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Neutropenia at the time of subcutaneous port insertion may not be a risk factor for early infectious complications in pediatric oncology patients.

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Abstract

Background: The risk of infection associated with subcutaneous port (SQP) placement in patients with neutropenia remains unclear. We reviewed the rate of early infectious complications (<30 days) following SQP placement in pediatric oncology patients with or without neutropenia [absolute neutrophil count (ANC) <500/mm^3].

Methods: Baseline characteristics and infectious complications were compared between groups using univariate and multivariate analyses.

Results: A total of 614 SQP were placed in 542 patients. Compared to non-neutropenic patients, those with neutropenia were more likely to have leukemia (n=74, 94% vs n=268, 50%), preoperative fever (n=17, 22% vs n=25, 5%), recent documented infection (n=15, 19% vs n=47, 9%), and were younger (81 vs 109 months) (p values <0.01). After adjusting for fever and

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underlying-disease, there was a non-significant association between neutropenia and early post-operative infection (OR 2.42, 95% CI 0.82–7.18, p=0.11). Only pre-operative fever was a predictor of infection (OR 6.09, 95% CI 2.08–17.81, p=0.001).

Conclusion: SQP placement appears safe in most neutropenic patients.

Keywords

Pediatric; Oncology; Neutropenia; Infection; Venous access

INTRODUCTION

Tunneled central venous catheters are essential tools in the management of children with cancer.[1] These devices allow long-term vascular access thereby permitting administration of chemotherapy, antibiotics, supportive medications, total parenteral nutrition, and allowing for necessary blood draws during therapy.[2] When compared to other tunneled catheters with external components, the totally implantable subcutaneous port (SQP) offers the advantage of being completely covered by skin and soft tissue, and when not accessed, the patient may shower, swim, and engage in most regular activities. While use of these devices is desirable, many pediatric oncology patients present with severe neutropenia at diagnosis or become neutropenic during treatment with cytotoxic chemotherapy. Because of the potential for increased infectious and wound complications in patients with severe neutropenia, many centers do not place SQP in patients with an absolute neutrophil count (ANC) less than 500 per mm^3.[3] While this is a common practice, data are conflicting regarding the association of neutropenia and complications after SQP placement.[2,10–16]

Early infection (within 30 days of central venous catheter insertion) is the most notable and frequently reported complication, occurring in 8–22% of pediatric patients with hematologic malignancy.[4–6] SQP are associated with the lowest rate of long-term infectious complications among central venous catheters.[7] Despite less infectious risk with SQP, the consequences of infection may be more significant due to increased complexity of infection, more difficult device removal, or a surgical wound resulting from removal. Catheter-related or surgical site infections often necessitate removal of the SQP under general anesthesia and may additionally delay therapy. [8,9]

Efforts have thus been made to optimize timing for insertion of SQP to minimize the risk of early postoperative infection. There is currently no standard protocol for SQP placement in the setting of neutropenia and therefore practices vary widely between centers. For example, in pediatric hematologic malignancies, SQP insertion may occur at the time of initial diagnosis, beginning of remission induction therapy, or following resolution of neutropenia. [2,3,10,11] Waiting for neutropenia to resolve prior to definitive venous access placement may result in a delay in therapy and multiple venipunctures. The literature is inconsistent regarding the association of neutropenia and complications after SQP placement, with some studies documenting increased infectious risk,[10–14] and others demonstrating no significant increased risk.[2,15,16]

The purpose of this study was to examine the association between neutropenia and the development of early post-operative infectious complications (30 days following the initial procedure) in pediatric oncology patients who underwent SQP insertion in a single cancer center. Our secondary objectives were to document the incidence of early post-operative infectious complications and to identify risk factors associated with SQP-related infectious complications. Furthermore, we sought to describe the type of infectious complications that occurred and the associated interventions, such as antibiotics and port removal.

METHODS

Patient cohort

An Institutional Review Board-approved retrospective review was performed. Electronic medical records of all pediatric oncology patients undergoing SQP placement at St Jude Children's Research Hospital between January 2013 and December 2016 were reviewed. The time period of this study reflects a culture shift at our institution. Prior to 2013, an ANC value of $<500/mm^3$ was considered a contraindication to SQP placement. However, after 2013 SQP were placed regardless of the neutrophil count.

