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CLINICAL RESEARCH

Comparison of perioperative practices for placement of central venous access devices (CVAD) in children with haemophilia

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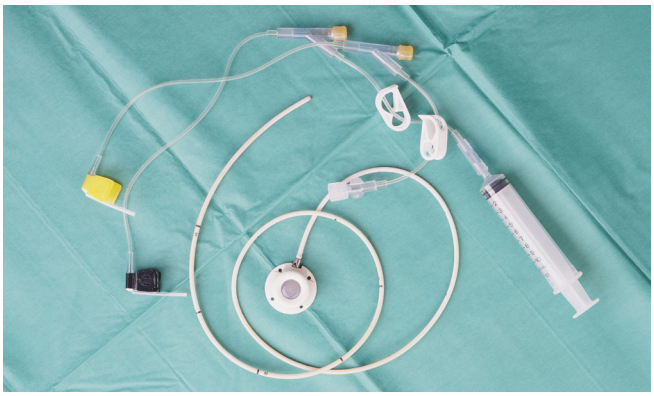

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A multi-centre study in Singapore and Canada found variations in perioperative practices around CVAD placement in children with haemophilia (CwH) with and without inhibitors. Further studies are recommended to support the development of guidelines for optimal CVAD placement in CwH.

Background: In children with haemophilia (CwH), central venous access devices (CVADs) are frequently placed to aid in the delivery of factor concentrates. In those who develop inhibitors, CVADs also allow for easy venous access and facilitation of immune tolerance therapy. **Aim:** In this study, we compare perioperative practices for CVAD placement in children with haemophilia to assess similarities and differences in practices across centres in two countries (Singapore and Canada). **Methods:** Retrospective chart review was conducted involving CwH (with and without inhibitors) who underwent CVAD placement from January 2007 to September 2017 at two centres in Singapore and at one centre in Hamilton, Canada. Data obtained included demographics, operative details, preoperative investigations, perioperative factor replacement, use of bypassing agents, antibiotic and

J Haem Pract 2022; 9(1). doi: 10.2478/jhp-2022-0013

antifibrinolytic use, length of stay, complications and need for CVAD revision. **Results:** Twenty-one CwH were included in the data analysis. Amongst those without inhibitors, the mean preoperative factor dose was 50.0 IU/kg (SD=7.6) in Singapore, and 72.4 IU/kg (SD=12.5) in Hamilton (p=0.002); mean total factor use in the perioperative period was 425.0IU/kg (SD=114.9) in Singapore and 646.8IU/kg (SD=118.1) in Hamilton (p=0.004); mean duration of clotting factor replacement was 5.3 days (SD=0.9) in Singapore and 6.9 days (SD=0.7) in Hamilton (p=0.004). Amongst those with inhibitors, the mean preoperative dose of rFVIIa was 160.5 mcg/kg (SD=99.9) in Singapore and 88.2 mcg/kg (SD=3.8) in Hamilton (p=0.244); mean total rFVIIa used from surgery to discharge was 3,008.0 mcg/kg (SD=2305.9) in Singapore and 2,640.2 mcg/kg (SD=134.1) in Hamilton (p=0.842); mean duration of rFVIIa cover was 5.3 days (SD=1.7) in Singapore and 9.5 days (SD=2.1) in Hamilton (p=0.054). None of the CwH without inhibitors developed postoperative complications, compared to 57% in those with inhibitors (p=0.006). **Conclusion:** Amongst CwH without inhibitors, significant variations were seen in perioperative factor replacement. Amongst those with inhibitors, there were also differences in perioperative practices across centres, although not statistically significant. Across centres, CwH with inhibitors were found to have more postoperative complications.

Keywords: *Haemophilia A, Haemophilia B, Inhibitors, Perioperative management, Recombinant factor VIIa, Vascular access devices*

Haemophilia is a bleeding disorder caused by a deficiency or complete absence of coagulation factors, specifically factor VIII (FVIII) in haemophilia A, and factor IX (FIX) in haemophilia B [1]. This X-linked bleeding disorder can be classified based on the clotting factor levels: mild (>5–40%), moderate (1–5%), or severe (<1%) [1]. In those with severe haemophilia, recurrent bleeding into joints and soft tissues can occur, leading to arthropathy [2]. There is evidence to support the use of prophylactic factor replacement in people with severe haemophilia to prevent joint damage and decrease the frequency of bleeding episodes [2,3]. As prophylactic factor replacement therapy requires venepuncture, often frequently, a central venous access device (CVAD) may be required to enable reliable venous access and aid in delivery of factor concentrates, especially in young children who may have difficult venous access [4].

