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Maintaining Adequate Anticoagulation on Extracorporeal Membrane Oxygenation Therapy: Hemochron Junior Low Range versus Hemochron 400

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Abstract: Extracorporeal membrane oxygenation (ECMO) therapy requires that patients be anticoagulated to prevent clotting and thrombotic complications. There are several bedside whole blood microcoagulation systems available to determine activated clotting time (ACT) levels. Many ECMO centers use Hemochron (International Technidyne, Edison, NJ) products to determine ACT levels. During the study period, we used the Hemochron 400 and then changed to the Hemochron Junior Low Range. There were two specific aims of this study. First, to determine if there was a difference in ACT levels measured by these two distinct Hemochron products both marketed for the use in ECMO therapy. Second, to determine if the differing ACT levels produced by these two devices affected clinical outcomes. We compared ACT levels between two devices on 70 paired blood specimens obtained from four neonatal ECMO patients receiving heparin. A retrospective review of 77 ECMO patients was performed to analyze frequency of circuit emergencies and length of ECMO circuit life while using the two products. In lower ACT ranges, the Hemochron Jr. LR consistently yielded higher ACT values than the Hemochron 400. In higher ACT ranges, the Hemochron Jr. LR consistently yielded lower ACT values than the Hemochron 400. Without calibration, after changing devices, this discrepancy led to shorter circuit life and more circuit clotting complications. After calibration and adjustment in target ACT values, there was a trend toward longer circuit life, and there were fewer clotting complications. There is a difference in the ACT values produced by Hemochron 400 and Hemochron Jr. LR. Failure to calibrate target ACT levels after changing machines may lead to shorter circuit life and more clotting complications. **Keywords:** hemochron, anticoagulation, ECMO, clotting. *JECT 2003;35:35–38*

Extracorporeal membrane oxygenation (ECMO) therapy requires that patients be anticoagulated to prevent clotting and thrombotic complications. A heparin infusion is titrated to achieve a predetermined target activated clotting time (ACT) level. Optimal target ACT ranges for neonates on ECMO have been reported between the ranges of 180–220 sec. There are several bedside whole blood microcoagulation systems available to determine ACT levels. A whole blood microcoagulation system is designed to be at the point of care to measure rapidly and accurately the effective amount of anticoagulation a patient is receiving. Many ECMO centers use Hemochron (International Technidyne, Edison, NJ) products to determine ACT levels. Because of the discontinuation of the Hemochron 400 product line, our institution changed to the Hemochron Jr. LR in 1999. Our perception of an increase in circuit complications when using the Hemochron Junior LR led us to investigate the true incidence of these complications and the accuracy of the device.

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METHODS AND MATERIALS

Hemochron Junior Calibration

We compared ACT levels between two devices on 70 blood specimens obtained from 4 neonatal ECMO patients receiving heparin. The Hemochron 400 and Hemochron Jr. LR were the two bedside microcoagulation systems used for the comparison. Both machines were quality control tested using test material provided by the manufacturer to ensure accuracy. A qualified ECMO specialist familiar with both systems processed the tests. No patients

received aminocaproic acid or aprotinin. The values generated by the two different bedside microcoagulation devices were analyzed using linear regression modeling [StatView 5.0 software (SAS, Cary, NC)].

Clinical Outcomes

We retrospectively reviewed the medical records of 77 neonates at our institution between 1995 and 2001 that received ECMO therapy. Two different bedside whole blood microcoagulation systems were used. Between 1/95 and 5/99, the Hemochron 400 was used. We used the Hemochron Jr. LR from 6/99 until the end of the study period. ACT target parameters were typically 200–220 sec while using the Hemochron 400. We continued to use similar ACT target parameters for heparin infusion with the Hemochron Jr. LR. There was an observation that we were experiencing shorter circuit life and more clotting complications with the Hemochron Jr. LR. Therefore, after regression analysis of paired blood samples, we increased our ACT targets ranges to 220–240 sec. There were three separate groups during the study period. Group 1 ($n = 41$) was treated with the Hemochron 400 with ACT ranges from 200–220 sec. Group 2 ($n = 22$) was treated with the Hemochron Jr. LR with ACT ranges of 200–220 sec. Group 3 ($n = 13$) was treated with the Hemochron Jr. LR with ACT ranges of 220–240 sec.

ECMO circuits were changed electively at the discretion of the attending physician. This was typically done for: evidence of consumptive coagulopathy, appearance of multiple clots in the circuit, or increasing circuit pressure secondary to clots in the circuit. A circuit emergency was defined as an immediate need to replace the ECMO circuit secondary to significant clots within the circuit or blood loss attributable to circuit malfunction.

We collected pretreatment and ECMO characteristics, anticoagulation data, bleeding and clotting complications. Analysis of variance (ANOVA) was used to analyze continuous variables and chi-square was used to compare categorical variables among the groups. Results are expressed as mean values with standard deviation for continuous variables.

