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Catheter-related atrial thrombosis: prevalence and risk factors in the pediatric age group—a retrospective study

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Abstract

Background: Catheter-related right atrial thrombosis (CRAT) is an under-studied complication of a long-term implantable venous access devices (IVAD), particularly in children with incidence rates extrapolated from the adult literature ranging between 2 and 29%. This is a single-center retrospective review of electronic medical records of children who underwent insertion of IVADs and had at least one echocardiogram performed prior to catheter removal between 2008 and 2018. Data collection included demographic information, development of CRAT, systemic infection, and administration of thrombogenic chemotherapeutic agents. We identified six patients who developed CRAT and compared them to 120 control patients. We also performed a detailed chart review for the patients who developed CRAT. Data was entered and analyzed using SPSS.

Results: A total of 764 patients underwent IVAD placement between 2008 and 2018. Six (0.79%) patients developed CRAT, and 120 patients were identified as controls that match the CRAT patients based on definitive criteria that include age, gender, chemotherapy type, steroid therapy, reason of line insertion, site of catheter insertion, tip-location at insertion, and history of systemic infections. In the CRAT group, 3 (50%) patients had their catheter tips placed in the superior vena cava-right atrial junction and 3 (50%) in the right atrium, whereas in the control group, all patients had their catheter tips placed in the superior vena cava-right atrial junction (p=0.000). Five (83.3%) patients in the CRAT group received L-asparaginase as compared to 75 (62.5%) patients in the control group (p=0.301). In the CRAT group, all patients had a history of systemic infection compared to 47 (39.2%) in the control group (p=0.180).

Conclusion: We identified 6 (0.79%) children with CRAT. Catheter-tip location within the right atrium is a potential risk factor for CRAT development in children.

Keywords: Central venous catheter, Venous access, Central venous catheter thrombosis, Atrial thrombosis

Background

Implantable venous access devices (IVADs) were first introduced in the early 1980s [1]. IVADs are long-term access venous devices that are either implantable such as port-a-cath (also known as polysite) or partially implantable catheters. IVADs have remarkably improved the day-to-day care of patients of all age groups requiring long-term central venous access, such as patients on chemotherapy and renal replacement therapy [2].

Although IVADs are generally considered safe, there exists a long list of potential complications such as hemothorax, pneumothorax, cardiac arrhythmias, and air embolism in the immediate postoperative period, and late complications that include infection, vascular erosion, catheter migration, and catheter-related thrombotic events [2–5].

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Catheter-related thrombotic complications are not rare, with an incidence rate during the first 1–2 years post-insertion ranging between 14 and 36% [5]. Symptoms may range from none to life-threatening thromboembolic events. Common locations of the thrombus include the catheter itself, the central vein containing the catheter, and the superior vena cava and right atrium.

The exact prevalence rate of catheter-related right atrial thrombosis (CRAT) is not well established, with published rates in the adult literature ranging between 2 and 12.8% [6] and up to 29% in a prospective postmortem study [7]. The asymptomatic nature of many CRAT cases may be the reason behind the difference in the documented incidence rates in the literature [6].

Different authors have proposed several risk factors for CRAT, but no consensus has been established particularly in the pediatric population. These include catheter-related bloodstream infection, systemic infection, hypercoagulable status, thrombogenic medications, and catheter-tip location [6, 8, 9].

The diagnosis of CRAT is commonly established incidentally on echocardiograms performed for unrelated indications. Several non-specific signs and symptoms such as dyspnea, fever, hemoptysis, chest pain, swelling, palpitations, syncope, and catheter malfunction may prompt physicians to request echocardiograms and look for catheter-related complications including CRAT [6].

Despite the plethora of publications on long-term central venous catheters, the prevalence rate and risk factors of CRAT in patients with IVADs remain largely unknown particularly in the pediatric age group. This project is to identify rate of CRAT development and potential risk factors at our institution.

Methods

We underwent a retrospective review of electronic medical records of all patients between 0 and 18 years of age who underwent long-term central venous access device insertion followed by at least one echocardiogram prior to device removal at our institution between 2008 and 2018.

In our institution, baseline echocardiograms are performed routinely for all children with cancer before the administration of agents with known thrombogenic potentials. Ethical approval was obtained from our local Institutional Review Board (IRB). Data collected included demographic information, associated comorbidities including congenital heart disease and hypercoagulable conditions, and administered chemotherapeutic agents and steroids, in addition to the characteristics of the IVADs (insertion site and catheter-tip location). If present, information regarding CRAT clot size, presenting symptoms, management approach, time from the initial catheter placement to the diagnosis of CRAT, and diagnosis of catheter-related bloodstream and systemic infections were all collected. We also performed a detailed chart review for the patients who developed CRAT.

