Timing of Central Venous Line Insertion During Induction in Children With Acute Lymphoblastic Leukemia

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Purpose: Central venous lines (CVL) in children with acute lymphoblastic leukemia (ALL) provide comfortable administration of intensive chemotherapy and blood sampling. The optimal time for the insertion of CVL in patients with ALL during induction therapy is controversial. This study aimed to investigate the frequency of CVL-related complications in children with ALL concerning the time of CVL insertion.

Patients and Methods: We reviewed the records of 52 pediatric ALL patients with CVL. CVL placement before or on treatment day 15 was defined as "early insertion", and after treatment day 15 was defined as "late insertion". Demographics, preoperative blood counts, type of central line, time of CVL placement, CVL-related complications, and blood counts during complications were all noted. All the data were collected from those with the first catheter use.

Results: CVL was placed $\leq$15 days in 26 patients (50%) and after 15 days in 26 patients (50%). Regarding the infection rates, no statistical difference was found between early and late CVL-inserted groups (P = n.s.). Five patients developed thrombosis, and risk was found to be similar between early and late CVL-inserted groups (P = n.s.). Catheter-related mechanical complications were recorded in 7 patients (3 in early and 4 in late CVL-inserted group, (P = n.s.).

Conclusion: The present study showed no relation between the timing of CVL placement during induction therapy and the occurrence of infection and thrombosis. Our results suggest that CVL can be placed safely at the time of diagnosis or early induction treatment to provide a comfortable administration of chemotherapy and decrease painful blood samplings.

Key Words: ALL, central venous catheter, catheter-related infections

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Acute lymphoblastic leukemia (ALL) is the most common cause of cancer in children, with a current 5-year overall survival rate estimated at >85%.[1] Because of the nature of the disease and intensive chemotherapy protocols, patients with ALL require frequent needle sticks for blood draws and intravenous access. In the last 30 years, central venous lines (CVL) have been increasingly used to manage children with ALL.[2] CVL provides a safe administration of intensive chemotherapy, antibiotics, blood products, and blood sampling in children with ALL. On the other hand, CVL can cause various adverse events like infections, deep venous thrombosis (DVT), and mechanical complications.[2–4]

There is a clinical variation in the optimal time for the insertion of CVL in patients with ALL. Some clinicians insert the CVL at the beginning of the treatment to comfort having CVL during the remission induction. At the same time, some clinicians wait until the end of induction, the time of remission, or recovery of neutropenia to decrease the risk of CVL-related complications.[5–7] The optimal timing of CVL placement in children with ALL has been investigated in different studies. Most of the studies reported no difference in the rates of infection or thrombosis between early and late CVL placement.[7] However, in 1 of the biggest studies performed by the Pediatric Oncology Group, 362 patients were analyzed retrospectively. They have found that the placement of CVL within the first 15 days of induction was associated with an increased risk of infectious complications.[6]

This study aimed to investigate the frequency of CVL-related complications in children with ALL according to the time of CVL insertion during induction therapy. We, therefore, hypothesized that CVLs placed during the first 15 days of induction were more likely to become infected than those inserted subsequently.

PATIENTS AND METHODS

This study was performed retrospectively in our pediatric hematology center. Fifty-two ALL patients newly diagnosed and treated according to ALL-BFM 95 or ALL-BFM 2000 study protocols between January 2006 to January 2016 with CVL were included. Data at the time of the first CVL insertion during induction chemotherapy were evaluated from the patients' medical records. Patients' demographics, hemoglobin level, white blood cell count (WBC), absolute neutrophil count (ANC), CVL type, time of CVL insertion, complications of CVL (infections, thrombosis, and mechanical complications), time and cause of CVL removal, type of infection, and culture results were noted. *Complications* developed in the first month after the first CVL insertion were defined as early complications, and late complications were evaluated until the time of removal or death of the patient with a CVL. Development of DVT in these patients was observed from the first CVL insertion to the last follow-up until January 2021. Thrombophilia testing for genetic risk factors was analyzed in patients who developed DVT.

