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Original Article

Incidence and risk factors of port related infections in patients with hematological malignancy

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Abstract: The aim of this study was to determine the incidence and risk factors of infections associated with implantable venous access ports (IVAPs) in adult patients with hematological cancer. A retrospective analysis was made of patients with hematological malignancies in the adult Hematology Department between December 2014 and December 2016. IVAP was inserted in a total of 87 patients in the Interventional Radiology Department. Evaluation was made of the incidence of port-related infections, patient characteristics, bacteriological data and patient progress. Univariable analyses (Chi-square test and Mann-Whitney U test) and multiple logistic regression analyses were used to determine the risk factors for IVAP-related infection. The study included 87 patients applied with IVAP. There was a total of 21823 catheter/day follow-up. IVAP-related infection was observed in 13 cases (14.9%). Total incidence of IVAP-related bloodstream infections (BSIs) was 0.595 events/1000 catheter days. Coagulase-negative staphylococci were the pathogens most commonly isolated. In logistic regression analysis, factors that increased the risk for IVAP-related infections were neutropenia on the day of implantation (OR = 4.139; $P < 0.05$) and the number of chemotherapy lines received after IVAP insertion (OR = 2.126; $P < 0.05$). The median time without IVAP-related BSI was 62 days (range, 10-382 days). Neutropenia on the day of implantation and the number of chemotherapy lines after IVAP insertion were independent risk factors for IVAP-related BSIs. Therefore, it can be suggested that, as far as possible, ports should be inserted after the neutropenia period in these patients.

Keywords: Port, infection, hematological malignancy, neutropenia

Introduction

Patients with hematological malignancies are at increased risk of infections. It is because of the malignancy itself and also because of neutropenia induced by intensive chemotherapy [1]. One of the most important risk factors for bacteremia in hematological malignancies is the use of central venous catheters [2]. Totally implanted venous access devices was first described in 1982 [3], after which the use of central venous catheters became a routine procedure. Recently, implantable venous access ports (IVAPs) for the administration of intravenous chemotherapy have been reported and they have progressively improved the quality of life for patients. They are currently part of the standard medical care for oncohematology patients [4]. The major complications of IVAPs placement include infection, thrombosis, catheter obstruction, extravasation, and catheter migration [5, 6]. Central venous cathaters (CVCs) or IVAP-related infection is the most common cathater and port complication and the most common cause for explantation, and the rates range from 0.8% to 7.5% in recent studies [5, 7-10]. Contamination of the device by extraneous pathogens occurs less in IVAPs than in CVCs [11]. IVAP-related infections are also known to be associated with increased hospital length of stay and healthcare costs [10, 12].

Hematological malignancy itself increases the infectious complications [13, 14]. Another major factor is the neutropenia, which is secondary to disease or chemotherapeutic agents [2]. It has also been previously seen in a study

Table 1. Baseline characteristics of the patients

Baseline Characteristics	All (n: 87), Median (range)
Age (years)	60 [19-86]
Sex	
Female	40 (46.0%)
Male	47 (54.0%)
Diagnosis	
Non-Hodgkin Lymphoma	30 (34.5%)
Acute Myeloid Leukemia	19 (21.8%)
Multiple Myeloma	10 (11.5%)
Acute Lymphoid Leukemia	10 (11.5%)
Hodgkin Lymphoma	6 (6.9%)
Myelodisplastic Syndrome	4 (4.6%)
Aplastic Anemia	3 (3.4%)
Chronic Lymphocytic Leukemia	3 (3.4%)
Chronic Myelomonocytic Leukemia	1 (1.2%)
Plasma Cell Leukemia	1 (1.2%)
Autologous Stem Cell Transplantation	
Multiple Myelom	5 (5.8%)
Non-Hodgkin Lymphoma	1 (1.1%)
IVAPs implanted (n)	87
Follow-up (cathater/day)	21823

Abbreviations: IVAPs: Implantable Venous Access Ports.

of 1642 patients with solid tumors that monthly catheter-stay duration (number of catheter utilization days per month) was a risk factor for IVAP-related bloodstream infections (BSIs) [15]. It is important to identify the risk factors of IVAP-related BSIs for appropriate management of patients with central venous ports. Many recent investigations of risk factors for port-related infections have examined whether there is any factor other than those reported previously. Therefore, in this study, an analysis was made of IVAP-related infections and risk factors in adult patients with hematological malignancies.

