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ORIGINAL ARTICLE

The impact of clinical practice on the outcome of central venous access devices in children with haemophilia

K. KHAIR,* S. RANTA,† A. THOMAS‡ and K. LINDVALL¶ PEDNET STUDY GROUP
**Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK; †Karolinska University Hospital, Stockholm, Sweden; ‡Royal Hospital for Sick Children, Edinburgh, UK; and ¶Skåne University Hospital, Malmö, Sweden*

Introduction: Central venous access devices facilitate home treatment in boys with haemophilia. These are usually fully implanted lines, referred to as ports. Caregivers are taught to manage the port using sterile techniques and maintaining patency by flushing with saline or heparin solution. National and international guidelines for the home care of ports are lacking. **Aim:** To evaluate if infection or occlusion rates differ between home care regimens used for ports in children with haemophilia. **Methods:** Children with ports were identified from the PedNet registry. Data on the homecare policy were acquired from each centre. To ensure a complete data set for each port, only ports that had been removed were included in the study. Three care groups were defined: 'aseptic non touch technique', 'sterile technique' and 'fully sterile technique'. Outcomes within and between the groups were analysed. **Results:** A total of 240 children with 352 ports were studied. Insertion occurred at a median age of 1.32 years. The median port duration was 2.94 years with a total of 215 688 port days in children without and 183 852 in children with inhibitors. Infection was the most common cause of port removal (34%); there was no significant difference with infection as reason for removal between the different care groups. Occlusion was not more frequent in centres that did not use heparin. **Conclusion:** Use of sterile gloves and gowns did not reduce the risk of port infection. Using less stringent sterile techniques for accessing ports is easier for caregivers and in addition may have health economic benefits.

Keywords: central venous access device, children, haemophilia, nursing practice

Introduction

Children with haemophilia A and B have deficiencies of clotting factor VIII (FVIII) or factor IX (FIX) respectively. Those with severe haemophilia (levels <0.01 IU mL^{-1}) can be treated with prophylactic therapy, which involves repeated injections of factor concentrate to prevent bleeding, joint disease and intracranial haemorrhage [1,2]. Children with moderate and mild haemophilia are commonly treated on-demand after a bleed has occurred, with factor concentrate usually being given via peripheral venous access. For children who develop inhibitors against the deficient coagulation factor and undergo immune tolerance, intensive intravenous therapy is required [3].

In order to secure more reliable venous access for early prophylactic treatment, immune tolerance therapy, and to facilitate home therapy, central venous access devices (CVADs) can be used. These can be either fully implanted subcutaneous injection ports (referred to as ports) or external lines. External lines are not recommended for long-term treatment of children with haemophilia [4]; ports are preferred because of their lower rate of infectious complications and expected usage of several years [5,6]. Parents or care givers are taught how to manage the port and administer treatment at home [7]. The use of ports requires adherence to sterile techniques, flushing with saline or heparin solution and periodic monitoring of the caregiver's ability to perform these procedures adequately [8]. No national or international guidelines for the home care of ports in haemophilia exist; care differs between haemophilia centres, dependent upon local guidelines [9]. Indication for insertion of ports also varies between centres: some centres insert ports routinely to initiate primary prophylaxis allowing timely

Correspondence: Kate Khair, Consultant Nurse Haemophilia, Great Ormond Street Hospital, Visiting Professor of Health and Social Care, London South Bank University, London, UK.
Tel.: +44 20 7829 8846; fax: +44 20 7829 8872;
e-mail: Kate.Khair@gosh.nhs.uk

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and secure venous access, while others teach the more demanding technique of peripheral venous access when introducing primary prophylaxis. Early port insertion can be particularly helpful for those patients living at a longer distance from the treatment centre. In addition not all centres have resources to teach the parents to inject factor concentrates via a peripheral vein. Other centres insert ports only when peripheral venepunctures are difficult to perform or in children with inhibitors to enable daily, high-dose treatment. The 'European Paediatric Network for Haemophilia Management' (PedNet) registry provides a unique data source to study the variability of port care in a large paediatric population with haemophilia [10]. Data for the registry are collected from birth cohorts of consecutive patients diagnosed with haemophilia from 31 haemophilia treatment centres in 16 countries. The aim of this study was to evaluate if the infection or occlusion rates differ between the different home care regimens in children with haemophilia across the PedNet cohort.

