Received: 21 July 2023 | **Accepted:** 08 Aug 2023 **Genel Tıp Derg. Volume** 33/**Issue** 5 (October), 588-593
DOI: 10.54005/geneltip.1330759

ORIGINAL ARTICLE

Investigation of the Adequacy of 100 IU/Kg Unfractionated Heparin Loading Dose by Activated Clotting Time In Children With Congenital Heart Disease During Cardiac Catheterization

Doğumsal Kalp Hastalıklı Çocuklarda Kalp Kateterizasyonu Sırasında Aktive Edilmiş Pıhtılaşma Zamanı Testi ile 100 IU/Kg Fraksiyone Olmayan Heparin Yükleme Dozunun Yeterliliğinin Araştırılması

[1]Mahmut Gokdemir, [1]Nimet Cındık

[1]Baskent University Faculty of Medicine, Division of Paediatric Cardiology, Konya, TÜRKİYE

Correspondence

Mahmut Gokdemir, Baskent Üniversitesi Konya Uygulama ve Araştırma Merkezi, Hoca Cihan Mah. Saray Cad. No:1, Selçuklu, Konya/TÜRKİYE

E-Mail: mgokdem@hotmail.com

How to cite ?

Gokdemır M. , Cındık N. Investigation of the Adequacy of 100 IU/Kg Unfractionated Heparin Loading Dose by Activated Clotting Time In Children With Congenital Heart Disease During Cardiac Catheterization. Genel Tıp Dergisi. 2023; 33(5): 588-593.

ABSTRACT

Purpose: This study investigated whether an activated clotting time (ACT) between 200 and 300 sec could be achieved with a100 IU/kg unfractionated heparin (UHF) loading dose in patients with congenital heart disease (CHD) during pediatric cardiac catheterization.
Materials and Methods: We included 264 patients aged 0-18 years with CHD undergoing cardiac catheterization between January 2022-March 2023. Data on patient characteristics, UHF doses, and ACT values were retrospectively obtained. The patients were intravenously administered 100 IU/kg UFH after sheath placement. We aimed to obtain a value between 200 and 300 sec according to the ACT measured at the 5th minute. If the measured ACT value at the 5th min was < 200 sec, additional heparin doses between 20 and 50 IU/kg were administered such that the total heparin loading dose did not exceed 150 IU/kg. Patients were divided into two groups based on whether the ACT value was below or above 200 sec.
Results: Median age, weight, and ACT value at procedure were 6.41(IQR:2.01–32.21) months, 6.13(IQR:3.79-11.9) kg, and 212(IQR:190-240) sec, respectively. The ACT value of 170(64.4%) of the 264 patients was between 200-300 sec, which was considered the target value. The ACT value of 86(32.6%) of the 264 patients was below the target value and that of eight (3%) patients was above the target value. Hematoma occurred at the access site in four patients (1.5%). We did not detect retroperitoneal hematoma, other bleedings at location, or thromboembolism in any of the patients. No significant differences were observed in comparisons between age subgroups and ACT distribution, or between age subgroups and ACT subgroups (p>0.05)
Conclusion: This study revealed that a 100 IU/kg UFH loading dose produced the target ACT value in 64.4% of the patients and that the UFH loading dose should be individualized according to the ACT value in the remaining patients.

Keywords: Congenital heart disease,, Cardiac catheterization, Unfractionated heparin, Activated clotting time