Port placement and post-operative care

All procedures were performed under sterile technique in the operating room or interventional radiology suite. Prophylactic antibiotics (intravenous cefuroxime or clindamycin in the case of penicillin allergy) were administered to all patients within 30 minutes of skin incision. All catheters were inserted percutaneously under general anaesthesia. Ultrasound guidance was used to guide internal jugular vein access, and anatomic landmarks were used to guide the subclavian approach. The choice of vessel accessed was determined by the surgeon, or interventional radiologist placing the line. Subcutaneous ports were either tunnelled and placed on the parasternal chest wall or placed in the subclavicular position. Correct position of the intravenous catheter was confirmed using fluoroscopy during the procedure and a standard chest radiograph was obtained immediately following port placement. The choice of diameter of catheter tubing was determined based on the weight of the patient, favoring 6.6 French catheters for patients < 30 kg.

Post-operative subcutaneous port care and maintenance were performed according to the nursing policy and procedure manual of this institution. While not in use, the subcutaneous port was locked with heparin (100 units/ml). While in use, the Huber needle accessing the port was changed weekly under sterile technique. Chlorhexidine-impregnated sterile line dressings were applied over port access needles as per hospital policy.

Data collection

Electronic medical records of all pediatric oncology patients undergoing subcutaneous port placement were reviewed. We recorded age at insertion, body mass index (BMI), underlying disease (e.g. leukemia, lymphoma, or solid tumor), history of previous central catheter placement, documented preoperative infection (within two weeks of procedure),, date of initiation of chemotherapy, location of port placement, size of catheter tubing, and service

placing subcutaneous port (Interventional Radiology or General Surgery), presence of fever within 24 hours of port insertion. Fever was defined as a temperature (measured by temporal scanner) of >38.5 degrees Celsius, in the absence of an isolated pathogen occurring within 24 hours of SQP placement. Most recent laboratory values were also collected prior to port insertion and included: white blood cell count (WBC), platelet count, hemoglobin, glucose, and absolute neutrophil count (ANC). A delay in therapy was noted if a scheduled chemotherapy session was not started; the exact duration of the delay was not consistently available in patient records. Baseline characteristics and infectious complications were compared between neutropenic and non-neutropenic patients.

Neutropenia was defined as ANC<500/mm^3. ANC values were recorded as continuous measures but then categorized into a dichotomous variable (<500/mm^3 vs. ≥500/mm^3) for data analysis. The primary outcome was early infectious complications (e.g. within 30 days of SQP placement). This was defined as: 1) bacteremia (e.g. isolation of a pathogen from a blood culture drawn through the lumen of the SQP [17–19]); 2) surgical site infection (e.g. presence of erythema, induration, and/or tenderness or evidence of purulent discharge at the surgical incision); or 3) tract infection (e.g. presence of erythema, induration, and/or tenderness within 2 cm of the port or catheter tubing.[20,21]

Statistical analysis

Descriptive statistics were calculated for patient characteristics with means and standard deviations for continuous variables and frequency (percentage) for categorical variables. All calculations were done using SAS software version 9.4 (Cary, NC). All tests were two-sided, and the significance level was set at a p-value of less than 0.05. A t-test was performed to compare continuous variables, and a Pearson chi-square test was performed to compare categorical variables between patients with and without neutropenia.

Logistic Regression Analysis

The association between neutropenia and early post-operative infection rate was examined using logistic regression analysis. Five potential confounding variables were pre-selected for analysis: preoperative fever (within 24 hours of port insertion), receipt of preoperative chemotherapy, history of previous central line, underlying disease (leukemia, lymphoma, or solid tumor) and body mass index (BMI). Underlying disease (hematologic malignancy vs. solid tumor) was pre-selected as the only potential effect modifier.

