Enoxaparin for perioperative warfarin bridging in patients on chronic hemodialysis: a retrospective study

Wynnie Lau, Pharm D; Hyoung Jun Kim, Entry-to-Practice PharmD.; Renée Dagenais, Pharm.D.; Myriam Farah, M.D., FRCP(C)
Departments of Pharmacy and Nephrology

Background

- Patients taking warfarin may require temporary interruption of therapy when undergoing invasive procedures
- Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are often used during the period of interruption
- LMWHs have more predictable pharmacokinetic properties, lower incidence of heparin-induced thrombocytopenia, and convenient administration compared to UFH
- Enoxaparin has been the LMWH of choice for perioperative bridging for intermittent hemodialysis (IHD) patients at St. Paul's Hospital.

Study Objective & Outcomes

- To describe safety and efficacy outcomes associated with enoxaparin for perioperative bridging of warfarin in patients receiving IHD.
- **Primary Outcomes** (within 30 days of last enoxaparin dose):
  - Major bleeding defined as:
    - Drop in hemoglobin (Hgb) of ≥ 20 g/L
    - Need for blood transfusion
  - Prolonged bleeding from the arteriovenous fistula/grafts (AVF/AVG)
  - Hospitalization for any bleeding event
- **Secondary Outcomes** (within 30 days of last enoxaparin dose):
  - All-cause mortality
  - Need for early discontinuation of enoxaparin
  - Prolonged hospitalization related to bleeding
  - Symptomatic thrombotic event (VTE, stroke)

Methods & Statistics

- Retrospective, non-comparative chart review; Sept 2009 to Sept 2019
- Inclusion criteria:
  - Age ≥ 18 years
  - IHD ≥ 3 months at one of PHC hemodialysis (HD) unit
  - Invasive procedure or surgery requiring interruption of warfarin
  - Received enoxaparin as peri-operative bridging agent
  - Warfarin re-initiated following the procedure.
- Exclusion criteria:
  - Enoxaparin used as a bridging for initiation of warfarin
- Statistics:
  - Descriptive statistics
  - Univariate analysis with Wilcoxon test and Fisher's or Chi-square test when appropriate for all binary variables
  - General linear mixed effects model used for multivariate analysis analyzing all procedures in the time period

Results

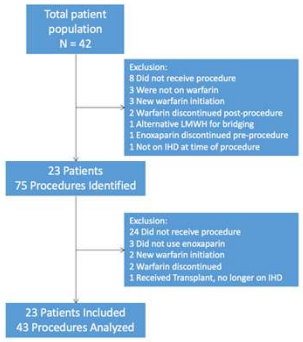

Table 1: Baseline Characteristics

Patient Characteristics (n=23)	
Age mean ± SD (years)	61 ± 14
Female, n (%)	7 (30)
Comorbidities [n (%)]	
Mechanical or bioprosthetic valve	13 (57)
Prior renal transplant recipient	10 (43)
Hx of GIB in past 12 months	5 (22)
Concomitant Medications [n (%)]	
ASA	4 (17)
Oral corticosteroids	7 (30)
PPI	11 (48)
H2RA	3 (13)
Characteristics at time of procedure (n=43)	
BMI ± SD (kg/m^2)	24.9 ± 2.2
Warfarin Indication [n (%)]	
VTE treatment	7 (16)
VTE prophylaxis	4 (9)
Stroke prevention secondary to atrial fibrillation/flutter	22 (52)
Thromboprophylaxis for mechanical mitral valve	7 (16)
Other	3 (7)
Thromboembolic Risk* [n (%)]	
Low	6 (14)
Moderate	7 (16)
High	30 (70)
Bleeding Risk [n (%)]**	
Low	5 (12)
Moderate	22 (51)
High	3 (7)
Unknown	13 (30)
Relevant Warfarin data (n=43)	
Mean INR up to 2 days prior to surgery ± SD	1.28 ± 0.34
Mean Warfarin free days	3.9 ± 3.3
Mean days to achieve therapeutic INR ± SD	9.2 ± 4.9
Relevant enoxaparin data (n=43)	
Mean dose ± SD (mg/kg)	0.97 ± 0.17
Mean number of doses received ± SD	9.7 ± 4.4

*Thromboembolism risk defined as low, moderate, and high as per CHEST 2012 guidelines
**Bleeding risk defined as low, moderate, high as per Thrombosis Canada 2019

Table 2: Primary Outcome

	Per patient (n=23)
Drop in hemoglobin ≥ 20g/L	3
Need for blood transfusion	1
Prolonged bleeding from AVF/AVG	0
Hospitalization for any bleeding event	3

Table 3: Univariate Analysis Summary

Variable of Interest	All procedures (n=43)	No major bleeding events (n=32)	Major bleeding events (n=11)	p-value
Dose mg/kg, mean (SD)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	0.43
Number enoxaparin doses (mean, IQR)	7 (7, 13)	7 (7, 11)	12 (7, 15)	0.09
History of GIB within past 12 months, N (%)	8 (19)	8 (25)	0 (0)	0.09
Concomitant PPI medication, N(%)	16 (37)	16 (100)	0 (0)	0.003
Concomitant H2RA medication, N(%)	7 (16.3)	3 (9.4)	4 (36.4)	0.058
Transplant history, N (%)	15 (35)	13 (41)	2 (18)	0.28

Wilcoxon test; Fisher's or Chi-square test when appropriate for all binary variables.

Table 4: Multivariate Analysis Summary

	OR (95% CI)	p-value
Dose mg/kg	6.9 (0-12047.5)	0.62
Number Enoxaparin doses	1.1 (0.91-1.32)	0.34
Concomitant PPI or H2RA	0.17 (0.02-1.35)	0.11

Results Continued

- 23 patients identified over 10 years
  - 3 index major bleeding events during time period (1 required a blood transfusion)
  - 11 total procedures resulted in a major bleeding (2 required a blood transfusion)
  - No 30-day mortality observed
- 37% enoxaparin doses were > 1mg/kg
- 2 (67%) of the high, 5 (23%) of the moderate and 2 (40%) of the low bleeding risk procedures had a bleed
- 1 symptomatic thromboembolic episode (PE) was observed during the bridging period

Conclusion

- Bleeding rates from this study are higher than reported in the literature (13% vs 6%, respectively); difference may be dose related (1 mg/kg vs 0.7 mg/kg, respectively)
- Need for bridging with enoxaparin appear to be uncommon, resulting in a significantly small sample size despite the large time interval sampled
- This study did not find any statistically significant risk factors to explain bleeding events
- Concomitant PPI use was observed to decrease the risk of a major bleed
- Suggest decreasing dosage of enoxaparin closer to 0.7mg/kg if needed for peri-operative bridging in HD pt