To identify the control patients, we excluded patients with potential confounding variables from the control group to eliminate any non-comparability between the cases and controls. These variables included the presence of congenital heart disease, the administration of 5-FU and cisplatin, reasons for line insertion other than chemotherapy administration (hemodialysis and difficult venous access), sites of catheter insertion other than the right internal jugular and right external jugular veins, and catheter-tip location at the distal superior vena cava at time of IVAD insertion. The justifications for choosing these variables are outlined in Fig. 1.

Eligible control patients within the same gender and age categories, type of chemotherapy treatment, reason for line insertion, and catheter-tip location at time of insertion were matched resulting in matching three case-to-control patients. Inclusion and exclusion criteria of the search methodology are outlined in Fig. 1.

Data were analyzed using SPSS version 25. Quantitative variables were reported as mean SD and qualitative data as percentages. Statistical significances were assessed using the chi-square test and odds ratio, and significance was reported for a p value less than 0.05 and a 95% confidence interval.

Results

We initially identified 784 patients under 18 years of age who have undergone IVAD placement and at least one echocardiogram before device removal between 2008 and 2018 (Table 1). Twenty patients were excluded from the study because of incomplete medical records (Fig. 1). Case-control sorting resulted in a total of 126 patients (6 CRAT and 120 controls) on whom the study analysis was based on.

Catheter-related atrial thrombosis (CRAT) developed in 6 (0.79%) patients. Five (83.3%) patients in the CRAT group were females as compared to 44 (36.7%) in the control group (p=0.022). The mean age at the time of catheter insertion was 4.116 ± 2.713 and 6.758 ± 4.122, respectively, for the CRAT and control groups (p=0.124). Patient demographics are depicted in Table 1.

Hematologic malignancies were the most common indications behind the IVAD placement in 113 (94.2%) of the control patients followed by non-hematologic malignancies 7 (5.8%). Similarly, hematologic malignancies were the most common reasons behind catheter insertion in 5 (83.3%) of the CRAT patients. The majority of the catheters were placed in the right