RESULTS

Hemochron Jr. Calibration

Paired determinations were performed on clinical blood samples with a range of ACT values from 160–300 sec. Heparin infusion doses were titrated to achieve ACT values within target range. In the typical target ACT ranges for neonatal ECMO between 180 and 220 seconds, the Hemochron Jr. LR yielded a value of 15–32 sec higher than that produced by the Hemochron 400. In higher ranges of ACT measurements, the Hemochron Jr. LR yielded values lower than that produced by the Hemochron 400. The ACT values generated by the Hemochron 400 and Hemochron Jr. LR (Table 1) were compared using linear regression. As expected, these measurements were highly correlated, but neither the slope nor the intercept was consistent with the null hypothesis that they were identical.

Clinical Outcomes

The clinical characteristics of the three groups were similar. There were no clinically significant differences in diagnosis, gestational age, or aminocaproic acid use (Table 2). There was no difference in the total number of hours on ECMO among the three groups. Of the patients who required more than one ECMO circuit, there was a shorter time in hours to the first circuit change in Group 2 (85.4 ± 46) compared to Group 1 (121 ± 34.8, $p = .035$). When we changed our target ACT parameters with the Hemochron Jr., there seemed to be a trend toward longer circuit life, Group 2 (85.4 ± 46) vs. Group 3 (99.0 ± 15.9, $p = .49$). The mean ACT values of the three groups, respectively, were (208.5 ± 12.7, 222.8 ± 27.9, and 232.7 ± 4.7). There were significantly more circuit clotting emergencies per patient in Group 2 (0.54 ± 0.86) vs. Group 1 (0.175 ± 0.55, $p = .0312$) and Group 3 (0.091 ± 0.31, $p = .049$). There was no difference in the rate of new central nervous system hemorrhages while on ECMO among the three groups (Table 3).

DISCUSSION

The goal of anticoagulation on ECMO is to avoid thrombosis in the ECMO circuit without increasing the risk of bleeding complications. The physiology of the coagulation system is altered while on ECMO. There is contact activation of factor XII and the intrinsic pathway either secondary to or independent of platelet adherence to the foreign surface of the circuit. There is also subsequent activation of the fibrinolytic system (1–5). The optimal ACT target may depend upon patient characteristics including gestational age, the presence of a central nervous

Table 1. Calibration Between Hemochron 400 and Hemochron Junior Low Range.

Hemochron 400 ACT (in sec) Used in Group 1	Hemochron Jr. LR ACT (in sec) Used in Groups 2 and 3	Difference
160	201	+41
180	212	+32
200	223	+23
220	235	+15
240	246	+6
260	257	−3
280	268	−12
300	279	−21

Hemochron Jr. LR value = 112 +0.558 (Hemochron 400 value).

Table 2. Demographic Data.

Variable	Group 1 Hemochron 400 ACT 200–220 (N = 41)	Group 2 Hemochron Jr. ACT 200–220 (N = 22)	Group 3 Hemochron Jr. ACT 220–240 (N = 13)	p-Value Group 1 vs. 2 1 vs. 3 2 vs. 3
Gestational age in weeks	38.8 (±1.9)	38.7 (±1.7)	37.2 (±3.2)	0.892 0.025* 0.051
Age in days when cannulated	2.2 (±2.4)	9.4 (±22.8)	6.8 (±13.4)	0.047* 0.306 0.586
Amicar used	18	13	5	0.40
Central nervous system bleed before ECMO	3	0	3	0.05
Diagnosis				0.171
1. PPHN	5	4	5	
2. Sepsis	9	4	3	
3. MEC	16	5	1	
4. CDH	5	4	2	
5. Cardiac	6	5	1	
6. Metabolic	0	0	1	
Type of ECMO				0.220
VA	28	16	6	
VV	13	6	7	

Table 3. Outcome Data.

Variable	Group 1 Hemochron 400 ACT 200–220 (N = 41)	Group 2 Hemochron Jr. ACT 200–220 (N = 22)	Group 3 Hemochron Jr. ACT 220–240 (N = 13)	p-Value Group 1 vs. 2 1 vs. 3 2 vs. 3
ACT mean (sec)	208.5 (±12.7)	228.8 (±27.9)	232.7 (±4.71)	.0001* .0001* .546
New CNS bleed on ECMO (N and % of patients)	6 (14.6)	4 (18.1)	1 (7.7)	.67
Number of patients who survived to discharge (N and % of patients)	33 (80.5)	14 (63.6)	11 (85.8)	.22
Total time of ECMO (in h)	140 (±78.1)	137.5 (±97.2)	145.4 (±99.9)	.892 .866 .798
Time on circuit #1 (in h)	114 (±45)	88 (±45.9)	94 (±26.5)	.025* .136 .715
Time to circuit change #1 (in h)	121 (±34.8)	85.4 (±31.9)	99.0 (±15.9)	.035* .244 .490
Number of circuits used per patient	1.39 (±0.77)	1.64 (±1.09)	1.62 (±0.961)	.310 .438 .948
Number of clotting emergencies/Pt	0.175 (±0.55)	0.545 (±0.86)	0.091 (±0.31)	.031* .700 .049*

system hemorrhage, or the need for an operation while on ECMO. Factors that may develop while on ECMO that influence target ACT includes: consumptive coagulopathy, clinical evidence of bleeding, and slow pump flow rates.