To identify other potential risk factors for the development of early post-operative infectious complications following SQP insertion, a univariate logistic regression analysis was performed. Fourteen pre-selected variables of interest were examined: preoperative fever, underlying disease, location of catheter (internal jugular vein vs. subclavian vein), location of port (chest wall vs. subclavicular), chemotherapy use prior to port insertion, service placing the SQP (interventional radiology vs. surgery), history of previous central line, history of non-central line infection within two weeks of SQP insertion, BMI, age, gender, glucose, hemoglobin, and catheter size (diameter). All variables with a p-value <0.3 in the univariate analyses were entered into the multivariable model and backwards selection was used to identify potential predictors of infection. All variables with a p-value <0.25 were

retained in the multivariable model. Odds ratios and 95% confidence intervals were determined.

RESULTS

Patients

In our study period, 614 subcutaneous ports were placed in 542 pediatric oncology patients (Table 1). The majority (79%) of ports were first-time insertions with the remainder being second (16%), third (5%), or fourth (1%) devices. There were 272 (44%) ports placed in children with solid tumors and 342 (56%) were placed in children with a diagnosis of leukemia or lymphoma. The study cohort included 79 ports (13%) placed in neutropenic patients and 535 (87%) placed in those who were non-neutropenic. Statistically significant baseline differences between nonneutropenic and neutropenic patients included age (mean age 109 vs 81 months, p=0.0002), presence of fever within 24 hours of port placement (n=25, 5% vs n=17, 22%, p<0.0001), underlying disease: leukemia/lymphoma (n=268, 50% vs. n=74, 94%), and solid tumor (n=267, 50% vs n=5, 6%), respectively (p<0.0001, Table 1). The following variables were also found to be significantly different between the two groups: chemotherapy prior to SQP insertion (35% vs. 23%, p=0.0359), previous central line insertion (40% vs. 20%, p=0.0024), and hemoglobin concentration (10.9 vs. 9.0 g/dL, p<0.0001; Table 1).

Infections

There were 18 total post-operative infections (Table 2). In univariate analysis, the rate of early post-op infectious complications was found to be significantly greater in neutropenic patients (n=7, 9%) compared to non-neutropenic patients (n=11, 2%, p<0.0001; Table 1). No patient in our data set had more than one infection. The median time to infection was 14.5 days following subcutaneous port placement (range, 2 – 30 days). Of those with infection, most patients developed bacteremia (n=12, 67%), with the remainder having port site infection (n=4, 22%) or the presence of both port site infection and bacteremia (n=2, 11%). The most common organism isolated was *Staphylococcus aureus* (n=4, 28%). The majority of patients (n=14, 78%) were neutropenic at the time of the early post-operative infectious complication. Treatment of infectious complications included antibiotics only (n=10, 56%), surgery only (e.g. removal of subcutaneous port, n=2, 11%), and both surgery and antibiotics (n=6, 33%, Table 2). The majority of infectious complications resulted in a delay of therapy (96%).

Regression Analysis

Baseline characteristics and infectious complications were compared between neutropenic and non-neutropenic patients (Table 3). No interaction was found between neutropenia and underlying disease (p=0.97). The multivariate regression model did find the presence of preoperative fever and underlying disease (solid tumor vs. leukemia/lymphoma) to be significant confounding variables. After adjusting for underlying disease and the presence of fever within 24 hours of port placement, the increased risk of early post-operative infection in the presence of neutropenia was not significant (OR 2.42, 95% CI 0.82–7.18, p=0.11; Table 3).

Univariate logistic regression was used to identify other potential risk factors for early postoperative infection following SQP placement (Table 4). Pre-operative fever was found to be associated with increased risk of infection (OR 7.78, 95% CI 2.76–21.93, p=0.0001). A diagnosis of hematologic malignancy (leukemia/lymphoma) was similarly found to be associated with increased risk of infection (OR 3.92, 95% CI 1.12–13.69, p=0.0321). Finally, lower hemoglobin levels were also found to be associated with increased risk of infection, with a 25% decrease in odds of infection for every one unit (g/dL) increase in hemoglobin (OR 0.75, 95% CI 0.58–0.96, p=0.025; Table 4).