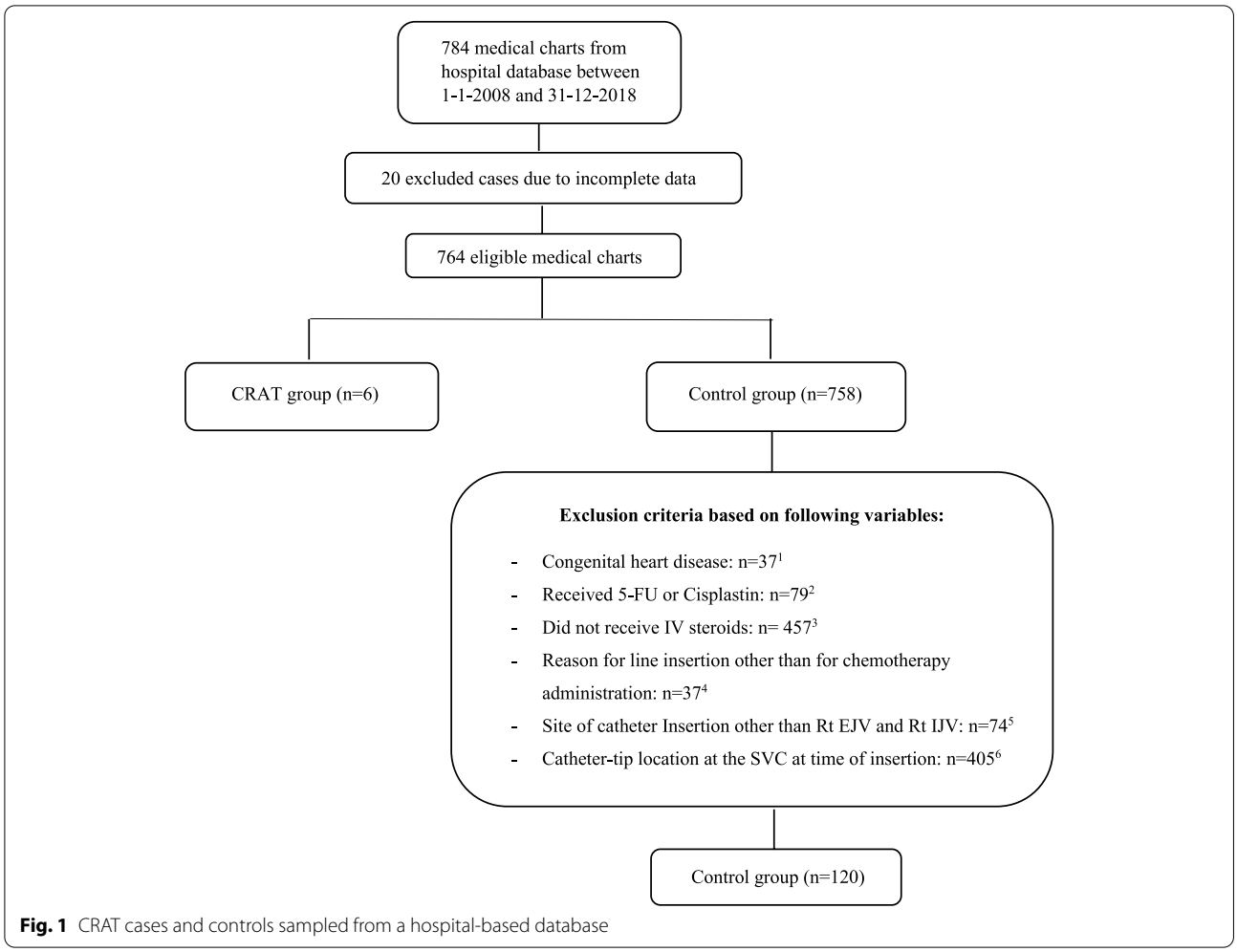

Fig. 1 CRAT cases and controls sampled from a hospital-based database

external jugular vein in both the control 70 (58.3%) and CRAT 5 (83.3%) groups.

All 126 patients received chemotherapy. Seventy-five (62.5%) patients in the control patients received L-asparaginase compared to 5 (83.3%) patients in the CRAT group, and this did not reach statistical significance (P=0.301). None of the identified CRAT patients received 5-FU or cisplatin. All patients in both groups received intravenous steroids while the catheters were in place (Table 1).

All control patients had their catheter-tips located at the superior vena cava-right atrial junction confirmed at the time of insertion via intraoperative fluoroscopy as compared to 3 (50%) of the CRAT patients. Three (50%) of the CRAT patients had their catheters placed in the right atrium. The difference was statistically significant (P=0.000). Forty-seven (39.2%) patients in the control group had history of systemic infection whereas all 6 (100%) CRAT patients were reported to have a history of systemic infection (P=0.180) while the catheters were in place (Table 1).

Table 2 depicts the demographic and clinical variables of the six patients with catheter-related atrial thrombosis including age, gender, indications for IVAD placement, site of placement, location of the catheter-tip at insertion, and history of positive microbiology cultures while the catheter was in place. All patients in this group had documented systemic infection in the bloodstream and/or urine. After the clot detection, all patients underwent extensive hypercoagulable state work including prothrombin time, activated partial thromboplastin time, serum protein C and protein S levels, antithrombin-III levels, factor VIII, lupus anticoagulant test, factor V Leiden, and MTHFR gene mutations; all of which were within normal limits.

Patient 1, with a brain tumor, received carboplatin, vincristine, vinblastin, and vinorelbine around the time of clot detection. Patients diagnosed with acute lymphoblastic leukemia (ALL) were treated on a protocol adapted

Table 1 Demographic distribution of patients

	Matched control (*n*=120)	CRAT (*n*=6)	*p* value
Age in years (mean ± S.D)	6.758±4.122	4.116±2.713	0.124
Age			
Female	44 (36.7%)	5 (83.3%)	0.022
Male	76 (63.3%)	1 (16.7%)	
Chemotherapy type			
L-asparaginase	75 (62.5%)	5 (83.3%)	0.301
Reason of line-insertion			
Hematologic malignancy	113 (94.2%)	5 (83.3%)	0.288
Non-hematologic malignancy	7 (5.8%)	1 (16.7%)	
Site of catheter insertion			
Right internal jugular	50 (41.7%)	1 (16.7%)	0.223
Right external jugular	70 (58.3%)	5 (83.3%)	
Tip location at insertion			
SVC-RAJ	120 (100%)	3 (50.0%)	0.000
Right atrium	0 (0%)	3 (50.0%)	
History of blood infection			
Yes	47 (39.2%)	6 (100%)	0.180

