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Original study

Exploring predictors of activated clotting time after unfractionated heparin administration in elective interventional neuroradiology

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Abstract

Background: **Thromboembolic complications are the most frequent risk in endovascular treatment of intracranial pathology. To prevent this, unfractionated heparin (UFH) is used. The effect of heparin is difficult to predict. Therefore, bedside monitoring is necessary by measuring activated clotting time (ACT).**
Objectives: **The aim of this study is to explore which factors are contributing to the variability in ACT values and to assess if a more individualized approach is potentially beneficial.**
Design: **A retrospective, single-center study at Ghent University Hospital.**
Methods: **All patients who underwent an elective interventional neuroradiologic procedure with the administration of heparin between January 2018 and December 2023 were enrolled. A baseline measurement of ACT was done before heparin administration. A second measurement was taken five minutes after administration. A retrospective analysis was conducted to identify potential predictors of ACT levels and their association with heparin dosing.**
Results: **285 patients (193 males, age 55 ± 12 years) were included. Patients with higher weight ($p < 0.001$), higher body mass index (BMI) ($p < 0.001$) and patients already taking acetylsalicylic acid ($p < 0.001$) and thienopyridines ($p < 0.001$) received higher doses of heparin. In univariate analysis gender, height, weight, BMI, use of acetylsalicylic acid or thienopyridines, creatinine, AST, aPTT, baseline ACT and heparin dose (p: <0.001, 0.004, <0.001, 0.004, <0.001, <0.001, 0.019, 0.038, 0.003, <0.001, <0.001 resp.) were associated with ACT values. In multivariate analysis baseline ACT, heparin dose, weight and use of thienopyridine (p: <0.001, <0.001, <0.001, <0.001 resp.) were retained as significant independent predictors.**
Conclusion: **Significant interindividual variability exists in ACT response after a loading dose of heparin. A more accurate estimation of the appropriate dose may be possible by considering other influencing factors, such as weight, baseline ACT and preoperative use of antiplatelet therapy. Nevertheless, some level of unpredictability is likely to persist.**

Key words: **Heparin, Activated Clotting Time, Interventional radiology, Intracranial Aneurysms, Intracranial Arteriovenous Malformations.**

Introduction

The most frequent risk in endovascular treatment of intracranial aneurysms or vascular malformations are thromboembolic and hemorrhagic complications. In coiling procedures, the overall risk of complications ranges from 1.3% to 9.2%, with 80% of these complications being thrombotic and 7.5% being hemorrhagic[1]. In contrast, the endovascular treatment of arteriovenous malformations (AVM) is most frequently complicated by bleeding (4-

The study has been conducted in the University Hospital of Ghent and was approved by its ethics committee (Corneel Heymanslaan 10, 9000 Ghent, Belgium, Chairperson: Prof. Dr. R. Peleman), reference number ONZ-2024-0329. Approval was obtained on 28st of August 2024. Data was used from the 1st of January 2018 until the 31st of December 2023.

15%)[2], while thrombotic events occur in 3% of cases[3]. The balance between thrombotic and hemorrhagic risks is a critical consideration in interventional neuroradiology. Perioperative rupture and bleeding occur less frequently but are associated with higher morbidity and mortality[1,4]. Interventional radiology relies on unfractionated heparin (UFH) as a key anticoagulant to minimize thromboembolic risks during procedures. Its rapid onset of action, short half-life and the availability of a reversal agent (protamine sulfate) make it an attractive choice in this setting.

UFH is a heterogeneous mixture of glycosaminoglycans. It binds to antithrombin and catalyzes the inactivation of thrombin and other clotting factors[5,6]. UFH has a complex working mechanism and has rather unpredictable pharmacokinetic and pharmacodynamic properties[6]. Therefore, a major limitation of UFH is the considerable interpatient variability in response to a standard dose. The response to UFH is influenced by multiple factors, including patient characteristics, baseline coagulation status, plasma protein levels and antithrombin III activity. Matsushita et al.[7] identified age over 80 years and New York Heart Association (NYHA) class IV as factors associated with reduced heparin sensitivity, whereas thrombocytopenia was associated with increased heparin sensitivity in multivariate analysis.

