Risk factors for complications of implantable venous access port usage among young pediatric patients with a solid tumor in China: a single-center retrospective study

Short title: Pediatric venous access port with solid tumor

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Abstract

Background and Objectives: This study aimed to evaluate the utilization of totally implantable venous access ports (TIVAPs) and identify risk factors for complications associated with their usage in young pediatric patients with a solid tumor.

Methods: We retrospectively investigated the clinical characteristics and procedure records of all patients admitted with a solid tumor who underwent TIVAP implantation and removal as well as line patency maintenance in our clinic from 2016 to 2019 at the Shanghai Children's Medical Center.

Results: Overall, 144 patients were evaluated over 28,444 catheter days. There was a greater risk of central line-associated bloodstream infection (CLABSI) in patients with neuroblastoma who were older in age and whose body mass index was lower. The rate of CLABSI was relatively increased in high-risk than low-risk and intermediate-risk neuroblastoma according to the Children's Oncology Group (COG) classification system. There were no significant differences in complications between the TIVAP implantation group and the combined surgery group.

Conclusions: Older age, lower BMI, and high COG risk are great risk factors of CLABSI in patients with neuroblastoma, thus requiring vigilant surveillance. Combining TIVAP insertion with biopsy and/or resection surgery should be given due consideration.

Keywords:

totally implantable venous access port, solid tumor, pediatric, complication, neuroblastoma

1. Introduction

Totally implantable venous access ports (TIVAPs) are frequently used to provide central venous access in cancer chemotherapy, and they play an important role in the long-term management of pediatric oncological diseases[1]. TIVAPs are designed to provide safe and comfortable central line access to avoid frequent painful blood punctures of peripheral veins, thereby improving patient quality of life[2,3]. Moreover, TIVAPs have lower failure and complication rates, rendering their cost-effectiveness superior to that of other central venous access device types[4].

Although the use of TIVAPs has greatly improved the quality of care in pediatric patients with cancer, it can also lead to severe complications, such as infection, thrombosis, and dislodgement[1,5]. Previous studies of TIVAPs have mainly focused on leukemia in adult or pediatric populations[6–8]. However, factors affecting the safety and efficacy of TIVAPs in pediatric patients with solid tumors may represent a distinction. Pediatric solid tumors are a group of non-hematologic cancers occurring during childhood, which are either embryonic or developmental malignancies in young children or adolescents resulting from alterations in the process of organogenesis or normal growth. This heterogeneous group of tumors represents approximately 40% of all pediatric cancers[9]. Although pediatric leukemia and solid tumors are both malignant cancers, they require very different approaches in terms of therapy and prognosis. Leukemia is mainly treated by chemotherapy, whereas pediatric solid tumors usually require surgery. Chemo- and radiotherapy could also be considered as viable treatment options depending on the tumor type and stage and the patient's age. Therefore, differences in cancer origin and biological characteristics may lead to various complications of TIVAP usage.

Investigations have been conducted to determine the risk factors of venous access device complications in pediatric patients. In a pediatric leukemia population, unexplained line malfunction, the preoperative dosage of packed red blood cells, and the presence of a bloodstream infection (BSI) were found to be significant predictors of premature central venous access device removal[10]. Younger age at diagnosis, female sex, left-side placement, and the duration of TIVAP usage were also found to increase the risk of thrombosis in pediatric oncological patients with TIVAP[11].

Similarly, despite the significantly different disease courses typical of pediatric solid tumors, we hypothesized that there would be identifiable risk factors associated with TIVAP complications in the pediatric population with solid tumors. Therefore, we analyzed the utilization and premature removal of TIVAPs and its complications in pediatric patients with a solid tumor who underwent surgery or chemotherapy via a TIVAP and were followed up at our center.

2. Materials and Methods

2.1 Patients

We conducted a retrospective analysis on 144 pediatric patients who underwent TIVAP implantation from June 2016 to December 2019 at Shanghai Children's Medical Center. All of the patients had solid tumors and underwent insertion and complete removal of TIVAP at our hospital. The exclusion criteria were as follows: device insertion or removal at a different institution, failure to maintain line patency, use of port access by other consultant services, patient death, or incomplete treatment with a TIVAP. Written informed consent was obtained from each patient's guardian.