Materials and methods

Patients

A retrospective analysis was made of patients with hematological malignancies in the adult Hematology Department between December 2014 and December 2016. A total of 87 patients were applied with IVAP for the administration of chemotherapy. Evaluation was made of the incidence of port-related infections, patient demographic information, chemotherapy regimens, laboratory test results, microbiological data and clinical progresses by reviewing the medical records and hospital database. All the diagnoses were classified in four different diagnosis groups. Group 1 was the lymphoma group [Hodgkin (n = 30) and Non-Hodgkin lymphoma, n = 6)], Group 2 was the acute leukemia group [acute myeloid leukemia (n = 30) and acute lymphoid leukemia, n = 10)], Group 3 was the myeloma group [multiple myeloma (n = 10) and plasma cell leukemia (n = 1)] and Group 4 was others [myelodisplastic syndrome (n = 4) aplastic anemia (n = 3), chronic lymphocytic leukemia (n = 3) and chronic myelomonocytic leukemia (n = 1). The clinical diagnosis of port-related infection was based on temperature of > 38°C, an IVAP in use 48 hours prior to the development of infection, and a positive blood culture with isolation of the same micro-organism from the catheter and bloodstream. IVAP-related BSI was defined according to The Center for Disease Control definition [16].

Statistical analysis

SPSS Statistics 19 software (IBM, Armonk, NY, USA) was used for statistical analysis. In the comparison of variables distributed homogeneously, the Independent Sample-t test was used for parametric variables and data were expressed as mean ± standard deviation. The Chi-Square test was used for non-parametric variables. For variables not showing homogeneous distribution, the Mann Whitney U test was used. Data were expressed as median [Min-Max] values. When the relationships of two qualitative variables were examined, "X^2-cross tables" were used according to the expected value levels. Binary Logistic Regression analyses were used to determine the risk factors for IVAP-related infection. In the adjusted module for logistic regression, correct categorization ratio was 81.6%, and the module was significant according to Hosmer-Lemoshow statistics of X^2 test (X^2 = 12.683; P = 0.123). A value of $P < 0.05$ was accepted as statistically significant.

Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amend-

Table 2. Characteristics of IVAP-related infections

IVAPs related infections	All (n: 13), n (%)
Incidence of BSI (event/1000 cathater days)	0.595
IVAP-BSI microorganisms	
Coagulase-negative staphylococcus	8 (61.5)
Pseudeumonas Aeruginosa	2 (15.4)
Escherichia coli	1 (7.7)
Klebsiella pneumoniae	1 (7.7)
Acinetobacter baumannii	1 (7.7)
Causes of IVAPs removal	
IVAP-related BSI	3
Lokal Exit Site Infection and Skin Necrosis	2
End of Treatment	1
Culture of Cathater Tips	
Burkholderia Cepacia	2
Escherichia Coli	1
None	3

Abbreviations: IVAPs: Implantable Venous Access Ports, BSI: Blood stream infection.

ments or comparable ethical standards. As a standard of care/action of the Ankara Diskapi Yildirim Beyazit Research and Training Hospital, it was confirmed based on the patient records that all of the studied patients gave the informed consent at the time of hospitalization and before the administration of chemotherapy and other relevant diagnostic/therapeutic standards of care.

Results

Baseline characteristics of the patients

The study included a total of 87 patients inserted with IVAP. The total follow-up was 21823 catheter/day. The most common diagnoses were Non-Hodgkin lymphoma (34.8%) and acute myeloid leukemia (22%). Autologous stem cell transplantation was performed in 6 cases during follow-up (5 multiple myeloma cases, 1 mantle cell lymphoma case). No thromboembolic complications occurred. The baseline characteristics of the patients are presented in **Table 1**.

