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Central venous lines in haemophilia

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Summary. Infections and technical problems are the most frequent complications when using implantable central venous access devices in patients with haemophilia. There are two major experiences reported concerning infections in noninhibitor patients: one is approximately 0.2 infections per 1000 days and the other approximately 1.0 (0.7–1.6) per 1000 days. Infections are more frequent in inhibitor patients and approximately one infection per 6–12 months of use can be expected. The figures are low for clinically apparent thrombosis in the larger series on record, but routine venograms were not carried out in most of these series. In studies where this has been done, a high frequency of abnormalities on venograms has

been seen in some but not in others. The final decision to use a central line has to take into account the medical goal, the patient's bleeding tendency, the social situation and the expected risk of complications at the particular haemophilia centre. Some of the complications may be reduced by adequate aseptic measures both during implantation and in subsequent use, and by clear basic routines for surveillance of the systems and repeated education of the users.

Keywords: haemophilia A, haemophilia B, factor VIII, factor IX, catheter

Introduction

Treatment of haemophilia A or B with, respectively, factor VIII (FVIII) or factor IX (FIX) concentrates, irrespective of whether this is done in the event of a bleed or as a prophylactic infusion, requires uncomplicated venous access. If the patient is treated on a prophylactic regimen, infusions are usually given three times per week or every other day in haemophilia A and twice per week or every third day in haemophilia B. Ideally, primary prophylaxis should be started at an early age, and it should be possible for the parents to administer the concentrate at home [1]. This may be very difficult using a peripheral vein in a small boy. If the child is treated on demand, the administration of concentrate for a bleed should preferably be done immediately by the parents at home, a situation in which safe and easy access to a vein is necessary. Several reports have been published describing varying experiences with the use of central venous catheters in patients with haemophilia [2–13]. There is a diversity of opinions among clinicians concerning the benefits and adverse effects of central

venous catheters. Some clinicians are in favour while others are more critical due to the frequency of complications. The aim of this paper is to give an overview of the experiences so far with the use of central venous lines in patients with haemophilia.

Evaluating the studies on record

When evaluating previous studies on central venous lines for treatment in haemophilia, several aspects need to be considered. First, some series include both patients with external catheters and those with implanted subcutaneous ports [6]. It has been clearly shown in a large series of non-haemophilia children that implantable systems have a much lower risk of infection compared with external catheters: 0.7 infections per 1000 patient days for subcutaneous ports vs. 4.3 for external catheters ($P < 0.0001$) [14].

Secondly, many series include haemophilia patients both with and without inhibitors. It has been shown in many series that the frequency of infection is higher in patients with inhibitors [3,6,11]. In one series with a median follow-up time of 30 months, 23% (nine of 39) of noninhibitor patients had complications, corresponding to 0.23 complications per 1000 patient days. In comparison, 64% (seven of 11) of inhibitor patients manifested complications [9].

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Thirdly, some series include patients with HIV infection who may be immunocompromised and thus naturally have a higher risk of infection than the HIV-negative patients [6]. Series that include many HIV-infected persons do not give an accurate risk figure for the otherwise healthy haemophilia patient considering a venous device. Another relevant consideration in assessing risk is that many series also include patients with other coagulation disorders [4,8], and we do not know if experiences from other coagulation disorders are transferable to haemophilia.

Most series with implantable catheters have been using the Port-A-Cath system, and almost all reports of larger series in haemophilia patients are with this system. However, some series also report peripheral intravenous access devices (P.A.S. Ports™, Slim-Ports™) [8]. These seem to be well accepted by the children and parents. In young children it is less threatening to insert a needle in the periphery of the body, and they can avoid the visible profile of the port on the chest. However, peripheral ports have been associated with a higher frequency of thrombophlebitis and thrombosis, and the average time that the patient may benefit from the device is probably shorter [8]. The Percuseal® device (Percuseal Medical, Huskvarna, Sweden) is implanted into the subcutaneous tissue, with the top portion protruding from the surface of the skin. The advantage is painless clotting factor application without skin puncture [15]. Although interesting, since it is based on a new technique, its usefulness needs to be demonstrated in larger series.

This overview will be mainly focused on the Port-A-Cath system, since most data from larger series are based on this device. The most frequent complications with implantable ports are infections and technical problems. Thrombosis is a serious potential adverse effect.

Infections

Infection is the most frequent complication when using a central venous line. Table 1 shows some of the larger studies from recent years. Unfortunately, it is usually not possible to study exclusively a cohort of haemophilia children who are HIV negative and to separate inhibitor from noninhibitor patients. Some series distinguish local infections around the port from proved bacteraemia/septicaemia. When discussing infections or other complications it should be emphasized that many systems have been used for prolonged periods before the complication occurred.

