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Factors Associated with Continuous Low Dose Heparin Infusion for Central Venous Catheter Patency in Critically Ill Children Worldwide

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Abstract

Objective—To identify patient, hospital and central venous catheter (CVC) factors that may influence the use of low dose heparin infusion (LDHI) for CVC patency in critically ill-children.

Design—Secondary analysis of an international multicenter observational study.

Setting—59 Pediatric Intensive Care Units (PICUs) over four study dates in 2012, involving 7 countries.

Patients—Children less than 18 years of age with a CVC, admitted to a participating unit and enrolled in the completed PROTRACT study were included. All overflow patients were excluded.

Interventions—None.

Measurements and Main Results—Of the 2,484 patients in the PROTRACT study, 1,312 patients had a CVC. 507 of those patients used LDHI. The frequency of LDHI was compared across various patient, hospital and CVC factors using chi-squared, Mann-Whitney and Fisher's exact tests. In the multivariate analysis, age was not a significant factor for LDHI use. Patients

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with pulmonary hypertension had decreased LDHI use while those with active surgical or trauma diagnoses had increased LDHI use. All central CVC insertion sites were more likely to use LDHI when compared to peripherally inserted CVCs. The Asia-Pacific region showed increased LDHI use, along with community hospitals and smaller ICUs (<10 beds).

Conclusion—Patient, CVC, and hospital factors are associated with the use of LDHI in critically ill children. Further study is needed to evaluate the efficacy and persistence of LDHI use.

Keywords

Pediatrics; Critical Care; Central Venous Access Device; Anticoagulation; Venous Thromboembolism; Intensive Care Units; Pediatric

Introduction

Central venous catheters (CVCs) are widely used in the care and management of critically ill children. However, CVCs have the potential to lose functionality from occlusion if they are not kept patent (1). Current studies in neonates find that the use of low dose heparin infusion (LDHI), to maintain CVC patency is of some benefit, in that it reduces catheter occlusion and prolongs CVC usability without increasing adverse effects (2) (3) (4) (5). However, there is minimal evidence supporting the efficacy of LDHI use for CVC patency in critically-ill children outside the neonatal period. Multiple studies in this population were inconclusive (6) (7) (8) (9) (10) (11) (12) (13) or found no significant effect on the patency of CVCs with LDHI (14). Additionally, no studies were found to detail the frequency of LDHI use to maintain CVC patency in pediatric medicine. In this study we aimed to identify the global prevalence of LDHI (defined as <10U/hr of unfractionated heparin) and the factors associated with LDHI, as a secondary analysis of the Prophylaxis against Thrombosis Practice (PROTRACT) study, a multinational, point-prevalence study of thromboprophylaxis practice in critically-ill children (15). Documenting the use of LDHI using the large and diverse population represented in PROTRACT, presented the opportunity to improve the global knowledge of care and maintenance of CVCs in children. We hypothesized that patient, hospital, and CVC factors would influence the use of LDHI as a technique for maintaining CVC patency.

Materials and Methods

We performed a secondary analysis of the PROTRACT study, a prospective, observational study involving seven countries, over four study dates (February 1, May 1, August 1, and November 1, 2012) to account for the seasonality of admissions to the Pediatric Intensive Care Unit (PICU) (15). The study enrolled children less than 18 years of age that were hospitalized in one of the 59 participating PICUs.

Overflow patients and those who received extracorporeal membrane oxygen, continuous renal replacement therapy, vascular assist devices or therapeutic anticoagulation at the time of study were excluded. At the local time of 9 am on each study date the following data were collected for each PROTRACT study patient: demographics, preadmission history, and ongoing factors presumptively associated with venous thromboembolism (VTE) risk,

including the number, type and location of CVCs. Pharmacologic and mechanical VTE prophylaxis were recorded. Data were gathered from the medical records into standardized case report forms by trained abstractors, who were typically physicians or nurses, complying with a manual containing detailed descriptions of each data point.