In addition to patient-related factors, differences in the biochemical composition of UFH itself may also affect its anticoagulant effect. Heparin from different sources, including distinct manufacturers or batches, may result in inconsistent anticoagulant responses. This can further complicate the predictability of ACT following standard dosing[8,9].

Therapeutic anticoagulation with UFH requires close monitoring to ensure adequate anticoagulation while minimizing the risk of bleeding. The most commonly used methods are measuring the activated partial thromboplastin time (aPTT) or antifactor Xa testing, both requiring laboratory processing. Antifactor Xa is less affected by preanalytic or biological variables[10]. During interventional procedures, real-time monitoring is essential to enable rapid adjustments. In this setting, ACT is preferred and commonly used as a point-of-care (POC) test, as it is immediately bedside available, making it more suitable for dynamic anticoagulation management.

ACT is a relatively simple whole-blood test that measures the time required for the formation of a measurable fibrin clot after mixing fresh blood with a contact activator, which initiates the coagulation pathway. The type of activator (e.g. kaolin, celite) depends on which device and cartridge is used[5]. However, ACT is influenced by factors such as hemodilution, hematocrit, platelet count, coagulation disorders and several medications, which may impact its accuracy. Despite these limitations, it remains the preferred monitoring tool in the interventional setting[5,11].

Despite its broad clinical use in several therapeutic interventions, there is a wide variety of heparin dose protocols for non-cardiac interventional procedures[8]. The optimal dosing strategy for UFH remains uncertain in interventional neuroradiologic procedures and target levels of ACT vary across institutions and procedures.

This study aims to explore factors associated with ACT variability following UFH administration in elective interventional neuroradiology procedures. By identifying key predictors, we seek to contribute to a more personalized approach to anticoagulation management in this setting.

Methods

Study Design

This study is a retrospective, single-center analysis of patients who underwent elective interventional neuroradiologic procedures with the administration of heparin. This study included patients treated between January 2018 and December 2023, a period that began following the implementation of the i-STAT device at the end of 2017. The aim was to assess the correlation between explanatory parameters and heparin dosing, as well as to identify predictors of activated clotting time (ACT) levels. This study was approved by the Ethics Committee of Ghent University Hospital on 28st of August 2024, reference number: ONZ-2024-0329.

Patient Selection

Inclusion criteria for this study consisted of adult patients (> 18 years) undergoing elective interventional neuroradiologic procedures in which heparin was administered. Patients were excluded if they underwent emergent procedures, were already receiving heparin before the procedure, or had known bleeding disorders. Patients receiving multiple interventions during the inclusion period were only included once.

Data Collection

Clinical and laboratory data were obtained from medical records, including laboratory values, patient height and weight, gender and coagulation medication history. We classified the anticoagulants into three categories: acetylsalicylic acid (ASA), thienopyridines (clopidogrel and ticlopidine) and anticoagulants (low molecular weight heparin [LMWH], direct oral anticoagulants [DOACs] and vitamin K antagonists). The treating interventional radiologist was responsible for determining the heparin dose and coordinating preoperative preparation with ASA and thienopyridines, starting with clopidogrel and transitioning to ticlopidine when necessary. ACT was assessed using the i-STAT kaolin-based assay at two specific time points: the baseline measurement before heparin administration and a second measurement taken five minutes after heparin administration.