Characteristics of IVAP-related infections

Of the 87 patients with hematological malignancies, IVAP-related infection was observed in 13 cases (14%) and the total incidence of IVAP-related BSIs was 0.595 events/1000 catheter days. The median period from port implantation to the episode of port-related infection was 62 days (10 to 382 days). Of the 13 infectious cases, 11 (84.6%) had neutropenia on the day of IVAP-related BSI detection. Coagulase-negative staphylococci were the pathogens most commonly isolated (8 cases, 61.5%). All patients with BSI were treated with antibiotics, and removal of the catheter was only indicated for 6 patients (6.8%). There was no isolated microorganism in the catheter tip culture of 3 cases where the IVAP was removed for reasons other than infection. The characteristics of IVAP-related infections and IVAP removal are shown in **Table 2**.

Comparison of patients with and without IVAP-related BSI

In the comparison of patients with and without IVAP-related BSI, the patients in the infectious group were younger than those in the non-infectious group ($P < 0.021$). There was no difference between the groups in respect of gender and diagnosis subgroups. The number of chemotherapy lines in the infectious group was significantly higher than in the non-infectious group ($P < 0.05$). Autologous stem cell transplantation was performed in 6 cases during the port follow-up period and there was no relationship between autologous stem cell transplantation and IVAP-related BSI. Median platelet count on the day of IVAP insertion was lower in the infectious group than in the non-infectious group but there was no statistical difference ($P = 0.06$). Neutropenia was present on the day of IVAP insertion in 11 (84.6%) of 13 infectious patients, and in 1 (1.4%) of 74 non-infectious patients, with a statistically significant difference determined between the two groups ($P = 0.00$). The median port follow-up days were similar in both groups. The comparisons of all these parameters are shown in **Table 3**.

Logistic regression analysis revealed that neutropenia on the day of IVAP insertion, number of chemotherapy line and age were independent risk factors of IVAP-related infection (**Table 4**). The adjusted odds ratio of infection for neutropenia was 4.139 (95% confidence interval (CI) = 1.037-16.512), for number of chemotherapy line was 2.126 (95% CI = 1.152-3.924), for age

Table 3. Comparison between Infectious Group and Non-infectious Group

Parameters (N = 87)	Patients with IVAP-related BSI All (n: 13), n (%), Median (range)	Patients without IVAP-related BSI All (n: 74), n (%), Median (range)	*P*
Age (years)	50.0 [20.0-68.0]	61.0 [19.0-86.0]	0.021
Sex			
Male	6 (46.2%)	34 (45.9%)	0.989
Female	7 (53.8%)	40 (54.1%)	
Diagnosis			
Lymphoma (HL-NHL)	5 (38.5%)	31 (41.9%)	0.429
Acute Leukemia (AML-ALL)	6 (46.1%)	23 (31.1%)	
MM and PCL	-	11 (14.9%)	
Others	2 (15.4%)	9 (12.1%)	
Chemotherapy Line	2.0 [1.0-4.0]	1.0 [0.0-5.0]	0.004
ASCT			
Yes	1 (7.7%)	5 (6.8%)	
No	12 (92.3%)	69 (93.2%)	0.902
Platelet count on day of IVAP insertion ($\times 10^6$/l)	70000 [11000-292000]	171000 [7000-471000]	0.063
Neutropenia on day of IVAP insertion			
No	2 (15.4%)	73 (98.6%)	
Yes	11 (84.6%)	1 (1.4%)	0.000
Port Follow-up (days)	208.0 [33.0-614.0]	223.0 [7.0-692.0]	0.757

Abbreviations: HL: Hodgkin lymphoma, NHL: Non-hodgkin lymphoma, AML: Acute myeloid leukemia, ALL: Acute lymphoid leukemia, MM: Multiple Myeloma, PCL: Plasma cell leukemia, ASCT: Autologous stem cell transplantation, IVAP: IVAPs: Implantable Venous Access Ports.