Design

After local IRB approval was obtained, we conducted a retrospective secondary analysis of the PROTRACT Study. Children less than 18 years of age with a CVC, who were admitted to a participating PICU and enrolled in the PROTRACT study were included. Data from the four study dates were combined for analysis. The primary outcome measure was the prevalence of LDHI. Secondary outcomes were patient, CVC and hospital factors associated with LDHI use.

Data Collection

The following data were collected on each study date:

Patient factors: gender, race, ethnicity, age, weight, diagnoses, bleeding tendency (platelet count, international normalized ratio [INR], partial thromboplastin time [PTT]), family history, patient history and therapeutic interventions.

CVC factors: CVC type and anatomic site of insertion.

Hospital factors: PICU size and type, geographic location, hospital/institution type.

Definitions

LDHI was defined as administration of <10U/hr of unfractionated heparin through the CVC presumably for line patency. Higher doses were considered prophylactic anticoagulation.

Practitioners have identified the presence of cardiac disease, surgery or bleeding tendency of patients as factors that influence the decision to prescribe pharmacologic prophylaxis (16). As these factors may also influence the decision to prescribe LDHI, combined categories were created. *Bleeding tendency* included diagnoses of cerebrovascular accident, non-intracranial hemorrhage, and intra-cranial hemorrhage. *Heart disease* included patients with cyanotic congenital heart disease, acyanotic congenital heart disease, dilated cardiomyopathy and those listed for heart transplant. *Surgical/Trauma* included patients with burns, spinal cord Injury, lower extremity fracture, craniotomy, traumatic brain injury, lower extremity surgery, scoliosis repair/spine surgery, and solid organ transplant.

Analysis

Using chi-squared, Mann-Whitney and Fisher's exact tests, the frequency of LDHI use was compared across each patient, hospital and CVC factor. For patient factors, frequencies were generated in terms of LDHI use, as well as the percentages of LDHI use with specific patient, CVC and hospital factors present and absent. Chi-square/Fisher's Exact test was used to compare the proportion of LDHI usage across the predictor (patient related, central venous catheter related and hospital related) categories. A multivariable logistic regression was used and a stepwise selection method (with $\alpha = 0.10$) was applied to find the best set of

predictors for the LDHI usage. P value <0.05 was considered significant. SAS v9.4 (SAS Institute Inc., Cary, NC) was used for the analyses.

Results

Prevalence of Low Dose Heparin Infusion

One thousand three hundred twelve critically-ill children with CVCs out of the 2,484 patients that met the inclusion criteria for PROTRACT study enrollment, were included in this secondary analysis. Of these, 507 used LDHI (38%; 95% CI: 36.0%-41.3%). The median LDHI concentration was 1 U/ml (IQR 1-2). This did not change with age.

Factors Associated with Low Dose Heparin Infusion

Patient factors associated with LDHI use from univariate analysis are presented in Table 1. LDHI was associated with younger patients, with ages >13 years having the lowest percentage of LDHI use (30%). Patients of Asian race were more likely to use LDHI (54% with odds ratio [OR] = 2.03) compared to other races, and Hispanic/Latino ethnicity showed greater likelihood of LDHI use (45.2% with OR=1.36) than non-Hispanic/Latinos.

Patients with diagnoses of heart disease, craniotomy, and sickle-cell disease, had increased LDHI use (54% with OR=2.63, 52% with OR=1.75, and 83% with OR=7.46 respectively) while those with pulmonary hypertension and cancer had decreased use (28% with OR=0.60 and 27% with OR=0.56 respectively). Patients with bleeding tendencies, including stroke, non-intracranial hemorrhage, or intracranial hemorrhage, had no significant association with LDHI use. Patients receiving prophylactic anticoagulation (aspirin, low molecular weight heparin, intravenous heparin, or vitamin K antagonists) were more likely to receive LDHI (49.3% with OR=1.70).