Abbreviations: *Rt* right, *Lt* left, *EJV* external jugular vein, *IJV* internal jugular vein, *SCV* subclavian vein, *RAJ* right atrial junction, *SVC* superior vena cava, *ALL* acute lymphoblastic leukemia, *RA* right atrium

from the St. Jude Total XV therapy [10]. The induction phase of 6 weeks was the same for all patients and consisted of oral prednisone, L-asparaginase; daunorubicin; vincristine; cyclophosphamide; 6-mercaptopurine; and cytarabine. After induction, patients were stratified into two protocol arms (low risk and intermediate/high risk). The consolidation phase of 8 weeks of high-dose methotrexate in combination with 6 MP. The continuation phase consisted of 120 weeks for females and 146 weeks for males and included a more intensive therapy termed "reinduction" I and II phases occurring at weeks 7–9 and 17–19, respectively, during continuation therapy. Patients received additinal L-asparaginase in combination with dexamethasone in each reinduction phase. Most cases of CRAT in ALL patients (80%) occurred in the postinduction phases of treatment while receiving a combination of asparaginase and dexamethasone.

Table 3 demonstrates the mode of presentation, size of the thrombus, and timing of the clot appearance since insertion, as well as outlines the management provided for each of the identified six patients with CRAT. The mean timing of the diagnosis of the atrial clot since insertion was 5.00 ± 3.2 months. Three patients were asymptomatic, two presented with swelling over the upper chest area, and one with catheter malfunction.

Discussion and review of the literature

CRAT is an under-described yet growing problem [11]. Several studies report a broad range of prevalence rates of CRAT in adults [12] between 2 and 12.8% [6] and even up to 29% in a prospective postmortem study [7]. The difference in the published incidence rates could be explained by the asymptomatic nature of many CRAT cases [6]. The available statistics from the pediatric literature are scarce. In their retrospective review of 156 children with cancer, Korones et al. reported an incidence rate of 8.8% of CRAT in their cohort diagnosed on routine echocardiograms [13]. We identified CRAT only in 6 (0.79%) patients in our cohort of 764 children. We are not able to explain the discrepancy between our and Korones et al.'s results, but it could be related to the site catheter-tip location whereby we showed that the risk of CRAT development is increased in patients in whom the catheter tips were located within the right atrium at the time of the catheter insertion; most of the CRAT cases reported in Korones et al.'s paper had their catheter-tips placed within the right atrium.

Table 2 Demographic and clinical variables of the CRAT cases

Patient	*Gender*	*Age (Y)*	*Indication*	*Catheter-tip location*	*L-Asparaginase*	*Positive cultures*
1	F	2	Brain tumor	RA	No	Urine: *Klebsiella pneumoniae*
2	F	8	Low-risk; Pre-B ALL	SVC-RAJ	Yes	Urine: *Klebsiella pneumoniae*
3	F	3	Standard risk; Pre-B ALL	SVC-RAJ	Yes	Blood: Non-enterococcus group D
4	F	6	Standard risk; T cell ALL	RA	Yes	Urine: *E. coli* Blood: Staph species, coag. negative
5	M	5	Standard risk; T cell ALL	SVC-RAJ	Yes	Blood: *Chryseobacterium indolgenes*
6	F	7	High risk; Pre-B ALL	RA	Yes	Blood: *Streptococcus viridians* group *Streptococcus mitis*

Abbreviations: *F* female, *M* male, *Rt* right, *Lt* left, *EJV* external jugular vein, *IJV* internal jugular vein, *SCV* subclavian vein, *RAJ* right atrial junction, *SVC* superior vena cava, *ALL* acute lymphoblastic leukemia, *RA* right atrium

Table 3 Clinical variables of the CRAT cases

Patient	*Presentation*	*Size of clot at detection*	*Interval to clot diagnosis*	*Management approach*
1	Swelling	Data missing	7 months	SC enoxaparin sodium catheter removal
2	Asymptomatic	10×12 mm	4 months	SC enoxaparin sodium catheter preserved
3	Catheter malfunction	3×12 mm	5 months	SC enoxaparin sodium catheter removal
4	Asymptomatic	7×11 mm	23 months	SC enoxaparin sodium catheter preserved
5	Asymptomatic	3×4 mm	5 months	SC enoxaparin sodium catheter preserved
6	Swelling	Data missing	1 month	SC enoxaparin sodium catheter removal

Abbreviations: *SC* subcutaneous

Three (50%) patients in the CRAT group were diagnosed incidentally on routine echocardiograms, and three had symptoms that prompted the echocardiogram including two patients with anterior chest swelling and one patient with catheter malfunction. This is in agreement with many previous published studies that concluded that many of the CRAT cases are asymptomatic [6]. In this study, we observed a statistically significant preponderance of female gender in the CRAT group as compared to the control group: 44 (36.7%) versus 5 (83.3%) with a p value of 0.022 (Table 1). In the previously published literature, there appears to be no statistical difference in the propensity of developing CRAT between the male and female genders [13, 14].