CVLs were inserted under general anesthesia in the operating room mainly by the same surgeon. All manipulations were applied with sterile techniques. External double-lumen catheters were preferred for high-risk patients who needed intensive care or who may need bone marrow transplantation; otherwise, internal port catheters were

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used. We are not using PICC in our clinic. All CVLs were managed according to the international standards; a bio-occlusive dressing was applied to the insertion area and changed every third day. At the same time, the skin at the insertion area was cleaned with chlorhexidine. Perioperative prophylactic antibiotics were not used during catheter insertion.

Many of the patients with ALL are febrile at presentation, and neutropenia that occurs within a few days of starting therapy persists for 2 to 3 weeks. Our hypothesis based on clinical experience was that CVLs placed during the first 2 weeks are more likely to become infected than those inserted subsequently. Also, we reviewed the previous studies about the timing of catheter insertions. According to these results and our clinical impression, we selected the cut-off point as day 15. CVL placement before or on treatment day 15 was defined as "early insertion", and after treatment day 15 was defined as "late insertion".

Infections were classified as bloodstream infection and local infection. Catheter-related bloodstream infection was diagnosed when 1 of the following criteria was positive: (1) Growth of the same pathogen from blood culture of the peripheral vein and culture of CVL, (2) Growth of skin contaminant in 2 or more blood cultures, (3) Growth of skin contaminant in 1 blood culture with symptoms of fever (>38°C;), chills, and hypotension.[8] Empirical first-line antibiotic therapy consisted of meropenem or piperacillin-tazobactam therapy. Antibiotic therapy was adjusted according to the patient's culture results and clinical response. Catheter lock therapy was given if a catheter-associated infection was suspected.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS software version 21). Descriptive analyses were presented using medians, means, and SD. The proportions of patients with early CVL placement and late CVL placement experiencing infections and other complications were analyzed using the χ^2 test. Student T test was used to compare the total catheter days in these groups. A P value of <0.05 was considered statistically significant.

RESULTS

The clinical properties of the patients are listed in Table 1. Two patients developed pneumothorax after catheter insertion in the operating room, but they regressed spontaneously. No other surgical complications occurred.

A total number of 18,590 catheter days was identified. The mean catheter days was 371.8 ± 251.48 days for a patient. There was no statistical difference between the early and late CVL-inserted groups according to catheter days (mean 343.4 ± 231.4 days in early CVL-inserted group; mean 400.2 ± 271.8 days in the late CVL-inserted group, P = n.s.). Patient characteristics according to the time of CVL insertion and CVL infections are given in Table 2. Median WBC and ANC value at diagnosis while inserting the CVL and at diagnosis of CVL infection are given in Table 3.

Catheter-related local and bloodstream infections occurred in 24 patients (46.2%), including 12 patients in the early and 12 in the late CVL-inserted group. No difference was found between the early and late CVL placement groups (P = n.s.) regarding the infection rates. When we evaluate the time of infections, in the early CVL-inserted group, 4 of 12 patients developed an infection in the first 30 days. On the other hand, in the late CVL-inserted group, 2 of 12 patients developed an infection in the first 30 days. During infections, the median WBC was 1100/mm^3 (IQR:625 to 2300), and the median ANC was 150/mm^3 (IQR:0 to 1150). Most of the infections (n = 17) were due to coagulase-negative Staphylococcus aureus (2 E.coli, 1 Candida, 1 S.maltophilia, 1 Enterococcus, 1 Pseudomonas, and 1 Klebsiella infections). Catheter lock therapy was given to 2 patients, 2 from the early and the other one from the late insertion group.