ÖZ

Amaç: Çalışmanın amacı pediatrik kalp kateterizasyonu sırasında konjenital kalp hastalığı (CHD) olan hastalarda 100 IU/kg fraksiyone olmayan heparin (UHF) yükleme dozunun 200-300 saniye aralığında aktif pıhtılaşma zamanı (ACT) değerine ulaşılabilirliğin araştırılmasıdır.
Gereç ve Yöntemler: Ocak 2022 ve Mart 2023 tarihleri arasında kardiyak kateterizasyon yapılan 0-18 yaş arası CHD'li 264 hasta çalışmaya alındı. Hasta özellikleri, UHF dozları ve ACT değerleri retrospektif olarak elde edildi. Kılıf yerleştirildikten sonra hastalara 100 IU/kg intravenöz UFH yükleme yapıldı. 5. dakikadaki ACT değerinin 200 ve 300 saniye aralığında olması hedeflendi. 5. dakikada ölçülen ACT değeri <200 saniye ise toplam heparin yükleme dozu 150 IU/kg'ı geçmeyecek şekilde 20-50 IU/kg ek UFH yükleme dozları yapıldı. Hastalar ACT değerlerinin 200 saniye altı ve üstünde olmasına göre iki gruba ayrıldı.
Bulgular: İşlem sırasında medyan yaş, ağırlık ve 5. dakikadaki ACT değeri sırasıyla 6.41(interquartile range (IQR): 2.01–32.21) ay, 6.13(IQR: 3.79-11.9) kg ve 212(IQR: 190-240) saniye belirlendi. 264 hastanın 170'inde (%64,4) ACT değeri hedef değer olarak kabul edilen 200-300 saniye aralığında ölçüldü. 264 hastanın 86'sında (%32,6) ACT değeri hedef değerin (<200 sn) altında ve sekiz (%3) hastada ise hedef değerin (>300 sn) üzerinde ölçüldü. Dört hastada (%1,5) giriş yerinde hematom belirlendi. Retroperitoneal hematom, kanama ve tromboembolizm hiçbir hastada belirlenmedi. Yaş alt grupları ile ACT dağılımı ve yaş alt grupları ile ACT alt grupları arasındaki karşılaştırmalarda gruplar arasında anlamlı fark belirlenmedi (p>0,05).
Sonuç: Bu çalışma, kardiyak kateterizasyon sırasında 100 IU/kg UFH yükleme dozunun CHD'lı hastaların %64,4'ünde hedef ACT değer aralığını sağlayabildiğini ve geri kalan hastalarda UFH yükleme dozunun 5. dakikada ölçülen ACT değerine göre ek UHF dozları ile bireyselleştirilmesi gerektiğini gösterdi.

Anahtar Kelimeler: Konjenital kalp hastalığı, Kalp kateterizasyonu, Fraksiyone olmayan heparin, Aktif pıhtılaşma zamanı

Introduction

Unfractionated heparin (UFH) is widely used to reduce thromboembolic complications during pediatric cardiac catheterization (PCC) (1). The UFH dose and its pharmacological efficacy may differ in children owing to differences in the maturation of the coagulation system and faster heparin clearance (2,3). Therefore, determining the optimal dose and monitoring the effects of UFH is necessary to reduce thromboembolism and bleeding complications (4). Although intravenous UFH loading doses between 50 and 150 IU/kg are recommended during PCC after sheath placement (2,5-9), the commonly administered loading dose is 100

Peer-Review: Double anonymized - Two External
Plagiarism Checks: Yes - iThenticate
Complaints: geneltip@selcuk.edu.tr

IU/kg (1,2,4,10-17). The activated clotting time (ACT) (1), activated partial thromboplastin time (aPTT) (9), anti-factor Xa (anti-FXa) (1,2,15), anti-factor IIa (anti-FIIa) (18), fibrinopeptide-A (2), and prothrombinase-induced clotting time (9) were used to monitor the degree of heparinization (1,3,4,6,7,10,11,13,14,16,17,19).

Many studies have recommended that the ACT should be > 200 sec and maintained as an indicator of adequate anticoagulation during PCC (2,10,11,13,18). Data indicating whether a 100 IU/kg UFH loading dose is sufficient after sheath placement are limited to the PCC. Hence, we hypothesized that the UFH loading dose to achieve and maintain an adequate ACT value may differ on an individual basis.

The primary aim of this novel study was to investigate whether ACT levels of 200 and 300 sec could be achieved at a loading dose of 100 IU/kg UFH in patients with CHD during PCC. The secondary aim of this study was to determine the UFH loading dose required to provide an ACT value between 200 and 300 sec in patients with an ACT value <200 sec after a loading dose of 100 IU/kg UFH.

