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Efficacy And Safety Profile Of Double Lumen Femoral Venous Catheters In Pediatric Stem Cell Apheresis

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Abstract:
Introduction: *Autologous peripheral blood stem cell (PBSC) harvests are increasingly being conducted in pediatrics patients for specific haematolymphoid and solid malignancies. A high-flow Central Venous Catheter is essential for the procedure. Many centers commonly utilize a femoral sheath and a peripherally inserted vein (PIV) for apheresis procedures. However, there is limited published data on the performance and safety of using a double-lumen femoral central venous catheter (CVC) in pediatric PBSC collection. This approach has traditionally been discouraged due to concerns about a higher risk of infections and thromboembolic complications*
Methods: *This retrospective observational study examines pediatric PBSC harvests in patients less than 15 years of age, conducted between December 2021 and June 2023. It evaluates the efficacy and safety of 23 short-term, double-lumen polyurethane femoral central venous catheters (CVCs) used for PBSC collection.*
Results: *There were a total of 23 patients with male to female ratio 2:1 with a mean age of 8 years. A total of 38 apheresis procedures were performed. The target CD 34 count was kept 6-10 X 10^6.*
Fifty-two percent of patients achieved the target or higher in a single session, and approximately 78% reached the target within one to two sessions. Half of the cases involved refractory or progressive Hodgkin lymphoma, while the other half comprised neuroblastoma, along with one case of relapsed Wilms tumor.
The mean CD34+ cell yield per session was 9.3 × 10^6 cells/kg, with an inlet flow rate exceeding 0.7 ml/kg/min in 94% of procedures. Flow-related adverse events (AEs) were observed in 17% of cases. Importantly, there were no insertion-related complications, and no cases of infection or thrombosis were reported. Central venous catheter (CVC) removal was uneventful in all patients.
Conclusion*: The short-term use of standard double-lumen femoral venous catheters appears to be a safe and effective option for PBSC collection, offering procedural simplicity, enhanced patient comfort, and reduced costs.*

Keywords: *femoral vein; central venous catheter; vascular access; dual lumen polyurethane catheter; PBSC collection.*

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I. Introduction:

Obtaining a sufficient number of stem cells in as few apheresis sessions as possible is ideal with respect to both patient convenience and economics. In order to decrease the required number of sessions, it is necessary to increase the volume of blood treated during each session which mandates a good vascular access with high flow rates. This is challenging in pediatric patients. In children, the peripheral veins can rarely accommodate minimal inlet flows (20–40 mL/min) required. A CVC is therefore necessary.

The long-term tunnelled dialysis CVC's have been used for stem-cell harvesting and high-dose chemotherapy, with the intention of reducing the number of peripheral venous cannulas or CVCs inserted in patients requiring PBSC transplantation. But most of them get removed before the start of high-dose treatment because of the infection. The non tunnelled CVCs have been found to be an excellent cost-effective alternative as it is intended for short term access. [1]

The location of apheresis catheters in the superior vena cava entered through the subclavian or internal jugular vein forms an ideal option because of its large calibre. It ensures high inlet flow rate and it can

withstand pressure. However insertion related problems such as pneumothorax, hemothorax, brachial plexus injury and positional problems have limited its use.[2]

The femoral vein catheterization is an alternative. The use of femoral venous access has traditionally been discouraged due to the high incidence of infection, thrombosis, mechanical occlusion secondary to kinking and patient discomfort. However, since it is used for a short duration of time during apheresis, it is still an optimal choice in the vast majority of patients. The anatomy is simpler, arterial pulse provides a reliable landmark, the technique doesn't require too much expertise, it is easy to achieve hemostasis by direct compression and doesn't require radiologic confirmation of placement. In adults, HD catheters which are large-gauge and hard-bodied are used. In paediatric age group, to find an appropriate size femoral HD catheters is often a challenge, hence many centres use a single lumen femoral sheath to serve as an inlet and a PIV in cubital fossa to serve as an outlet. Femoral sheath are stiffer catheters which can withstand pressure and ensures good flow rates. Although polyurethane double lumen femoral catheters can serve both as an inlet and outlet, not requiring an additional PIV with improved patient comfort and relatively sturdier compared to silicone catheters, they are not routinely used mostly because of the possibility of loss of procedure efficiency secondary to recirculation, resulting in suboptimal yield. The literature regarding this is very scarce.

As a new BMT centre, we performed pediatrc apheresis with the double lumen CVCs and we present our experience regarding its efficacy and safety.

II. Patients And Methods:

This analysis includes the pediatric (<15 years) PBSC records from a new Bone marrow transplant setting over a period of one and half year from December 2022 to June2023. The following data were reviewed: demographic characteristics of the patients, details of each PBSC collection and any catheter-related complication until catheter removal.