Patients who participated in the study with a history of multiple cardiac catheterizations, complex surgical cardiac repair, and/or cavopulmonary anastomosis, had increased LDHI use (51% with OR=1.70, 58% with OR=2.96 and 65% with OR=3.17 respectively) while patients on home parenteral nutrition showed decreased LDHI use (10.3% with OR=0.18). Personal or family history of thrombosis did not influence the use of LDHI.

LDHI use varied by CVC anatomic site and type, with transthoracic and umbilical cord locations as the most common CVC sites associated with LDHI use (85% with OR=17.73 and 69% with OR=7.26 respectively). Atrial and Umbilical CVC types were associated with increased LDHI use (85% with OR=5.39 and 69% with OR=2.21 respectively). Patients with more than one CVC were more likely to receive LDHI compared to those with one CVC (53% vs. 37%, $p<0.001$) (Table 2).

Patients in cardiac ICUs had increased LDHI use (74% with OR=3.92) in comparison to those in medical/surgical, and mixed ICUs (20% with OR=0.34 and 42% respectively). Smaller ICUs had greater use of LDHI than larger ICUs (70% vs. 27%, $p<0.001$) (Table 3).

Geographic location influenced LDHI use, with the Asia-Pacific region having the highest usage of LDHI (60% with OR=2.79) and Canada having the least use (19% with OR=0.46) (Table 3).

Multivariable Analysis

In the multivariable analysis of patient related predictors, age was not a significant factor for the use of LDHI. Asian and Black race, and Hispanic/Latino ethnicity remained significant for increased use of LDHI (OR= 2.44, 1.61 and 1.52 respectively). Patients with active pulmonary hypertension remained significant with decreased LDHI use (OR= 0.54). Patients with a diagnosis of surgical trauma continued to be associated with increased LDHI use (OR= 1.58). Other factors associated with increased LDHI use were cryoprecipitate transfusion and the use of vasoactive agents (OR=4.65 and 1.48, respectively) (Table 4). Patient history of complex surgical cardiac repair remained a significant factor for increased LDHI use (OR=2.23) while patients on home parenteral nutrition continued to be a significant factor for decreased LDHI use (OR=0.29). Pre-study history of sickle-cell disease, multiple cardiac catheterizations, and cavopulmonary anastomosis were no longer significant patient factors.

Amongst the hospital related predictors, the Asia-Pacific region remained significant for increased LDHI use (OR=3.31) (Table 4). Hospital and institution type also showed significance; community hospitals (both with and without academic affiliation) were more likely to use LDHI compared to the academic institutions (OR= 1.84 and 2.78 respectively) and children's hospitals were less likely to use LDHI (OR= 0.40) (Table 4). When compared to mixed ICUs, medical or surgical pediatric ICU types were less likely to use LDHI (OR= 0.62), whereas cardiac ICUs were more likely to use LDHI (OR=4.40) (Table 4). Using an ICU size of >30 beds as a reference, smaller ICUs (<10 beds) showed a greater likelihood of using LDHI (OR=3.40) (Table 4).

An alternative model (not shown) which included CVC insertion site, but not CVC type (due to the small numbers in some of the types) allowed inclusion of transthoracic and umbilical vein categories of CVC site. After this analysis, all CVC sites were more likely to use LDHI when compared to peripherally located CVCs (OR= 8.27-transthoracic, 4.43-umbilical, 3.81-femoral, 2.24-internal jugular vein, 1.7-subclavian).

Discussion

In this multi-national post-hoc analysis of the PROTRACT study, the prevalence of LDHI was 38%, with varying patient, CVC and institutional factors associated with its use. The regional and geographic variation in practice is not unexpected, and is reflective of the inconsistent literature on the efficacy of LDHI. Some neonatal studies support LDHI for prolonging CVC patency (2) (3) (4) (5). This contrasts with adult evidence which conveys that there is no benefit of heparin prophylaxis vs. saline (17). The limited pediatric evidence is varied, with most studies unable to draw distinct conclusions or showing no benefit (6) (7) (8) (9) (10) (11) (12) (13) (14). The small volume of patients at any institution, along with the technical and financial difficulties of carrying out large-scale clinical trials, forces practitioners to make patient-management decisions in spite of limited evidence. This

decision-making appears to be influenced as much by hospital and geographic culture as by patient factors. This is consistent with a previous survey of pediatric intensivists, where the second most common criterion to initiate heparin prophylaxis was *attending preference*, 42% (18).