It is obvious that the frequency of infections is higher in patients with inhibitors. In the series by Ljung *et al.* [9], 64% of the inhibitor patients (seven of 11) manifested infections after 1–47 months of use (mean, 15 months; median, 15 months). In the series by McMahon *et al.* [11], 23 infections occurred in 18 central venous lines in patients with inhibitors, a rate of one infection per 8.5 patient months or 4.3 infections per 1000 patient days, which is a considerable higher frequency than in the other study. In a review, van den Berg [16] found that in various studies 50%–83% of patients with inhibitors can be expected to get an infection. Collins *et al.* calculated that children with inhibitors develop one infection per 8.3 months compared with one per 50 months for noninhibitor patients [17]. In the Spanish registry of central venous lines, 54% (19 of 35) of the patients with inhibitors had infections, compared with 30% (six of 20) of the patients without inhibitors (Tusell *et al.*, personal communication and World Federation of Haemophilia (WFH) Congress, Seville, 2002). One reason for the higher frequency of infections in inhibitor patients may be that these patients have small haemorrhages around the port after an injection that will stimulate bacterial growth in the subcutaneous tissue. Another

Table 1. The rate of infection in recent series with haemophilia patients using central venous lines [6,8–11].

Study	Number of patients (<i>n</i>)	Rate of infection per 1000 patient days	Comment
Blanchette <i>et al.</i> 1996 [6]	19	0.7	3 patients with inhibitors, 3 HIV+
Perkins <i>et al.</i> 1997 [8]	35	1.2 (central) 0.7 (peripheral device)	7/32 inhibitors, 2/32 vWD
Ljung <i>et al.</i> 1998 [3]	53	0.19	11 patients with inhibitors
Sanagostino <i>et al.</i> 1998 [13]	15	0.3	2 inhibitor patients, 13 on prophylaxis
Miller <i>et al.</i> 1998 [10]	41	0.14	Includes external
McMahon <i>et al.</i> 2000 [11]	58	1.6 (without inhibitor) 4.3 (with inhibitor)	77/86 devices Port-A-Cath; 37/58 patients haemophilia
Tusell (personal communication, 2002)	20 35	0.28 (prophylaxis) 0.68 (ITI)	Port-A-Caths used for prophylaxis/on demand or ITI

explanation could be that the inhibitor patient is often on an immune tolerance induction programme with one or two injections per day. The noninhibitor patient on prophylaxis accesses the port at most every other day. In the Spanish series, the patients with inhibitors had on average a period of 17.5 months free of infections compared with 41.5 months for the patients without inhibitors (Tusell *et al.*, personal communication and WFH Congress, 2002). However, in one study no relationship could be found between the number of punctures of the Port-A-Cath and the frequency of infections [9]. A reasonable conclusion from the different experiences with Port-A-Cath in patients with inhibitors is that one infection per 6–12 months of use can be expected. However, these patients need uncomplicated, easy venous access both for the treatment of acute bleeds and for immune tolerance induction programmes, and the above-mentioned risk of infection has to be judged in that context.

For noninhibitor patients the need for a port has to be considered together with the risk of complications. As judged from the series in Table 1, there seem to be two major experiences concerning infections in noninhibitor patients: one is approximately 0.2 infections per 1000 days and the other approximately 1.0 (0.7–1.6) per 1000 days. Sanagostino *et al.* found 0.33 infections per 1000 entries to the port in a small prospective series of 15 patients, of whom 13 were on prophylaxis [13]. Whether this is an acceptable frequency of infections for this group of patients depends on the situation for the individual patient and the treatment regimen. The child prone to spontaneous bleeds who should start primary prophylactic treatment from the age of 1 year is a greater challenge for venous access than the child receiving on-demand treatment for infrequent bleeds. A central catheter is only an option for those patients in frequent need of an uncomplicated venous access where the benefits have been calculated to be greater than the risks. The indication has to be discussed with the parents, with the social situation and the need for home treatment to be taken into the decision making. Most centres probably start with a peripheral vein with the hope that it will be sufficient. In the best of hands, the patient with a Port-A-Cath, without inhibitors and on regular prophylaxis, will have a maximum of one catheter-related infection in approximately 10 years (Table 1).

The most frequent pathogens in all series seem to be *Staphylococcus epidermidis* or *aureus*. The use of antibiotics in the peroperative period varies between centres and remains controversial. Most of the experience is from cancer patients and in some

studies antibiotics have been of value [18], while in others no benefit was found [19]. A more important issue may be the general use of antibiotics in the environment and the resulting frequency of resistance to antibiotics. Of course, vigorous education in aseptic techniques, follow-up and re-enforcement of the education are fundamental in reducing the risk of infection. It has also been speculated that the common use of EMLA[®] anaesthetic cream may play a role [8]. A reduction in infections was found after the parents were instructed to scrub with soap and water rather than using an ordinary medical swab to remove the residual lipid from the skin. This is probably worth noting in the education of aseptic techniques.

