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Use of implantable venous access devices in children with severe hemophilia: benefits and burden

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A B S T R A C T

Background and Objectives. Since venous access in small children can be difficult to obtain, implantable venous access devices (IVAD) are used to administer clotting factor in such patients with severe hemophilia. The aim of our study was to evaluate how many children in our center needed an IVAD in order to be able to start early prophylaxis, what the differences were between children who needed an IVAD and those who did not and what the complications of the IVAD were.

Design and Methods. All 70 patients with severe hemophilia born between January 1987 and October 2000 treated at our center before they were 6 years old were studied.

Results. An IVAD was placed in 23 children (33%). Children with an IVAD started prophylactic treatment at a mean age of 2 years (SD 1.3), those without at a mean age of 3.6 years (SD 1.6) ($p< 0.001$). Home treatment was feasible at a mean age of 2.8 years (SD 1.3) in children with an IVAD and at 4.5 years in those without an IVAD (SD 1.8) ($p = 0.001$). Infection was the most frequent complication; the mean number of infections per IVAD was 0.61. Thrombosis was more common than initially thought (15%). The infection rate in children with inhibitory antibodies was 3.1 per 1000 patient-days; in children without an inhibitor it was 0.72 per 1000 patient-days.

Interpretation and Conclusions. In 33% of the children in our cohort an IVAD was needed in order to start early prophylaxis. IVAD are needed more frequently when prophylaxis is started at an early age, but have the advantage that home treatment is feasible earlier. Infection is the most common complication, particularly in children with inhibitors.

Key words: hemophilia, Port-a-Cath, prophylaxis.

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Hemophilia is an X-linked recessive disease, which is characterized by a deficiency of factor VIII or IX for, respectively, hemophilia A and B. In severe hemophilia there is a total absence of clotting factor (factor VIII or IX < 0.01 IU/mL) resulting in recurrent bleeding, mainly in joints. Intravenous clotting factor administration is often needed. Two different treatment strategies can be used; 1) administration of factor VIII or IX when bleeding occurs (on demand), 2) prophylactic treatment, in which the factor is given at regular intervals with the aim to prevent bleeding. Several groups have demonstrated that primary prophylactic treatment may prevent arthropathy.[1,2] Ideally, prophylaxis consists of clotting factor administration two to three times a week before the first joint bleed.[3]

Since venous access in small children can be difficult to obtain and is often needed, implantable venous access devices (IVAD) are used for administration of the clotting factor. The benefits of these IVAD are clear: uncomplicated venous access and blood withdrawal. Besides benefits, the following disadvantages can occur; infection, which is the most common complication with reported infection rates varying between 0.23 and 1.8 per 1000 patient-days,[4-9] and thrombosis.[10-14] In patients with antibodies against factor VIII or IX (inhibitors) frequent administration of clotting factor is needed in order to acquire immune tolerance. It has been suggested that these patients are more prone to obtain infections of their IVAD than are patients without inhibitors.[7,8,15,16]

The aim of this study was to investigate the frequency of the use of IVAD and early prophylaxis in a single cohort of children with severe hemophilia. The clinical parameters of children with and without an IVAD

were compared. In addition the complications of the IVAD were evaluated.

Design and Methods

In our clinic we started implanting IVAD in the early 1990s. All patients born between January 1987 and October 2000 with severe hemophilia, who first attended the Van Creveldkliniek before they were 6 years old, were included in this study.

