A clinically significant incidence of bleeding in critically ill children receiving therapeutic doses of unfractionated heparin: a prospective cohort study

Stefan Kuhle, Pablo Eulmesekian, Brian Kavanagh, Patricia Massicotte, Patricia Vegh, Lesley G. Mitchell

From the Division of Haematology/Oncology (SK); Departments of Critical Care Medicine & Anesthesia (PE, BK); Department of Population Health Sciences, The Hospital for Sick Children, University of Toronto, Toronto (PV, LGM); Department of Pediatrics, Stollery Children's Hospital, University of Alberta, Edmonton, Canada (SK, PM, LGM).

The study was supported by a grant-in-aid from the Canadian Institutes Of Heath Research (MOP 77742) and by an "Erwin Schroedinger-Auslandsstipendium" from the Austrian Science Fund (FWF), Project # J-2038 (S.K).
Stefan Kuhle is the recipient of the Baxter BioScience Pediatric Hemostasis Fellowship 2002/2003 at the Hospital for Sick Children, Toronto.

Manuscript received August 6, 2006. Accepted December 6, 2006.

Correspondence: Lesley Mitchell, Stollery Children's Hospital, Dept of Pediatrics, Pediatric Thrombosis Program, Dentistry Pharmacy Centre, Rm 1130, 11304-89 Avenue, Edmonton, AB T6G 2C7.
E-Mail: LesleyMitchell@cha.ab.ca

ABSTRACT

Unfractionated heparin (UFH) is frequently prescribed for children for the prevention and treatment of thrombosis; however, its safety and efficacy have not been assessed. The aim of this single center, prospective cohort study was to determine the incidence of major bleeding and recurrent thrombosis in children receiving UFH. Major bleeding was defined a priori as: central nervous system or retroperitoneal bleeding, bleeding resulting in UFH being stopped or overt bleeding causing a drop in hemoglobin >20 g/dL in less than 24 h. Major bleeding events occurred in 9/38 children (24%, 95% CI 11-40%) and 2/38 (5%, 95% CI 0-18%) developed thrombosis. In conclusion, there is clinically significant bleeding in children receiving UFH.

Key words: unfractionated heparin, children, bleeding.

Haematologica 2007; 92:244-247

Unfractionated heparin (UFH) is frequently used for the prevention and treatment of thromboembolic events in critically ill children. UFH has a short half-life and its anticoagulant effect can be rapidly reversed by protamine in the case of bleeding or if an urgent invasive procedure is required.[1] A major drawback of UFH therapy in children is the absence of clinical studies determining a pediatric therapeutic dose range. Studies have suggested that extrapolation of adult treatment guidelines to pediatric care may not be optimal.[2-5] Therefore, the primary purpose of the current study was to determine the incidences of bleeding and thrombosis in pediatric patients receiving UFH.

Study design and population

A prospective cohort study was performed at the Critical Care Unit (CCU) of the Hospital for Sick Children, Toronto, Canada. The primary outcomes were objectively proven major bleeding events and new or recurrent thromboembolic events. The study population consisted of unselected children requiring therapeutic doses of UFH. Patients were eligible for the study if they were >36 weeks gestation and <18 years of age and required therapeutic doses of UFH. Patients were excluded if they received UFH for <24 hours or were receiving extracorporeal membrane oxygenation. The study was approved by the hospital's Ethics Review Board and informed consent was obtained from parents/guardians and/or patients.

UFH dosing and monitoring

Dose adjustments were made according to a revision of a previously published nomogram[1,6] in which anti-Xa levels where followed in infants <1 year; in children >1 year of age, aPTT and anti-Xa levels were used. If aPTT and anti-Xa levels corresponded, the aPTT was used, if there was no correspondence, anti-Xa levels were used.

Outcomes and statistical analysis

Outcome events were assessed by two of the investigators (*PE, BK*). Major bleeding was defined *a priori* as: (i) any overt bleeding associated with a decrease in hemoglobin of >20 g/dL in less than 24 h, (ii) any bleeding into the central nervous system or retroperitoneal area, iii) bleeding attributed to heparin treatment by the attending physician that resulted the heparin therapy being

Table 1. Demographic and clinical data of children with and without major bleeding events. Data are reported as median (range) or relative frequencies (n) where applicable.

	Major bleeding event (n=9)	*No bleeding event (n=29)*
Age	84 days (5 days-15.0 years)	8 days (2 days-15.4 years)
Male gender	3/9	18/29
Duration of UFH therapy [days]	4.5 (1-5)	7 (1-29)
Diagnosis		
Hypoplastic left heart syndrome	45% (13)	22% (2)
Tetralogy of Fallot	10% (3)	0
Transposition of the great arteries	7% (2)	22% (2)
Pulmonary embolism	0%	22% (2)
Other cardiac disorders	34% (10)	11% (1)
Other non-cardiac disorders	3% (1)	22% (2)
UFH dose [U/kg/h]	24 (7-30)	28 (16-33)

stopping. Thromboembolic events were identified by clinical symptoms and subsequently confirmed by appropriate objective radiographic tests. The statistical analysis was performed using Stata 9.2 software (StataCorp, College Station, USA).

