

Effect of New Heparin Potency on Activated Clotting Time during Pediatric Cardiac Surgery: A Retrospective Chart Review

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Abstract: In 2009, the U.S Food and Drug Administration (FDA) announced a two-phase change in unfractionated heparin to reduce contamination and create a new potency reference. The FDA announced the change would bring about a 10% decrease in potency from the old heparin (OH) to new heparin (NH). The purpose of this article is to compare heparin in pediatric patients undergoing cardiac surgery before and after the FDA changes. After Institutional Review Board approval, a retrospective chart review was conducted with pediatric patients ($n = 266$) undergoing cardiac surgery. All patients received a heparin loading dose of 400 IU/kg and data collected included patient demographics, baseline activated clotting time (ACT), ACT after initial heparin dose, and heparin dose–response. These data were then further broken down into age blocks consisting of neonates (<1 month), 1–12 months, 1–5 years old, and older than 5 years old. In

17.3% of cases in the NH group, the ACT after the initial heparin dose did not reach the critical value of 400 seconds necessary for initiation of cardiopulmonary bypass (CPB). This is significantly higher than the 8.9% of cases in the OH group ($p < .05$). There was an overall trend among age groups that the NH was less potent than OH. However, only the 1–5 years of age group showed significance at $p < .05$. Given the median ACTs 591 seconds for OH and 484 seconds for NH, the calculated percentage difference was 18.1%. The results from this retrospective pediatric chart review indicate that the change in heparin potency greatly deviates from the 10% change reported by the FDA. In conclusion, NH has a trend of lower potency and frequent monitoring is necessary to maintain a safe level of anticoagulation during CPB. **Keywords:** unfractionated heparin, activated clotting time, pediatric, cardiopulmonary bypass. *JECT.* 2014;46:224–228

Unfractionated heparin (UFH) is routinely used for anticoagulation during cardiopulmonary bypass (CPB). On October 1, 2009, the U.S. Food and Drug Administration (FDA) announced there would be a change in UFH in response to the 2007–2008 deaths related to contaminated heparin. According to the U.S. Pharmacopeia, there was a two-phase change to UFH. Phase 1 developed new quality tests to identify oversulfated chondroitin sulfate in the heparin. The second phase addressed a new potency assay and potency reference standard that would be more universally accepted as defined by the World Health Organization (1–4). The FDA reported “. . .it is essential that health care professionals be aware

of the potential difference in potency between the old and new vials of heparin when administering the drug,” because the new UFH has a 10% decrease in potency (3). This decrease in heparin potency was suggested to have minimal to no effect, unless administered through an intravenous bolus or when immediate anticoagulation is needed, both of which pertain to operating room procedures (1–5).

Requirements for additional heparin to achieve an activated clotting time (ACT) greater than 400 seconds to initiate CPB as well as having lower ACT values during CPB have been a topic of discussion among perfusionists. Anderson et al. looked at the change in UFH potency in the adult population and found that to achieve adequate anticoagulation with the new heparin (NH), a total increase of 12.1% in dose based on weight was required. Additionally, this study found that the post-NH loading dose ACTs had a 9.3% decrease when compared with old heparin (OH) ACTs (4). Inadequate anticoagulation resulting from the decrease in UFH potency can lead to ineffective

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thrombin inhibition in the pediatric population, thus resulting in coagulation activation and hemostatic abnormalities. As a result of the immature coagulation system of pediatric patients, this population is then more susceptible to administration and exposure to homologous blood products attributable to postoperative bleeding complications (6–8).

The goals of the present study were to investigate whether the reduction in UFH potency has reduced the level of anticoagulation in pediatric patients as measured by ACTs after initial heparin loading and evaluate the FDA-reported 10% potency difference between “new” and “old” heparin. The hypothesis of this study is that the change in heparin potency is significantly different than 10% as reported by the FDA.

MATERIALS AND METHODS

After receiving Institutional Review Board approval, a retrospective chart review was conducted of pediatric patients undergoing heart surgery at the Medical University of South Carolina (MUSC). Data were retrospectively collected from the charts of 266 patients: “new” unfractionated heparin ($n = 98$) and “old” unfractionated heparin ($n = 168$). The OH patients were from 2009 and NH from 2011. Each of the years was divided into 6-month blocks, January through June and July through December. The first 50 consecutive patients in each block were included in the OH and NH groups. There were no exclusions based on type of surgery. Patients were excluded from this study if pertinent data were missing from the chart. A total of 10 patients was excluded from this study. Further classification (Table 1) based on age was divided into neonate younger than 30 days old (class I), 1–12 months (class II), 1–5 years of age (class III), and older than 5 years of age (class IV).

