Bivalirudin monitoring by dilute thrombin time is cost-efficient in pediatric ECMO patients

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Background

Use of the parenteral anticoagulant bivalirudin, a direct thrombin inhibitor, is increasing for pediatric patients requiring mechanical circulatory support (MCS) because of its reported favorable safety (bleeding, blood transfusions) and efficacy (thrombosis) outcomes, compared to unfractionated heparin (UFH).

Recent publications have documented favorable or equivalent clinical costs for patients on MCS who are anticoagulated with bivalirudin vs UFH, however these publications have included the cost of the activated partial thromboplastin time (aPTT) for bivalirudin monitoring.

Our group has recently demonstrated that the aPTT is an unreliable marker of bivalirudin's anticoagulant effect in both extracorporeal membrane oxygenation (ECMO) and ventricular assist device (VAD) patients; the dilute thrombin time (dTT) provides superior reliability.[1] Furthermore, a drug-calibrated dTT could offer the opportunity for multicenter collaboration to identify a true therapeutic range for bivalirudin anticoagulation using relevant clinical outcomes.

Concern remains among clinicians that the dTT is largely unavailable for use in monitoring bivalirudin due to access and/or cost issues at their institutions.

We hypothesize that, given a robust and established platform for running the dTT, dTT monitoring of bivalirudin in ECMO patients is cost efficient compared with monitoring of UFH.

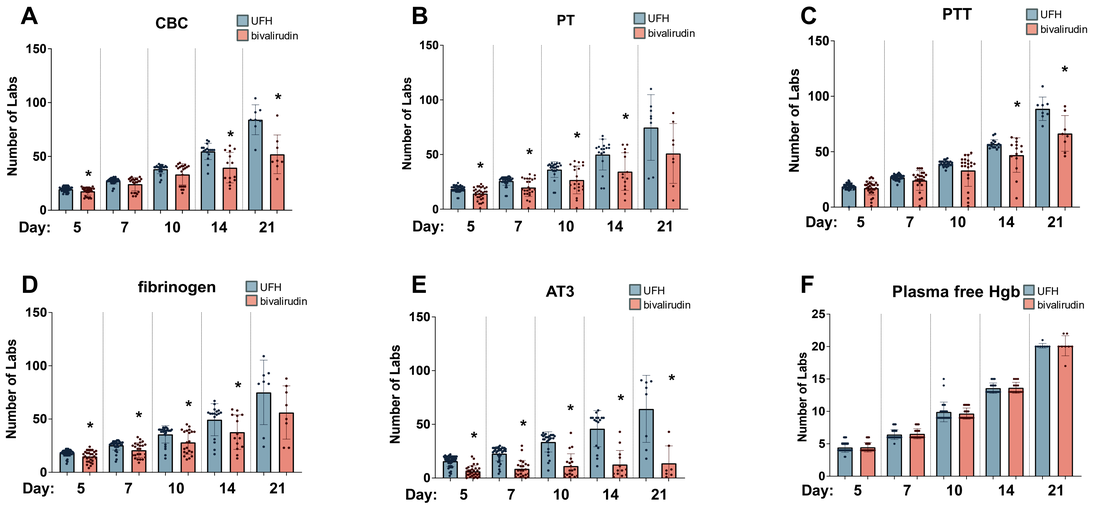
Here, we report a cost analysis of monitoring ECMO patients anticoagulated with bivalirudin versus UFH.

[1]Engel ER, Perry T, Block M, Palumbo JS, Lorts A, Luchtman-Jones L. Bivalirudin monitoring in pediatric ventricular assist device and extracorporeal membrane oxygenation: Analysis of single-center retrospective cohort data 2018-2022. *Pediatr Crit Care Med*. 2024 Jul 1;25(7):e328-e337. PMID: 38713010.

Study Design

As part of a larger, IRB-approved, retrospective clinical study, we collected clinical and laboratory data for children admitted to Intensive Care Units at Cincinnati Children's Hospital and Medical Center on ECMO and anticoagulated with UFH or bivalirudin between January 16, 2018 and August 30, 2023. We performed cost analysis by identifying the total number of laboratory tests (CBC, PT, aPTT, fibrinogen, AT3, UFH level, dTT, serum Creatinine, and plasma free Hgb) ordered for patients. We collected data on lab tests ordered over multiple time points, including 5 days, 7 days, 10 days, 14 days, and 21 days of ECMO. Cost analysis was performed using the 2024 institutional list prices for each test.

Results



Figures A-F: Analysis of the number of the stated lab drawn in patients anticoagulated with either UFH (blue bars) or bivalirudin (red bars) across the time points listed. Each point represents one patient. Error bars represent standard deviation. *p<0.05 by Mann-Whitney test.

