#48 Evaluating the Effectiveness of a Bivalirudin Titration Protocol in Achieving Therapeutic Anticoagulation Levels

UNIVERSITY of MARYLAND

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BACKGROUND

Bivalirudin is a direct thrombin inhibitor currently approved in patients with known or suspected heparin-induced thrombocytopenia (HIT) undergoing percutaneous coronary intervention (PCI). Outside of the setting of PCI, the use of bivalirudin for treatment of HIT has not yet been established.[1]

Though bivalirudin is not approved for the treatment of HIT, several studies have confirmed its use in this disease state. In a study conducted by *Kiser and Fish*, bivalirudin was considered to be safe and effective for the treatment of HIT in critically ill patients with hepatic dysfunction, renal dysfunction or both.[2] Additionally, a study by *Dang et al*, concluded that bivalirudin reached therapeutic activated partial thromboplastin time (aPTT) levels in a shorter period of time compared to argatroban and lepirudin in the treatment of HIT.[3] These studies expand upon the clinical evidence supporting the use of bivalirudin in HIT. Thus the University of Maryland Medical Center (UMMC) implemented guidelines for the use of bivalirudin in patients with HIT in April 2008.

PURPOSE & OUTCOMES

Purpose

Evaluate institution implemented dosing and titration guidelines

Primary Outcome

Evaluate dosing and therapeutic outcomes with bivalirudin use in patients with (suspected) HIT before and after implementation of guidelines

Secondary Outcome

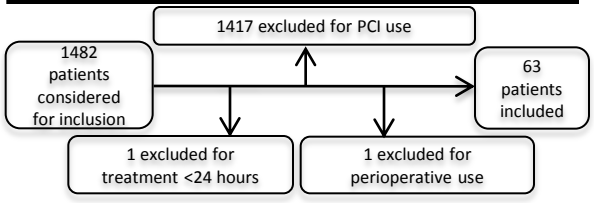
Describe the complications secondary to bivalirudin use

METHODS

Retrospective chart analysis

Inclusion Criteria	Exclusion Criteria
• Age ≥18 • Received bivalirudin for ≥ 24 hours • Admitted to UMMC between January 1, 2005 and June 30, 2010	• PCI use • Perioperative use

PATIENT POPULATION



UMMC GUIDELINES

BIVALIRUDIN TITRATION PROTOCOL

aPTT	Hold Infusion (min)	Normal Hepatic and Renal Function	Renal OR Combined Hepatic and Renal Dysfunction
		Initial dose: 0.15 mg/kg/hr	Initial dose: 0.03 mg/kg/hr
<30	0	Increase by 50%	Increase by 50%
31-46	0	Increase by 25%	Increase by 25%
47-76	0	No change	No change
77-100	60	Decrease by 25%	Decrease by 25%
>100	120	Stop infusion and notify physician	

BASELINE DEMOGRAPHICS

	Pre-Guidelines (n=16)	Post-Guidelines (n=43)	*p* value
Age (years)*	52.9 ± 9.9	55.3 ± 13.2	0.236
Male Gender⁺	8 (50.0)	30 (67.8)	0.159
Race⁺			
African American	6 (37.5)	19 (44.2)	0.644
Caucasian	9 (56.3)	22 (51.2)	0.728
Other	1 (6.3)	2 (4.7)	0.804
Height (cm)*	172.7 ± 14.9	172.1 ± 10.4	0.450
Actual body weight (kg)*	93.3 ± 26.5	91.9 ± 26.3	0.430
Ideal body weight (kg)*	66.4 ± 15.4	66.3 ± 10.5	0.489
Renal Function			
SCr (mg/dL)*	2.1 ± 1.5	2.0 ± 1.4	0.410
CrCl (ml/min)*	50.8 ± 27.4	58.9 ± 40.2	0.192
Renal Replacement⁺	8 (50.0)	20 (46.5)	0.811
Hepatic Function			
AST (IU/L)*	202 ± 383.0	92.8 ± 159.0	0.129
ALT (IU/L)*	165 ± 307.0	55.2 ± 76.8	0.080
Tbili (mg/dL)*	7.5 ± 11.0	5.9 ± 9.8	0.265
Albumin (g/dL)*	2.2 ± 1.1	2.1 ± 0.9	0.103

*[mean ± SD]; ⁺[n (%)]; $fecal occult stool or urinalysis positive for blood
SCr, serum creatinine; CrCl, creatinine clearance; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Tbili, total bilirubin

REFERENCES

1.Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: american college of chest physicians evidence-based clinical practice guidelines (9th edition). Chest 2012;141:495S-530S.
2.Kiser TH, Fish DN. Evaluation of bivalirudin treatment for heparin-induced thrombocytopenia in critically ill patients with hepatic and/or renal dysfunction. Pharmacotherapy 2006;26:452-60.
3.Dang CH, Durkalski VL, Nappi JM. Evaluation of treatment with direct thrombin inhibitors in patients with heparin-induced thrombocytopenia. Pharmacotherapy 2006;26:461-68.

DISCLOSURES

The investigators have no disclosures to report.

PRIMARY OUTCOME

	Pre-Guidelines (n=16)	Post-Guidelines (n=43)	*p* value
Initial dose (mg/kg/hr)*	0.10 ± 0.12	0.08 ± 0.10	0.287
Minimum dose (mg/kg/hr)*			
at 24 hours	0.05 ± 0.05	0.06 ± 0.06	0.324
at 48 hours	0.05 ± 0.06	0.06 ± 0.06	0.421
Maximum dose (mg/kg/hr) *			
at 24 hours	0.11 ± 0.13	0.11 ± 0.12	0.411
at 48 hours	0.08 ± 0.09	0.10 ± 0.13	0.251
Time to first therapeutic aPTT (hours)	10.2 ± 26.7	8.0 ± 22.0	0.303
aPTT (seconds)*			
First level post initiation	52.6 ± 28.7	66.2 ± 22.3	0.103
at 24 hours	48.9 ± 15.3	62.9 ± 17.4	**0.013**
at 48 hours	41.2 ± 16.8	64.6 ± 22.7	**0.004**
Average INR [minimum/maximum]			
at 24 hours	1.6/2.2	1.7/1.9	-
at 48 hours	1.8/2.0	1.6/1.7	-
Platelet count (K/mL)*			
Baseline	138.7 ± 119.2	98.9 ± 77.1	0.114
At 24 hours	142.1 ± 122.3	105.4 ± 78.4	0.139
At 48 hours	149.9 ± 128.6	109.9 ± 79.0	0.133
HIT confirmed by SRA⁺	0 (0)	1 (2.3)	-

SECONDARY OUTCOME

Adverse Events

	Pre-Guidelines (n=16)	Post-Guidelines (n=43)	*p* value
Documented bleeding⁺	4 (25.0)	7 (16.3)	0.444
Hemoglobin decrease by ≥ 3g/dL⁺	2 (12.5)	4 (9.3)	0.718
Blood product transfusions⁺	9 (56.3)	27 (62.8)	0.780
Other signs of bleed⁺$	1 (6.3)	4 (9.3)	0.708

DISCUSSION & CONCLUSIONS

Compared to the pre-implementation period, during the post implementation period:

- Time to first therapeutic aPTT was 2.2 hours faster
- Average aPTT at the 24 and 48 hour period was within therapeutic range
- There were no differences in bleeding rates
- More appropriate initial doses

Utilization of a standardized titration protocol for bivalirudin:

- May lead to more rapid achievement of therapeutic levels
- Leads to persistent attainment of goal aPTTs