The occurrence of an infection does not mean that the catheter has to be removed. There are several reports in the literature to show that many catheters may be used after the treatment of an infection. Usually these are cases of an early infection around the port. It may be advisable not to use the port in the immediate postoperative period to ensure that no infection develops in the area around the port that may be transferred to the inside of the system. There are anecdotal reports of a beneficial effect with the instillation of antibiotics in the catheter between injections during treatment of bacteraemia. After treatment of bacteraemia/septicaemia the system has to be checked repeatedly before it may be considered free from bacterial contamination. In many cases it has to be removed, and it may be advisable not to insert a new system at the same operative procedure.

Thrombosis

Infections are the main adverse effect associated with central venous catheters. However, several other complications have to be considered, as shown in Table 2. Thrombosis has been a major concern when discussing indwelling catheters. The incidence figures are very low for clinically apparent thrombosis in the larger series on record (Table 2). However, one should be aware that routine venograms were not done in most of these series. In cases where this has been done for various reasons, a fibrin clot at the tip of the catheter has sometimes been seen, the clinical significance of which is not clear. Some series have reported a high frequency of abnormalities on venograms [20]. In the series by Journeycake *et al.* [20], eight of 15 children with haemophilia and central venous catheters (tunnelled subclavian) had evidence of thrombosis on routine venograms, and all those with clinical problems (five of 15) had abnormal venograms. However, before 48 months of use none

Table 2. Complications of implantable central venous catheters other than infections in various studies with an estimate of risk.

Complication	Frequency	Study
Technical problems (blockade or buckling of catheter, damage from trauma)	Blockade after a mean of 13 months	3/16 complications Ljung <i>et al.</i> [9] McMahon <i>et al.</i> [11]
	Catheter splitting or disconnection after a mean of 2 years	McMahon <i>et al.</i> [11]
Short catheter	1/16	Ljung <i>et al.</i> [9]
	1/19	Blanchette <i>et al.</i> [6]
Erosion of skin over port	0/53	Ljung <i>et al.</i> [9]
	3/86	McMahon <i>et al.</i> [11]
	3%	Perkins <i>et al.</i> [8]
Thrombosis	0/53	Ljung <i>et al.</i> [9]
	1/19	Blanchette <i>et al.</i> [6]
	0/86	McMahon <i>et al.</i> [11]
	0/19	Medeiros <i>et al.</i> [21]
	2/55	Tusell <i>et al.</i> (Spanish registry)
	7/181	Tusell <i>et al.</i> (17 int. paediatric centres)
	8/15	Journeycake <i>et al.</i> [20]

of the patients had abnormal venograms, ie the risk of thrombosis increases after years of use. The clinical implications of this study for the patient with a Port-A-Cath are not clear. Medeiros *et al.* studied venograms in 13 of 19 young haemophiliacs (of whom many later in the course were included in the series by Journeycake *et al.* [20]) with implantable central venous devices and reported no clinically relevant findings [21]. Tusell *et al.* reported clinical thrombosis in two of 55 cases (one verified by imaging) in the Spanish registry and in seven of 181 (six verified by imaging) cases in a survey of 17 paediatric centres in nine countries (Tusell *et al.*, personal communication and WFH Congress, 2002). There are reports in the literature of thrombosis even in inhibitor patients [22] and also a case of bacterial endocarditis [23]. The risk of thrombosis in haemophilia patients seems to justify only routine clinical surveillance of this potential complication. It is important that the tip of the catheter is in the right atrium or in the superior vena cava, where the flow of blood diminishes the risk, compared with positioning in a smaller vessel. Annual routine X-rays of the position of the catheter tip seems warranted in this context, and perhaps a routine venogram at the same time should be recommended after a few years of use. One should also consider assaying for thrombophilic factors in the patient before making the decision to implant a central venous catheter, since catheter-related thrombosis in haemophilia patients has to be considered a multifactorial disorder [24].

Other complications

The risk of blockade of the catheter may be diminished by proper education in the use of saline flush

and a 'heparin lock' after use (a few millilitres heparin 100 U mL⁻¹, depending on the system used). If not used, the catheter should be flushed and a new heparin lock should be administered at least every second month. Another prophylactic measure is the routine use of instillation of urokinase in the catheter (eg 2–3 mL 5000 U mL⁻¹ for 1–2 h). How often this has to be done depends on the use of the catheter, but it should be at least when injection in the catheter becomes less smooth.

Erosion of the skin over the port has occurred in a few reported cases and has to be considered as a potential serious complication. Inhibitor patients with bleeding and subsequent infection around the port seem to be at particular risk.