TABLE 1. The Clinical Characteristics of the Patients

	n = 52 (%)
Sex	
Female	23 (44.2)
Male	29 (55.8)
Age	
Median	6.1 y (1.2-16.9 y)
Immunophenotype	
T-ALL	12 (23)
B-ALL	40 (76.9)
Risk group	
Standard	11 (21.2)
Intermediate	25 (48.1)
High	16 (30.8)
Catheter type	
Internal	48 (92.3)
External	4 (7.7)
Catheter insertion time	
Early (≤15 d)	26 (50)
Late (>15 d)	26 (50)

In our study group, 21.2% of patients were in the SR group, 48.1% of patients in the MR group, and 30.8% of patients in the HR group. The infection risk was higher in the HR group compared with the SR-MR group (OR: 1.94, 95% CI: 0.83 to 4.56).

Five patients developed thrombosis during therapy (9.6%). Two were from the early (thrombosis in the distal part of CVL and jugular vein thrombosis), and 3 were from the late CVL-inserted group (thrombosis in the distal part of CVL, intracardiac, and sagittal sinus thrombosis). All of the thrombosis developed after the first 30 days. In thrombophilia testing, a patient with intracardiac thrombosis was found to have heterozygous Factor V Leiden mutation; other patients' results were unremarkable. Patients with CVL-related thrombosis received low molecular weight heparin (LMWH) during the rest of the intensive chemotherapy period. On follow-up of these patients, recurrence of thrombosis was not observed during leukemia treatment and after cessation of therapy.

Catheter-related mechanical complications were recorded in 7 patients with internal catheters (3 in the early and 4 in the late CVL-inserted group, P = n.s.); leakage in 1 patient, the accidental removal of CVL in 1 patient, line rupture in 1 patient, and line occlusion in 4 patients. When we evaluate the time of complications, 2 patients developed mechanical complications in the first 30 days. The other 5 patients developed mechanical complications after the first 30 days. A new catheter was inserted in 6 of them. Local skin infections developed in 6 patients, all with port catheters. In 3 patients, local infection developed in the first 30 days. In the other 3 patients, local infections developed late. Wound dehiscence developed in 1 patient after the first 30 days of catheter insertion. CVL had to be removed in 17 patients (32.7%) before the end of the chemotherapy protocol for

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TABLE 2. Patient Characteristics According to the Time of CVL Insertion and CVL Infections

First Catheter Insertion Time	Time of CVL Infections Early ≤30 d, %	Time of CVL Infections Late >30 d, %	No Infectious Complication, %
Early (≤15th day)	4	8	14
	15.5	30.7	53.8
Late (>15th day)	2	10	14
	7.8	38.4	53.8
Total	6	18	28
	11.5	34.6	53.8

various reasons (catheter-related infection in 6, local skin infections in 4, and other catheter-related mechanical complications in 7 patients). Four patients died due to sepsis in remission or relapsed ALL (2 in the early and 2 in the late CVL-inserted group).

DISCUSSION

The CVL for vascular access is frequently utilized in children with cancer, severe systemic infection, congenital heart disease, traumatic injury, and intensive care unit admission. Placement of CVL is the most frequent cause of DVT in childhood since CVL adversely influences altered blood flow, hypercoagulability, and endothelial injury.[9–11] DVT may develop quickly in children with ALL and CVL since most of the patients have other concomitant risk factors such as a hypercoagulable state due to the disease itself, inflammation, infection, dehydration, decreased mobility, surgery, obesity, and thrombogenic medications such as steroids and L-asparaginase.[10–14]

The optimal timing of CVL placement in children with ALL has been investigated in different studies. While some studies have found that early placement of CVL at diagnosis increased the risk of complications, others reported no increased risk of CVL-related complications due to early CVL insertion.[6,7,12,15] Recently there has been an interinstitutional variation concerning the time of the CVL placement; some receive it at the time of ALL diagnosis, and others await the remission phase.[15] Our study wanted to investigate the rate of CVL-related complications in children with ALL concerning the time of CVL insertion during induction therapy to compare the complication rates between the early and late CVL-inserted groups.