The Hemochron product line is widely used for point-of-care anticoagulation monitoring. More than 90% of the ECMO centers (n = 81) in the United States use a Hemochron device, while the remaining centers use the Hemotec device (Medtronic Hemotec, Inc, Englewood, CO) (6). It is crucial to have accurate ACT measurements because of the altered physiology of the coagulation system and reliance on ACT values for titration of the anticoagulant. It has been shown that instability of ACT levels while on ECMO may be an early indicator of an intracranial hemorhage (7,8). ACT levels as analyzed by whole blood coagulation systems must be accurate and reproducible between patients and between centers. Titration and infusion rates of heparin are a matter of protocol at our insti-

tution. We changed anticoagulation devices without changing target ACT parameters. There was a clinical observation that we were experiencing more clotting complications and shorter circuit life after changing from the Hemochron 400 to the Hemochron Jr. LR. Because of this observation, the paired blood sample analysis was performed. We used the resultant regression line to adjust our target ACT parameters. In this study, we retrospectively examined the results of these changes. The calibration between the Hemochron 400 and Hemochron Jr. LR show that they yield different ACT values for a given blood sample. For the target ACT typically used for ECMO, the Hemochron Jr. LR yielded consistently higher values than those produced by the Hemochron 400. These were paired samples from the same patients, obtained at the same time, and processed with a similar technique. The differences in ACT values produced suggest a difference in technology between the two machines. The Hemochron 400 is an older machine and required a larger amount of blood (2 mL) for analysis. To process a sample for the Hemochron 400, blood was added to a test tube containing a procoagulant (celite), and the machine was monitored for clot formation. The Hemochron Jr. LR uses newer technology and requires a smaller volume of blood (2–3 drops) and uses a different procoagulant (silica). Our findings clearly suggest the critical need for calibration and testing of a new measurement device when it is introduced into clinical care.

Our failure to anticipate the discrepancy in ACT values between the two devices seems to have had an effect on longevity of circuit life. The comparison of the mean number of hours to the first circuit change showed that the circuits needed to be changed sooner in Group 2 than in Group 1. Although not statistically significant, after the ACT parameters were changed, the time to the first circuit change increased in Group 3 versus Group 2. These data suggest that the combination of Hemochron Jr. LR with ACT targets of 200–220 seconds led to a shorter circuit life when compared to the combination of Hemochron 400 with similar target ACT goals. It also suggests that the circuit life may be increasing with a higher ACT goal of 220–240 sec on the Hemochron Jr. LR. The frequency of circuit clotting emergencies per patient is indicative of the difference in the anticoagulation status among the three groups. There was an increased frequency of clotting complications per patient in Group 2, as compared to both Groups 1 and 3. This suggests that the elevated ACT value generated by Hemochron Jr. LR when compared to Hemochron 400 may have ineffectively anticoagulated the patients on ECMO. Once the ACT target was increased to 220–240 sec with the Hemochron Jr. LR, the frequency of circuit clotting emergencies was not different than what we experienced with the Hemochron 400 with ACT goals of 200–220. Our data do not suggest that there was an increase in bleeding complications as a result of increasing heparin infusion rates to maintain an increased target ACT. There was not a statistically significant difference in the frequency of new central nervous system hemorrhages among the three groups. The sample size in the three groups is small and must be considered in interpretation of the lack of difference in new central nervous system bleeds among the three groups.

That other factors that affect coagulation and viscosity were not investigated in this study is a limitation of our study. The number of blood product infusions, including platelet, fresh frozen plasma, and cryoprecipitate was not analyzed. The incidence of a documented coagulopathy was not recorded. The composition of the ECMO prime was not reviewed. The number of patients who received aminocaproic acid was similar among groups, but patients' antithrombin III levels and the number of patients who received antithrombin III was not investigated. In addition, we were limited by our sample size. Despite these limitations, the findings validate a clinical observation that inadequate anticoagulation as a result of spuriously high ACT values may have resulted in an increased frequency of circuit clotting emergencies and shorter time to the first circuit change. After calibrations between machines was completed and ACT parameters adjusted, the number of circuit clotting emergencies decreased, and there was a trend suggestive of longer circuit life.

This study serves as a reminder to centers that monitor bedside whole blood-activated clotting times of patients while on ECMO. When initiating use of a new whole blood coagulation system, even if the manufacturer remains the same, it is necessary to compare parameters from the new system to the old system. This will ensure that patients on ECMO receive adequate, but not excessive, anticoagulation therapy to avoid bleeding and clotting complications and optimize circuit life.

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