Multiple co-morbidities were collected and analyzed for impact on LDHI use as part of the PROTRACT study. These included chronic disease, thrombosis history, obesity, TPN use, as well as current diagnoses and interventions. These variables are listed in full in Table 1. After multivariable analysis, most patient co-morbidities including chronic disease and thrombosis history did not impact LDHI use, while hospital and geographic factors retained significance. The presence and use of hospital or unit-wide protocols for LDHI use was not collected. The existence and compliance with such protocols would have the potential to minimize the role of factors such as ethnicity, age or pathology as indications for LDHI use.

Patient age was not associated with LDHI after multivariable analysis despite the neonatal evidence for LDHI to prolong catheter patency (2) (3) (4) (5). This could be reflective of some intensivists weighting the adult study conclusions over the neonatal studies, or a preference to standardize treatment practice despite varying patient age. This is also consistent with survey results, where only 38% of intensivists used patient age as a criterion for the initiation of heparin prophylaxis (18).

The divergence between adult and neonatal evidence regarding the efficacy of LDHI could be due to difference in CVC and blood vessel sizes. Accordingly, mechanical obstruction in the smaller vessels of neonates with adverse effects on blood flow is more probable, and may explain the reported efficacy of LDHI for CVC patency in this age group.

Patients with increased LDHI use through transthoracic and umbilical vein sites may reflect a comfort with neonatal evidence, which has showed prolonged patency of CVCs with LDHI. As the neonatal studies provide the only evidence for efficacy of LDHI, it is reasonable to speculate that this may influence providers caring for patients at the highest risk for compromise if CVC patency is lost. The increased use of LDHI in patients with complex surgical cardiac repair, may reflect a heightened specialty-specific (cardiovascular surgery, cardiac intensivist) concern for thrombosis and sequelae such as CVC occlusion.

Multivariable analysis showed independent association of LDHI use by geographic location, with increased use in the Asia-Pacific region. These effects may be due to differences in institutional practice, policy and training techniques. However, increased LDHI in certain races (Black, Asian) remained significant after multivariable analysis, suggesting this patient factor still plays a role in LDHI use.

The amount and details of medication and fluids delivered were not collected in this study, which may have influenced the use of LDHI. For instance, patients requiring continuously infused medications or central venous pressure monitoring may be more likely to receive LDHI than those with CVC-administered intermittent medications. This is supported by the increased association of LDHI with those on vasopressor support. We can speculate that practitioners did not feel the need for LDHI in patients at 'baseline' risk, as patients on home TPN had decreased use of LDHI.

This study is limited by its post-hoc analysis of an original study. The patients' need for the CVC and the rationale for LDHI, were not known. In a previous survey by Clarke, intensivists often prescribed LDHI without a clear rationale. As multiple benefits including CVC patency, line infection and patient thrombosis were postulated (18), indications for LDHI may be difficult to assess even in future prospective study. Other limitations include the a priori definition of LDHI (heparin of <10 U/hr) that may not reflect all practices. The PROTRACT study found that pharmacologic thromboprophylaxis was used in 43% of the children with cyanotic heart disease which included heparin infusion with rates >10U/hr. However, this definition may not entirely distinguish the dosing of LDHI for CVC patency from heparin infusion for systemic prophylaxis, as some providers may have overlapping indications and various subtleties to their use of LDHI. Additionally, outcomes including CVC patency, thrombosis, bleeding, and hospital length of stay were not collected.