Data for this study were collected from the patients' files. The following items were studied: 1) age at start of prophylactic treatment, 2) age at first joint bleed, 3) the frequency of prophylaxis and 4) age at start of home treatment. We studied in detail all 23 children in whom an IVAD was positioned. The following items were investigated: indication for IVAD implantation, time between implantation and start of home treatment, prophylaxis, presence of inhibitors of factor VIII or IX, infections, thrombosis and other complications. Our prophylactic treatment regimen has been intensified since its introduction in the early 1970s.[3] Today we aim at starting prophylaxis early after the first joint bleed. However in earlier years two to three joint bleeds were accepted before prophylaxis was started. To find antibodies against factor VIII or IX three monthly blood samples were taken and laboratory examinations were performed. Until 1-12-1996 inhibitor concentrations of > 1.0 Bethesda units (BU)/L were considered positive; after 1-12-1996, due to the Nijmegen modification the threshold for inhibitors was taken to be > 0.2 BU/L.[17,18] Patients with an inhibitor were defined as patients who had a positive inhibitor test twice in combination with a decreased recovery.

During the implantation of the IVAD, coagulation was completely corrected by continuous infusion and this was continued for at least one week after surgery. Recombinant products were used in all children. In the case of bleeding in patients with an inhibitor, NovoSeven® was used. Antibiotics were not given routinely. Vascular access for the IVAD was gained by subclavian puncture. The implanted device was a Port-a-Cath (Pharmacia Deltic Inc., USA) in all cases. After every infusion through the IVAD, saline and a 5 mL bolus of heparin (1000 IU/10 mL) were given. When the IVAD was not used for a longer period, heparin was given once per month. Data were recorded until the date of the patients' last visit to our outpatient clinic for 3 children who had further treatment in an other center. For all other children we used the date of evaluation (01-05-2001), when the IVAD was still *in situ* or the date when the last IVAD was removed as the end-point. Patients were instructed to contact our clinic in case of any problems. Infections were defined as a positive blood culture test in combination with clinical manifestations of septicemia. Venography or ultrasound was performed in patients who presented with mechanical dysfunction of the IVAD (no blood return, no product infusion, discomfort with access), prominent chest wall veins, enlarged jugular veins or swelling or erythema of the neck, face or ipsilateral arm.

The children who had an IVAD implanted were evaluated separately according to whether they did or did not have an inhibitor.

t-tests and χ^2 tests were used to compare patients without an IVAD and patients with an IVAD.

Results

The cohort consisted of seventy children with severe hemophilia, born between January 1987 and October 2000. An overview of the study population is shown in Table 1.

Children without an IVAD versus children with an IVAD

Of this cohort 23 children (33%) were given an IVAD and 47 were not. Prophylactic treatment was started in 22 of 23 children (96%) children with an IVAD, whereas at the time of evaluation prophylaxis had been started in 30 of 47 children (64%) without an IVAD. Two of the children without an IVAD developed an inhibitor; however, peripheral vein access was adequate to allow immune tolerance therapy in these patients.

Children with an IVAD tended to have their first joint bleed at a younger age, although the difference was not statistically significant ($p = 0.48$). Children with an IVAD started prophylactic treatment earlier ($p < 0.01$) and in these children home treatment was feasible at a younger age ($p < 0.01$) (Table 1).

Children with an IVAD

Overall, 23 children had 34 IVAD implanted. One child was lost from follow-up after implantation of his first IVAD. He was excluded from further analysis, leaving 22 children with 33 IVAD. Before implantation of the IVAD 14 children had been treated on demand and 8 prophylactically; after implantation of the Porth-a-Cath only one child was treated on demand and 21 prophylactically. In two children prophylaxis was started relatively late; 1.3 and 2.5 years after implantation.

Three patients had severe hemophilia B and 19 had hemophilia A. The median age at implantation of the first IVAD was 1.7 years (range 0.7-5.3). Obtaining venous access was the main reason for implantation. Additional reasons for port insertion were start of prophylactic treatment in 13 patients, continuation of

Table 1. Characteristics of the total study population according to the use of the IVAD or not.