Table 4. Logistic regression analysis for risk factors of IVAP-related infection

Risk Factor	OR	95% CI	B	*p*
Neutropenia	4.139	1.037-16.512	1.420	0.044
Chemotherapy Line	2.126	1.152-3.924	0.754	0.016
Age	0.963	0.928-1.000	-0.037	0.048

Note: Neutropenia existence on day of IVAP insertion was chosen as a reference category for neutropenia. Abbreviations : B: Beta coefficient, CI: Confidence Interval, OR: Odds Ratio.

was 0.963 (95% CI = 0.928-1.000). The most effective variables were neutropenia on the day of IVAP insertion and number of chemotherapy line.

Discussion

In this single institution-based study, the incidence and risk factors of infections associated with IVAPs in patients with hematological cancer were investigated. IVAP-related infection was observed in 13 cases (14%) and the total incidence of IVAP-related BSIs was 0.595 events/1000 catheter days. In recent studies it has been shown that IVAP-related infection rates range from 0.8% to 7.5% [5, 7-10]. According to the results of a review that analyzed 200 published studies of adults in which every device in the study population was prospectively evaluated for evidence of associated infection, it was suggested that the risk of intravascular device (IVD)-related BSI be expressed per 1000 IVD days rather than BSIs per 100 IVDs for more meaningful estimates of the risk [12]. In that literature review, which included patients with solid tumors, surgical and traumatic causes and acquired immunodeficiency syndrome not only hematological cancer, the incidence was 0.1 per 1000 port. In other studies, the incidence of BSI has been reported to range from 0.091 to 2.77 per 1000 catheter-days and it appears to differ according to the specific underlying illness [17-19]. Therefore, the incidence rate in the current study was higher than that of recent studies based on both BSIs per 100 IVDs and BSI per 1000 IVD days. This could be attributed to the patient selection of the current study being only those diagnosed with hematological malignancy as it has been shown in many previous studies that hematological malignancy itself is a much more highly significant risk factor for infection than other types of solid cancers [13, 14, 17, 19, 20]. In studies including only

patients with hematological malignancies, the incidence of CVC-related bacteremia not IVAP-related BSI has been analysed and reported to range from 6.5 to 19 per 1000 catheter days [2, 21, 22]. In a study including both hematological and non-hematological cancer patients, the IVAP-related BSI rate was 0.66 episodes per 1,000 port days in hematological tumors [23]. There are conflicting reports about the pathogens most commonly isolated from IVAP-related BSI. Many studies have shown gram-positive microorganisms to be the most common pathogens [2, 10, 13-15, 18, 20, 21], whereas others have reported gram-negative microorganisms [19, 24]. In the current study, coagulase-negative staphylococci were found to be the pathogens most commonly isolated (61.5%).

There have been many studies and investigastions related to the risk factors for port-related infections because infection related to intravenous devices results in significant increases in hospital costs, duration of hospitalization, and patient morbidity [10, 12, 25]. In the current study, neutropenia on day of port insertion, younger age and number of chemotherapy line were observed to be significantly associated with an increased risk of BSI. It was proven many years ago that neutropenia is the most prominent and important risk factor for bacteremia in hematological cancer patients [26]. The effect of neutropenia on IVAP-related BSI has also been frequently investigated. In a case-control study by Pagano et al., one of the risk factors for bacteremia in patients with hematological malignancies was found to be neutropenia for more than 6 days [2]. Another study attributed the higher rate of BSI in the hematology group to profound neutropenia [23]. In the current study, neutropenia on the day of port insertion was determined as the most significant risk factor for IVAP-related BSI (OR: 4.139, P < 0.05). Similar to our result, it is recently reported that neutropenia on the day of implantation increases the risk of IVAP-related BSI in a study with pediatric oncology patients and in another study including children with acute leukemia [27, 28]. In contrast, a study of 1642 patients with solid cancer revealed that neutropenia did not increase the risk of IVAP-related BSI [15]. In addition to these findings, 85% of the cases in our study were neutropenic on the day of infection detection. Infectious patients who had neutropenia on the day of IVAP insertion also had neutropenia on the day of infection detection. Therefore, it can be considered that neutropenia both at the beginning and during the follow-up period might play a major role in IVAP-related BSI.