The conflicting neonatal and adult evidence concerning the efficacy of LDHI along with the scarcity of data within the pediatric population, corroborates the need for further research, such as a randomized controlled study to determine if there is a specific age that LDHI is no longer beneficial. The inclusion of outcomes such as the number of CVC occlusions, the days of line patency, incidence of venous thromboembolisms, and the need for CVC replacements, would help to determine the efficacy of LDHI use and to clarify why it has mixed implementation in PICUs.

Conclusion

LDHI remains a common method for the maintenance of CVC patency in critically-ill children despite the lack of substantial data supporting its efficacy. In our analysis of the PROTRACT study, we showed that LDHI use has global prevalence, as 38% of patients with CVCs in this study received LDHI. Various patient, hospital and CVC factors are associated with LDHI use. With randomized controlled trials, we hope to shed more light on the effectiveness of LDHI in comparison to other methods of CVC patency such as saline infusion.

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Table 1

Patient-related Predictors of Low Dose Heparin Infusion (Univariate)

	Total N	LDHI ^a (yes)%	OR	95/ CI (OR)	p
Race					
White = Ref	923	339 (36.7%)			
Black	193	78 (40.4%)	1.17	0.85-1.60	0.34
Asian	61	33 (54.1%)	2.03	1.21-3.42	0.008
Other	135	57 (42.2%)	1.26	0.87-1.82	0.22
Ethnicity					
Hispanic/Latino	221	100 (45.2%)	1.36	1.01-1.82	0.04
Non-Hispanic/Latino=Ref	982	372 (37.9%)			
Unknown	109	35 (32.1%)	0.78	0.51-1.18	0.24
Age					
0-1 =Ref	740	313 (42.3%)			
1 - 12	417	148 (35.5%)	0.75	0.59-0.96	0.03
13	155	46 (29.7%)	0.58	0.40-0.84	0.004
Active Diagnosis					
Acyanotic CHD ^b	175	94 (53.7%)	2.03	1.47-2.80	<0.0001
Cyanotic CHD ^b	234	135 (57.7%)	2.59	1.94-3.45	<0.0001
Dilated Cardiomyopathy	28	11 (39.3%)	1.03	0.48-2.21	0.94
Listed for Heart Transplant	7	2 (28.6%)	0.53	0.08-3.40	0.51
Cerebrovascular accident	28	14 (50%)	1.60	0.76-3.39	0.22
Pulmonary Hypertension	117	33 (28.2%)	0.60	0.39-0.91	0.02
Cancer	104	28 (26.9%)	0.56	0.36-0.88	0.01
IBD	4	2 (50%)	1.59	0.22-11.32	0.64
Sepsis/Bacteremia	189	72 (38.1%)	0.97	0.71-1.34	0.87
Nephrotic Syndrome	6	3 (50%)	1.59	0.32-7.92	0.57
End Stage Renal Disease	20	9 (45%)	1.30	0.54-3.17	0.56
Burns	8	2 (25%)	0.53	0.11-2.62	0.43
Spinal Cord Injury	11	5 (45.4%)	1.33	0.40-4.37	0.64
Lower Extremity fracture	15	2 (13.3%)	0.24	0.05-1.07	0.06
Craniotomy	54	28 (51.8%)	1.75	1.02-3.02	0.04
Traumatic brain injury	43	14 (32.6%)	0.76	0.40-1.45	0.41
Lower Extremity Surgery	9	4 (44.4%)	1.27	0.34-4.76	0.72
Scoliosis Repair/ Other Spine Surgery	42	11 (26.2%)	0.55	0.28-1.11	0.10
Intra-cranial hemorrhage	49	19 (38.8%)	1.01	0.56-1.81	0.98
Non-intracranial hemorrhage	34	15 (44.1%)	1.26	0.64-2.50	0.51
Solid Organ Transplant	32	13 (40.6%)	1.09	0.53-2.23	0.81
Grouped Diagnoses					