It has been suggested in the literature that children with ALL are more prone to catheter-related thrombosis when compared to children with other types of malignancies [13]; this is due to hemostatic alterations in patients with ALL that are apparent prior to therapy with a cumulative effect that leads to a hypercoagulable state in the patients [15]. In addition to hemostatic changes, ALL patients are at an increased risk of thrombotic events due to the chemotherapeutic agents' effect on hemostatic proteins and endothelium [16]. Similarly, in our study, 5 out of 6 patients who developed CRAT had active ALL.

Male et al. concluded that the risk of catheter-related atrial thrombosis is increased in patients with left-sided catheters (p=0.048) and when catheters are inserted in the subclavian vein (p=0.025) [17]. On the other hand, Chick et al. showed no statistically significant difference in the risk of CRAT development in relation to the site and laterality of catheter insertion (p=0.23 and p=0.52, respectively) [18]. In our study, most of the patients who developed CRAT had a catheter placed in the right external jugular vein 5 (83.3%); however, this is probably related to our local preference of line placement, whereby we place most of our catheters through the right external jugular vein.

Korones et al. demonstrated a significantly higher prevalence of CRAT in patients in whom the catheter tips were placed within the right atrium as compared to the superior vena cava (20 versus 2%, p=0.004) [13]. Other authors showed up to a 46.2% increase in the incidence of CRAT when the tip was placed in the right atrium [19]. The thrombogenic phenomenon is initiated by the right atrial wall endothelial damage that is seen because of the mobile catheter tip that is free-floating in the beating right atrium [8, 20]. None of our patients who developed CRAT had their catheter tips positioned in the distal superior vena cava, and three patients (50%) had their catheter-tips in the right atrium and three (50%) at the superior vena cava-right atrial junction. However, in the control group, 120 (100%) had their catheter-tips placed at the superior vena cava-right atrial junction at the time of placement; this difference statistically significant (p value=0.000). This relatively higher tendency of CRAT development in patients in whom the catheter tips are placed in the right atrium could be explained by the fact that in these situations, the catheters might change position from the initial insertion placement because of physical activity, thus promoting thrombus formation [8]. On the other hand, in patients in whom the catheters are placed within the distal SCV, the catheters tend to stay in place, hence the lower chances of developing CRAT [8].

Multiple risk factors have been identified for the development of catheter-related thrombotic complications [21]. Various chemotherapeutic agents have been recognized in the literature as independent thrombogenic risk factors in cancer patients particularly 5-fluoro-uracil, cisplatin, and L-asparaginase [22]. L-asparaginase, a widely used chemotherapeutic agent, has a well-established risk of

thrombosis. L-asparaginase increases the risk of thrombosis by decreasing the formation of proteins implicated in coagulation and fibrinolysis such as plasminogen, anti-thrombin III, and the anticoagulant proteins C and S [23]. Steroids are also given with chemotherapeutic agents for the treatment of malignancies, which further increases the risk of thrombosis. Steroids can lead to an increase in Von Willebrand factor, clotting factor VIII, prothrombin, and antithrombin III [24]. In our study, we have identified five out of six patients with CRAT who received both L-asparaginase and steroids at the time when the right atrial clot was diagnosed.

Catheter-related bloodstream infection has been identified in the literature as a risk factor for catheter-related atrial thrombosis [25]. The infectious process can initiate the thrombosis cascade or the thrombus itself can be a medium for infection [26]. The inflammatory process associated with systemic infections has also been implicated in the development of thrombi. While 47 (39.2%) of patients in the control group developed systemic infection while the catheter was in place, all the patients who developed CRAT had either positive blood cultures, urine cultures, or both in the presence of the central venous catheter. This, however, did not reach the level of statistical significance (p value=0.180).