The use of Port-A-Cath systems

A survey of the actual use of Port-A-Cath systems in children was done in 20 centres in 16 European countries [25]. In three of 19 centres >50% of the boys under the age of 6 had a Port-A-Cath, while none had the device in seven of 19 centres. A few children at some centres used ports after the age of 6 years. The treatment regimen is one reason for differences, but the most important factor is the clinical experience of the centre with central venous lines.

In summary, for immune tolerance induction with daily infusions, a central venous line is often necessary and unavoidable, especially in children. A higher frequency of complications, especially infections, is to be expected as a calculated risk of the overall procedure. In prophylactic treatment, a central venous access device is recommended as an option when access to a peripheral vein is difficult or infeasible for the modern frequent treatment of

haemophilia from an early age. The alternative is usually a less frequent prophylactic treatment, especially in small boys, using a peripheral vein. The final decision to use a central line in a child has to be a compromise between the medical goal, the patient's bleeding tendency, the social situation and the expected risk of complications at the particular haemophilia centre. Some of the complication rates on record may be reduced both by adequate aseptic measures during implantation and by the subsequent use of clear basic routines for surveillance of the systems and for the repeated education of the users.

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Open discussion following the presentation by Dr Rolf Ljung

Dr Amy Shapiro: Do you have a preferred method for implanting the port? Is it subclavian or internal jugular implantation?

Dr Ljung: External jugular. In the small kids, it's the internal, because the other is too small. But it is the surgeon's decision, really. Our surgeon always tries to put it in the jugular vein, first the external, or if that doesn't work, the internal.

Dr Shapiro: In the USA, most ports are put in the subclavian vein, and I think that leads to more problems with thrombosis. If you look at the literature, the number of passes that they make at the subclavian does more damage and can lead to more thrombotic episodes.

Dr Victor Blanchette: We are repeating the studies now on our cohort using bilateral arm venograms and ultrasounds. We have a figure that's high from our series [*Blood Coagulation Fibrinolysis* 1996; 7 Suppl 1: S39–44] and from Buchanan's series [*J Pediatr* 1998; 132: 934–8]. The true incidence is probably somewhere in the middle, and it is going to require a larger number of patients to be studied to give confidence limits. It could be set up as a prospective study doing the correct imaging techniques in good centres, and then you would come up with the real incidence of this complication. But a number of these clots are silent.

Dr Marilyn Manco-Johnson: I think when you see data like that, it is primarily either a difference in surgical technique or a more sensitive detection method that, as Dr Blanchette is suggesting, will show that the other studies have more cases also. Centres that see a higher prevalence have to ask themselves: Are we doing something differently in our surgical technique or are we just detecting more silent cases?

Dr Blanchette: There are a lot of questions: what is the best technique, where should it be placed, when should you take it out. I think a cooperative study could probably get at those issues.

Dr Manco-Johnson: We used urokinase every 2 weeks for years and we never had one infection and we never had one clinical thrombosis. Then it was taken off the market in the USA. Because of the cost,

tPA is not available for home use. It comes in a 5 mg vial that costs \$5,000, which can be divided under a hood into 100 doses, and then it's only \$50 a dose to clear the catheters. Since we stopped using it because of the practical issues, we have had some infections. If we could somehow make that convenient for home use, tPA is very helpful.

Dr Ljung: I'm glad you say so. I don't do that routinely, but I have been considering it because I think it makes sense to do it.

Dr Alessandro Gringeri: I want to remind you of our experience with the venous fistulas that we are doing in the proximal forearm in our patients after what we judged to be bad experiences with Port-A-Cath. Now we have more than 20 children with the fistulas, and in our experience it is something that adds no risk of infection at all.

Dr Ljung: What happens with the growth in that arm?

Dr Gringeri: Our experience in children with haemophilia is still short-term, about 2 or 3 years, but there is a long experience in other young patients; with an appropriate surgical procedure, we do not have any problems. The only side effect is that in some patients it will close up by itself, but actually, this event happens in 10%, no more.

Dr Ljung: On the other hand, when you look at infections, for example, usually the child had benefit of the Port-A-Cath for perhaps 1 or 2 years before the infection. If a child is implanted with a Port-A-Cath at the age of 1, and at 3 and a half I take away the Port-A-Cath, I think it was a successful case, because they had use of it for 2 years.

Dr Blanchette: Do you or others feel that the data are sufficiently persuasive to suggest that the line be placed in the jugular venous system?

Dr Ljung: I don't think we have the data to justify such a recommendation. You could comment on other things, such as look for thrombophilic factors, flush every month, use urokinase every second month, but we don't have data to support the choice of surgical method.

Dr Shapiro: We don't have proof about urokinase either.

Dr Ljung: No. The only thing we know is that it helps to smooth the injections.