The estimated heparin concentrations ([heparin]) and heparin dose–responses (HDR) were calculated with the following formulas:

$$\text{HDR} = \frac{\text{ACT initial-Baseline ACT}}{[\text{heparin}]}$$

$$[\text{heparin}] = \frac{\text{Initial heparin anesthesia loading dose}}{\text{patient blood volume}}$$

Initial heparin dose given to the pediatric patient before bypass was determined by patient weight as per MUSC protocol (400 IU/kg). Heparin was also added to the perfusion circuit before bypass initiation, and the amount added is determined by the amount of prime volume. Per MUSC protocol, 2000 IU of heparin is added to the prime volume whenever fresh-frozen plasma (FFP)

Table 1. Age classifications.

Age Classifications	Old Heparin (n = 168)	New Heparin (n = 98)
I (neonates)	30	18
II (infants)	79	35
III (1–5 years)	37	29
IV (>5 years)	22	16

is used. For all patients under 8 kg, FFP is incorporated into the prime. If the patient is above 8 kg, then the perfusionist adds enough heparin to the prime to achieve an estimated circulating level of 4 units heparin/mL of total blood volume. An ACT measurement greater than 400 seconds was necessary for initiation of CPB. All ACT measurements from 2009 and 2011 were performed using kaolin activation and all blood samples were analyzed by i-STAT Handheld (Abbott Point of Care Inc., Princeton, NJ). Additionally, the software for the ACT machines was the same for both years included in this retrospective study. Per MUSC protocol, ACT testing is done every 30 minutes to ensure that the patient is adequately heparinized. Additional heparin is dosed per the perfusionist’s own judgment.

All statistical analysis was performed using IBM SPSS Statistics software (Version 19.0; IBM Corporation, Armonk, NY). Statistical significance was assessed at the $\alpha = .05$ level. Collected data points were tested for normality and compared using descriptive statistics such as age classification, age, weight, and body surface area. Because most of the data was not normally distributed, nonparametric statistics were used as represented by median and interquartile range. Continuous data were tested using the Mann Whitney U test or χ^2 test of independence as appropriate.

To calculate percentage difference in the ACTs after initial heparin dose between OH and NH, the following formula was used:

$$\text{Calculated \% difference} = \frac{\text{OH ACT after initial heparin dose} - \text{NH ACT after initial heparin dose}}{\text{OH ACT after initial heparin dose}} \times 100$$

RESULTS

The patient demographics of this study are shown in Table 2. The age range of patients ranged from 0 to 19 years. The OH group contained 168 patients and NH group = 98 patients (Table 2). There were no statistically significant differences between demographic variables including: age classification, age, weight, and body surface area.

Each age group within OH and NH was compared for statistical significance in the baseline ACT and postheparin

Table 2. Patient demographics.

	Old Heparin (n = 168)	New Heparin (n = 98)	p Value
	Median (IQR)	Median (IQR)	
Age (years)			
I (neonates)	.02 (.02, .03)	.03 (.01, .08)	.29
II (infants)	.42 (.25, .58)	.42 (.33, .50)	.57
III (1–5 years)	3.00 (2.00, 4.25)	3.00 (1.67, 4.25)	.19
IV (>5 years)	10.00 (7.00, 13.25)	8.00 (6.00, 14.50)	.49
BSA (m ²)			
I (neonates)	.22 (.20, .23)	.21 (.20, .23)	.78
II (infants)	.32 (.27, .35)	.30 (.28, .34)	.31
III (1–5 years)	.58 (.48, .66)	.56 (.44, .63)	.12
IV (>5 years)	1.20 (.91, 1.60)	1.11 (.91, 1.79)	.87

IQR, interquartile range; BSA, body surface area.

Table 3. Heparin potency by groups.

	Baseline ACT Median (IQR)	Postheparin Loading Dose ACT, Median (IQR)	Percent Postheparin Loading Dose ACT <400 Seconds
Group I			
OH	137 (119, 160)*	682 (519, 848)*	2/30 (6.7%)
NH	158 (146, 178)	487 (431, 611)	1/18 (5.6%)
Group II			
OH	117 (98, 126)	577 (459, 746)*	11/79 (13.9%)
NH	114 (102, 133)	484 (415, 572)	6/35 (17.1%)
Group III			
OH	112 (103, 126)	543 (500, 662)*	2/37 (5.4%)
NH	120 (104, 134)	446 (398, 582)	9/29 (31.0%)
Group IV			
OH	117 (112, 126)	580 (487, 691)	0/22 (0%)
NH	118 (114, 128)	498 (454, 635)	1/16 (6.25%)

ACT, activated clotting time; IQR, interquartile range; OH, old heparin; NH, new heparin.