Statistical Analysis

All statistical analyses were conducted using SPSS software. Correlation analysis was performed to examine relationships between explanatory parameters and heparin dosing. Binary parameters were analyzed using the paired Student's t-test, while continuous variables were assessed through univariate linear regression. To address non-normally distributed variables, we employed a natural logarithmic transformation when appropriate. If the natural logarithm exhibited a normal distribution, the transformed data were used for statistical analyses. Predictors of ACT levels were evaluated using both univariate and multivariate linear regression with forward inclusion. A significance level of $p < 0.05$ was considered statistically significant for all analyses.

Results

Patient Enrollment and Baseline Characteristics

A total of 617 procedures were assessed for eligibility, with 590 conducted in adults being evaluated. After exclusion (urgent/multiple procedures, no/continuous heparin administration, coagulation disorder or missing data), 285 patients were included in the univariate analysis, and 259 in the multivariate analysis (Figure 1). Baseline characteristics for the entire study cohort are detailed in Table I, with data presented both for the overall group and separately for subgroups defined by heparin dosage. An analysis of the relationship between these baseline characteristics and the administered heparin dosage was performed. The analysis revealed that interventional radiologists tended to request higher heparin bolus doses in patients with higher weight ($p < 0.001$) and body mass index (BMI) ($p < 0.001$). Additionally, patients taking acetylsalicylic acid ($p < 0.001$) and thienopyridines ($p < 0.001$) were also administered higher heparin doses.

Univariate Analysis of Predictors of ACT Values

The mean ACT (s) after heparin administration was 183 s, with a standard deviation of 26.8 s, while 56% of the patients achieved an ACT of 180 s or more. Univariate analysis (Table II) revealed significant associations between ACT values and patient characteristics such as gender ($p < 0.001$), height (cm) ($p = 0.004$), weight (kg)

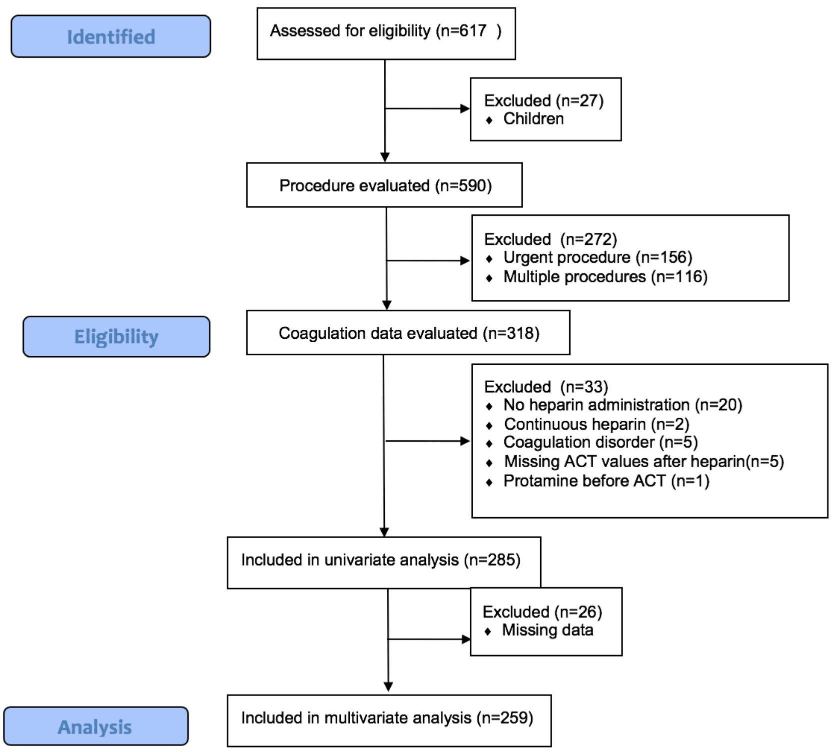

Fig. 1 — CONSORT Flow Diagram.

Table I. — Baseline characteristics.