A second multivariate logistic model was constructed to examine the association between these selected risk factors and early post-operative infection followed by a Wald test for the overall effects of ANC on infection. This process identified two significant variables (fever and underlying disease) and thus a final model adjusting for these two variables was created. This final model found the presence of fever within 24 hours of SQP placement was significantly associated with an increased risk of infection (OR 6.09, 95% CI 2.08–17.81, p=0.0010) after adjusting for underlying disease (Table 5).

DISCUSSION

In this study, which is the largest single-center series examining the topic, we demonstrated no statistically significant relationship between neutropenia and early post-operative infection following SQP placement. Univariate analysis showed that neutropenia, pre-operative fever, underlying diagnosis (leukemia versus solid tumor), previous chemotherapy, and anemia were significantly associated with increased early post-operative SQP infection. However, multivariate analysis showed that only pre-operative fever was independently associated with increased early-postoperative SQP infection. These finding are in keeping with several other studies that examined early post-operative wound infections in the setting of neutropenia following placement of tunneled lines.[3,15]

In our study period, the incidence of early post-operative infections following SQP placement was 2.9% (18/614). This is comparable to the incidence of infections found in the literature (0.712.6%).[9] Treatment of infectious complications required surgical removal of the SQP in just under half of these patients (44%, 8/18). This is in contrast to the literature that has demonstrated antibiotic treatment failure rate ranging from 11% [2] to 14%.[9] This difference may be secondary to the higher incidence of local infections (e.g. port site or surgical site) noted in our group of patients (6/18). This may also be secondary to poor wound healing in the context of neutropenia. Almost all of our patients with infections, whether salvaged with antibiotics or not, had a documented delay in therapy (17/18).

Neutropenia is a common occurrence in the setting of cancer, both at the time of diagnosis and throughout therapy. The optimal timing of placement of tunneled central venous lines with regard to preoperative neutropenia has been an area of interest in several studies. Historically, placement of SQP in the setting of severe neutropenia has been discouraged due to the potential increased risk of serious infections, given the crucial role which neutrophils play in the process of wound healing.[14] Some studies have demonstrated that neutropenia (defined variably as ANC ≤500–1000/mm^3) at the time of tunneled central venous line

insertion is associated with an increase in post-operative infection and line removal and therefore recommend delaying central line placement until ANC recovery.[25,26] Conversely, other studies have demonstrated that neutropenia is not a significant risk factor for infection following central line placement.[3,15] Our study, which is the largest series to date, did not demonstrate a significant association between pre-operative neutropenia and early post-operative SQP infectious complications.

Pre-operative fever was independently associated with early post-operative SQP infection in this study. The importance of pre-operative fever in the absence of an isolated pathogen and the risk of post-operative wound infection following line placement in the pediatric oncology patient remains poorly defined. Fever is common in children with leukemia. It is hypothesized to be secondary to the release of cytokines from leukemic cells, the administration of certain drugs, or even the transfusion of blood products.[32] While fever in an oncology patient is often multifactorial, and may not be an indication of acute infection, it has been found to be associated with a higher rate of post-operative infections following SQP insertion.[2] Similarly, our study demonstrated a significantly increased risk of infection following SQP placement in patients that had a documented fever in the 24 hours preceding surgery.

Other factors that have been studied with regard to infectious risk and central line placement include site of line placement (internal jugular vein versus subclavian vein), type of catheter used (subcutaneous port versus tunneled central access devices), and the age of patient.[15,28,29,32] In keeping with the literature, we found that the choice of vessel (internal jugular vein versus subclavian vein) did not influence infectious risk. Prior studies found an increased risk of infectious complications following line placement in children less than 10 years of age. However, in our population, age was not a predictive factor for early post-operative infection following SQP placement. Our study did find that for every g/dL increase in hemoglobin, the odds of developing a post-operative wound infection decreased by 0.75. This is not surprising, given the extensive literature demonstrating an association between anemia and increased risks of postoperative complications (including infection). This is thought to be secondary to lower oxygen carrying capacity and the subsequent lower oxygen tension in tissues, resulting in poor wound healing and decreased local immunity.[30,31]

Historically, tunnelled central venous catheters were placed exclusively by surgeons. Over the past 15 years, however, these lines are now more frequently placed by interventional radiologists at many centers. Our study found that the service placing the SQP (interventional radiology versus surgery) was not a risk factor for early infection. This lack of a difference may be due to a standardized approach within the institution to line care both at the time of insertion and post-operatively.