2.2 Data collection

Demographic data, disease and treatment course, surgical details, and complications related to TIVAP usage were obtained from medical charts. The sociodemographic variables included the age at the time of insertion and removal, sex, and body mass index (BMI). The clinical variables included the type of cancer and complications such as catheter dislodgement and leakage, BSI, and central line-associated bloodstream infection (CLABSI). In this study, only laboratory-confirmed BSI or CLABSI was taken into consideration, with the endpoint being any positive blood culture result. Patients with a clinically diagnosed BSI or CLABSI but with a negative blood culture were excluded from the analysis. The surgery-related variables consisted of the duration of insertion, number of revisions required, methods of revision, and TIVAP condition at removal.

2.3 Statistical analysis

Statistical analysis was performed using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). All analyses were two-tailed, and a difference was considered to be statistically significant if the p value was < 0.05. Differences between groups were assessed using the chi-squared test or Fisher's exact test for categorical data. Continuous variables were analyzed using Student's t-test for normally distributed data and the Wilcoxon rank-sum test for nonparametric data. Binary logistic regression analysis served as a univariate or multivariate model to quantify the independent contribution of one or more factors of interest to removal, expressed as the risk ratio with 95% confidence interval (CI). The local significance level was set to 5% for statistical analysis.

3 Results

3.1 Demographic characteristics

During the study period, 171 children with solid tumors had undergone both insertion and removal at our institution; however, 27 patients were excluded because they did not undergo chemotherapy or line patency maintenance at our hospital. The final analysis consisted of data from 144 patients with a total of 28,444 catheter days. In total, 64% of the patients were female. The TIVAPs remained in place from insertion to removal for an average of 198±102.8 days. All catheters were inserted into the internal jugular vein. The average age at the time of insertion was 1.2 years, whereas the average age at the time of removal was 1.9 years old. A majority of participants had a diagnosis of neuroblastoma (35.4%), hepatoblastoma (29.9%), and sarcoma (15.3%). The baseline patient characteristics are presented in Table 1.

3.2 Premature removal

Overall, 135 TIVAPs were removed after completion of treatment, while 9 TIVAPs were removed prematurely in accordance with the Clinical Practice Guidelines for the Diagnosis and Management of Intravascular Catheter-Related Infection[12], 6 of which were removed prematurely for CLABSI, 2 for BSI, and 1 for multi-infection. All the children who had undergone premature TIVAP removal used a peripherally inserted central catheter to complete chemotherapy treatment. The characteristics of all premature removals are listed in Table 2. Prematurely removed TIVAPs tended to have a shorter indwelling time (p=0.016). However, there is no difference observed in terms of birth weight, male sex, BMI, diagnosis, and premature removal (Table 3). Multivariate logistic regression was used to estimate the risk of premature catheter removal. The variables included in the final model consist of sex, diagnosis, child growth

standard, age, BSI, and CLABSI. After adjusting for the other variables, BSI (odds ratio (OR), 695.848; 95% CI, 4.348-111365.915), CLABSI (OR, 283.932; 15.659-5148.191), and indwelling time (OR, 0.978; 95% CI, 0.957-0.999) were found to be associated with an increased risk of premature catheter removal (Supplementary Table 1).

3.3 Complications

Among the 144 cases, there were 24 cases (16.7%) of TIVAP-related complications, including 3 cases of physical catheter damage, 4 cases of catheter leakage, 6 cases of BSI, and 11 cases of CRBSI (catheter-related blood- stream infection) (Figure 1). There was no case of catheter obstruction or episodes of venous thrombosis. BSI and CRBSI were diagnosed in 17 patients (11.8%). Gram-negative microorganisms were the pathogens most commonly isolated and the most common cause of TIVAP removal (Table 4). All patients with BSI and CLABSI were treated with systemic antibiotics, but TIVAP removal was indicated in the case of 11 patients (64.7%). The incidence rates of fungal infection and multi-infection were lower than those of bacterial infections; however, once infection develops, TIVAP removal was inevitable.