Patients:

The cohort consisted of 23 consecutive pediatric patients who underwent stem cell harvest. The demographic details, the treatment history, weight, height and vitals of each patient were accurately documented. Since most of these patients were previously treated with anthracycline based chemotherapy, cardiac fitness was obtained. 21of 23 patients were chemomobilised. Post chemotherapy cycle, granulocyte-colony-stimulating factor (GCSF) 5 mg/kg/day was given subcutaneously, daily until harvest. The CBC count was monitored daily from day 10, post chemotherapy cycle. Plerixafor (Mozifor) injection (0.24 mg/kg) was used pre-emptively in 17 out of 23 patients, 12 hours prior to the procedure. The harvest was done around day 14 (range 9-19) of the chemotherapy cycle. The CD34 cell analysis from peripheral blood prior to apheresis was done only in 5 patients and the target CD 34 count for starting the collection was >20 cells/μL. In 2 patients of the 23, only GCSF (10 mg/kg per day subcutaneous) was given and CD34 collection was done on the fifth day. The complete blood count, biochemistry, coagulation panel, serology was investigated prior to the procedure.

Vascular Access:

Vascular access was achieved through the femoral vein catheters, (standard double-parallel-lumens polyurethane catheter, non cuffed (Arrow/B Braun).These were placed by an experienced pediatric intensivist under conscious sedation, on the day of planned collection. The size of lumen was decided individually prior to the procedure by ultrasound screening of femoral vein diameter. Usually, 1 -2 sizes higher than routine recommendation was used as mentioned in the table 2.The cannulation was done according to the Seldinger technique, at the bedside, using aseptic precautions, under ultrasound guidance. No prophylactic antibiotic or antithrombotic therapy was used. For those patients requiring more than one apheresis, the catheter was left in situ. Both lumens were flushed with heparin and the site of insertion was cleaned and covered with a sterile dressing after each manipulation. Catheters were removed after completion of the apheresis when the target CD 34+ cell counts had been met. Following removal, the patients were observed for a minimum of 1 hour.

PBSC collections:

A total of 37 apheresis sessions were undertaken. The SPECTRA OPTIA (Terumo BCT, Lakewood, CO, USA), version 11 was used for all collections. The extracorporeal volumes (ECVs) ranged from 140 to 450 ml. In children, when the ECVs was greater than 15% of total blood volume, the circuit was primed with 300ml packed red cell, to avoid hypotension and impaired oxygen delivery. The whole blood volume processed, inlet flow volume, run time, inlet flow rate, collect volume was documented. The ACD-A ratio was 1:13(1:10-1:15).All patients were given IV calcium during mid procedure at 30 mg/kg. The flow related issues having an impact on PBSC collection were identified. The manipulation needed to improve blood flow or catheter functions were documented. These included flushing each catheter limb with saline, reversing lines, immobilising the limb with padded support etc. Full or partial rinse back was given in few selected cases.

Flow cytometry:

A FACS Lyric flow cytometer (Becton Dickinson, San Jose´, CA, USA) was used to obtain absolute CD34 count. The flow cytometry was performed by adding 20 µL of BD® Stem Cell reagent, 20 µL of 7-AAD(7-Aminoactinomycin D -a dye to assess cell viability)solution and 100 µLofspecimen (by reverse pipetting) to a BDTrucount™ tube cap and vortex which was incubated in the dark at room temperature for 20 minutes. To this 2 mL of 1X ammonium chloride - a lysing solution was added and further incubated in the dark at room temperature for 10 minutes. Later these tubes were immediately placed on wet ice in the dark, until ready to acquire samples which was done almost immediately within 1 hour after lysing.

Catheter-related complications:

Catheter-related complications were documented as follows:

Infection: local: skin erythema, purulent drainage, and pain at the site of catheter insertion; Systemic: fever and bacteremia.

Catheter malfunction: inadequate blood flow for the procedure or failure of blood withdrawal.

Vascular thrombosis: clinical and/or ultrasound evidence of catheter-associated thrombosis.

Bleeding: haemorrhage or hematoma.

Data analysis: Quantitative data were reported as the mean ± standard deviation (SD), median and range. *Categoricaldata were analyzed by chi-square and odds ratio, linear regression, t-test (Paired, unpaired) using SPSS 22 software.* A p value < 0.05 was considered statistically significant.