Material and Methods

We recruited 264 patients aged 0-18 years with CHD who underwent PCC at our institution between January 2022 and March 2023. The following data were extracted retrospectively from our preformed pediatric cardiology digital database for each patient; sex, age, weight at procedure, cardiac diagnosis, UFH dose, ACT value, whole blood parameters, duration of cannulation, duration of hemostasis, and complications at the access site. The exclusion criteria included patients with prematurity, syndromic, thrombocytopenia, liver failure, hematocrit values < 25% and > 55%, antiaggregant and anticoagulant drugs, and indwelling central catheters. We converted our first ACT values, which were obtained 5th minute after intravenous UFH loading dose administration, to a dichotomous variable using 200 sec as the cut-off point. Patients were divided into two groups based on whether the ACT value was < or > 200 sec Accordingly, the two-group comparison statistics were used. The procedures were performed under general anesthesia or deep sedation provided by an anesthesiologist.

This study was approved by the Baskent University Institutional Review Board (Project no: KA23/188) and was supported by the Baskent University Research Fund.

Anticoagulant Protocol with UFH

Unfractionated heparin (Biemparin, 25000 IU/5 mL, Biem İlaç San.ve Tic.AŞ. Tandoğan, Ankara) was administered to the patients at an initial loading dose of 100 IU/kg UFH (maximum dose: 5000 IU) through the peripheral vein immediately after sheath placement. The sheaths and catheters were flushed with heparinized saline (1U/mL) before usage. During catheterization, we aimed to obtain an ACT between 200 and 300 sec and to maintain this value. We planned our maintenance dose and ACT controls according to the ACT value at the 5th minute after the UFH loading dose. According to our institutional protocol, no additional loading dose was administered when the ACT value was measured over 200 sec If the measured ACT value at the 5th minute was < 200 sec, additional heparin doses were administered so that the total heparin loading dose did not exceed 150 IU/kg. Additional UFH loading doses were given to 20 IU/kg for ACT value between 180-199 sec, 30 IU/kg for 170-179 sec, 40 IU/kg for 160-169 sec, and 50 IU/kg for <160 sec Control ACT measurements were routinely performed 5 minutes after each additional and maintenance dose. ACT control was performed 30 minutes later when the ACT value was between 200-250 sec When the ACT value was measured between 250-300 sec, ACT value was assessed after 60 min and maintenance doses were administered according to the measured values. To determine the effect of 100 IU/kg UFH on ACT values in different age groups, we categorized our patients into five main groups: 0-28 days, 29-90 days, 91 days-1 years, 1.01 years-5 years and > 5.01 years. Hemostasis was achieved by manual compression after the sheath was removed. The duration of hemostasis was defined as the time from sheath removal to bleeding control. If arterial and venous access were performed simultaneously in the same patient, the hemostasis duration was accepted as the average arterial and venous bleeding control time

Measurement of Activated Clotting Time

Approximately 4-5 ml of whole blood was drawn from the catheter or sheath five minutes after intravenous UFH administration to avoid contamination from the flush solution. Subsequently, 0.6 ml blood samples were drawn into non-heparinized syringes for ACT measurements and immediately placed in a standby ACT device using a double-chambered cartridge (Medtronic ACT Plus, Medtronic Inc. Minneapolis, MN 55432 USA) in the catheterization laboratory. Blood samples were collected from catheters or sheaths to avoid contamination and were reinfused into the patients after sampling. The average double count was considered as the final ACT value.

Statistical Analyses

Continuous variables were expressed as medians with interquartile ranges (IQR) (25th-75th) and categorical variables were expressed as numbers (percentages). The Kolmogorov-Smirnov test was used to assess the normality of the distribution of continuous variables. The Kruskal-Wallis and Mann-Whitney U tests were used to compare variables between independent groups as continuous variables did not exhibit a normal distribution. Statistical comparisons of categorical variables were performed using Chi-square or Fisher's exact tests. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using BM SPSS statistical software (version 25.0: IBM Corp. 25.0, Armonk, NY, USA).