Methods

Patients and data

The PedNet registry provided data for this observational cohort study. All patients were treated according to local protocols. Ethical approval and written informed consent was obtained before inclusion into the PedNet registry. More details of the design of the PedNet Registry have been described elsewhere [10]. The children in the CVAD study cohort were born between January 1st 2000 and December 31th 2013 and were followed up until 13th January 2016. As the purpose of this study was to compare different care regimens, we only included children with ports that had been removed so that complications and outcomes for the full life span of the port were known. For the same reason, only ports inserted before January 1st 2015 were included. External catheters were not included in the analysis as they comprised only 5.0% of all CVADs. Data routinely collected as part of the PedNet registry included details of port complications and reason for removal such as infection (culture positive or clinically diagnosed), occlusion, mechanical problems and 'no longer required', the point when children moved on to peripheral venous access for treatment. Additional information was requested from each centre detailing port care. As most centres performed no formal imaging to assess for evidence of thrombosis, 'occlusion' is used for a line reported as blocked, rather than 'thrombosis'.

Classification of port care groups

Data were collated on a centre-by-centre basis to describe standard port care including skin cleansing, use of protective clothing (sterile or non-sterile gloves, mask and/or gown) and heparin or saline flushing after factor administration. Three distinct home care groups were described:

1. 'Aseptic non-touch technique (ANTT) group': ANTT is a technique that maintains asepsis in a non-touch manner rather than with sterile barriers such gowns and gloves [11].
2. 'Sterile technique (ST) group' where sterile gloves, sterile field and aseptic techniques were used.
3. 'Fully sterile technique (FST) group' where sterile gloves, sterile field, aseptic technique and gowns and/or masks were used.

Statistical analysis

Statistical analyses were performed with SPSS, Version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Comparison of continuous variables between the two groups was performed with the non-parametric Mann–Whitney *U* test and categorical variables with a chi-square or Fisher's exact test as appropriate. The outcome of different groups was compared using Kaplan–Meier survival analysis and the log-rank test, with the start time as that of insertion of the port. Outcome variables were calculated based on the registry data. Time was defined as the time from insertion of port until its removal. Two-sided P values <0.05 were considered significant.

Results

Patients and ports

The total cohort of children born 2000–2013 from the 31 PedNet centres was 1480; 372 (25%) had a CVAD of whom 356 had one or more ports and 16 had one or more external lines. Forty nine ports in 39 patients from six centres were excluded from analysis due to incomplete data sets. Of the remaining 25 centres, 333 children had 482 ports and 28 external lines. One hundred and thirty ports were excluded as they either were inserted after January 1st 2015 (10 ports), still *in situ* (86 ports), or the date or reason for removal were missing (34 ports). The final study group included 240 children with 352 ports. Two hundred and twenty-seven children had severe haemophilia, 11 moderate and two mild; 124 (52%) had inhibitors. One hundred and forty-seven patients (61%) had only a single port with the remaining 93 (39%) having at least one port replacement.

The median age at first port insertion was 1.32 years (mean 1.60, range 0.02–7.94 years). At the first port insertion 150/240 (63%) had no inhibitors and the reason for insertion was presumed to be to initiate prophylaxis or to allow easier access for those with poor peripheral veins. Twenty three percent (34/150) of these

patients later developed an inhibitor. An inhibitor was present in 90/240 (38%) cases at the time of port insertion: 87 were known and the reason for the port was presumably to initiate immune tolerance therapy (ITT); in three cases, inhibitors were detected shortly prior to planned port insertion. Clinical characteristics of the study group are shown in Table 1.

The median port duration was 2.94 years (range 0.02–10.03). The total number of port days was 399 540 (215 688 for non-inhibitor and 183 852 for inhibitor patients). Complications were frequently reported as the reason for removal: 66% (159/240) of first ports and 67% (236/352) of all ports; only 33% (116/352) were removed when there was adequate peripheral venous access and thus no longer required (NLR) and in five of those, a catheter complication precipitated removal. Where more than one reason was given for removal, they are counted in each appropriate group (Fig. 1) thus 347 ports were removed for either complications, NLR or both. A further five ports were removed for other reasons such as centre practice to remove or replace ports after >1000 punctures, or replacement by an arteriovenous fistula or peripherally inserted central catheter. Of the 236 ports that were removed due to a complication, only 143 (61%) were replaced by a new port.