			Heparin (IU) >3001 (177)	Heparin (IU) 3001-4001 (35)	Heparin (IU) >4001 (73)	
	N	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	P-value **
Age (yr)	285	55 (12)	54 (13)	59 (12)	54 (10)	0.416
Height (cm)	284	168 (8)	167 (8)	168 (11)	170 (8)	0.51
Weight (kg)	285	73.1 (15.5)	70.7 (13.8)	73.1 (17.9)	79.0 (16.7)	<0.001
BMI	284	25.8 (4.6)	25.2 (4.2)	25.5 (4.8)	27.4 (5.2)	<0.001
Hemoglobin (mg/dL)	285	13.8 (1.4)	13.7 (1.4)	13.7 (1.3)	14.0 (1.26)	0.07
INR	274	0.96 (0.09)	0.97 (0.09)	0.97 (0.1)	0.96 (0.07)	0.395
aPTT (s)	261	33 (4.3)	32.8 (4.6)	34.1 (5)	32.8 (3.2)	0.904
Platelets ($10^3/\mu L$)	282	255 (68)	254 (69)	259 (77)	257 (62)	0.78
Baseline ACT (s)	283	125 (13)	124 (14)	127 (11)	127 (11)	0.088
eGFR (mL/min/1.73 m²)	285	83.6 (18.7)	82.8 (20.7)	82.2 (16)	86.1 (14.5)	0.274
Heparin (IU)	285	3619 (884)	2980 (134)	3957 (142)	5007 (132)	/
		Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	P-value
ALT * (U/L)	285	18 (12-26)	18 (13-27)	17 (12-23)	16 (11-23)	0.868
AST * (U/L)	284	19 (16-24)	20 (16-24)	19 (16-29)	18 (16-23)	0.67
Creatinine * (mg/dL)	285	0.79 (0.7-0.92)	0.8 (0.71-0.95)	0.76 (0.69-0.87)	0.8 (0.71-0.88)	0.69
		N (%)	N (%)	N (%)	N (%)	
Gender	285	92 (67.7)	118 (66.7)	24 (68.6)	51 (69.9)	0.723
		193 (32.3)	59 (33.3)	11 (31.4)	22 (30.1)	
ASA	285	99 (34.7)	76 (42.9)	9 (25.7)	14 (19.2)	<0.001
		186 (65.3)	101 (57.1)	26 (74.3)	59 (80.8)	
Thienopyridines	285	171 (60)	125 (70.6)	16 (45.7)	30 (41.1)	<0.001
		114 (40)	52 (29.4)	19 (54.3)	43 (58.9)	
Anticoagulants	285	272 (95.4)	169 (95.5)	33 (94.3)	70 (95.9)	0.987
		13 (4.6)	8 (4.5)	2 (5.7)	3 (4.1)	

* Natural logarithm was used.
** For statistical analysis no grouping was used.
IU (International Unit), SD (Standard Deviation), BMI (Body Mass Index), INR (International Normalized Ratio), aPTT (activated Partial Thromboplastin Time), ACT (Activated Clotting Time), eGFR (estimated Glomerular Filtration Rate), IQR (Interquartile Range), ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase), ASA (Acetylsalicylic Acid).

($p < 0.001$) and body mass index (BMI) ($p = 0.004$). Additionally, laboratory values, including creatinine (mg/dL) ($p = 0.019$) and AST (U/L) ($p = 0.038$), were significant predictors of ACT values. Medication use, such as acetylsalicylic acid ($p < 0.001$) and thienopyridines ($p < 0.001$), as well as pre-existing coagulation status, indicated by aPTT (s) ($p = 0.003$) and baseline ACT value (s) ($p < 0.001$), were also significantly linked to ACT values. As expected, heparin dose (IU) ($p < 0.001$) also demonstrated a strong association..

Multivariate Analysis of Predictors of ACT Values

To determine the independent predictive value of these factors, multivariate linear regression analysis was performed (Table III). The final model, adjusted for potential confounders, demonstrated that baseline ACT value (s) ($p < 0.001$) and heparin dose (IU) ($p < 0.001$) were significant predictors of ACT values. Additionally, patient weight (kg) ($p < 0.001$) and thienopyridine use ($p < 0.001$) were also identified as significant independent predictors of ACT values. The model explained 43.4% of the variance in ACT values (Adjusted R-squared = 0.434, $p < 0.001$).