	Total N	LDHI ^a (yes)%	OR	95/ CI (OR)	p
Bleeding ^c	92	40 (43.5%)	1.24	0.81-1.90	0.32
Heart Disease ^d	419	228 (54.4%)	2.63	2.07-3.34	<0.0001
Surgical/Trauma ^e	179	69 (38.6%)	0.995	0.72-1.38	0.98
Interventions					
Parenteral Nutrition	368	154 (41.8%)	1.20	0.94-1.54	0.14
Packed RBCs ^f	232	103 (44.4%)	1.34	1.00-1.78	0.05
Fresh Frozen Plasma Transfusion	100	48 (48%)	1.51	1.01-2.28	0.05
Platelet Transfusion	107	48 (44.9%)	1.32	0.89-1.97	0.17
Cryoprecipitate transfusion	20	16 (80%)	6.52	2.17-19.63	0.0008
Invasive mechanical ventilation	783	317 (40.5%)	1.21	0.97-1.52	0.10
Non-invasive mechanical ventilation	187	62 (33.2%)	0.76	0.55-1.05	0.10
L-asparaginase therapy	8	3 (37.5%)	0.95	0.23-4.00	0.95
Complete bed rest	633	246 (38.9%)	1.02	0.82-1.27	0.87
Vasoactive agent	411	233 (56.7%)	3.00	2.35-3.81	<0.0001
Anticipated surgery	97	44 (45.4%)	1.35	0.89-2.04	0.16
Prior Surgery	478	223 (46.6%)	1.69	1.35-2.13	<0.0001
Anticoagulant Use					
Aspirin	93	43 (46.2%)	1.40	0.92-2.14	0.12
Low Molecular Weight Heparin	83	28 (33.7%)	0.80	0.50-1.27	0.34
Intravenous Heparin	61	43 (70.5%)	4.05	2.31-7.11	<0.0001
Subcutaneous heparin	7	3 (42.9%)	1.19	0.27-5.35	0.82
Vitamin K antagonistic	9	3 (33.3%)	0.79	0.20-3.18	0.74
Grouped Anticoagulant ^g	223	110 (49.3%)	1.70	1.27-2.27	0.0004
Patient History/Pre-Study Info					
Personal History Thrombosis	83	35 (42.2%)	1.01	0.64-1.59	0.95
Congenital thrombophilia	5	2 (40%)	0.97	0.16-5.85	0.98
Acquired Hypercoagulability	6	2 (33.3%)	0.70	0.13-3.85	0.68
Sickle Cell Disease	6	5 (83.3%)	7.46	0.87-64.02	0.04
Family Hx of Thrombosis	3	2 (66.7%)	2.98	0.27-33.05	0.37
Obesity	23	8 (34.8%)	0.84	0.36-2.01	0.70
Home Parenteral Nutrition	29	3 (10.3%)	0.18	0.05-0.58	0.004
Multiple Cardiac Catheterizations	113	58 (51.3%)	1.70	1.15-2.50	0.008
Complex Surgical Cardiac Repair	345	200 (58%)	2.96	2.30-3.82	<0.0001
Cavopulmonary Anastomosis	69	45 (65.2%)	3.17	1.91-5.27	<0.0001

Note: Extracorporeal Membrane Oxygenation, Continuous Renal Replacement therapy, Ventricular Assist Device, Allergy to Heparin, Heparin-induced Thrombocytopenia, Granulocyte Transfusion, Diabetic Ketoacidosis and Pregnancy/Lactation had 0-1 cases in study with no use of LDHI

^aLDHI = Low Dose Heparin Infusion

^bCHD = Congenital Heart Disease

^cBleeding = Cerebrovascular accident, Non-intracranial hemorrhage, Intra-cranial hemorrhage

^dHeart Disease = Cyanotic CHD, Acyanotic CHD, Dilated Cardiomyopathy, Listed for Heart Transplant