Catheter care

Five centres used ANTT (53 children, 79 ports), 15 ST (154 children, 211 ports) and five FST (31 children, 62 ports). The median catheter age in the ANTT group was 2.55 years (range 0.02–9.05), 2.38 years (range 0.04–9.02) in the FS group and 2.02 years (range 0.05–10.03) in the FST group.

Table 1. Clinical characteristics of patients with haemophilia and ports according to inhibitor status.

Patients (n = 240)	Negative inhibitor (n = 116)	Positive inhibitor (n = 124)	P
Age at insertion in years (median and range)	1.4 (0.02–6.3)	1.3 (0.3–7.9)	0.596
Type and severity of haemophilia (%)			
Severe A	88 (44)	112 (56)	
Moderate A	3 (33)	6 (67)	
Mild A	1 (50)	1 (50)	
Severe B	23 (82)	5 (18)	
Moderate B	2	0	
Inhibitors at insertion	NA	90	
First ports, median catheter time in years (range)	3.96 (0.04–9.02)	2.50 (0.05–10.03)	≤0.001
Reason for removal, first port (%)*			
Any complication	64 (40)	95 (60)	0.001
Infection	24 (32)	52 (68)	
Occlusion	14 (47)	16 (53)	
No longer required	53 (64)	30 (36)	

*Five patients without inhibitors and seven patients with inhibitors had more than one reason for removal.

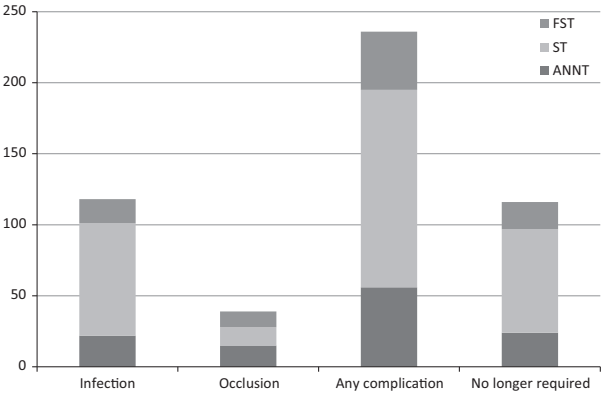

Fig. 1. Reasons for port removal according to home care groups. Fourteen ports had more than one reason for removal. ANTT, aseptic non-touch technique; ST, sterile technique; FST, fully sterile technique.

There was no difference in complication rates as a reason for removal of the port between different care regimens in the whole cohort (P = 0.711), or when the patients with and without inhibitors were analysed separately (Tables 2 and 3).

All ports were flushed with normal saline post factor infusion. Data on heparin flushing were available from 24 centres (comprising 231 children with 341 ports), and heparin flushing after the saline flush was routine practice for 21 centres (215 children 310 with ports) with three (16 children with 31 ports) using the saline flush only. The strength, volume and frequency of heparin flushing varied between centres but the majority used 100 U mL^{-1} strength.

Comparison of infection rates in different home care groups

Infection was the most common reason for port removal with 34% (118/352) of ports being removed due to infection (Fig. 1). There was no difference in the rate of infection between the care groups [22/79 (28%) ANTT, 79/211 (37%) ST and 17/62 (27%) FST, P = 0.163] corresponding to 0.27, 0.30 and 0.33 infections per 1000 catheter days respectively. Neither was there any difference in cumulative incidence of infection as a reason for catheter removal (P = 0.848). When ports placed in children with no inhibitors at the time of insertion were analysed separately, there were no reported infections as the reason for removal in the 16 ports removed in the FST group which was superior to the other two groups [9/46 (20%) ANTT and 37/131 (28%) ST, P = 0.032] (Fig. 2, Table 2). The frequency of infusions of coagulation factor concentrates was available for 154 patients (212 ports) of whom 70 had inhibitors and 84 did not. There was no difference in total mean days of infusions between ports in patients with and without inhibitors (680 and 622 days respectively; P = 0.762) but the 70 patients with inhibitors had an infection rate of 0.68/1000

Table 2. The outcome of all subcutaneous ports in patients without inhibitors at the time of insertion according to care groups.