Our univariate analysis revealed that patients with a diagnosis of leukemia or lymphoma appeared to be almost four times more likely to develop an early post-operative infectious complication as compared to patients diagnosed with a solid tumor. However, this relationship was not statistically significant in multivariate analysis. When compared to solid tumor patients, the hematologic malignancy population typically presents more systemically ill, and often with profound bone marrow suppression. Further, both groups differ

significantly with regards to timing of initiation of chemotherapy as well as the types of chemotherapeutic agents used to treat the underlying disease. Finally, the observed increased risk of infection associated with the leukemia/lymphoma group may be exaggerated given our low event rate and resulting wide confidence intervals (only 3 infections occurred in solid tumor patients with neutropenia).

Ultimately, an important finding of this study was the overall low rate of post-operative infection following port placement in a group of both neutropenic and non-neutropenic patients. However, this low event rate also resulted in wide confidence intervals for many of our analyses. Our small event rate also limited our ability to fit multiple variables into our second multivariate regression model due to over-fitting and likely contributed to the wide confidence intervals seen throughout our analyses. A second limitation of this study is the retrospective design which may result in inherent bias. An example of this was our definition of central-line associated blood stream infection. We chose to accept all infections wherein a pathogen was isolated from a culture drawn through the central line. However, a more restrictive definition would have involved comparing cultures between central and peripheral venous samples and documenting a 5:1 ratio in microbe counts. This would have eliminated the potential for contaminated specimens. Not all patients had peripheral and central blood cultures drawn, and therefore this comparison could not be made.

Conclusions

The optimal timing of SQP placement in the pediatric oncology patient remains poorly defined. Our results did not demonstrate an adverse association of neutropenia with early post-operative infection following SQP placement. However, fever within 24 hours prior to port placement was found to carry a six-fold increase in the risk of infection. Given these findings, we believe it may be safe to place SQP in neutropenic patients without fever in last 24 hours. The presence of fever in the immediate pre-operative period, however, should prompt consideration of delaying placement to reduce risk of infection. Given our low event rate, and wide confidence intervals, further studies are required to assess the relationship between neutropenia and modifiable risk factors on early post-operative wound infections following central line placement in pediatric oncology patients.

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How this study will improve care:

Our review of subcutaneous infusaport placement in pediatric oncology patients did not reveal a significant association between neutropenia and early post-operative infection. These data suggest that port placement does not need to be delayed until the neutrophil count normalizes.

Table 1.

Patient characteristics by ANC.

	ANC ≥= 500/mm^3 N = 535	ANC <500/mm^3 N = 79	OR, 95% CI	p-value
Age (months; mean, SD)	109.3 (74.7)	81.0 (58.7)		0.0002[1]
Gender				0.904[2]
Female	232 (43%)	37 (47%)	F:M	
Male	303 (57%)	42 (53%)	1.51 (0.72,1.85)	
BMI (mean, SD)	23.0 (70.0)	18.2 (5.5)		0.1217[1]
Disease				<0.0001[2]
LL	268 (50%)	74 (94%)	LL:ST	
ST	267 (50%)	5 (6%)	13.99 (5.57,35.16)	
Fever				<0.0001[2]
No	510 (95%)	62 (78%)	Y:N	
Yes	25 (5%)	17 (22%)	5.59 (2.86,10.94)	
Chemo Prior*				0.0359[2]
No	348 (65%)	61 (77%)	Y:N	
Yes	186 (35%)	18 (23%)	0.55 (0.32,0.96)	
Previous Catheter				0.0024[2]
No	323 (60%)	62 (78%)	Y:N	
Yes	212 (40%)	17 (22%)	0.42 (0.24,0.73)	
Service Placing				0.6885[2]
IR	140 (26%)	19 (24%)	Surgery:IR	
Surgery	395 (72%)	60 (76%)	1.12 (0.64,1.94)	
Location Catheter				0.1490[2]
IJ	172 (32%)	19 (24%)	SCV:IJ	
SCV	363 (68%)	60 (76%)	1.50 (0.87,2.58)	
Port site*				0.7061[2]
Chest	265 (50%)	41 (52%)	CW:SCL	
Sub clavicular	269 (50%)	38 (48%)	1.09 (0.68,1.76)	
Hemoglobin (g/dL; mean, SD)	10.97 (2.11)	9.00 (1.32)		<0.0001[1]
Post-op Infection				<0.0001[2]
No	524 (98%)	72 (91%)	Y:N	
Yes	11 (2%)	7 (9%)	0.22 (0.08,0.57)	