CLABSI was the most common complication associated with the use of TIVAP, accounting for 53.33% of the total complications (Figure 1). In the bivariate analysis, we observed that the diagnosis of neuroblastoma was associated with an increased rate of CLABSI (p=0.026) (Table 5), while that of Wilms' tumor or yolk sac tumor was associated with a greater risk of BSI (p=0.036 and p=0.04, respectively) (Supplementary Table 2). These types of solid tumors were more vulnerable to infections; however, there was no obvious difference between the increased rate of infections and other diagnoses of solid tumors. In addition, no obvious relationship was noted

between different types of solid tumors and the rate of premature removal (data not shown), as 52% (9 in 17) of TIVAP infections could be cured by conservative treatment with combined systemic antibiotics. Further investigation revealed that in the group of pediatric patients with neuroblastoma, there was an increased rate of CLABSI associated with older age, high-risk status according to the Children's Oncology Group (COG) classification system[13], and lower BMI at the time of insertion (p=0.017, p=0.017, and p=0.048, respectively). The BMI of patients with neuroblastoma falling below the 50th percentile of the World Health Organization (WHO) child growth standards was a great risk factor of CLABSI (p=0.045) (Table 6). However, there was no obvious relationship between age or BMI at the time of insertion and the rate of CLABSI in patients with different types of solid tumors (Table 5). These specific clinical characteristics influencing the rate of CLABSI were only observed in patients with neuroblastoma.

Every patient with a solid tumor required one or more operations such as tumor biopsy and/or resection, excluding TIVAP insertion. There was no significant difference in complications between patients who underwent simultaneous TIVAP implantation with tumor biopsy/resection and those who underwent a separate procedure for TIVAP insertion (Supplementary Table 3). There were also no significant differences observed in complications in terms of the varied lengths of operation (data not displayed).

4 Discussion

In this retrospective study, we analyzed the data of pediatric patients with solid tumors who underwent TIVAP insertion and removal over a period of 3 years. Our study showed that the total rate of complications was 16.7%, and the rate of premature removal was 6.25%, which were

comparable to the results of some previous studies[14–16] but were significantly lower than those of studies involving a pediatric leukemia population[10,11,17]. Our results demonstrated that the premature removal of TIVAPs is associated with a significantly increased rate of infection, including BSI and CLABSI, among children with solid tumors. Gram-negative bacteria are the most commonly found pathogens in blood cultures of patients with infections. Nevertheless, most gram-positive infections can be successfully managed with systemic antibiotics without TIVAP removal particularly in pediatric cancer patients[18], as confirmed in our patient population. Gram-negative microorganisms, fungal infection, and multi-infection were also observed as reported in other studies[19,20]. In our study, the majority of TIVAPs required removal in cases of gram-negative infection, whereas premature removal became inevitable in cases of fungal infection and multi-infection. Infection-related complications are considered significant in TIVAP usage. In addition, unlike other studies on adult[2,21] and pediatric hematological patients[8,10] with TIVAPs, we were not able to analyze data on thrombosis due to the absence of catheter obstruction or episodes of venous thrombosis.

The present results show that patients with neuroblastoma had a greater risk of CLABSI, whereas patients with Wilms' tumor or yolk sac tumor had a greater risk of BSI. However, there was no obvious difference between the increased rate of infections and other diagnoses of solid tumors, such as hepatoblastoma and sarcoma. The association between CLABSI and BSI complications and diseases themselves could also be attributed to the different chemotherapy regimens. In studies of patients undergoing chemotherapy, the administration of cytotoxic drugs reportedly increase the risk of infectious complications and interfere with wound healing[22,23]. A univariate

analysis comprising cases of neuroblastoma with TIVAP usage identified older age and a high-risk status based on the COG classification system as risk factors for CLABSI, which corresponds with the diverse clinical behavior of neuroblastoma. In general, patients with neuroblastoma exhibit extremely heterogeneous clinical courses, which are mainly contingent on the age at diagnosis and the stage of the disease[24]. Neuroblastomas diagnosed after 1 year of age always have a poor prognosis[24]. Moreover, the most common induction therapy for patients with high-risk neuroblastoma is intensive chemotherapy, whereas treatment regimens for patients with low- and intermediate-risk neuroblastoma have been designed to further decrease the therapeutic intensity and to reduce associated toxicity[25]. The toxicity of chemotherapy for high-risk neuroblastoma is associated with serious infections[26,27], which might explain the high risk of CLABSI among older patients with neuroblastoma. Furthermore, our study also established that a low BMI at the time of insertion is a risk factor of CLABSI in patients with neuroblastoma, particularly those falling below the 50th percentile of the WHO Child Growth Standards[28,]. Weight loss is a systemic symptom of patients with neuroblastoma, whose population is more likely to be underweight[29]. According to the Childhood Cancer Survivor Study, underweight subjects were more likely to report adverse health conditions and major medical conditions than those with normal weight[30]. Interestingly, Taveira et al.[6] found an association between CLABSI and chronic malnutrition, whereas the literature reviews of Rogers et al. and McLean et al. revealed no studies involving pediatric oncological patients in which this association was reported[31,32]. It appears that both reports [6], [31,32] gave a reasonable account as they included patients with different types of cancer. This was consistent with our result that malnutrition increased the risk of CLABSI in patients with neuroblastoma, although there was no obvious