*P < 0.05.

loading dose ACT. The reported data are presented as median and interquartile range (25%, 75%). For baseline ACT, the only age group that was statistically different was group 1 (neonates <30 days). Postheparin loading dose

Table 4. Heparin dose–response and estimated heparin concentration.

	Old Heparin (n = 168)	New Heparin (n = 98)	p Value
	Median (IQR)	Median (IQR)	
HDR (sec/unit/mL)			
I (neonates)	120.70 (82.02, 152.64)	71.94 (60.97, 91.78)	.005
II (infants)	98.82 (70.45, 123.04)	74.46 (62.73, 94.45)	.007
III (1–5 years)	89.30 (79.20, 108.01)	67.80 (54.61, 90.23)	.002
IV (>5 years)	82.56 (67.94, 150.98)	64.31 (56.78, 90.29)	.101
Estimated heparin (IU/mL)			
I (neonates)	4.71 (4.70, 4.71)	4.71 (4.70, 4.74)	.733
II (infants)	4.71 (4.70, 4.74)	4.71 (4.70, 4.78)	.995
III (1–5 years)	5.00 (4.96, 5.00)	4.98 (4.71, 5.02)	.361
IV (>5 years)	5.66 (5.00, 6.15)	5.75 (5.12, 6.12)	.484

IQR, interquartile range; HDR, heparin dose–response.

Table 5. χ^2 test of independence between old and new heparin.

	ACT <400 seconds	ACT ≥400 seconds	Total
Old heparin	15	153	168
New heparin	17	81	98
Total	32	235	266

ACT, activated clotting time.

Table 6. Percent change in potency between old and new heparin.

	Baseline ACT, Median (IQR)	Postheparin Loading Dose ACT, Median (IQR)
Old heparin	117 (104, 131)	591 (494, 728)
New heparin	123 (110, 141)	484 (420, 593)
p value	.023	.0001

ACT, activated clotting time; IQR, interquartile range.

ACT between OH and NH was statistically different for group I (neonates <30 days), group II (1–12 months), and group III (1–5 years of age). The percent of patients that did not reach 400 seconds was significant in group III (1–5 years; $p < .01$; Table 3).

When comparing the HDR between OH and NH among age groups, there was a significant difference in groups I, II, and III. There was no statistical significance among any age groups or between OH and NH for the estimated heparin concentration (Table 4).

A χ^2 test of independence (Table 5) was used to analyze the amount of patients that did or did not reach the ACT requirement of 400 seconds to initiate bypass. In the OH group, a total of 15 patients (8.9%) did not reach the ACT requirement to initiate CPB. In the NH group, a total of 17 patients (17.3%) had an ACT less than 400 seconds after the initial anesthesia heparin dose. These data proved to be statistically significant ($p = .04$).

The median postheparin loading dose ACT for OH was 591 seconds versus 484 seconds for new heparin. This represents an 18% decrease in potency (Table 6). It is

important to note that the data did show a statistical difference between the overall old and new heparin groups for baseline ACT. The NH had a statistically higher baseline than OH; however, the 6-second difference is probably not clinically significant.

DISCUSSION

This investigation was modeled on the methods of data collection and statistical analysis used by Guzzetta et al. and Anderson et al. (1,4) The methodical difference between the Guzzetta et al. study and the current study is that Guzzetta et al. used 480 seconds as the ACT after the initial heparin cutoff for determining potency, and this current study used 400 seconds. The results achieved from both studies indicate that NH is not as potent as OH for all three age groups. Guzzetta et al. found a higher incidence of ACT <480 postheparin with NH for patients 1–12 months and >1 year of age. Our study showed similar results in patients >1 year of age. Importantly, both studies indicated that there was a greater incidence of ACTs not reaching bypass initiation requirement after the heparin loading dose when comparing OH and NH (1).

Anderson et al. conducted a similar retrospective study looking at ACTs and heparin dosing for NH but in the adult population. Although this study did find similar results in which NH is less potent than OH and a need for additional dosing is required to achieve adequate anticoagulation, one must consider the differences in adult and pediatric physiology (4). Therefore, parameters such as patient physiological maturity and weight-based dosing could contribute to different heparin responses. A study conducted by Honchel et al. in both monkeys and young pigs found that the mean ACTs for the NH were generally lower than the mean ACTs for the OH. Although animal responses cannot be an exact clinical comparison to humans, this study found the general trend that NH is less potent than OH when measured with anticoagulation test responses (6).