Subcutaneous ports (n = 193)	ANTT (n = 46)	ST (n = 131)	FST (n = 16)	P
Median catheter time in years (range)	2.71 (0.19–9.05)	4.11 (0.04–9.02)	3.25 (0.05–10.03)	0.022
Reason for removal (%)				
Any complication	32 (70)	76 (58)	8 (50)	0.268
Infection	9 (20)	37 (28)	0 (0)	0.032
Occlusion	12 (26)	11 (8)	3 (19)	0.008
Not required any longer	17 (37)	56 (43)	8 (50)	0.628

Four ports with a complication at removal were no longer required.

Table 3. The outcome of all subcutaneous CVADs according to care groups in patients with inhibitors at the time of insertion.

Subcutaneous ports (n = 159)	ANTT (n = 33)	ST (n = 80)	FST (n = 46)	P
Median catheter time in years (range)	2.32 (0.16–5.81)	2.28 (0.06–8.34)	1.61 (0.07–5.41)	0.059
Reason for removal (%)				
Any complication	24 (72)	63 (79)	33 (72)	0.623
Infection	13 (39)	42 (53)	17 (37)	0.180
Occlusion	3 (9)	2 (3)	8 (17)	0.013
Not required any longer	7 (21)	17 (21)	11 (24)	0.934
Other[†]	2 (6)	1 (1)	2 (4)	

*Seven ports had several reasons for removal.
[†]Two PACs in the ANTT were removed due to use of arteriovenous fistula, one in the ST group for inserting an external line to facilitate ITI and in the FST group two due to centre practice to remove PACs after >1000 punctures.

infusion days compared to an infection rate of 0.38/1000 in the 84 without inhibitors (Kaplan–Meier, P = 0.030). However, there was no difference in infection rate per number of infusion days in patients with and without inhibitors between different catheter care groups (P = 0.756).

Occlusions

Occlusions were not more frequent in the group that used normal saline as a locking solution post factor infusion rather than heparin; occlusion occurred in 1/31 (3%) ports in the normal saline group and 38/310 (12%) in the heparin group (P = 0.230). Ten centres reported occlusion as the reason for catheter removal. The incidence varied between the care groups and was independent of inhibitor status. The ST group had the fewest occlusions, 13/211 (1.4%) compared to 15/79 (19%) occlusions in the ANTT group and 11/62 (18%) in the FST group (P = 0.002) (Tables 2 and 3). Only one patient with occlusion was reported to have simultaneous infection.

Discussion

The findings of this study show that 67% of ports were removed due to complications but does not show any clinically significant difference in infection rate between the different techniques used for port care. Interestingly, 39% of ports removed due to complications were not replaced and the patient was successfully managed subsequently with peripheral venous access.

The infection rate in this large cohort was comparable or somewhat higher than those from previously published data [12–20]. This may be because only