Results

The patients' median age and weight of the patient

at procedure were 6.41(IQR:2.01-32.21) months and 6.13(IQR:3.79-11.90) kg, respectively. Of the 264 patients, 53(20%) were newborns and 101(38.3%) were between one and 12 months old. Thirty-two (12.1%) patients were <3 kg, 67(25.4%) patients were between 3.01-5 kg, 88(33.4%) patients were between 5.01-10 kg and 77(29.1%) patients were > 10.01 kg. Before catheterization, 40(15.2%) patients were intubated for respiratory and/or heart failure. The median cannulation time was 22 min (IQR:15-37) in all patients, >30 min in 79(29.9%) of the 264 patients, and >60 min in 27(10.2%) patients. The demographic, clinical, and laboratory data of patients with CHD who underwent ACT monitoring during cardiac catheterization are summarized in Table I.

The median ACT value was 212(IQR:190-240) sec at the 5th minute for all patients. The ACT value of 170(64.4%) of the 264 patients was between 200-300 sec, which is considered the target value. The ACT value of 86(32.6%) of the 264 patients was < the target value (<200 sec) and required an additional UFH loading dose. The ACT values of eight (3%) of the 264 patients were above the target value (>301 sec). The ACT values of these 86 patients were measured at ≤ 160 sec in 14 patients, 161-170 sec in eight patients, between 171-180 sec in 19 patients, and between 181-200 sec in 45 patients. The relationship between age subgroups and the distribution of the ACT values is depicted in detail in Figure 1, and the relationship between the age subgroup and the ACT subgroup is summarized in Table 2. No significant differences were observed in comparisons between age subgroups and ACT distribution, or between age subgroups and ACT subgroups (p=0.217 and p=0.209, respectively)

According to these ACT values, additional doses of 50 IU/kg for 14 patients with ACT values ≤160 sec, 40 IU/kg for eight patients with ACT values between 161-170 sec, 30 IU/kg for 19 patients with ACT values 171-180 sec, 20 IU/kg for 45 patients with 181-200 sec were administered. In addition, three patients with ACT values of 170, 185, and 194 required second additional doses, and their total doses were completed at 150 IU/kg. Consequently, 17 patients required a 150 IU/kg UFH loading dose. In two of the 17 patients who received 150 IU/kg loading as the total dose, the ACT values were measured less than 200 sec and could not be failed to reach the target ACT value. The ACT values of 83 among the 86 patients who received additional UFH loading doses were 200-300 sec. Only one patient who received an additional UFH loading dose exhibited an ACT value > 300 sec (ACT value was 384 sec). Additionally, the patient was administrated protamine sulfate to prevent prolonged bleeding.

After catheterization, temporary femoral artery occlusion developed in 26(9.8%) patients and permanent femoral artery occlusion in five patients (1.9%). Hematoma occurred at the access site in four patients (1.5%). No significant differences were observed between the groups (p>0.05). We did not detect retroperitoneal hematoma, other bleedings at location, pseudoaneurysm, arteriovenous fistula, or thromboembolism in any of the patients. In the univariate analysis, no statistical difference was noted between the two groups, except for bleeding control time. As statistically significant variables were not obtained between the groups in the univariate analysis, appropriate modeling for logistic regression analysis could not be established in the patient group whose ACT value was below the target value, therefore, independent risk factor analysis was not performed in our patient group with ACT value of < 200 sec.

Table 1: Demographic, clinical and laboratory of patients with CHD who underwent ACT monitoring during cardiac catheterization.

Characteristics of the patients	All patients n: 264	Patients with ACT < 200 sec, n: 86(32.6%)	Patients with ACT ≥ 200 sec, n: 178(67.4%)	p-value
Gender, female / male (n)	123/141	37/49	86/92	0.419
Age at procedure (month)	6.41(2.01-32.21)	7.80(2.76-42.89)	5.63(1.75-27.76)	0.122
Weight at procedure (kg)	6.13(3.79-11.90)	6.08(3.85-13.65)	6.28(3.69-11.45)	0.465
Cyanotic heart disease, n(%)	79(29.9)	25(29.1)	54(30.3)	0.833
Intubation before procedure, n(%)	40(15.2)	10(11.6)	30(18.9)	0.267
Interventional procedure, n(%)	81(30.7)	23(26.7)	58(32.6)	0.335
Activated clotting time (sec)	212(190-240)	181(170-190)	225(212-252)	<0.001
Hemoglobulin (g/dL)	12.4(10.8-13.0)	12.3(10.8-14.0)	12.4(10.8-14.0)	0.938
Hematocrit (%)	37.7(32.6-42.1)	37.2(32.5-41.8)	37.8(32.7-42.2)	0.991
Platelet count (10^9/L)	287(231-358)	280(237-372)	290(230-358)	0.706
White blood cell (10^9/L)	9515(7560-1260)	10200(7550-13200)	9250(7570-12200)	0.461
Cannulation duration (min)	22(15-37)	21(17:25-39:45)	22:00(15:22-36:50)	0.575
Haemostasis duration (min)	8:00(6:07-13:45)	8:30(5:30-10:00)	10(6:00-14:30)	0.045
Hematoma at access site, n(%)	4(1.5)	1(1.2)	3(1.7)	1.000
Temporary arterial occlusion, n(%)	26(9.8)	11(12.8)	15(8.4)	0.265
Permanent arterial occlusion, n(%)	5(1.9)	2(2.3)	3(1.7)	0.662