Pediatric heart surgery produces parameters that must be considered when looking at adequate anticoagulation and reaching target ACTs: CPB influences, pediatric physiology, and heparin weight-based dosing deduced from adult protocols. As a result of changes in blood viscosity, plasma clotting factor concentrations, platelet function, and hypothermic temperature on CPB, a falsely high ACT could be measured (1,6–11). Additionally, the developing immune system of neonates reacts with a variety of CPB contact activation factors such as factor XII, factor XI, prekallikrein, and high-molecular-weight kininogen, which can also lead to misinterpreting prolonged ACTs. Another factor to consider when

looking at the neonatal population is the recognition of congenital heart defects and the administration of prostaglandin E1, an inhibitor of platelet aggregation, may prolong the ACT (1,9). Overall, the influences of CPB and physiology can lead to a prolongation of ACT, which could result in error and risks of inadequate anticoagulation (1,6–9).

A major limitation in pediatric cardiac surgery is that many of the heparin protocols for pediatrics are deduced from weight-based adult dosing. Therefore, errors in anticoagulation may arise when dosing heparin for this specific pediatric patient population (6,7). Additionally, it has been suggested that commercial ACT machines cannot accurately measure the lower plasma concentrations of clotting factors in pediatric patients, especially neonates. For pediatric populations, monitoring heparin effect has proven to be difficult as a result of discrepancies in solely using ACT and not a defined heparin concentration (1,6–8,10,11). Various publications have suggested the use of alternative monitoring techniques that have more accurate anticoagulation measurement such as antifactor Xa assay or the Hepcon HMS instrument (Hepcon Hemostasis Management System Plus; Medtronic, Minneapolis, MN) (1,6). In a study done by Guzzetta et al. it was suggested that a “patient specific heparin concentration based protocol” should be used for patient younger than 6 months old rather than a traditional weight-based protocol to better protect against thrombin formation (as measured by F1.2 test) and preserving clotting factor VIII. The new protocol called for more heparin in the prime and additional boluses with the Hepcon HMS while on CPB. However, the mean heparin concentrations were higher from rewarming to end of bypass when compared with the weight-based protocol patients (6).

The use of the Hepcon HMS for pediatric cardiac surgery has also been controversial, although Guzzetta et al. found that the Hepcon HMS does show a strong correlation with laboratory-measured antifactor Xa plasma heparin concentrations, especially in patients younger than 6 months old. Guzzetta et al. even clarified the agreement of the Hepcon HMS and laboratory antifactor Xa levels by using a test of agreement and found that samples were more than 95% within the limits of agreement of within two standard deviations (8). However, there has been opposition for the support of using the Hepcon HMS. Gruenwald et al. found that the Hepcon HMS did not accurately correlate with antifactor Xa levels in patients younger than 1 year of age. This study clarified that there are some factors that may show differences in the Hepcon’s ability to correlate antifactor Xa including hemostatic system immaturity, level of hemodilution from the bypass circuit, and decreased levels of coagulation factors. The Hepcon HMS testing works by doing a protamine titration of thromboplastin, which most likely is

in lower concentration in pediatric populations. Therefore, Gruenwald et al. made its conclusions and opposed the idea of heparin concentration-based protocols for anticoagulation on bypass (11).

In conclusion, this study demonstrated that when comparing new and old heparin in the pediatric population, the NH produces a decreased level of anticoagulation as measured by the ACT. Additionally, the results of this study indicate a greater percentage difference in the potency of old and new heparin than the 10% decrease that the FDA reported. There is clinical significance to the potency change and if suboptimal anticoagulation occurs, the patient may be placed at a higher risk for adverse outcomes.

QUALITY CONTROL STUDY

The results of this present study led to a change in heparin loading dose protocol at the MUSC's Children's Hospital. Per surgeons' request, the heparin loading dose increased from 400 IU/kg to 500 IU/kg as a result of the decrease in potency. The increase in heparin loading dose was implemented to reduce coagulopathies related to inadequate heparinization for complex pediatric cases. This called for a subsequent retrospective chart review to compare the adequacy of new heparin's anticoagulation by analyzing the 400 IU/kg from 2011 versus 500 IU/kg dosing protocol from 2013. Data have yet to be analyzed for this study.

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