Continuous variables are presented as means and standard deviations. Tests used [1]TTest; [2]Pearson X^2 test. BMI (Body Mass Index). LL (Leukemia, Lymphoma). ST (Solid Tumor). IR (Interventional Radiology). IJ (Internal Jugular Vein). SCV (Subclavian Vein). CW:SCL (Chest Wall, Subclavicular)

* 1 patient with missing data

Table 2.

Early post-operative infectious complications

	N	N (%)
Type of infection	18	
Bacteremia		12 (67%)
Port Site		4 (22%)
Tunnel/track		0 (0%)
Bacteremia and port		2 (11%)
Organism Isolated	1	
Capnocytopagea		1 (7%)
Coag Neg Staph + Candida		1 (7%)
Escherichia coli		3 (21%)
Moraxella non-liquefaciens		1 (7%)
Pseudomonas aeruginosa		1 (7%)
Rothia mucilaginosa		1 (7%)
Staphylococcus epidermidis		1 (7%)
Staphyloccocus aureus		4 (29%)
Streptococcus viridans		1 (7%)
ANC at time of infection	18	
0		10 (56%)
100		2 (11%)
300		1 (6%)
400		1 (6%)
500		1 (6%)
600		1 (6%)
900		1 (6%)
2500		1 (6%)
Intervention	18	
Antibiotics		10 (56%)
Surgical removal SQP		2 (11%)
Antibiotics and surgery		6 (33%)
Delay in therapy	18	
Yes		17 (94%)
No		1 (6%)

Table 3.

Association between neutropenia and infection adjusting for fever, and underlying disease.

	Odds Ratio	95% CI	P-value
Neutropenia	2.42	0.82–7.18	0.1106
Presence of pre-operative fever	4.72	1.55–14.37	0.0063
Disease (LL:ST)	2.33	0.61–8.86	0.2158

LL (Leukemia, Lymphoma). ST (Solid Tumor)

Table 4.

Univariable analysis: predictors of infection

	Odds Ratio	95% CI	P-value
Fever (Y:N)	7.78	2.76–21.93	0.0001
Disease (LL:ST)	3.92	1.12–13.69	0.0321
Location Catheter (SCV:IJ)	1.18	0.41–3.36	0.7570
Port Site (CW:SCL)	1.45	0.54–3.85	0.4588
Chemo Prior (Y:N)	0.42	0.12–1.48	0.1780
Service Placing (Sx:IR)	1.23	0.40–3.79	0.7185
Previous Catheter (Y:N)	0.64	0.22–1.82	0.4003
Preop Infection (Y:N)	1.11	0.25–4.97	0.8849
BMI	1.00	1.00–1.00	0.6987
Age	1.00	1.00–1.00	0.3795
Gender (F:M)	1.63	0.63–4.18	0.3124
Glucose	1.00	0.99–1.02	0.5379
Hemoglobin	0.75	0.58–0.96	0.0251
Catheter Size	1.08	0.79–1.50	0.6343

LL(Leukemia, Lymphoma). ST (Solid Tumor). IR (Interventional Radiology). IJ (Internal Jugular Vein). SCV (Subclavian Vein). CW:SCL (Chest Wall, Subclavicular). Y (Yes). N (No)

Table 5.

Multivariable analysis: predictors of infection

	Odds Ratio	95% CI	p-value
Disease (LL:ST)	4.37	0.96–19.86	0.0564
Presence of pre-operative fever	6.09	2.08–17.81	0.0010

* LL (Leukemia, Lymphoma). ST (Solid Tumor).