difference between low BMI and the incidence of CLABSI in all children with different types of solid tumor. This is an important finding because TIVAP insertion may contribute to infection in patients with neuroblastoma having older age, lower BMI, and a high-risk status based on the COG classification system, despite the fact that immunosuppression often occurs in all cancer patients undergoing chemotherapy treatment. These findings further emphasize the need for intensive nutritional support and careful management in this critical patient group.

Multiple surgeries are inevitable in children with solid tumors requiring surgery for port insertion. Surgical resection is the first choice of treatment for most pediatric solid tumors, and biopsy surgery is important for diagnosis and guidance of chemotherapy[33]. Although the operation time was longer when TIVAP insertion was combined with biopsy and/or resection surgery and internal jugular vein damage was increased by catheterization during the second surgery, there were no significant differences in terms of complications between the TIVAP implantation group and the combined surgery group. To reduce the frequency of anesthesia administration and improve cost-effectiveness, combined surgery could be considered; however, prospective trials should be performed to evaluate its benefits.

There are a few limitations to this study. First, the individual chemotherapy regimens were not included in the analysis, which could have had an impact on the complications. Second, this study was a retrospective single-center study, rendering it impossible to control for the type of operative procedure (whether combined or not), which was determined by different experienced surgeons. Thus, the optimal operative procedure for TIVAP placement in pediatric patients with solid tumors remains to be defined in future prospective studies.

5 Conclusions

In summary, the most common complication of TIVAP usage in young pediatric patients with solid tumors is infection, namely, BSI and CLABSI, which are also considered as significant predictors of premature TIVAP removal. Therefore, the prevention of infections will greatly benefit pediatric patients. In this study, only the diagnosis of neuroblastoma was found to be associated with a greater risk of CLABSI. Older age, lower BMI, and a high-risk status based on the COG classification system are great risk factors of CLABSI in the neuroblastoma population. We believe that the varied clinical courses of neuroblastoma and the toxicity of chemotherapy might play an important role in the development of complications, hence the need for improved clinical surveillance in this population. Because of the lack of evidence suggesting that combined surgery increases the risk for complications, we recommend performing combined surgery to reduce the frequency of anesthesia administration and lessen the financial burden associated with the procedure. Nevertheless, the present findings warrant further confirmation through a prospective randomized study in the future.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Conflict of interest disclosure

All authors confirm that there is no conflict of interest.

Ethics approval statement

This retrospective study received approval from the Institutional Review Board of Shanghai

Children’s Medical Center.

Patient consent statement

Written informed consent was obtained from each patient’s guardian.

Credit Authorship contribution Statement

Shanshan Qiu Ming Hu, Ping Guan, Chenchen Li, Nan Bao, Jun Chu: Conceptualization, Methodology, Project administration, Writing - original draft, and Project administration. Ming Hu: Investigation, Formal Project administration, Writing - original draft. Ping Guan: Investigation, Validation, Data curation. Chenchen Li: Investigation, Visualization, Data curation. Nan Bao: Review, Funding acquisition, Supervision. Jun Chu: Conceptualization, Formal analysis, Writing - review & editing, Supervision.

Abbreviations

BMI body mass index

BSI bloodstream infection

CI confidence interval

CLABSI central line-associated bloodstream infection

COG Children’s Oncology Group

OR odds ratio

TIVAP totally implantable vascular port

WHO World Health Organization

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Figure Legend

Figure 1. Complication rates. CRBSI=catheter-related blood- stream infection; BSI=bloodstream infection