One of the main complications of prophylactic factor replacement therapy in people with haemophilia is the development of anti-factor neutralising alloantibodies, or inhibitors, which make them resistant to the replacement therapy [5]. To eradicate inhibitors, immune tolerance induction (ITI) treatment is usually attempted [6]. This treatment consists of frequent, uninterrupted exposure to intravenous infusions of factor concentrates over a period of months to years to induce antigen-specific tolerance [5,6]. Hence, in children with haemophilia (CwH) who have developed inhibitors, CVADs allow for easy venous access and facilitation of immune tolerance therapy.

Although CVADs have the benefit of providing reliable venous access, they also come with risks of complications, such as infection, thrombosis, blockage and disconnection, which may lead to device removal or replacement [4].

AIM

Despite the prevalent use of CVADs in CwH, the literature on perioperative practices for CVAD placement in these children, especially those with inhibitors, is scarce. Moreover, to our knowledge, there has not been a multi-centre comparative study investigating similarities and differences in perioperative practices for CVAD placement across countries in people with inhibitors. In this study, we describe and compare perioperative practices for CVAD placement in CwH to assess similarities and differences in practices across three centres in two countries (Singapore and Canada).

METHODS

Retrospective review of medical records was conducted involving CwH (with and without inhibitors) who underwent CVAD placement from January 2007 to September 2017 at two centres in Singapore (KK Women's and Children's Hospital and National University Hospital) and at one centre in Hamilton, Ontario, Canada (McMaster Children's Hospital). Data obtained included demographics (age, type of haemophilia, severity of haemophilia, preoperative treatment details), operative details (including age at CVAD insertion, weight at insertion, inhibitor titres at insertion if applicable, reason for CVAD placement, type of CVAD used, vessel used, number of attempts and estimated blood loss), preoperative investigations, perioperative factor replacement (if applicable), perioperative use of bypassing agents (if applicable), antifibrinolytic use, perioperative antibiotic use,

Table 1. Characteristics and operative details of CwH included in the study, from all centres

Number of CwH	21
Median age at insertion, months (range)*	20.5 (12–110)
Haemophilia A (%)	20 (95%)
Haemophilia B (%)	1 (5%)
Deficient factor <1% (%)	21 (100%)
Number of patients with inhibitors (%) Median preoperative inhibitor titres (range)	7 (33%) 5 BU (1.5–210 BU)
Preoperative treatment** • Prophylaxis (%) • On-demand (%)	 9 (64%) 5 (36%)
Indication for CVAD insertion • Prophylaxis (%) • ITI (%) • Revision (%) • Difficult venous access (on-demand treatment) (%)	 13 (62%) 4 (19%) 2 (9.5%) 2 (9.5%)
Type of CVAD • Portacath (%)	 21 (100%)
Vessel used for CVAD • Internal jugular vein (%) • Subclavian vein (%) • External jugular vein (%)	 9 (43%) 9 (43%) 3 (14%)
Mean number of CVAD insertion attempts, including successful attempt (range)	1.4 (1–4)

*missing 1 data point; **missing 7 data points

length of hospital stay, perioperative complications and need for CVAD revision. Postoperative infection was defined as an infection that occurred within 30 days of the procedure. Statistical calculations were performed using Microsoft Excel Program, Office 365 version (Microsoft, Redmond, Washington, USA) and SPSS Version 19 (IBM, Armonk, New York, USA), with a p-value of <0.05 considered statistically significant. Local ethics boards approved this study. Participants in the study gave informed consent.

RESULTS

Overall participant characteristics

Between January 2007 and September 2017, 25 CVADs were inserted in 25 CwH: 16 in Singapore, 9 in Hamilton. Four cases in Singapore underwent CVAD insertion at a time when they were being treated for other bleeds, so their data were excluded. Hence, 21 patients were included in the analysis (see Table 1 for characteristics).