Results and Discussion

Between April 1, 2002 and June 30, 2003, 38 children were enrolled in the study, of whom 22 (56%) were males. Their median age was 15 days (2 days-15.4 years). The most frequent diagnoses were hypoplastic left heart syndrome (39%, n=15), transposition of the great arteries (11%, n=4), tetralogy of Fallot (8%, n=3), pulmonary embolism and Shone complex (each 5%, n=2). Twenty-nine percent of patients (n=11) received UFH for treatment of venous thrombosis, 5% (n=2) for arterial thrombosis, and 66% (n=25) for prophylaxis. Specific reasons for prophylaxis included Blalock-Taussig shunt (60%, n=15), right ventricle-pulmonary artery conduit (12%, n=3), prosthetic valves (8%, n=2), and other (20%, n=5). The median dose of UFH was 27 U/kg/h (range: 7-33). Patients received UFH for a median of 6 days (range: 1-29).

There were nine (24%, 95% CI 11-40%) major bleeding events during the study period. The incidence of major bleeding events was 3.33% per person day on UFH, corresponding to 23.1% (95% CI 12-1;44.8%) per patient week on UFH. The characteristics of patients who did or did not have bleeding event are displayed in Table 1. Seven out of the nine patients who had a major bleeding event required one or more transfusions of red blood cells. Details on the bleeding events are shown in Table 2.

Two patients developed thromboembolim while on therapy, resulting in an incidence of 5.2% per patient week on UFH (95%CI 1.3;20.7). The thromboembolism were located in the femoral and internal jugular veins. The aPTT, anti-Xa activity and platelet count in these two patients at the time of the thromboembolic event were 101 and 29s; not determined and 0 U/mL; and 239 and 290/nL, respectively.

Post-hoc census data from the CCU patient database indicated potentially eligible patients had been missed during recruitment. A retrospective descriptive analysis of 28 patients who received therapeutic doses of UFH during the study period showed no difference in baseline clinical characteristics (*data not shown*).

The current study found an incidence of major bleeds in critically ill children of 24% (95%CI 11-40%). This incidence represents a major increase compared to previously reported incidences for children (1.5%)[6] and adults (2%)[7] on UFH. Andrew *et al*. reported only one major bleed in a cohort of 65 children (1.5%).[6] Other studies report similar findings: the Canadian registry on venous thrombosis found no significant bleeds in 115 children with venous thrombosis from different institutions[8] and Manco-Johnson *et al*. reported no major bleeds in 32 non-neonatal children with venous thromboembolism treated with a combination of UFH and fibrinolytics.[9] The most likely explanation for this discrepancy is a shift in the patient populations receiving UFH. The most commonly used anticoagulant in children 10-15 years ago was UFH and the population receiving the drug comprised all children, as in the studies by Andrew *et al*. and Manco-Johnson *et al*.[6,9] Today, low molecular weight heparin is the preferred anticoagulant in clinically stable children, while UFH is almost exclusively used in critically ill children because its action can be reversed relatively rapidly. In keeping with this tendency, only four children (<10%) outside the CCU received therapeutic doses of UFH during the study period.

The lack of a proper monitoring test for UFH therapy in children may have further contributed to the clinically significant bleeding rate seen in the current study. Analysis of the patients' laboratory data[10] showed that there was little agreement between UFH dose, aPTT and anti-Xa activity. These findings were corroborated by a recent study by Ignatojvic *et al*.[11] In critically ill children with a severely compromised hemostatic system the individual response to UFH is extremely difficult to predict. This may have resulted in inappropriate dosing and may have contributed to the bleeding events in some patients. In the current study, the aPTT was in the therapeutic range for only 15% of the time compared to 43% in the study by Andrew *et al*.[6] There was no significant difference in the duration of UFH therapy or median UFH dose between children with and without major bleeds. In a few patients, an increased International Normalized Ratio and a decreased platelet count likely played a role in the etiology of their bleeding events

Table 2. Clinical and laboratory data of the nine patients at the time of their major bleeding events.

Age/Diagnosis	*Reason for UFH*	*Type of bleed*	*UFH dose [U/kg/h] APTT [s]*	*Anti-Xa [U/mL] INR*	*Platelets ($\times 10^9$/L)*		
3 months/Congenital diaphragmatic hernia	BT shunt	Hemothorax	31	>212	0.49	3.1	501
19 days/HLHS	BT shunt	Mediastinal bleed	33	138	0.39	1.3	294
6 months /AVSD	Arterial thrombosis	Gastrointestinal bleed	25	63	0.32	1.1	211
13 years/Pulmonary embolism	Pulmonary embolism	Retroperitoneal hematoma	30	116	0.56	1.6	90
14 years/Pulmonary embolism	Pulmonary embolism	Hemothorax	15	>212	1.6	0.14	302
6 years/Mucopolysaccharidosis	Venous thrombosis	Gastrointestinal bleed	24	65	0.36	0.94	59
5 days/TGA	Switch repair	Mediastinal bleed	28	>212	0.31	1.1	33
10 days /HLHS	RV-PA conduit	Hemothorax	28	148	0.28	1.3	127
12 days/TGA	Venous thrombosis	Hemothorax	31	121	0.19	1.3	8