To visually assess the model's predictive accuracy, a scatter plot comparing predicted ACT values with actual ACT values was generated (Figure 2). This plot demonstrates a moderate degree of correlation between predicted and actual values, with a tendency for the model to underestimate ACT values at higher ranges.

Table II. — Univariate analysis.

		95,0% Confidence Interval for B		
	Mean diff	Lower Bound	Upper Bound	P-value
Female gender	14.96	8.49	21.43	<0.001
ASA use	14.26	7.9	20.63	<0.001
Thienopyridines use	16.03	9.91	22.14	<0.001
Anticoagulants use	2.84	-12.18	17.85	0.71
		95,0% Confidence Interval for B		
	Beta	Lower Bound	Upper Bound	P-value
Age (yr)	0.085	-0.166	0.366	0.507
Height (cm)	-0.527	-0.888	-0.167	0.004
Weight (kg)	-0.382	-0.58	-0.184	<0.001
BMI	-1.004	-1.677	-0.331	0.004
Hemoglobin (mg/dL)	-0.587	-2.844	1.671	0.61
INR	-23.68	-59.83	12.47	0.198
aPTT (s)	1.161	0.4	1.922	0.003
Platelets (10^3/µL)	-0.14	-0.06	0.032	0.543
Baseline ACT (s)	0.874	0.654	1.093	<0.001
eGFR (mL/min/1.73 m²)	0.02	-0.147	0.188	0.811
Heparin (IU)	0.013	0.01	0.016	<0.001
ALT * (U/L)	-0.617	-6.107	4.873	0.825
AST * (U/L)	8.608	0.499	16.716	0.038
Creatinine * (mg/dL)	-13.244	-24.263	-2.225	0.019

* natural logarithm was used.
ASA (Acetylsalicylic Acid), BMI (Body Mass Index), INR (International Normalized Ratio), aPTT (activated Partial Thromboplastin Time), ACT (Activated Clotting Time), eGFR (estimated Glomerular Filtration Rate), IU (International Unit), ALT (Alanine Aminotransferase), AST (Aspartate Aminotransferase).

Discussion

This study identified several factors that appear to influence the dosing and effect of UFH in elective interventional neuroradiology. No standardized protocol existed for heparin dosing based on weight. However, patients with higher body weight and body mass index (BMI) were administered larger bolus doses of UFH ($p<0.001$). There was no significant correlation between baseline ACT value and given bolus dose of heparin ($p = 0.088$).

Heparin boluses were administered in this study at the interventional radiologist's discretion, aiming for a target ACT of 180 s or higher, which was reached in 56% of the patients. In other studies, considerable variability was observed in heparin dosing strategies as well as in target ACT levels. The World Federation of Interventional and Therapeutic Neuroradiology (WFITN) recommends a 5000 IU bolus, then 1000 IU/h continuously, with target ACT at about 200 s[12]. Varma et al.[13] wants to achieve two or three times baseline ACT after intravenous heparin loading dose of 70 IU.kg-1. Bracard et al.[4] reports monocenter studies using boluses ranging from 3000-5000 IU followed by continuous infusion to maintain ACT levels between 200 to 300 s. Jang et al.[14] have a target ACT level of 250 s.

Interestingly, patients who were on preoperative acetylsalicylic acid or thienopyridines also tended to receive higher initial bolus doses of heparin. The underlying rationale for this observation is not clear. One possible explanation could be that clinicians administer higher heparin doses in these patients to counteract any perceived risk of procedural thromboembolic events. As the endovascular treatment of unruptured aneurysms involving stents or coiling has been associated with a higher incidence of thrombotic complications, these patients typically receive preoperative oral antiplatelet therapy[1,15]. However, upon inquiry with the interventional radiologists, it appeared that this practice was not intentional.