Across the centres, all of the children had severe haemophilia (factor level less than 1%). The majority had haemophilia A (n=20); only one had haemophilia B. One third (n=7) had inhibitors at the time of CVAD insertion. The child with haemophilia B had inhibitors.

Operative details for all CwH across centres are summarised in Table 1. The median age at CVAD insertion of all included CwH was 20.5 months (data missing for 1). The median preoperative inhibitor titres were 5 BU (IQR=7.5). The most common indication for CVAD insertion was for ease of vascular access (n=15), followed by ITI (n=4). Two CwH needed the operation for revision purposes. All children in this study received a Portacath as their type of CVAD. The number of CVAD insertion attempts for each surgery ranged from one to four (including the successful attempt), with a mean number of 1.4, and median number of 1. None of the CwH had significant blood loss during the CVAD insertion procedure.

Amongst all CwH in this study, the average length of hospital stay was 6.1 days (range 3–25 days). The median length of stay was five days. Four of the 21 CwH had postoperative complications: three cases of port site haematoma and one case of bacterial infection. These cases of haematoma are more significant than superficial bruising and were noted in the immediate postoperative period.

Comparison between CwH with and without inhibitors

A comparison of perioperative practices between CwH with and without inhibitors across both countries can be found in Table 2.

When comparing preoperative investigations between the two groups, CwH without inhibitors received APTT (activated partial thromboplastin time) and factor assay testing more than the group with inhibitors (36% vs. 29%, and 64% vs. 14%, respectively), although not statistically significant. More CwH with inhibitors were checked for blood counts, factor VIII recovery study, and inhibitor screen compared to those without inhibitors (100 vs. 50%, 29 vs. 0%, and 100 vs. 64%, respectively); however, of these three investigations, only difference in the preoperative practice of checking blood counts was statistically significant.

Amongst CwH without inhibitors, 43% received antifibrinolytic therapy, compared with 57% of those with inhibitors (p=0.659). Across the centres, the only antifibrinolytic therapy used was tranexamic acid. The average length of hospital stay was 8.6 days for CwH with inhibitors and 4.9 days for those without inhibitors

J Haem Pract 2022; 9(1). doi: 10.2478/jhp-2022-0013

Table 2. Comparison of perioperative practices between CwH with and without inhibitors

	CWH WITHOUT INHIBITORS	CWH WITH INHIBITORS	P-VALUE
Number of CwH	14	7	—
Preoperative investigations performed			
• Full blood count (%)	7 (50%)	7 (100%)	0.047
• APTT (%)	5 (36%)	2 (29%)	1.000
• Factor assay (%)	9 (64%)	1 (14%)	0.063
• Recovery study (%)	0 (0%)	2 (29%)	0.100
• Inhibitor screen (%)	9 (64%)	7 (100%)	0.123
Antifibrinolytic use (%)	6 (43%)	4 (57%)	0.659
Mean length of stay in days (range)	4.9 (3–7)	8.6 (3–25)	0.096
Postoperative complications (%)	0 (0%)	4 (57%)	0.006
Need for CVAD revision (%)	0 (0%)	1 (14%)	0.333

Table 3. Preoperative investigations performed prior to CVAD surgery and details of perioperative factor VIII cover for CVAD surgery amongst CwH without inhibitors

	SINGAPORE (% PERFORMED)	HAMILTON (% PERFORMED)	P-VALUE
Investigations			
Full blood count	100%	0%	0.000
APTT	83%	0%	0.001
Factor assay	25%	100%	0.003
Inhibitor screen	25%	100%	0.003
Factor VIII cover			
Mean preoperative factor VIII dose (±SD)	50.0 IU/kg (±7.6)	72.4 IU/kg (±12.5)	0.002
Mean total dose used (±SD)	8642.9 IU (±6011.9) 425.0 IU/kg (±114.9)	8924.1 IU (±2488.6) 646.8 IU/kg (±118.1)	0.911 0.004
Mean duration of factor VIII cover (±SD)	5.3 days (±0.9)	6.9 days (±0.7)	0.004

(p=0.096). None of the CwH without inhibitors developed postoperative complications, whereas four of the seven CwH with inhibitors did develop postoperative complications (p=0.006). None of the CwH without inhibitors needed revision of their CVAD, while one of the seven CwH with inhibitors required CVAD revision (p=0.333).