^eSurgical/Trauma = Burns, Spinal Cord Injury, Lower Extremity Fracture, Craniotomy, Traumatic Brain Injury, Lower Extremity Surgery, Scoliosis Repair/Spine Surgery, Solid Organ Transplant

^fRBCs = Red Blood Cells

^gGrouped Anticoagulant = Aspirin, Low Molecular Weight Heparin, Intravenous + Subcutaneous Heparin, Vitamin K

Table 2

Central Venous Catheter Related Predictors of Low Dose Heparin Use (Univariate)

CVC Site and Type	Total N	LDHI ^a N (%)	OR	95% CI (OR)	P
CVC^b Site					
Transthoracic	13	11 (84.6%)	17.73	3.86-81.37	0.0002
Umbilical cord	26	18 (69.2%)	7.26	3.06-17.20	<0.0001
Subclavian vein	205	64 (31.2%)	1.46	1.01-2.12	0.04
Internal jugular vein	319	138 (43.3%)	2.46	1.79-3.38	<0.0001
Femoral vein	326	173 (53.1%)	3.65	2.66-4.99	<0.0001
Peripheral = Ref	414	98 (23.7%)			
CVC^b Type					
Hemofiltration/dialysis	6	3 (50%)	0.98	0.20-4.90	0.98
Atrial	13	11 (84.6%)	5.39	1.18-24.53	0.03
Umbilical	26	18 (69.2%)	2.21	0.94-5.15	0.07
Tunneled	166	41 (24.7%)	0.32	0.22-0.47	<0.0001
Peripherally inserted	493	128 (26%)	0.34	0.27-0.44	<0.0001
Untunneled = Ref	606	306 (50.5%)			

^aLDHI = Low Dose Heparin Infusion^bCVC = Central Venous Catheter

Table 3

Hospital Related Predictors of Low Dose Heparin Use (Univariate)

	Total N	LDHI ^a N (%)	OR	95% CI	P
Hospital Location					
Asia, Australia or New Zealand	168	100 (59.5%)	2.79	1.99-3.92	<0.0001
Canada	72	14 (19.4%)	0.46	0.25-0.84	<0.02
Spain or Portugal	173	83 (48%)	1.75	1.26-2.43	0.0008
United States = Ref	899	310 (34.5%)			
Hospital/Institution Type					
Community w/ Academic Affiliation	261	130 (49.8%)	1.80	1.36-2.36	<0.0001
Community without Academic Affiliation	48	20 (41.7%)	1.29	0.72-2.33	0.39
Academic = Ref	1003	357 (35.6%)			
Children's Hospital/Institution					
Yes	1090	387 (35.5%)	0.47	0.35-0.63	<0.0001
No = Ref	222	120 (54%)			
Pediatric ICU^b Type					
Medical or Surgical	397	79 (19.9%)	0.34	0.26-0.46	<0.0001
Cardiac	138	102 (73.9%)	3.92	2.61-5.88	<0.0001
Mixed medical or Surgical and Cardiac=Ref for all 3	777	326 (42%)			
Pediatric ICU^b Size					
10 beds	95	67 (70.5%)	9.34	5.45-15.99	<0.0001
11-20 beds	478	191 (40%)	2.60	1.82-3.71	<0.0001
21-30 beds	489	198 (40.5%)	2.66	1.86-3.79	<0.0001
>30 beds=Ref	250	51 (20.4%)			
Pediatric ICU^b Annual Admissions					
500	164	84 (51.2%)	2.86	1.97-4.14	<0.0001
501-1000	355	182 (51.3%)	2.86	2.13-3.85	<0.0001
1001-1500	350	122 (34.9%)	1.46	1.08-1.98	0.02
>1500 =Ref	443	119 (26.9%)			