	No IVAD (n=47)		IVAD (n=23)		Total (n=70)		p value
Hemophilia A	42	(89)	20	(87)	62		
Hemophilia B	5	(11)	3	(13)	8		
Age at evaluation (years)	5.9	(0.6-14.3)	6.2	(3.0-13.6)	5.9	(0.6-14.3)	0.85
Age at first joint bleed (years)	1.6	(0.6-6.0)	1.6	(0.7-4.6)	1.6	(0.6-6.0)	0.48
No joint bleed yet (n)	5	(11)	2	(9)	7		
Unknown (n)	2	(4)	1	(4)	3		
Age at start of prophylaxis (years)	3.7	(0.9-7.1)	1.6	(0.3-5.5)*	2.7	(0.3-7.1)	<0.01
Not on prophylaxis (n)	17	(36)	1	(4)	18		
Frequency of prophylaxis ≤ 2 x per week (n)	9	8	17				
Frequency of prophylaxis > 2 x per week (n)	21	14	35				
Age at start of home treatment (years)	4.5	(1.3-9.5)	2.4	(1.2-6.5)	3.4	(1.2-9.5)	<0.01
On home treatment (n)	27	(57)	21	(91)	48		

*IVAD: implantable venous access device; values are medians (range) or numbers (%) ; *two patients started prophylaxis 1.3 and 2.5 years after implantation of the IVAD.*

prophylaxis in 8 patients, start of immune tolerance therapy in one patient and major bleeding in one patient. Problems related to the surgical procedure were the development of a transient Horner's syndrome in one child and a punctured subclavian artery in another. No bleeding or other complications occurred.

In 21 patients the first IVAD was used for home treatment by the childrens' parents; in one patient professionals administered the clotting factor. The median interval between implantation of the IVAD and home treatment becoming feasible was 2.0 months (range 1.0-8.0).

Of 33 IVAD implanted, 20 have been removed, 10 are still *in situ* and we do not have follow-up data for the other 3. Data were recorded until the date of the last visit to our outpatient clinic for three children who had further treatment in another center. At the last visit no inhibitory antibodies had been present and the IVAD were still *in situ*. Table 2 presents an overview of the reasons for removal and the complications. Two IVAD were removed because they were no longer needed. The median time until the first complication was 1.0 year (range 2 days-3.8 years). The median time until the first infection (n=12) was 1.4 years (range 6.0 days-3.8 years). In 9 out of 12 patients this infection was successfully treated with antibiotics. In these patients the median time from first infection until removal was 0.24 years (range 10 days-0.62 years).

Five patients had a thrombosis. The median time from initiation of the IVAD until the first thrombosis was 0.37 years (2 days-1.8 years).

In patients with an inhibitor, subcutaneous bleeding around the device occurred in two out of four IVAD. In children without an inhibitor, this occurred in 5 out of 18 IVAD. The results of the children with and without an inhibitor are shown separately, because children with an inhibitor tend to have more complications, particularly infectious ones.

Children without an inhibitor

In 18 children no inhibitor was detected; a total of 24 IVAD were implanted in these children. The median age at implantation of the first IVAD was 1.6 years (0.7-3.9 years). Of these 24 IVAD, 14 were removed. The reasons for removing the devices are shown in Table 2. Seven IVAD were still *in situ* and data were not available for three IVAD. The median time from insertion until the first infection (n=8) was 2.2 years (10 days-3.8 years).

The following bacteria were found in cultures of specimens: *S. aureus* (n=6; line loss in n=3), *S. epidermidis* (n=3; line loss in n=2), *Klebsiella oxytoca* (n=2; line loss in n=1), *Streptococci* (n=2; line loss in n=1) and *Streptococci* in combination with *Corynebacterium* group B (n=1, resulting in line loss).

Children with an inhibitor

In four children an inhibitor was present at the time of implantation of the IVAD. Three of these children had one IVAD with an inhibitor at implantation and one child had four IVAD.

Of the seven IVAD implanted, five had been removed by the time of this study.

One child had a total of six infections in the first three IVAD implanted: all these IVAD were removed.