Comparison between centres – CwH without inhibitors

Amongst CwH without inhibitors, 11 CVADs were placed in Singapore centres, and 7 placed in the Canadian centre. Four cases from Singapore underwent CVAD insertion at a time when they were being treated for other bleeds, so their data were excluded. The mean age at first CVAD insertion was 51.0 months (SD=36.8) in Singapore and 32.7 months (SD=26.9) in Hamilton (p=0.309). The average number of CVAD insertion attempts per surgery (including the successful one) was 1.6 for both countries (SD=1.1 in Singapore; SD=0.8 in Hamilton).

There were differences between the centres in terms of the preoperative investigations performed (Table 3). In Singapore, all the CwH without inhibitors (100%) had full blood counts, 83% had APTTs, 25% had factor assays and 25% had inhibitor screens. In Hamilton, none of the CwH without inhibitors had full blood counts or APTTs, but all (100%) had factor assays and inhibitor screens.

When comparing between centres, there were also differences in perioperative factor replacement (Table 3). The mean preoperative factor dose immediately prior to surgery was statistically significant between centres, at 50.0 IU/kg (SD=7.6) in Singapore, and 72.4 IU/kg (SD=12.5) in Hamilton (p=0.002). The mean total factor use in the perioperative period was 8,642.9 IU (SD=6,011.9) (425.0 IU/kg; SD=114.9) in Singapore and 8,924.1 IU (SD=2,488.6) (646.8 IU/kg; SD=118.1) in Hamilton (p=0.911 for total dose; p=0.004 for dose per weight). Mean duration of clotting factor replacement was significantly different, with 5.3 days (SD=0.9) in Singapore and 6.9 days (SD=0.7) in Hamilton (p=0.004). Antifibrinolytic therapy was administered in 83.3% in Singapore, compared to none in Hamilton. Perioperative antibiotics were administered

Table 4. Details of perioperative rFVIIa cover for CVAD surgery in CwH with inhibitors

RFVIIA COVER	SINGAPORE	HAMILTON	P-VALUE
Mean preoperative rFVIIa dose (±SD)	160.5 mcg/kg (±99.9)	88.2 mcg/kg (±3.8)	0.244
Mean total dose used from pre-operative dose to discharge (±SD)	3008.0 mcg/kg (±2305.9)	2640.2 mcg/kg (±134.1)	0.842
Mean duration of rFVIIa cover (±SD)	5.3 days (±1.7)	9.5 days (±2.1)	0.054

in 41.6% in Singapore, compared to none in Hamilton. Average length of hospital stay was similar: 4.6 days (SD=1.3) in Singapore and 4.1 days (SD=1.7) in Hamilton (p=0.600). No perioperative bleeding or infective complications within 30 days were recorded in any CwH across the centres. None of the CVADs needed to be revised across the centres.

Comparison between centres – CwH with inhibitors

Amongst CwH with inhibitors, 5 CVADs were placed in Singapore and 2 were placed in Hamilton. The mean preoperative inhibitor titre was 6.2 BU (SD=4.7) in Singapore and 106.9 BU (SD=145.8) in Hamilton (p=0.507). Preoperatively, both CwH in Hamilton were on prophylactic factor replacement therapy until the development of inhibitors; after the development of inhibitors, one continued with prophylactic FVIII replacement as immune tolerance, and the other switched to on-demand therapy with rFVIIa. In Singapore, one of the five CwH (20%) was on prophylactic factor replacement therapy; four were receiving on-demand factor replacement therapy. When comparing preoperative investigations, all CwH with inhibitors had full blood counts and inhibitor assays checked across the centres. The only child (1) to have their factor assay investigated was in Hamilton. Two of the five CwH with inhibitors in Singapore had their APTT checked, compared to none in Hamilton.