In previous studies, different cut-off points have been reported for the timing of catheter insertions. In Abbas et al[16] study, early placement was defined as catheter insertion before day 21, whereas Handrup et al[15] defined it as before day 20. Early placement was not a risk factor for infection in these 2 studies. However, Mclean et al[6] defined catheter insertion before day 15 as early and found a higher risk of infection. Many of the patients with ALL are febrile at presentation, and neutropenia that occurs within a few days of starting therapy persists for 2 to 3 weeks. Our hypothesis based on clinical experience was that CVLs placed during the first 2 weeks are more likely to become infected than those inserted subsequently. According to these results and our clinical impression, we selected the cut-off point as day 15. As a result of our study, we did not find any statistical difference in the rate of thrombosis, CVL-related infection, and other mechanical complications between these 2 groups.

TABLE 3. Laboratory Features of the Patients

	n (minimum-maximum)
Median WBC at diagnosis (mm^3)	8350 (1300-59,500)
Median WBC while inserting the catheter (mm^3)	3000 (500-35,300)
Median ANC while inserting the catheter (mm^3)	950 (0-12,000)
Median WBC at diagnosis of infectious complication (mm^3)	1100 (200-20,600)
Median ANC at diagnosis of infectious complication (mm^3)	150 (0-17,700)

DVT is a frequent and well-known complication during ALL treatment, with an incidence ranging from 1% to 37%.[16,17] The most common sites for thrombosis during ALL treatment have been reported as cerebral sinovenous and catheter-related DVT.[12,13,16] In patients with catheter-related DVT, even though the mortality risk is very low, morbidity is frequent with postthrombotic syndrome (reported up to 68%).[18,19] Five patients (9.6%) developed thrombosis during therapy in our study. Two were from early (thrombosis in the distal part of CVL and jugular vein thrombosis), and 3 were from the late CVL-inserted group (thrombosis in the distal part of CVL, intracardiac, and sagittal sinus thrombosis). In thrombophilia testing, a patient with intracardiac thrombosis was found to have heterozygous Factor V Leiden mutation. A recent study investigated the association between thrombophilia and recurrent CVL-related DVT and suggested that thrombophilia testing to predict recurrence in those patients may be unnecessary.[20] However, young age at the time of CVL insertion and lack of administration of treatment or prophylactic doses of anticoagulant were found to be predictive for recurrent events.[20]

Our patients with CVL-related thrombosis received LMWH for thromboprophylaxis during the rest of the intensive chemotherapy period, and reoccurrence of thrombosis was not observed. When CVL-related DVT occurs, the American College of Chest Physicians Pediatric Guidelines recommend giving anticoagulation for ≤3 months but consider more prolonged treatment for persistent risk factors.[21]

In our study, the mean number of catheter days was 371.8 ± 251.48 days for a patient. According to catheter days, there was no statistical difference between the early and late CVL-inserted groups. Catheter-related local and bloodstream infections occurred in 24 patients (46.2%), including 12 patients in the early and 12 in the late CVL-inserted group. No difference was found in the early and late CVL placement groups regarding the infection rates. Some studies reported that an ANC ≤500-1000/mm^3 on the day of CVL insertion is a major risk factor for infection, and the procedure should be delayed.[6,22] On the other hand, some other studies demonstrated that patients who had severe neutropenia on the day of insertion did not have a higher incidence of CVL-associated

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infection.[15,23–25] Gonzales et al[25] reported that CVL-related infection is not influenced by a patient's ANC, age, body mass index, or fever. Early placement of a CVL is safe in children with ALL, even when their ANC is <500/mm^3, the rate of mechanical complications is low, and no CVL has to be removed due to early infection.

The most important limitation of our study was its retrospective design and a limited number of patients. Because of a limited number of patients, statistically, it is impossible to compare some groups. Likewise, only 7 patients had early complications when we tried to evaluate only the early complications (in the first 30 d). We, therefore, evaluated all complications until the catheter removal. Another limitation of our study was that we did not record the presence of concurrent mediastinal mass at the time of diagnosis.

In conclusion, the present study showed no relation between the timing of CVL placement during induction therapy and the occurrence of infection and thrombosis. Our results suggest that CVL can be inserted safely at diagnosis or early induction treatment to provide a comfortable administration of chemotherapy and decrease painful blood samplings.

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