In the univariate analysis, several variables were significantly associated with post-heparin ACT values, including heparin dose, gender, height, weight, BMI, preoperative use of acetylsalicylic acid or thienopyridines, aPTT, baseline ACT, AST and creatinine. However, when controlling for

Table III. — Multivariate analysis.

Model	Unstandardized Coefficients	95,0% Confidence Interval for B		P-value
	B	Lower Bound	Upper Bound	
Intercept	71.849	43.61	100.271	<0.001
Baseline ACT (s)	0.811	0.613	1.008	<0.001
Heparin (IU)	0.013	0.009	0.016	<0.001
Weigth (kg)	-0.54	-0.711	-0.368	<0.001
Thienopyrdines use	9.617	-3.314	24.915	<0.001
	Adjusted R square	F		
Model	0.434	50.553		<0.001
ACT (Activated Clotting Time), IU (International Unit).				

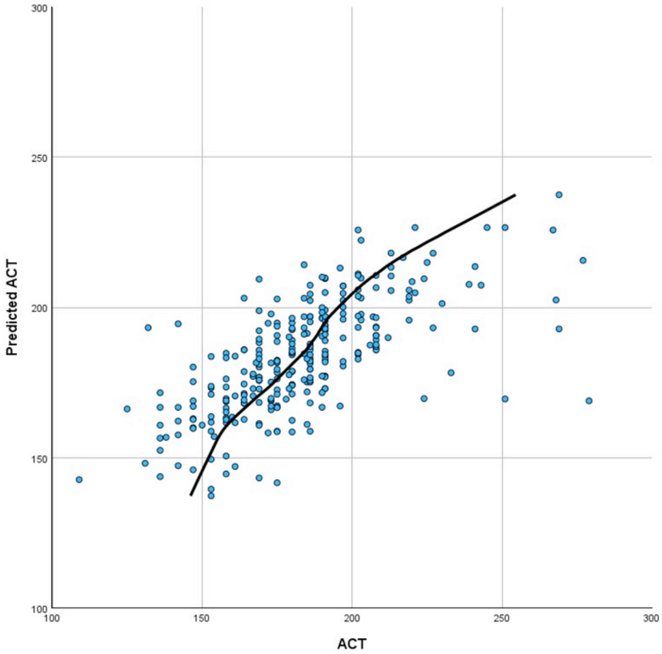

Fig. 2 — Plot of estimated versus actual ACT values.

confounders in the multivariate analysis, only baseline ACT, weight and preoperative intake of thienopyridines remained significant predictors. These findings suggest that, while multiple factors may initially appear to influence ACT, the effect of some may be explained by underlying correlations. These observations partially align with the findings of Oshita et al.[16], who reported correlations between gender, estimated glomerular filtration rate (eGFR) and hematocrit and the ACT response after heparin administration.

In our study, age did not have a significant impact on ACT values, in contrast to previous studies where elderly had an increased heparin resistance[7]. This discrepancy may be explained by the relatively small number of younger and older patients in our cohort, possibly masking a true effect of age on ACT values.

The use of other anticoagulant medications preoperatively did not show a statistically significant effect on post-heparin ACT values. However, it is important to note that, according to current practice, anticoagulant medications were stopped preoperatively in these cases. This subgroup included only 13 patients, which limits the statistical power to detect a meaningful association. Therefore, conclusions regarding the impact of these agents should be interpreted with caution.