Numerical variables were presented as median with IQR. ACT: Activated clotting time

Table 2: Relationship between the age groups and ACT subgroups according to the ACT value at the 5th minute.

	Age group distribution of patients					
Distribution of the ACT groups	0-28 days, n(%)	29-90 days, n(%)	3.01-12 months, n(%)	1.01-5 years, n(%)	>5.01 years, n(%)	All patients, n(%)
< 160 sec, n	0	3(12)	7(9.2)	3(4)	1(2.9)	14(5.3)
161-170 sec, n	2(3.7)	1(4)	1(1.3)	2(2.6)	2(5.9)	8(3)
171-180 sec, n	3(5.7)	1(4)	6(7.9)	5(6.6)	4(11.8)	19(7.2)
181-200 sec, n	8(15.1)	4(16)	13(17.1)	12(15.8)	8(23.5)	45(17)
201-300 sec, n	37(69.8)	16(64)	46(60.5)	52(68.4)	19(55.9)	170(64.4)
301-350 sec, n	1(1.9)	0	3(40)	1(1.3)	0	5(1.9)
>351 sec, n	2(3.7)	0	0	1(1.3)	0	3(1.2)
All patients, n(%)	53(20)	25(9.5)	76(28.8)	76(28.8)	34(12.9)	264(100)

P0.209. ACT: Activated clotting time

Table 3: Relationship between the age groups and UFH requirement of patients according to the ACT value at the 5th minute.

	Age group distribution of patients					
Patients' UFH requirements	0-28 days, n(%)	29-90 days, n(%)	3.01-12 months, n(%)	1.01-5 years, n(%)	>5.01 years, n(%)	All patients, n(%)
100 IU/kg, n	40(75.5)	16(64)	49(64.5)	54(71.1)	19(55.9)	178 (67.4)
120 IU/kg, n	8(15)	4(16)	12(15.8)	10(13.2)	8(23.5)	42(15.9)
130 IU/kg, n	2(3.8)	1(4)	5(6.6)	5(6.5)	4(11.8)	17(6.5)
140 IU/kg, n	3(5.7)	1(4)	2(2.6)	1(1.3)	2(5.9)	9(3.4)
150 IU/kg, n	0	3 (12)	8(10.5)	6(7.9)	1(2.9)	18(6.8)
All patients, n(%)	53(20)	25(9.5)	76(28.8)	76(28.8)	34(12.9)	264(100)

P:0.271. UFH: Unfractionated heparin

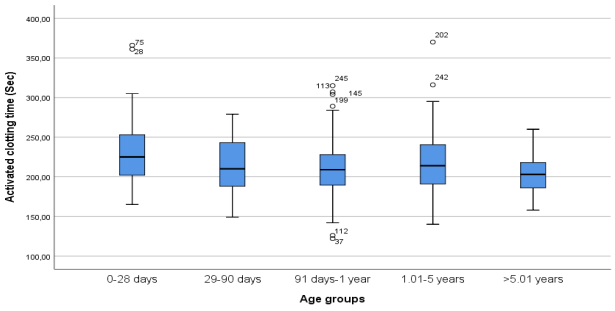

Figure 1: Relationship between age subgroups and distribution of the ACT value.

