiving chemotherapy, three cases of TIVAD infection were detected, as well as eight cases of occlusion and 12 other complications; in the group of patients receiving only follow-up care, however, four bacteraemia, three occlusions, one pocket infection, one cutaneous infection and seven other complications were detected. A total of four TIVADs were removed (0.7%). The authors therefore concluded that it was not necessary to wash the TIVAD every four weeks, although no definite evidence has emerged and further studies were suggested.

In 2009, Kefeli and colleagues conducted a retrospective study involving patients receiving chemotherapy to evaluate the effectiveness of irrigating the TIVADs every six weeks instead of the prescribed four-week interval. Patients with central venous catheters, those treated with anticoagulants or suffering some collateral effects as a result of the heparin use, were excluded. Eighty-nine patients were enrolled, and these were divided randomly into two groups: 1) 59 patients who received a TIVAD wash with 1000 IUs of heparin in 3 ml of normal saline every six weeks; and 2) 30 patients who received a TIVAD wash using 500 IUs of heparin in 3.5 ml of saline every four weeks. There were no clinically-relevant infections or thromboses in either group. According to the authors, an irrigation every six weeks with 1000 IUs of heparin was found to be safe, convenient, effective and less expensive than irrigation every four weeks: however, considering the limited sample and the retrospective nature of the study, the authors recommended further investigation.

Previously, Kuo et al. (2005) conducted a retrospective study including 82 patients—45 diagnosed with ovarian cancer, 23 with uterine cancer and 5 with cervical cancer. All patients had completed the prescribed chemotherapy at least six months prior, and were visiting their care location every 58 days on average (range: 29.5–244 days). Some continued to access the department for TIVAD irrigation once a month, while others never attended their appointments. A total of seven patients developed thrombosis, defined as an inability to aspirate blood through their TIVAD, although the device maintained its capacity for infusion; none of the patients reported fever, deep venous thrombosis or infection. The average irrigation intervals for patients with complications was 79 days while, for those who did not have complications, the average interval was 63 days; however, this difference was not statistically significant.

In light of the above-mentioned lack of evidence, the main aim of this study was to explore the effectiveness of irrigating TIVADs every eight weeks rather than every four weeks in maintaining the patency of the device and the differences, if any, in the time elapsed to the occlusion of the devices.

Materials and methods

Study design and setting

An explorative, pragmatic, prospective study was planned and undertaken in two day hospital centres located in the northeast of Italy from January 2011 to September 2012.

During 2011, the involved centres hosted a total of 698 first oncological visits and 3922 follow-up visits; the centres administrated 2455 cycles of chemotherapy and 961 TIVADs irrigations. The implanted TIVADs adopted by the centres were all produced by the same manufacturer, and were all of the same plastic reservoir diameter with perforated silicone septum connected to a central venous catheter (diameter: 1.0 mm internal, 6.6 Fr external). The standard wash interval of the TIVADs as adopted by the centres was every four weeks; moreover, given that the centres were located in a mountainous area characterised by transportation difficulties, not all patients were rigorous in adhering to their wash regimen: some came to the centres for a wash only every eight weeks, skipping an appointment in the interim.

Sampling and sample

A consecutive series of patients was included in the study. Patients were included who were older than 18, who had completed a chemotherapy treatment at least two months prior, with a need for TIVAD wash for at least six months and had given their informed consent. Patients with some contraindications to the use of heparin, with a central venous catheter, receiving parenteral nutrition or supportive care through the TIVAD, with infection manifested or suspected and those reporting previous device infection(s) were excluded.

On the basis of internal data, a total of 20 patients who had skipped a TIVAD wash appointment in the two months from completion of their chemotherapy treatment, and therefore receiving their TIVAD wash every eight weeks (exposed) instead of every four weeks, were identified and included in the study. During the same period, 17 patients who had strictly adhered to their wash regimen of appointments every four weeks (controls) in the two months following completion of their chemotherapy treatment were also included. A total of 27 patients were recruited from Day Hospital Centre '1' and 10 from Day Hospital Centre '2': the proportion of patients skipping their appointment was homogeneous between the Centres. According to the explorative nature of the study, the sample size was not defined *a priori*.

Diagram 1 describes the patient recruitment and the reasons for study withdrawal.

End-points, procedure and the data collection process

Based on the extant literature (e.g., Garofoli and De Nisco, 2007), TIVAD occlusion—defined as the inability of the device to aspirate blood and/or the inability to properly irrigate the device—was the study end-point. Patients were also evaluated for: a) sign(s) of infection and/or inflammation of the skin and tissue surrounding the TIVADs; b) tenderness at the site; c) presence of oedema; d) signs of extravasations surrounding the TIVADs; e) signs of local allergic reaction; and f) fever episodes reported after the last irrigation.

The TIVADs were irrigated at the time of study inclusion, with the aim of assessing their patency. Socio-demographic and clinical data for each patient was collected in a grid, including: patient age; cancer localisation; time elapsed from TIVAD implantation; anticoagulant/antiplatelet medication administered, if any; and whether or not the patient had experienced a fever episode since the last irrigation.

The device irrigation procedure (Vescia et al., 2008) was the same for all patients according to the protocols adopted at the centres: every four or eight weeks, a positive pressure and pulsating flush procedure with 20 ml of normal saline, followed by a locking procedure with 3 ml of sodium heparin (250 IUs/ml 5) for a total of 150 UIs of heparin was performed. The procedure was based on a protocol developed in accordance with recommendations made by: a)