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Letter to Editor

Outpatient Central Venous Access Device Insertion in Very Young Children with Severe Haemophilia

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Central Venous Access Devices (CVADs) are particularly useful in young children with severe haemophilia who receive multiple weekly infusions of Coagulation Factor Concentrates (CFC) for primary prophylaxis, and in children with inhibitors who require Immune Tolerance Induction (ITI). However, they have a high risk of complications, particularly infections, thrombosis and mechanical problems [1-5].

Here, we describe our experience with CVADs in young children with haemophilia regularly followed at the Haemophilia Treatment Centre (HTC) of Montpellier University Hospital. We analysed the causes of the recorded CVAD complications to develop strategies with the aim of reducing their rates and improving the quality of patient care. We also evaluated the safety and feasibility of CVAD insertion in such young children in a day surgery setting.

After approval by our local Institutional Review Board, we reviewed the medical records of all children younger than 10 years of age followed at our HTC (n=30) between March 2006 and September 2019. Among them, we excluded 14 patients for the following reasons: prophylaxis not yet initiated at the moment of the analysis (n=5), patients left Montpellier and were followed at another HTC (n=8), and prophylaxis using a peripheral vein (n=1). The 16 children included in the study had severe haemophilia A (n=14), severe haemophilia B (n=1), and type 3 von Willebrand disease (n=1 girl). During the study period, the same experienced paediatric anaesthetist inserted 28 internalized Port-A-Cath (Deltec, Inc., St Paul, PM, USA) in these 16 children using the same procedure (i.e., ultrasound-guided transcutaneous insertion of an implantable CVAD via the supra clavicular approach) and at the same day surgery unit.

The CVADs were placed for prophylaxis (full regimen with three infusions per week) in fourteen patients, and for ITI (peak titres >10 Bethesda Units) followed by prophylaxis in two patients (Table 1). The children's median age at CVAD implantation was 11 months (range: 8-34 months), and eleven children were younger than 12 months of age. Just before CVAD insertion in the operative theatre, all patients received CFC (50 IU/kg of factor VIII or von Willebrand factor, or 90 IU/kg of factor IX) or by-passing agents (270 µg/kg of activated recombinant FVII and/or 100 UI/kg of activated prothrombin complex concentrate). This was followed (8-12 hours post-insertion) by a second peripheral vein infusion in the paediatric outpatient unit because of the observation of minor chest wall bruising when the CVAD was accessed during the first 24 hours post-surgery. Prophylactic antibiotic coverage (cefazolin, 30 mg/kg) was performed only in patients with inhibitors. No complication related to CVAD insertion was reported, except one haematoma at the injection site, resolved by additional CFC infusions (n=2), in the girl with type 3 von Willebrand disease. In the absence of complications, patients were discharged after the second CFC infusion. A third CFC infusion (same dosage) was administered through the CVAD the day after when patients returned to the paediatric outpatient unit. Two days after surgery, the routine prophylaxis or ITI were started at the paediatric outpatient unit or at home by a specialist nurse. Each infusion was performed through a Hüber needle inserted after EMLA® analgesia and removed thereafter. Parents were asked to report promptly any signs of CVAD-related bleeding, occlusion or infection. During the routine haemophilia follow-up at the HTC, the CVAD was systematically monitored. CVADs remained in situ for a cumulative period of 20227 days (median duration = 799 days, range 123-1568), with a cumulative and median number of 8601 and 340 infusions (range 51-672), respectively. Seven patients underwent more than one CVAD insertion (two devices in three patients, three in three patients, and four in one patient) (Table 1).

During the follow-up, CVAD-related complications were reported in seven patients (median age 11 months) (Table 1): i) eight mechanical problems (0.25/1000 catheter days); ii) three bacterial systemic infections (coagulase-negative and methicillin-resistant *Staphylococcus aureus*) in the same patient who had high-titre inhibitors (0.12/1000 catheter days) and who was infused at home by specialist nurses. After CVAD removal, he received appropriate systemic antibiotics and activated recombinant FVII infusions at the paediatric outpatient unit (ITI was successful after 18 months); and iii) two cases of symptomatic CVAD-related thrombosis diagnosed by ultrasonography or computed tomography angiography because of CVDA malfunction (0.10/1000 catheter days). Analysis of the data for the first eight patients who received a CVAD showed that most complications occurred before 18 months of use and/or 500 infusions in patients younger than 12 months at the time of insertion. Therefore, we implemented the following modifications: i) CVADs are systematically replaced before 18 months of use and/or 500 infusions;

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Table 1: Patients' characteristics and Central Venous Access Device (CVAD) complications.