^aLDHI = Low Dose Heparin Infusion^bICU = Intensive Care Unit

Table 4

Multivariate Analysis of Patient, Central Venous Catheter and Hospital Factors

	Total N	LDHI ^a (yes)%	OR	95% CI (OR)	p
Patient related predictors					
Race					
Black	193	78 (40.4%)	1.61	1.07-2.43	0.02
Asian	61	33 (54.1%)	2.44	1.29-4.60	0.04
Other	135	57 (42.2%)	1.21	0.72-2.03	0.46
White = Ref	923	339 (36.7%)			
Ethnicity					
Hispanic/Latino	221	100 (45.2%)	1.52	1.00-2.32	0.05
Unknown	109	35 (32.1%)	0.78	0.43-1.42	0.42
Non-Hispanic/Latino=Ref	982	372 (37.9%)			
Active Diagnosis Yes vs No=Ref					
Pulmonary Hypertension	117	33 (28.2%)	0.54	0.31-0.92	0.02
Grouped Diagnoses: Surgical/Trauma^b	179	69 (38.6%)	1.58	1.06-2.36	0.02
Interventions (yes/no = Ref)					
Cryoprecipitate transfusion	20	16 (80%)	4.65	1.20-18.13	0.03
Vasoactive agent	411	233 (56.7%)	1.48	1.08-2.04	0.01
Patient History (yes/no=Ref)					
Home Parenteral Nutrition	29	3 (10.3%)	0.29	0.08-1.11	0.07
Complex Surgical Cardiac Repair	345	200 (58%)	2.23	1.55-3.20	<0.0001
CVC^c Related Predictors: Site and Type					
CVC^c Site					
Subclavian vein	205	64 (31.2%)	1.42	0.72-2.82	0.31
Internal jugular vein	319	138 (43.3%)	1.12	0.56-2.23	0.74
Femoral vein	326	173 (53.1%)	2.09	1.11-3.93	0.02
Peripheral = Ref	414	98 (23.7%)			
CVC^c Type					
Tunneled	166	41 (24.7%)	0.59	0.36-0.96	0.04
Peripherally inserted	493	128 (26%)	0.62	0.35-1.12	0.49
Untunneled = Ref	606	306 (50.5%)			
Hospital related predictors					
Hospital Location					

	Total N	LDHI ^a (yes)%	OR	95% CI (OR)	p
Asia, Australia or New Zealand	168	100 (59.5%)	3.31	1.86-5.89	<0.0001
Canada	72	14 (19.4%)	0.52	0.23-1.14	0.10
Spain or Portugal	173	83 (48%)	1.34	0.69-2.58	0.38
United States = Ref	899	310 (34.5%)			
Hospital/Institution					
Community w/ Academic Affiliation	261	130 (49.8%)	1.84	1.20-2.83	0.005
Community without Academic Affiliation	48	20 (41.7%)	2.78	1.18-6.53	0.02
Academic = Ref	1003	357 (35.6%)			
Children's Hospital/Institution					
Yes	1090	387 (35.5%)	0.40	0.25-0.65	0.0002
No = Ref	222	120 (54%)			
Pediatric ICU^d Type					
Medical or Surgical	397	79 (19.9%)	0.62	0.42-0.91	0.02
Cardiac	138	102 (73.9%)	4.40	2.52-7.67	<0.0001
Mixed medical or Surgical and Cardiac=Ref for all 3	777	326 (42%)			
Pediatric ICU^d Size					
10 beds	95	67 (70.5%)	3.40	1.42-8.10	0.006
11-20 beds	478	191 (40%)	0.92	0.53-1.60	0.78
21-30 beds	489	198 (40.5%)	1.39	0.86-2.26	0.18
>30 beds=Ref	250	51 (20.4%)			

Note: Some of the CVC data (transthoracic, umbilical vein CVCs) were excluded for ensuring multivariable model convergence

^aLDHI=Low Dose Heparin Infusion

^bSurgical Trauma= Burns, Spinal Cord Injury, Lower Extremity Fracture, Craniotomy, Traumatic Brain Injury, Lower Extremity Surgery, Scoliosis Repair/Spine Surgery, Solid Organ Transplant

^cCVC=Central Venous Catheter

^dICU=Intensive Care Unit