The mean age at port insertion was 42.5 months in Singapore, compared with 18.0 months in Hamilton (p=0.218) (there was 1 missing data point from Singapore). All CwH with inhibitors required only one CVAD insertion attempt for it to be successful. Surgical haemostasis was achieved using recombinant activated Factor VII (rFVIIa) in all children (including the one with haemophilia B), except for one case from Singapore who received activated prothrombin concentrate complex (FEIBA). There were differences in details of perioperative rFVIIa replacement (Table 4). The mean preoperative dose of rFVIIa was 160.5 mcg/kg (SD=99.9) in Singapore and 88.2 mcg/kg (SD=3.8) in Hamilton (p=0.244). The mean total rFVIIa used from surgery to discharge was 3,008.0 mcg/kg (SD=2305.9) in Singapore and 2,640.2 mcg/kg (SD=134.1) in Hamilton (p=0.842). Mean duration of rFVIIa cover was 5.3 days (SD=1.7) in Singapore and 9.5 days (SD=2.1) in Hamilton (p=0.054). Of note, these analyses of rFVIIa coverage include children with both haemophilia A and haemophilia B.

Antifibrinolytic therapy and perioperative antibiotics were administered in 80% of CwH with inhibitors in Singapore (four of five). No CwH with inhibitors in Hamilton received antifibrinolytic therapy or perioperative antibiotics. The average length of hospital stay was 9.8 days (SD=8.7) in Singapore and 5.5 days in Hamilton (p=0.547). Postoperative complications seen within 30 days were noted in two of five cases in Singapore (two cases of port site haematomas) and in both cases in Hamilton (one port site haematoma and one bacterial infection) (p=0.429).

DISCUSSION

Overall, this study describes perioperative practices for CVAD placement in CwH with and without inhibitors, comparing them across centres in Singapore and Hamilton, Canada. To our knowledge, this is the first multi-centre international study on perioperative practices for CVAD placement in CwH with inhibitors. When comparing postoperative complications between CwH with and without inhibitors across centres, those with inhibitors had significantly more complications, including both port site hematomas and infection. Although the mean length of hospital stay was longer for CwH with inhibitors, this did not reach statistical significance, likely due to the small sample size. Similarly, other studies and meta-analyses have found that the presence of inhibitors increased CVAD-related infection rates. In their retrospective nationwide study of 106 CVADs in 58 CwH, Vepsalainen et al. found that inhibitors enhanced CVAD-related infection rates three-fold [7]. Valentino et al. conducted a meta-analysis in 2004 including 48 studies and 2704 patients; this group also found that the presence of inhibitors was an independent risk factor for the development of CVAD-related infection, with an incidence rate ratio of 1.67 [8]. This higher infection rate may be due to more frequent CVAD usage during ITI, or due to potential small bleeds around the port after injection that could stimulate bacterial growth [9]. Likewise, in their study of 14 CwH,

Bollard et al. also found that children with inhibitors had more significant CVAD-related hematomas [10].

CwH without inhibitors

Amongst CwH without inhibitors, our study found similarities and differences across the centres in perioperative practices around CVAD placement, with variations seen in preoperative investigations, doses and duration of perioperative factor replacement strategies used, and in the use of antifibrinolytics and antibiotics. This is in keeping with Neunert et al.'s systematic review on factor replacement for CVAD procedures in people with haemophilia without inhibitors, which found that perioperative laboratory studies and factor administration varied greatly amongst their included articles [11]. Currently, the World Federation of Hemophilia (WFH) recommends inhibitor screening in all people with haemophilia prior to surgery and invasive procedures [12]. However, guidelines are scarce regarding other preoperative investigations prior to CVAD placement in CwH. The WFH also outlines the desired peak factor levels of clotting factor concentrate replacement for minor surgeries and duration of treatment, but factor replacement schedules and doses are lacking [12]. Recommendations on other perioperative practices for CVAD placement are also scarce. More studies are warranted to determine optimal perioperative practices for CVAD insertion in CwH. Clear guidelines on FVIII replacement therapy are also needed to achieve optimal haemostasis during CVAD placement, with the lowest dose possible to minimise the risk of inhibitor development.