III. Results:

There were a total of 23 patients with 15 males and 8 females; ratio of (2:1). The median age of the patients was 5 years (2 to 14 years).The weight of patients ranged from 9 to 86 kg, median being 15.5 kg. Of these 23cases, 11 were refractory /progressive Hodgkin Lymphoma, 11 were high risk Neuroblastoma and 1 was a case of relapsed Wilmstumor. Most children (21/23) were collected following chemo mobilisation. 17 out of 23 children received injection plerixafor (Mozifor), 10 hours prior to the 1st harvest and 33 /38 sessions were proceeded by injection plerixafor(Mozifor) **(Table 1).**

VARAIBLE	NO.OF PATIENTS
No of patients	23
Sex(M:F)	15:8(2:1)
Age(years)	6.5(2-14)
<2y	0
2-5 y	11
5-10y	7
>10 y	5
Weight(kg)	22(9-86)
<10	1
10-20	12
>20	10
Primary diagnosis	
Relapsed /Refractory Hodgkin lymphoma	11
High Risk Neuroblastoma	11
Relapse wilms tumor	1
Mobilization:	
Chemotherapy +GCSF	21
GCSF only	2
Plerixafor (Mozifor)	17
Pre apheresis SDP	7
Pre apheresis PRBC	5
No.of apheresis sessions	
1	12(52%)
2	6(26%)
3	4(17.3%)
4	1(4.3)

Table 1: Patient demographics

All patients had femoral lines placed under anesthesia without complications. In all, only 2 patients had 2 catheters each, one of whom required 2 different collections at different times to achieve the target count of CD34 + cells; in another case, since the initial catheter inserted was of a smaller size, he underwent

rethreading into a bigger lumen catheter. No other patient required more than one catheter for the same collection. All catheters were placed in the right femoral vein.

The CVC size for all the patients ranged from 5-12 Fr. The catheter size was decided individually considering the weight of the child, the built and ultrasound screening of femoral vein diameter. In <5 years, the median catheter size was 5 Fr (5-8). In children 5-10 years, the median size was 8 Fr(7-8). In those >10 years,the median size was 8 Fr(7-12).

When compared against weight, the median CVC size <10 kg is 5Fr; 10-20kg is 7 Fr (5-8) and 21-30 is 8 Fr (7-8); 31 to 40kg is 8 Fr and in>40 kg is 12 Fr. **(Table 2)**

Age (years)	No. of patients	Recommended size(Fr)	Catheter size(Fr): median/range
</=5	11	04-May	5(5-8)
06-Oct	7	5	8(7-8)
>10	5	7	8(7-12)
Weight(kg)	No. of patients	Recommended size(Fr)	Catheter size(Fr):
			Median/range
</=10	4	4	5
Nov-20	9	4	7(5-8)
21-30	6	4	8(7-8)
31-40	2	5	8
>40	2	07-Aug	12

Table 2: Size of femoral CVC used based on age and weight

A total of 38 sessions were performed, with a median of 2 (range 1–4) apheresis sessions for collection. 12 among 23 (52%) reached the target or beyond in only one session, 6 (26%) patients required 2 sessions; 4(17%) underwent 3 sessions each and 1 (4.3%) child required 4 sessions as his 3rd session was aborted due to hypotension).In total 78% patients required only one or two sessions(Table 1). Of the 11 patients who had > 1apheresis procedures, 9 were refractory progressive Hodgkin lymphoma who were heavily pre-treated. In 9 /11 patients requiring consecutive apheresis sessions, the GCSF dose was increased (10mg/kg) and additional plerixafor (Mozifor) injections were given.

The mean TBV (patient blood volume) processed per session was173ml/kg. A median of 2.2 patient blood volumes was processed per procedure, lasting 200 minutes, i.e 3.3 hours (range: 150-328 min).The median inlet flow rate for all procedures was 22.4ml/min (range 8.8–63). The adjusted inlet flow rate for body weight is 0.95 ml/min/kg (0.5-1.01). 34% of procedures were performed at an inlet rate of less than 0.9ml/min/kg. The mean numbers of CD34+ cells collected across all 36 sessions were 9.3 X 10^6/kg of body weight (range 0.8–42 X 10^6 cells /kg)**(Table 3).**

PBSC Collections(n=38)	**Range**	**mean**
Apheresis per patient	**01-Apr**	**1.7**
TBV *processed per apheresis(ml)	**1532-11963**	**4160**
TBV per kg per apheresis (ml/kg)	**70-275**	**173.4**
Inlet flow rate(ml/min)	**8.8-63**	**22.4**
Adjusted inlet flow rate(ml/kg/min)	**0.5-1.01**	**0.95**
#ACD –A ratio	**1:10-1:15**	**01:13**
Collect time duration(min)	**150-328**	**200**
Collect volume(ml)	**104-260**	**170**
Single CD 34+ cells result X 10^6/Kg	**0.8-42**	**9.3**
TBV: Total Blood Volume, ACD: Acid Citrate Dextrose		

Table 3: Apheresis results

The flow related Adverse Events (AE) was documented in 4 (17%) patients and on an average of 10(27%) procedures. Interface issues in 5 procedures. The slow inlet rate (<0.7ml/kg/min) and requirement for line reversals in 5 and 2 procedures respectively. These were corrected by line flushing; correcting the leg position, immobilisation and improving the hydration status. These were noticed more in children <5 years of age while coming out of sedation. There was prolongation of duration in 4/38 sessions due to flow related issues **(Table 4).**