Discussion

The UFH loading dose at the initiation of the procedure and the maintenance dose required for prolonged procedures should be based on anticoagulation monitoring to prevent thromboembolism and bleeding during PCC in patients with CHD. As the UFH dose and its pharmacological efficacy may differ in children due to variations seen in the maturation of the coagulation system (2,3), a fixed UFH loading dose may not be suitable in the pediatric population. However, we believe that a fixed UFH dose can result in over and under coagulation. Hence, the UFH loading dose should be individualized and carefully monitored for each patient. In 264 patients included in our study, the ACT value was measured in the range of the target value of 200-300 in 170(64.4%) patients, below the target value (<200 sec) in 86(32.6%) patients, and above the target value (>300 sec) in eight (3%) patients.

As the ACT allows point-of-care testing compared with other tests, it has been widely used as a whole-blood coagulation test during PCC (1,3,4,6,7,10,11,13,14,16,17,19). The aPTT, ant-FXa, ACT + and ACT-LR tests were performed in the PCC and congenital heart surgery settings. This study indicated that ACT plus (+) was more reliable than ACT-LR and was strongly correlated with anti-FXa (r=0.89, p = 0.001) (1). We used ACT +, which is more reliable at moderate and high UFH doses, has a high correlation with anti-FXa, and allows post-care in our catheterization laboratory. Since anti-FIIa, which provides important complementary information for monitoring UFH levels, especially in infants and at high UFH loading doses, was not available at our institution (18), the data on monitoring anti-FIIa were not measured.

A previous study reported that a 50 IU/kg UFH loading dose was similarly effective in preventing arterial thrombosis as 100 IU/kg. Though the study included 366 children, it did not follow ACT measurement and the incidence of arterial thrombosis was reported as 9.8% and 9.3%, respectively, between the groups. Furthermore, no bleeding or hematoma were observed at the arterial access site (5). In a similar study comparing 50 and 100 IU/kg UFH loading doses, thromboembolism, and bleeding risks were similar, and a 50 IU/kg UFH loading dose was sufficient for thromboembolism during PCC (8). In another study in which 60 patients weighing <10 kg was included, loading doses of 100 and 150 IU/kg were compared and the mean ACT value was observed as 199 ± 53 and 259 ± 113 sec, respectively at the 20th minute after UFH administration. Hence, it is safe to administer

a loading dose of 100 IU/kg or more and to maintain the ACT level for over 200 sec (6). Although different doses were administered in two studies, the reason for the similar clinical results may be that no significant difference could be detected. In these studies, the percentage of patients in whom the target ACT level was achieved after the UFH loading dose of different regimens during PCC was not reported.

In three different studies with a loading dose of 100 IU/kg UFH, the ACT control was performed for 30 min. for anticoagulation monitoring. The target ACT level was accepted as > 250 sec, and a 50 IU/kg UFH bolus was repeated in procedures lasting longer than 1h (13,14,19). In addition, in two studies with a UFH loading dose of 100 IU/kg, ACT was measured at 30-60 min intervals to maintain the target ACT value between 200 and 300 sec for anticoagulation monitoring and during the procedure (11,17). However, these studies did not report whether a loading dose of 100 IU/kg of UFH at the beginning of the procedure was sufficient to achieve the target ACT value. They focused on the need for repeated UFH loading doses in long-term procedures.

In a study conducted by Kim et al., in which ACT control was performed at the 5th minute after intravenous UFH, the age group and the presence of CDH did not affect the ACT value (1). In another study, in which a100 IU/kg UFH loading dose was administered and factors affecting the final ACT value were investigated, it was reported that patient age, interventional procedure, and cardiac diagnosis did not affect the ACT value. In our study, the patients were divided into five main groups based on their age at the procedure, two groups according to the presence of cyanotic heart disease, and two groups based on the interventional procedure There was no difference between age subgroups, interventional procedures, and cyanotic and acyanotic patients (all P > 0.05).