Overall, the model has a moderate degree of correlation as it explained 43.4% of the variance in ACT values, with an underestimation of higher ACT values (Adjusted R-squared = 0.434). This observation highlights the challenges in predicting the effect of a certain dose of UFH because of a non-linear dose-response curve and even differences between several brands and batches of the same brand[9]. Furthermore, there is a big interindividual variability in heparin response. Veerhoek et al.[11] identified a different response on a fixed dose of heparin in patients who underwent vascular surgery. The group with reduced sensitivity had higher pre-operative levels of platelet factor 4 and lower antithrombin III levels. Oshita et al.[16] identified that a body weight based dose is more reliable than a fixed dose, but other factors had a significant influence as mentioned before. Only 50% of the patients had an immediate adequate ACT level after the first weight-based dose of heparin. Bedside ACT measurement is already a measure to compensate for the unpredictability of UFH. A model incorporating various influencing factors may contribute to a more accurate estimation of post-heparin ACT values, however it will never allow for precise prediction. Despite the unpredictability of the effect of heparin, both under- and overdosing should be avoided to prevent associated complications.

To address this challenge, we derived a predictive formula for heparin bolus dosing aiming to individualize therapy and optimize anticoagulation:

ACT (s) (post heparin) = 71.849 + baseline ACT (s) x 0.811 + Heparin (IU) x 0.013 -Weight (kg) x 0.54 + Thienopyridines (0=no intake) x 9.617

Heparin (IU) = (Target ACT – 71.849 - baseline ACT x 0.811 + weight x 0.54 -Thienopyridines x 9.617) / 0.013

In the following example, we target an ACT of 180 in a patient weighing 70 kg with a baseline ACT of 120 who is not taking thienopyridines:

Heparin (IU) = (180 – 71.849 - baseline ACT x 0.811 + weight x 0.54 -Thienopyridines x 9.617) / 0.013

Heparin (IU) = (108.151 – 120 x 0.811 + 70 x 0.54 – 0 x 9.617) / 0.013 => 3740.85U

This formula is only applicable for the calculation of the initial heparin bolus dose in neurointerventional procedures employing the i-STAT device with a kaolin cartridge. It should be considered that approximately 50% of patients are likely to achieve an ACT below and 50% above the target value.

Until today, there is no consensus on the optimal ACT value across different medical disciplines. Establishing and comparing target ACT values is further complicated by the substantial variability among different ACT measurement devices. Dirkmann et al.[17] compared two different devices (i-STAT and Hemochron) and demonstrated inconsistencies not only between the two systems, but also between two separate Hemochron devices. This brings the suitability of ACT as the preferred method for intraoperative coagulation monitoring into question. At higher heparin dosages in cardiac surgery, ACT proves to be more reliable than aPTT, which quickly reaches its measurement limit. Kubalek et al.[18] investigated if aPTT was more reliable after lower doses of heparin. Following a heparin bolus of 2,500–7,500 IU, a usable result was obtained in only 33% of cases. Thus, even at lower doses, ACT is clearly the preferred method.

This study has several limitations. As described above, results cannot be extrapolated to other monitoring devices or cartridges as different systems give different results. Further investigation is warranted to establish a dosing formula incorporating most important influencing factors, followed by prospective validation to assess if this approach leads to a more rapid achievement of adequate ACT levels. Moreover, future research should also investigate the evolution of ACT values over time, the need for additional heparin doses and how to estimate the additional doses. This study did not examine all possible factors that may influence ACT levels after heparin, for example antithrombin III, which could have made the model more precise, but are not typically available in this clinical setting. Furthermore, some factors, such as renal function, showed little variation within the study population, thereby limiting their potential to demonstrate a significant influence. The study did not differentiate between factors potentially affecting intrinsic heparin sensitivity and those influencing the ACT measurement independently.

Conclusion

Without a consensus on target ACT values in interventional neuroradiology, achieving optimal anticoagulation is challenging, also due to interindividual variability in heparin response. While baseline ACT, weight, and thienopyridine use are significant predictors, unpredictability remains, highlighting the need for individualized monitoring and management. Future research should focus on refining dosing strategies, establishing evidence-based ACT targets and identifying additional influencing factors to improve patient outcomes.

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