CRAT may develop any time after the catheter placement; some authors have reported CRAT within a week after insertion [19, 21], while others have reported CRAT that was diagnosed around a year after the catheter was removed [13]. In our series, the mean timing for the diagnosis of the atrial clot was 5.00 ± 3.24 months after insertion.

Recommendations for screening patients with IVADs for CRAT are equivocal. Some authors have recommended echocardiograms in patients with catheter dysfunction [27]; others have recommended screening in high-risk patients such as in patients with the catheter tips situated in the right atrium and patients on pharmaceutical agents with known thrombogenic potentials such as L-asparaginase [28], while others went further and recommended routine screening echocardiographs in all patients with long-term central venous catheters.

Guidelines for thrombosis prophylaxis in children with long-term IVADs are not clear in the literature, with most evidence being not in favor of prophylaxis. A systematic review of more than 3000 children concluded that thromboprophylaxis in the pediatric population does not reduce the incidence of catheter-related thrombotic complications [29]. In our practice, we do not provide prophylactic anti-thrombotic agents to patients with IVADs and none of the identified patients with CRAT received any prophylaxis against thrombosis prior to the diagnosis of the complication.

The literature lacks high-quality evidence for the best treatment option for CRAT, especially when it comes to the pediatric population as most of the treatment protocols are derived from adult literature [30, 31]. The treatment approach depends mainly on the size of the clot and the medical status of the patient [6]. Clot size exceeding 2 cm, anti-coagulation contraindications, and hemodynamic instability favor surgical excision of the thrombus [6, 27]. Thrombolysis of the clot is not without risks, pulmonary embolism from the disintegration of the clot has been reported in the literature [27], systemic embolisms due to a patent foramen ovale can also occur [32]. Systemic anticoagulation and subsequent catheter removal are generally recommended as the first-line therapy in uncomplicated cases of catheter-related atrial thrombosis [6]. One study reported effective treatment of 20 adult hemodialysis patients with anticoagulation and catheter removal and positioning the new catheter-tip at a different location from the clot [9].

Some authors advocate for catheter removal regardless of the circumstances; Stavroulopoulos et al. concluded in their meta-analysis of 71 CRAT cases in hemodialysis patients that catheters of confirmed CRAT patients should be removed because of the high morbidity and mortality rates that accompany catheter preservation [6]. The worse outcomes correlated with retaining the catheter in place are potentially due to the mechanical damage caused by the catheter-tip on the atrial walls, especially when the tip is positioned in the right atrium instead of the distal superior vena cava, in addition to the possible bacterial colonization of the catheter. On the other hand, successful treatment of CRAT with anticoagulation without having to remove the catheter in stable and asymptomatic patients has been frequently reported in the literature [21]. Chick et al. reported successful preservation of 92% of the catheters in incidentally diagnosed CRAT [18]. All our CRAT patients received low molecular weight heparin (subcutaneous enoxaparin sodium) starting at a dose of 1mg/kg/dose twice daily with doses adjustment based on monitoring of anti-Xa levels and for a minimum of 3 months if the catheter remained in situ. The catheters were removed in the three symptomatic patients and preserved in the three asymptomatic patients.

Due to its retrospective nature, this study falls into inherent limitation gaps including missing data in the medical records and possibly inaccurate information due to the loss of some patients to follow-up.

Conclusion

We identified 6 (4.76%) patients with catheter-related right atrial thrombosis in a cohort of 126 patients under 18 years of age with long-term implantable central venous access devices. Catheter-tip location within the right atrium is a potential risk factor for the development of catheter-related atrial thrombosis in children.

Abbreviations

Rt: Right; Lt: Left; EJV: External jugular vein; IJV: Internal jugular vein; SCV: Subclavian vein; RAJ: Right atrial junction; SVC: Superior vena cava; ALL: Acute lymphoblastic leukemia; RA: Right atrium; 5-FU: 5-Fluoro-uracil; Y: Years; SC: Subcutaneous.

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Authors' contributions

SA is the senior author; AZ proposed the study; AHA and HN contributed equally to this paper and are both first authors; AZ, JH, AHA, and HN performed the literature review and wrote the first draft; AZ and JH collected and analyzed the data; DH and RJ critically revised the manuscript. AZ is the guarantor. All authors contributed to the design and interpretation of the study and to editing of the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

All data and materials are available from the corresponding author based on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval from institutional review board of the American University of Beirut (AUB). Consent from patient/parent are not applicable considering that this is a retrospective review and no personal identity was exposed.

Consent for publication

Not applicable

Competing interests

The authors declare no competing interests

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