In a study, in which 3859 patients who underwent femoral artery catheterization were included, patients were administered 100 IU/kg UFH loading dose, and the target ACT value was accepted as > 250 sec. Final ACT value <250 sec [Odds ratio: 1.9 (1.4-2.7), p=0.04] was stated as a risk factor for postprocedural acute occlusive arterial injury (10). In contrast, in another study in which 2388 femoral arterial catheterizations were performed, a 50-100 IU/kg UFH loading dose was administered, and the target ACT value was accepted as > 250 sec, it was reported that a final ACT value of > 250 sec did not prevent femoral arterial occlusion (7). Hence, the final ACT for UFH monitoring is important in planning the treatment of postprocedural femoral arterial occlusion after procedure (4).

Different studies have reported that initial UFH loading doses of 50-150 IU/kg are sufficient in pediatric cardiology practice (5-9,15). In a study by Grandy et al., in which bolus doses of 50 and 100 IU/kg UFH were compared between patients with CHD, basal and for two-hour fibrinopeptide A and ACT values were measured to monitor the heparin anticoagulation effect. A bolus dose of 100 IU/kg UFH resulted in a consistent >200 sec ACT level and trended toward lower fibrinopeptide A levels. As a result of this study, it is recommended to use a bolus of 100 IU/kg UFH and maintain the ACT for > 200 sec during PCC (2). As in this and previously reported studies (4,7,10,11,13,14,16,17,19), we administered an initial intravenous loading dose of 100 IU/kg UFH to our patients.

To our knowledge, it has not been investigated whether each patient requires a different UFH loading dose. In this novel study, we focused on determining the optimal UFH loading dose to achieve the target ACT value range. We administered initial UFH loading doses between 100 and 150 IU/kg to our patients, based on our predetermined clinical protocol and ACT values measured at the 5th minute after the 100 IU/kg UFH loading dose and the controls. Although 264 patients received an initial UFH loading dose of 100 IU/kg, 86 (32.6%) had an ACT value < 200 sec. Of the 86 patients, 45 required 120 IU/kg, 17 required 130 IU/kg, 9 required 140 IU/kg, and 18 required a total UFH loading dose of 150 IU/kg. While the target ACT value was not obtained in three of the 86 patients, the ACT value was measured for 384 sec in only one patient. In our study, no difference was observed in terms of bleeding, hematoma at site access, and femoral artery occlusion between patients requiring additional UFH loading doses and those requiring single dose loading according to the target ACT value (all p>0.05).

This study has main several limitations. First, this was a single-center, retrospective study. Second, at baseline, the prothrombin time, aPPT, and fibrinogen levels were not routinely measured before cardiac catheterization, except in patients with decompensated heart failure. Third, the factors affecting heparin resistance, mainly antithrombin, and activation of the intrinsic coagulation pathway were not investigated in patients who were administered a100 IU/kg UFH loading dose, but whose target ACT level could not be achieved and required additional UFH loading doses of 20-50 IU//kg.

Conclusion

In conclusion, this study revealed that an initial dose of 100 IU/kg of UFH produced the target ACT value in 64.4% of the patients, and 32.4% required additional loading doses of UFH in the range of 20-50 IU/kg. In patients who received a 100 IU/kg UFH loading dose and whose ACT is < 200 sec, the additional UFH loading dose should be individualized according to the measured ACT value. Hence, we believe that multicenter prospective randomized controlled trials are needed to investigate the clinical efficacy and safety of the ACT measurement measured in patients with CHD.

Conflicts of interest:

The authors declare no potential conflict of interest.

Financial disclosure

The authors received no financial support for the research.

Author contributions

Both authors contributed equally to the conceptual, design, data collection, statistical analysis, manuscript writing, editing, revision and final approval processes of the manuscript.

References

1.Kim GG, El Rouby S, Thompson J, Gupta A, Williams J, Jobes DR. Monitoring unfractionated heparin in pediatric patients with congenital heart disease having cardiac catheterization or cardiac surgery. J Thromb Thrombolysis 2010; 29:429-436

2.Grady RM, Eisenberg PR, Bridges ND. Rational approach to use of heparin during cardiac catheterization in children. J Am Coll Cardiol1995; 25:725-729

3.Gottlieb EA, Andropoulos DB. Current and future trends in coagulation management for congenital heart surgery. J Thorac Cardiovasc Surg 2017; 153:1511-1515