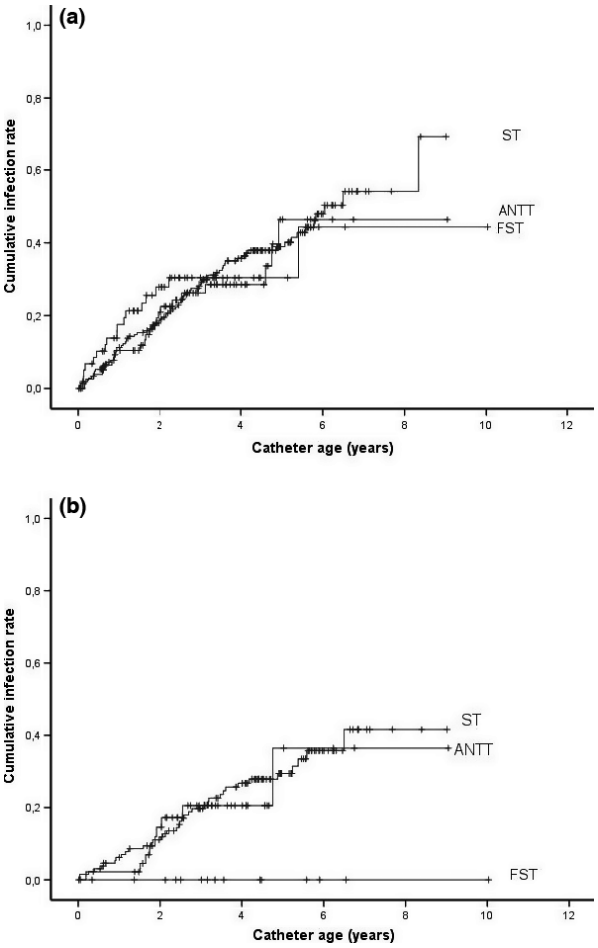

Fig. 2. Cumulative incidence of infections as reason for port removal in different home care groups. Top panel (a) demonstrates all ports and the lower panel (b) only ports in patients without inhibitors at insertion. ANTT, aseptic non-touch technique; ST, sterile technique; FST, fully sterile technique.

ports that had been removed were included and those that were still *in situ* without complications were excluded thus giving a selection bias towards increased infections. Also, both blood culture positive and clinically diagnosed infections as a reason for port removal were included. Further, several of the previous reports with very low infection rates have been smaller single centre studies [12,14,18]. It is of interest that those with inhibitors have an increased rate of infection as seen in other studies [12,17] despite there being no difference in the number of infusions of coagulation factor concentrates. This may be because in many of those with an inhibitor the port needle is left in for longer periods rather than removed immediately after infusion of factor concentrate or because of subcutaneous fibrin deposition from small bleeds at the site of needle removal [3].

In a Canadian study of children with haemophilia 4/25 ports were replaced due to complications, while 12 were removed due to adequate peripheral venous access [18]. Another single centre study in 18 children with bleeding disorders demonstrated complications in 24% (9/37) leading to removal of the port while 21% (8/37) patients outgrew their ports; only 5/37 were removed as the ports were not needed any more [12]. However, unlike our study, both studies included patients with catheters/ports still *in situ* and therefore the final rate of complications may be higher.

Data on the benefits of heparin vs. normal saline as a locking solution in ports are lacking [21]. In our study however, most of the centres used heparin to flush the ports and the number of patients in the group using only normal saline flushes was small. The centres using the sterile technique had the fewest port occlusions. This finding is unexplained but as this difference was not due to infections, the 'sterile group' was by far the largest and only ten centres reported occlusions there may be under reporting of this complication rather than a true difference between the care groups. Previous studies have shown that normal saline is effective in maintaining catheter patency without a higher infection risk [22–24] and our data support this. Flushing with only normal saline could eliminate one step in the process of administering factor concentrate and could be considered for both current and new patients.

Previous data on the optimal catheter care in patients with haemophilia are scarce, yet catheter care is an important part of the daily routine. In our study all the three care methods gave satisfactory results. The risk of complications may therefore depend more on the quality of the caregiver's education and training and the family's adherence to instructions than to the particular method chosen. Maintaining sterility using an aseptic non touch technique seems acceptable when performed correctly and may save time and effort. However, introducing a new care method for ports will create challenges for both staff and families and will require careful explanation and additional teaching to ensure those being treated have confidence in the change.

Conclusion

No significant differences in outcomes between the aseptic non-touch technique, the sterile technique and the full sterile technique subgroups were shown. Clinical practice is governed by local hospital rules and practice, however there may be health economic benefits for using less stringent sterile techniques, which may also be easier for parents to learn/perform at home. A greater risk of infection in children with inhibitors was demonstrated, which was independent of number of port punctures. Greater scrutiny of parental care techniques may be beneficial in this group this could be audited locally as a quality outcome measure, or could be part of future collaborative nurse research.

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Authorship

KL and KK designed the study and collected the data. SR performed the statistical analysis. KK, SR, and AT wrote the paper, read and approved the final manuscript.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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