Despite the differences in perioperative practices amongst CwH without inhibitors in our study, such as the differences in duration of clotting factor replacement between centres, no early complications were seen within 30 days in any centre. It would thus be interesting to investigate if the duration of clotting factor replacement can be reduced for CVAD insertions. Minna et al. published a multi-centre study in 2021 to evaluate whether haemostasis coverage under four days was as safe and effective as a longer duration of coverage in those undergoing CVAD insertion [13]. In a group of 144 children with severe haemophilia A without inhibitors who received their first CVAD, haemostatic coverage with coagulation factor concentrates (CFC) for four days or less was found to be as effective as coverage for five days or more [13]. Minna et al. also found that bleeding complications were rare; both groups only had one bleed related to the surgery [13].

Since bleeding complications are rare amongst CwH without inhibitors, as we have also found in our study, it would be interesting to investigate in a future study if the length of hospital stay can be decreased, or perhaps even switch the procedure to be undertaken in an outpatient setting. Neunert et al.'s retrospective study found that CVAD procedures could be done safely in an outpatient setting, which can reduce overall economic and emotional burdens on patients and families [11].

CwH with inhibitors

Amongst CwH with inhibitors, there were also differences in perioperative practices around placement of CVADs across centres, with variations seen in perioperative factor replacement strategies, length of hospital stay, and the use of antifibrinolytics and antibiotics. However, across centres, there was no statistically significant difference between the mean preoperative rFVIIa dose, duration of rFVIIa, or mean total rFVIIa dosage from surgery to discharge. There was also no statistical difference with length of stay and postoperative complications between centres. Similar to in those without inhibitors, guidelines on perioperative practices for CVAD placement in CwH with inhibitors are lacking. Hagglof et al. conducted a retrospective study on the perioperative treatment of 12 CwH with inhibitors with regards to CVAD insertion or removal [14]. This group used higher doses of rFVIIa but a shorter treatment time compared to others in the literature (median initial dose of 227mcg/kg; median total dose per kg per operation 3,980 mcg; median length of stay of 4 days) and found their treatment regimen to be safe and effective [14]. Further studies are warranted to determine optimal perioperative practices for CVAD insertion in CwH with inhibitors, perhaps in multi-centre studies to increase the sample size. It would be interesting to trial shorter duration of rFVIIa cover and investigate the clinical outcomes to minimise cost and emotional burden on families.

Limitations

Limitations of our study include the small sample size, especially the number of CwH with inhibitors, and its retrospective design. Furthermore, our study only included children with severe haemophilia, so the results are not generalisable to all CwH. The study can, however, help to inform future studies in this area.

CONCLUSION

Across the centres in our study, CwH with inhibitors were found to have more postoperative complications, including port site haematomas and infection, but

these complications did not significantly prolong their length of hospital stay. Amongst CwH without inhibitors, there were similarities and differences in perioperative practices around CVAD placement across the centres, with variations seen in preoperative investigations, doses and duration of perioperative factor replacement strategies used and in the use of antifibrinolytic therapy and antibiotics. Despite these differences, there was no significant difference in the average length of stay. There were also no early complications seen within 30 days in any centre for CwH without inhibitors. Amongst CwH with inhibitors, there were also differences in perioperative practices around placement of CVADs across centres, with variations seen in the use of antifibrinolytic therapy and antibiotics. Differences were also found in the doses of perioperative factor replacement strategies used and length of stay; however, these differences did not reach statistical significance.

More studies are required to determine optimal perioperative practices for CVAD insertion in CwH with and without inhibitors. It would be of interest to conduct prospective studies with larger sample sizes, perhaps in larger multi-centre studies, to develop guidelines on optimal perioperative practices on CVAD placement in CwH with and without inhibitors. Such guidelines would ideally help to improve care and outcomes, while also being cost-effective.

ACKNOWLEDGEMENTS

The authors have advised no interests that might be perceived as posing a conflict or bias.

Anthony KC Chan holds the McMaster Children's Hospital/Hamilton Health Sciences Foundation Pediatric Thrombosis and Hemostasis Endowed Chair.

Informed consent has been obtained from the participants in the study reported in this paper.

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HOW TO CITE THIS ARTICLE:
Kwan C, Chan AKC, Koh PL, Abdul Kadir NI, Decker K, Lim CY, Lam JCM. Comparison of perioperative practices for placement of central venous access devices (CVADs) in children with haemophilia. *J Haem Pract* 2022; 9(1): 96-102. *https://doi.org/10.2478/jhp-2022-0013*