4.Muster I, Haas T, Quandt D, Kretschmar O, Knirsch W. Factors influencing ACT after intravenous bolus administration of 100 IU/kg of unfractionated heparin during cardiac catheterization in children. Clin Appl Thromb Hemost 2017; 23:740-747

5.Saxena A, Gupta R, Kumar RK, Kothari SS, Wasir HS. Predictors of arterial thrombosis after diagnostic cardiac catheterization in infants and children randomized to two heparin dosages. Cathet Cardiovasc Diagn1997; 4:400□403

6.Bulbul ZR, Galal MO, Mahmoud E, Narden B, Solymar L, Chaudhary MA, et al. Arterial complications following cardiac catheterization in children less than 10 kg. Asian Cardiovasc Thorac Ann 2002; 10:129□132

7.Bansal N, Misra A, Forbes TJ, Kobayashi D. Femoral artery thrombosis after pediatric cardiac catheterization. Pediatr Cardiol 2021; 42:753□761

8.Hanslik A, Kitzmüller E, Thom K, Haumar M, Mlekusch W, Salzer-Muhar U, et al. Incidence of thrombotic and bleeding complications during cardiac catheterization in children: comparison of high-dose vs. low-dose heparin protocols. J Thromb Haemost 2011; 9:2353-2360

9.Chen D, Långström S, Petäjä J, Heikinheimo M, Pihkala J. Thrombin formation and effect of unfractionated heparin during pediatric cardiac catheterization. Catheter Cardiovasc Interv 2013; 81:1174-1179

10.Glatz AC, Shah SS, McCarthy AL, Geisser D, Daniels K, Xie D, et al. Prevalence of and risk factors for acute occlusive arterial injury following pediatric cardiac catheterization: a large single□center cohort study. Catheter Cardiovasc Interv 2013; 82:454□462

11.Alexander J, Yohannan T, Abutineh I, Agrawal V, Lloyd H, Zukrakowski D, et al. Ultrasound□guided femoral arterial access in pediatric cardiac catheterizations: A prospective evaluation of the prevalence, risk factors, and mechanism for acute loss of arterial pulse. Catheter Cardiovasc Interv 2016; 88:1098□1107

12.Herbert CE, Leshko J, Morelli D, Amankwah E, Hanson J, Stapleton GE. Use of Near-Infrared Spectroscopy to Monitor Lower Extremity Perfusion in Pediatric Patients Undergoing Cardiac Catheterization. Pediatr Cardiol 2019; 40:1523-1529

13.Backes CH, Cheatham SL, Deyo GM, Leopold S, Ball MK, Smith CV, et al. Percutaneous patent ductus arteriosus (PDA) closure in very preterm infants: Feasibility and complications. J Am Heart Assoc 2016; 5: e002923

14.Brotschi B, Hug MI, Kretschmar O, Rizzi M, Albisetti M. Incidence and predictors of cardiac catheterisation□related arterial thrombosis in children. Heart 2015; 101:948□953

15.Hanslik A, Kitzmüller E, Tran US, Thom K, Karapetian H, Prutsch N, et al. Monitoring unfractionated heparin in children: a parallel-cohort randomized controlled trial comparing 2 dose protocols. Blood 2015; 126:2091-2097

16.Gokdemir M, Cindik N. Risk factors and frequency of acute and permanent femoral arterial occlusion in neonates with CHD who undergo ultrasound-guided femoral arterial access. Cardiol Young 2022:1-7. doi:10.1017/S1047951122002608

17.Gokdemir M, Cindik N. Frequency and Predictors of Acute and Persistent Femoral Artery Occlusion in Infants with Congenital Heart Disease: A Study Using Ultrasonography for Arterial Access and the Diagnosis of Arterial Occlusion. Pediatr Cardiol 2023;44:1191-1200

18.Hanslik A, Kitzmüller E, Tran US, Thom K, Karapetian H, Prutsch N, et al. Anti-activated factor II assay for monitoring unfractionated heparin in children: results of the HEARTCAT study. J Thromb Haemost 2017; 15:38-46

19.Crameri O, Brotschi B, Achini F, Rizzi M, Albisetti M. Treatment of catheter-related arterial thrombosis in children: A 15-year single-center experience. J Pediatr 2021; 239:182-186