Patient	Disease	Indication	Age at first insertion (months)	Height at insertion (cm)	Number of infusions	Catheter days*	Height at removal (cm)	Complications Reason of removal
1	Severe haemophilia A	Prophylaxis, ITI	12	77 89 96	147 81 588	348 189 1374	89 96 125	Infection Infection Infection
2	Severe haemophilia A	Prophylaxis	8	69 116	591 672	1384 1568	116 136	Malfunction, rupture Choice
3	Severe haemophilia A	Prophylaxis	17	73 111 113	486 60 663	1137 141 1549	111 113 143	Malfunction, rupture Malfunction Choice
4	Severe haemophilia A	Prophylaxis	9	67 82	309 246	726 577	82 nd	Malfunction Choice
5	Severe haemophilia A	Prophylaxis Prophylaxis	10	71	381	895	95	Choice
6	Severe haemophilia A	Prophylaxis	11	75 90 110 120	312 261 324 213	609 759 498 1249	90 110 120 nd	Malfunction, rupture Malfunction Malfunction Choice
7	Severe haemophilia A	Prophylaxis	11	75 101 nd	534 396 579	1249 925 1352	101 nd nd	Thrombosis Malfunction Choice
8	Severe haemophilia A	Prophylaxis, ITI	34	97 100	63 207	153 486	100 nd	Thrombosis Choice
9	Severe haemophilia B	Prophylaxis	12	77	72	257	-	None
10	Severe haemophilia A	Prophylaxis	11	nd	162	383	-	None
11	Severe haemophilia A	Prophylaxis	11	nd	51	123	-	None
12	Type 3 von Willebrand	Prophylaxis	20	nd	312	730	-	None
13	Severe haemophilia A	Prophylaxis	21	72	252	501	-	None
14	Severe haemophilia A	Prophylaxis	18	78	216	382	-	None
15	Severe haemophilia A	Prophylaxis	15	71	180	358	-	None
16	Severe haemophilia A	Prophylaxis	11	73	132	279	-	None

nd: not determined; *at removal or at the end of the study

ii) infusions are performed at the outpatient paediatric unit during the first month post-insertion, and then, at home by specialist nurses whose procedural practices are regularly re-assessed. In addition, the need of a CVAD is questioned, at least once per year. Since the implementation of these modifications, the number of complications has decreased, and none occurred in the last eight patients (patient 9 to16). In seven patients, the CVAD was later removed because of suitable peripheral vascular access. Eight patients still had the CVAD at the end of the study follow-up. No joint bleed occurred during the studied period.

Consensus recommendations for the CVAD use in haemophilia have been published [6]. Literature data show that CVADs are safely inserted without perioperative complications [1-5]; however, the implantation setting (outpatient or inpatient surgery) was not systematically described. In a series of 15 patients with haemophilia discharged 24-48h after central venous port insertion, Santagostino *et al.* [6] reported only a port-site haematoma in one patient at day 7 post-surgery, when an inhibitor could be detected. Our data seems to confirm these results: all devices were inserted in an outpatient setting without any serious perioperative complication, mainly due to the high experience of the anaesthesiologist and specialist nurses.

Infection is the major complication associated with CVADs. In a meta-analysis including 48 studies on 2074 patients and 2973 CVADs, Valentino *et al* reported a pooled incidence of infection of 0.66/1000 CVAD days (CI 0.44-0.99) and identified several independent risk factors for infection (RR 1.67, CI, 1.15-2.43): presence of inhibitors, young age, and use of external CVADs [1]. Overall, we had a low infection rate, possibly because we used, as recommended, only fully implantable catheters. In the only patient with infection, we identified two known major risk factors: high-titre inhibitor [1-5] and young age [1,2]. However, Vepsalainen *et al*, suggested that young age does not increase the risk of infection [5]. Thrombosis is the other main complication of CVADs described in the literature [7]. In our series, thrombosis was associated with 2 of the 28 CADVs (7.1%). The reported frequency is highly variable, from 2% in the meta-analysis by Valentino *et al.* (pooled incidence: 0.054 per 1000 CVAD days, CI, 0.016-0.196) to 15% in the article by Van Dijk *et al.* [1,8]. Moreover, both clinical and radiological (of questionable clinical significance) thrombotic events are generally reported, making difficult to evaluate the real risk [9]. Neither age nor inhibitor presence affected thrombosis incidence in two studies [5,8]. As previously reported [4,5], mechanical problems (pinched or folded catheter), resulting in device malfunctions and replacement, were the most frequent complication in our series. These events may lead to catheter rupture when unblocking manoeuvres are repeatedly performed. This occurred three times in our series in patients who were perfused by nurses at home. Some situations could be explained by the children's increasing age and growth. All mechanical problems experienced with CVADs were the subject of a material vigilance report. Usually, mechanical problems lead to catheter removal [4,5], but they are considered to be less frequent than infections or

thrombosis [6].

Our cohort was relatively small. However, it is interesting to note that about 60% of patients were younger than 12 months of age at catheter insertion and that the median age was 11 months, which is younger than the age usually reported [3,8].

The development of extended half-life CFC and non-factor-based therapies that can be given subcutaneously, such as emicizumab (a bispecific antibody that mimics factor VIII), offer alternative approaches to overcome the venous access issue. Emicizumab, is now approved in several countries for patients with haemophilia A without inhibitors for all age groups. However, the French authorities highlighted the absence of specific studies in children younger than 12 years. Moreover, primary prophylaxis with CFC during the first 1-2 years of life is still the optimal treatment for complete prevention of joint bleeds with an objective of zero bleed in children with severe haemophilia. In this group, prophylaxis with extended half-life factor VIII concentrates may not allow a reduction of infusion frequency.

In conclusion, our findings emphasizes that, when strict precautions are implemented, CVAD insertion may be an option in very young children with severe haemophilia who have to be treated intensively [10].

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