UFH: unfractionated heparin; APTT: activated partial thromboplastin time; INR: International Normalized Ratio; BT: Blalock-Taussig; HLHS: hypoplastic left heart syndrome; AVSD: atrioventricular septal defect; PE: pulmonary embolism; TGA-. transposition of the great arteries; RV-PA: right ventricle to pulmonary artery.

(Table 2).

Two patients (5%, 95% CI 0-18%) developed a new thromboembolic episode during the study period while on UFH therapy. The risk of a new thromboembolic event during UFH therapy was lower than the risk of bleeding, raising questions of the risk/benefit ratio of UFH therapy. However, the attending physicians not infrequently considered the observed bleeding events less serious than the potentially dramatic consequences of a thromboembolic event, as illustrated by the fact that UFH therapy was continued or restarted after the bleeding event had been treated in seven out of nine children.

The current study has some limitations that need to be acknowledged. Firstly, we were not able to enroll all eligible patients during the study period; although recruitment rates were in keeping with those in other studies in this population,[12] this may have resulted in a biased population. A CCU database query identified patients who were missed for enrollment. The clinical characteristics (age, gender, diagnosis, duration of UFH therapy) of these children did not differ from those of the study sample. However, even after inclusion of the 28 missed patients with the most conservative assumption of zero bleeding events, the bleeding rate would still be clinically significant at 13%.

Secondly, the generalizability of the study may be limited as the study population described may not be representative of children receiving UFH at other hospitals. The Hospital for Sick Children is a quaternary care center; other centers may well see less severely ill children on UFH and thus a much lower bleeding rate. The results must, therefore, be interpreted with caution. Thirdly, the current study did not have a control group. Without a control group, it is difficult to determine whether surgical or other complications contributed to the bleeding risk. However, a surgical cause for the bleed could be excluded in at least four of the nine patients.

In summary, the current study found a clinically significant bleeding rate of 24% in critically ill children receiving therapeutic doses of UFH. This finding is probably related to the complexity of the patient population and/or dose of UFH.

Authors Contributions

SK: responsible for the integrity and analysis of the data, wrote the manuscript; PE: responsible for execution of the research and clinical management of the study patients; BK: responsible for execution of the research and clinical management of the study patients; PM: responsible for execution of the research and clinical management of the study patients; PV: responsible for execution of the research, integrity and analysis of the data; LM: responsible for the conception, design and execution of the research, integrity of the data and analysis of the data, wrote the manuscript.

Conflicts of Interest

The authors reported no potential conflicts of interest.

References

1. Monagle P, Chan A, Massicotte P, Chalmers E, Michelson AD. Antithrombotic therapy in children: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:645S-87S.
2. Andrew M, Mitchell L, Vegh P, Ofosu F. Thrombin regulation in children differs from adults in the absence and presence of heparin. Thromb Haemost 1994;72:836-42.
3. Schmidt B, Ofosu FA, Mitchell L, Brooker LA, Andrew M. Anticoagulant effects of heparin in neonatal plasma. Pediatr Res 1989; 25:405-8.
4. Vieira A, Berry L, Ofosu F, Andrew M. Heparin sensitivity and resistance in the neonate: an explanation. Thromb Res 1991;63:85-98.
5. Andrew M, Ofosu F, Schmidt B, Brooker L, Hirsh J, Buchanan MR. Heparin clearance and ex vivo recovery in newborn piglets and adult pigs. Thromb Res 1988;52: 517-27.
6. Andrew M, Marzinotto V, Massicotte P, et al. Heparin therapy in pediatric patients: a prospective cohort study. Pediatr Res 1994; 35: 78-83.
7. Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. Ann Intern Med 1999;130:800-9.
8. Andrew M, David M, Adams M, et al. Venous thromboembolic complications (VTE) in children: first analyses of the Canadian Registry of VTE. Blood 1994;83:1251-7.
9. Manco-Johnson MJ, Nuss R, Hays T, Krupski W, Drose J, Manco-Johnson ML. Combined thrombolytic and anticoagulant therapy for venous thrombosis in children. J Pediatr 2000;136:446-53.
10. Mitchell L, Kuhle S, Massicotte PM, Vegh P. Increase incidence of major bleeding in children receiving unfractionated heparin for clinical management: a prospective cohort study. Blood 2004;104:1772A.
11. Ignjatovic V, Summerhayes R, Than J, Gan A, Monagle P. Therapeutic range for unfractionated heparin (UFH) therapy: age-related differences in response in children. J Thromb Haemost. 2006 (in press)