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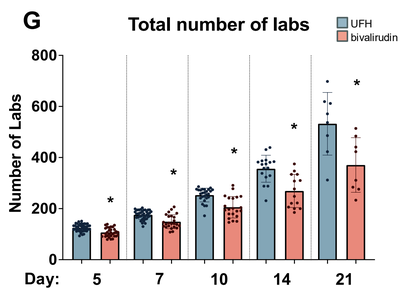

Figure G: Total number of labs collected (as stated in Study Design) in patients anticoagulated with either UFH or bivalirudin across the time points listed. Each point represents one patient. Error bars represent standard deviation. *p<0.05 by Mann-Whitney test. Of note, data represents the summation of all lab tests investigated in this study, including unfractionated heparin (UFH) in patients anticoagulated with bivalirudin, which may represent an error in ordering practices.

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Lab Test	Cost (USD)
CBC	65
PT	64
aPTT	120
Fibrinogen	92
AT3	418
UFH	211
dTT	126
Serum Creatinine	9.50
Plasma free Hgb	70

Table H: 2024 direct cost in US dollars to run each of the stated laboratory tests at our institution.

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UFH	Lab test	Day 5 cost	Day 7 cost	Day 10 cost	Day 14 cost	Day 21 cost
	CBC	1273	1772	2485	3552	5468
	PT	1192	1654	2321	3200	4784
	aPTT	2230	3212	4712	6833	10650
	Fibrinogen	1660	2340	3277	4546	6900
	AT3	6533	9496	14051	19203	26909
	UFH	4018	5654	8302	12101	18647
	dTT	-	-	-	-	-
	Serum creatinine	102	141	198	269	349
	Plasma free Hgb	310	451	694	951	1409
	Total lab cost	16127	24719	36041	50656	75116
	Avg lab cost / day	3226	3531	3604	3618	3577

Bivalirudin	Lab test	Day 5 cost	Day 7 cost	Day 10 cost	Day 14 cost	Day 21 cost
	CBC	1148	1579	2167	2572	3380
	PT	913	1272	1710	2203	3264
	aPTT	1996	2745	3983	5640	7980
	Fibrinogen	1364	1909	2589	3470	5164
	AT3	2619	3449	4240	4897	5016
	UFH	1386	1864	2381	2411	4537
	dTT	1886	2777	4002	5634	7214
	Serum creatinine	107	147	202	274	325
	Plasma free Hgb	313	458	677	955	1409
	Total lab cost	10819	16306	21950	28056	38287
	Avg lab cost / day	2164	2329	2195	2004	1823

Table I: 2024 total average cost (US dollars) at the time points listed of the analyzed laboratory tests across patients anticoagulated with UFH versus bivalirudin. "Total lab cost" represents the summation of all labs analyzed in this study. "Avg lab cost / day" represents the total lab cost divided by the total days of ECMO.

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Company	Instrument	Reagent	AMR/R.R.	dilution	dTT Price	APTT Price
Werfen*	ACL Top, Elite	Hemosil Thrombin	5-80 sec AMR /5-300sec R.R.	1:4 auto	$126	$120
Stago	StarMax, Compact	Sta-thrombin	8-150 sec R.R.	1:4 auto		
Siemens **	BCS XP, BF III	BC thrombin reagent, Batroxobin	35.2-506.2 sec R.R.	1:2 manual and 1:2 on BCS (total 1:4)	$126	$120
Roche	Cobas	TT Cobas				
Sysmex	CA, CS	Test thrombin				

*Currently performed at CCHMC
**Previously performed at CCHMC

Table J: Platforms available for running dilute thrombin time (dTT) and activated partial thromboplastin time (aPTT) with associated costs. Werfen product is currently used at CCHMC, Siemens product was previously used at CCHMC.

Conclusions

The dTT, previously demonstrated as superior to the aPTT for monitoring bivalirudin therapy, can be performed in clinical laboratories on an automated or semi-automated platform, as seen in Table J.

Clinical guidelines at many institutions (including Extracorporeal Life Support Organization [ELSO] members) continue to use aPTT for bivalirudin monitoring with concerns for cost and lack of expertise/availability for dTT in their clinical laboratories; at our ELSO member institution, multiple daily aPTTs are ordered, even as dTT is clinically used for managing bivalirudin. Monitoring cost and blood sampling volume savings will be enhanced by reducing aPTT orders to only clinically necessary.

These data demonstrate that bivalirudin monitoring by dTT in pediatric ECMO patients leads to overall fewer labs drawn (Figure G) and is significantly more cost-efficient for the main laboratory parameters tested across all time points tested (Table I).

Of note, bivalirudin anticoagulation monitoring in ECMO may be more cost efficient over time, as evidenced by a trend towards decreasing average lab cost per day when compared with UFH-anticoagulated MCS patients.

Furthermore, previous studies have reported decreased need for blood product transfusions and circuit changes with bivalirudin, with favorable or equivalent total costs in ECMO patients.

This work demonstrates that dTT monitoring of bivalirudin in pediatric ECMO patients at multiple points over time is cost-efficient and also potentially reduces total laboratory test/blood volume sampling.

Contact information

Please contact Lisa Dorn (lisa.dorn@cchmc.org) with questions.