There is no agreement on whether age is a risk factor for infection. A study showed that age > 65 was a risk factor for IVAP-related BSI [24]. However, in another study, age < 20 increased the risk of infection but not statistically significant [14]. In the current study, the median age of infectious patients was found to be lower than that of the non-infectious group. Logistic regression analysis revealed that age decreases the risk of infection but its impact was lower than other two factors (OR: 0.963, $P < 0.05$). This may have been due to the higher number of chemotherapy lines in the infectious group who were younger than the non-infectious group (2.0 [1.0-4.0] vs 1.0 [0.0-5.0], $P = 0.004$). Similarly, in a study by Panagiotis Samaras et al. including both hematological and solid tumor patients, it was reported that the only significant risk factor associated with a higher port complication rate was younger age [13]. In that study, infections were the main type of complication and age was related to hematologic neoplasm, since patients with hematologic neoplasms were significantly younger than solid tumor patients.

In the current study, analysis was made of the hematological malignancy subtypes, performing ASCT and number of chemotherapy lines during the port follow-up period in adult hematology patients. It was investigated whether or not there was any impact on the incidence of IVAP-related BSI. In 2006, it was reported that HSCT was associated with increased risk of both port and central venous catheter related BSI in pediatric hemato-oncology patients [29]. In our study, patients who had performed ASCT during port follow up period did not show any increase in IVAP-related BSI incidence. In a study that analyzed the risk factors of CVC-related bacteremia (not IVAP-related) in hematological patients, it was noted that acute myeloid leukemia (AML) is associated with increased risk of infection [22]. In the current study, the diagnoses of patients were classified in four groups; acute leukemia group, lymphoma group, myeloma group and others. No sig-

nificant difference was determined between the infectious and non-infectious groups in respect of the diagnosis subtypes. However, the results revealed that a higher number of chemotherapy lines given to patients during the port follow-up period was strongly associated with infection risk (OR: 2.126, $P < 0.05$). This may have been due to the increased frequency of chemotherapy-induced neutropenia in patients who recieved multiple chemotherapy lines. Previous studies on chemotherapy status have been limited to the nature of chemotherapy as curative or palliative, adjuvant or non-adjuvant, not the number of lines. In a study published in 2014, the incidence of IVAP-related infection was higher in hematooncology patients receiving palliative chemotherapy [14]. Another study including both solid and hematological cancer patients showed that chemotherapy in an adjuvant setting is associated with a lower risk of infection than for patients in a neoadjuvant setting [19]. It has also been shown that the neutropenia-inducing potential of the chemotherapy regimens administered affects the IVAP removal rates [30].

It is questionable whether the long-term placement of a port in patients with hematological malignancy may result in an increased frequency of infection or not. In the currrent study, no relationship was determined between the port follow-up period and infection. Similarly, a previous study including hematological and nonhematological cancer patients revealed that IVAP-related infection appeared to be attributable to profound neutropenia not port follow-up [23]. Another study about ports usage suggested that adherence to a 6-day interval between the insertion and first use of IVAPs for the administration of chemotherapy may reduce port removal rates due to the complications and especially infectious morbidity [30]. In another study, Guk Jin Lee *et al.* showed that longer duration of monthly catheter-stay increases the risk of IVAP-related BSI [15].

The limitations of this study were the retrospective design and the relatively small number of patients. The findings of this study should be confirmed by future, prospective studies of larger cohorts.

In recent years, IVAPs are part of the standard medical care for oncohematologic patients. The major complication of IVAPs is infection. To conclude, we herein showed that neutropenia on the day of implantation and number of chemotherapy line after IVAP insertion were most significant risk factors for IVAPs-related BSI in patients with hematological malignancy. Therefore, we proposed to insert ports after the neutropenia period of these patients as much as possible.

Disclosure of conflict of interest

None.

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