Table 2. Use and complications of the IVAD among 18 children without inhibitor and among 4 children with an inhibitor.

	*No inhibitor **		*n IVADs*	*Inhibitor*		*n IVADs*	*p value*
IVAD (n)	24			7			
Age at implantation of 1st IVAD (years)	1.6	(0.7-3.9)		2.4	(1.0-5.3)		0.14
Duration of use of the IVAD (years)							
removed because of a complication	2.1	(0.15-5.0)	12	0.63	(0.27-1.6)	5	0.02
still in situ	0.8	(0.12-4.0)	7	1.04	(0.52-1.6)	2	0.68
Number of infusions through the IVAD	218	(22-630)	20	147	(27-242)	7	0.05
Number of infusions through the IVAD per week	2.0	(0.48-2.99)	20	3.0	(0.48-5.75)	7	0.11
Reason for removal of the IVAD (total number removed)	(14)			(5)			
infection	7			4			
thrombosis	4			_			
infection and thrombosis	1			_			
other	2			1			
Number of infections per IVAD	0.57	(0-2)		1	(0-2)		0,07
Infection rate x 1000 patient-days	0.72			3.1			<0.001
Infection rate x 1000 patient-days until first infection†	0.45			1.44			0.12

*Values are medians (range) or numbers; *the IVAD implanted in children with an inhibitor after the inhibitor had disappeared are not included; †number of first infections divided by (the time from implantation of the IVAD until the first infection of the IVAD when an infection occurred + the total duration of use of the IVAD when no infection occurred).*

The duration of use of these three IVADs in this child varied between 0.27 years and 0.63 years. The median duration until the first infection (n=4) was 56 days (6 days-1.5 years).

The following bacteria were cultured; *S. aureus* (n=3; line loss in n=2), *S. epidermidis* (n=1, line saved), *Corynebacterium* group B (n=2; line loss in n=1) and *X. maltophilia* (n=1, resulting in line loss).

An IVAD was replaced in two children after the inhibitor had disappeared. No complications occurred in the other IVAD; one was removed after 2.4 years because it was no longer needed and the other is still *in situ* (2.7 years).

Discussion

A cohort of 70 patients born between 1-1-1987 and 1-10-2000 was studied. Of these children 33% had one or more IVAD implanted. Prophylactic treatment was started in 22 of 23 children (96%) children with an IVAD, whereas it was started in 30 of 47 children (64%) without an IVAD. Children who started prophylactic treatment earlier in life (2 years, SD 1.3) needed an IVAD more often than children who started prophylaxis later (3.6 years, SD 1.6). A major achievement of the implantation of an IVAD was that home treatment was feasible at a younger age (1.7 years) in patients in whom this strategy was used than it was in patients without an IVAD. Because patients are treated according to their phenotype, patients with a milder bleeding pattern started prophylaxis later in life, when venous access was better and IVAD were no longer necessary.

In 21 of the 22 children with an IVAD the IVAD was used for home treatment by the childrens' parents. This study was performed retrospectively; therefore it could be argued that patients or complications might have been missed. However this is not very likely, because children attend our center regularly (at least three times a year) and parents were instructed to contact our center in the case of any problems. The percentage of children who are given an IVAD could be an underestimate, because the youngest children in our population were 7 months old at evaluation and are still candidates to have an IVAD implanted.

The infection rate in our population is comparable to that reported in a meta-analysis by Santagostino *et al.*[8] The average rate was reported to be 0.48 (0.31-0.64) per 1000 patient-days, when only the first infection of each port was considered. In some patients there was a short period between surgery and first infection, which could, therefore, have been related to the surgical procedure. Routine use of antibiotics might have prevented these infections. We found a relatively large number of infec-