Patients procedures		
No. of patients with CVC related A/E	1	
Pain	1	
Bleeding/hematoma	0	
Thrombosis	0	
CLABSI	0	
No. of flow related AE	4(17%)	10(27%)
Difficulty in establishing interface	2	3
Slow inlet rate	2	5
Line reversal	2	2
Requirement of alternate IV access	0	0
Aborted procedures		**2**
Malfunction of program setting		**1**
Hypotension		**1**

Table 4: Incidence of Adverse Events (AE) during apheresis

There were no sedation related side effects. There was 1 patient who during his 3rd session developed hypotension with chills 20 minutes into the procedure which was terminated eventually. The child was managed symptomatically with Intravenous fluids and IV calcium. No other symptoms related to hypocalcaemia occurred in any other children. Only 1 child reported pain at femoral catheter side; however no local or systemic infection was observed. No evidence of venous thrombosis, limb swelling was recorded. There was 1 case where catheter was kept beyond 24 hours due to technical issues in the apheresis machine. The longest duration, a catheter was left in situ was 56 hours with an average duration of 29 hrs (9 hrs -56 hrs), making a total of 26 catheter days. No complications related to maintenance of the femoral catheter were recorded. Catheter removals were simple and safe, with no acute or delayed bleeding.

IV. Discussion:

In this study, we describe the experience of a new BMT centre, using a double lumen femoral CVC for stem cell collection in children, while vast majority use a femoral sheath and a PIV for the same. 78 % of our children achieved the target with 1or 2 procedures while 84% of the children achieved the same using femoral double lumen catheters in the series by Laura et[3] al and 89% cases in a study by ravagnani[4] et al, where target CD34+cell count was achieved in a single harvest. This could partly be explained due to the type of patients in the cohort and the lack of pre apheresis peripheral CD 34 + cells estimation which is reliable indicator for optimal harvest. 80% of those patients in our study, who required >2 sessions to achieve the target count were heavily pretreated refractory progressive Hodgkin lymphoma.

There are very few centres using double lumen femoral CVC for pediatric apheresis and hence there is limited published data regarding the catheter performance.

In our study, flow related issues were documented in17% cases. This was higher compared to Laura[3] et al(6.7% cases) and an adult study, Moreiras-Plaza[2] et al which encountered catheter-related flow issues in 12% (29/232 cases). However, our results were better compared to flow related AE in thoracic CVC (37% cases) from Laura et al[1] study. No procedures were abandoned because of these AE and all were corrected by routine manoeuvres. 70% of our flow related issues were noted in children <5 years who required correction in leg position. This was similar to Yocco et al [5] who anecdotally reported a high incidence of alarms, obstructions and kinked lines using femoral CVC in children < 3years of age, prompting them to use a soft leg splint to immobilize patients. Our study using polyurethane Double lumen catheter was better compared to Fishmeister et al[1] who used long-term, tunnelled, silicone CVCs (7-12 French) in 51 children and young adults undergoing PBSC but they were prone to collapse under the negative pressure and had increased risk of mechanical obstruction resulting in low inlet rates, reversal of draw and return lines, and line resulting in flow realted AE in 28% patients. Furthermore, these patients still required PIV for return to avoid recirculation due to the close proximity of the draw and return lumens unlike in our case where double lumens served as inlet and outlet.

Though there are no data available for determining the femoral catheter size for apheresis, using the standard size might not suffice for a good yield which we experienced with our first case that subsequently underwent rethreading into larger lumen catheter. We used 1-2 sizes larger than the routine recommendation based on weight or age. No AE like bleeding, hematoma or thrombus formation was experienced with larger size catheter.

Except for pain at the CVC insertion site in one case, no catheter related AE was noted in any of our patients as against Sevilla et al[6] who noted hematoma (8%) and bleeding (25%) in 12 children under < 10 kg

[31]. Bolan et al[7]used femoral CVC in 80%(31/38) of pediatric patients, with serious bleeding and hematoma formation in one patient.

Our study shows the safety and good performance characteristics of femoral Double-lumen polyurethane dialysis CVC in pediatric HPCC, especially in small and very young children. So, in conclusion using the appropriate sized double lumen femoral catheters for the purpose of apheresis reduces the necessity for placement of two lines and the complications associated with 2 lines. The patients are offered better positioning as they no longer need to keep the arm with fixed needle unmoved for extended period of time. With pre apheresis CD 34 + cells monitoring, which is henceforth planned to be used routinely, the yield can be obtained in as few apheresis sessions as possible. Thus, it improves patient comfort, simplifies PBSC collection and reduces the cost, duration of hospital stay, especially in resource limited setting.

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