tions in children with inhibitors. One child had a total of six infections in three IVAD. This problem was described earlier in several studies.[7,8,15,16] Different suggestions have been made to explain the higher infection rate. Bollard *et al.* suggested that the higher infection rate can be explained by more frequent use of IVAD for longer periods to treat difficult bleeding episodes.[19] This was not confirmed by a multicenter study.[7] However, in this study only the total number of infusions through the IVAD was considered and not whether there were periods when the IVAD was used more frequently (e.g. in a period with an inhibitor) and more infections did occur. In our population there was only a slight difference in the number of infusions per period (Table 2). Bollard *et al.* also suggested a relation with the use of Emla crème.[19] This was also mentioned in a study by Perkins.[5] Cleaning the skin with water and soap to wash away the crème before starting disinfection of the IVAD resulted in a decrease of infections. In our study this was not evaluated. Both Ljung and Collins suggested that the higher number of bleeds around the IVAD could play a role in patients with an inhibitor.[6,7,15] In our study bleeding around the IVAD occurred 7 times; 5/18 times in a child without an inhibitor and 2/4 times in a child with an inhibitor. This bleeding could enhance bacterial growth in the area, leading to infections.

Besides infections, thrombotic complications should also be considered. Thromboses should be divided into short-term thrombosis, when the tip of the catheter is blocked and long-term thrombosis, when endothelial damage occurs and thrombotic sheets are deposited on the outer surface of the catheter. This latter complication was not prospectively investigated in our study, but was reported by Journeycake *et al.*[14] In our study thrombosis occurred in five out of 33 IVAD (15%). All cases occurred in children without an inhibitor. Our data on thrombosis were evaluated only in patients with symptoms. The thromboses occurred between 2 days to 1.8 years after implantation after a median time of 0.37 years. The early thromboses might have been due to the surgical procedure. The percentage of thrombosis reported in the literature ranges from 0-17%.[7,17,20-22] However, from recent prospective studies, in which asymptomatic children were also screened, it became clear that thrombosis occurred more often than was previously thought.[10,12-14] Journeycake *et al.* evaluated the IVAD of 15 children with hemophilia by venography.[14] Eight of 15 patients were found to have thrombosis, although clinical symptoms were not present in any case. When present, clinical symptoms can be a larger diameter of the ipsilateral arm, prominent chest wall veins or dysfunction of the IVAD. No thrombosis was detected in patients who had their IVAD *in situ* for less than 4 years. Blanchette *et al.* examined 16 children with hemophilia by venography and ultrasound.[13] They detected thrombosis in 63%. When the IVAD is placed in the subclavian vein, venography is sufficient.[14] Koerper *et al.* performed bilateral venography in 11 asymptomatic children with hemophilia and an IVAD *in situ* for 1 to 5 years.[10] Two children (22%) had total occlusion of their left brachiocephalic vein with development of collateral vessels. Pulmonary embolism has not been described as a complication in these children.

The advantages of IVAD are clear, uncomplicated venous access and blood withdrawal. These advantages justify the disadvantages, such as the risk of infections and thromboses in some children. An experienced clinician should make the decision about implanting an IVAD for each patient individually, carefully weighing the need for early start of prophylaxis, the risks and the acceptability for the child and its parents. More prospective studies are needed to evaluate the use of IVAD in children with severe hemophilia. Venography may be performed regularly to detect asymptomatic thrombosis. However, this is an invasive procedure and the contrast agent used may induce phlebitis.[23] Journeycake *et al.* suggested removing the IVAD after 4 years or performing a venography if the IVAD is required for longer.[14] Implantation of an IVAD in children with an inhibitor remains a difficult decision. On the one hand an IVAD is almost indispensable because clotting factor must be administered frequently to induce immune tolerance, but on the other hand the chance of infectious complications in this group seems to be higher.

In conclusion, 33% of the children in our cohort needed an IVAD in order to start early prophylaxis. IVAD are needed more frequently in children who start prophylactic treatment at an early age. The advantage is that home treatment is feasible at an early age. Infection is the most common complication, particularly in children with inhibitory antibodies.

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