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

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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, tinzaparin, and dalteparin have all been studied in small studies as bridging agents in intermittent hemodialysis (IHD)
- Enoxaparin has been the LMWH of choice for perioperative bridging 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 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
  - Subtherapeutic enoxaparin dose (<0.5 mg/kg)
- Statistics:
  - Descriptive statistics
  - Univariate and multivariate analysis to compare patients who experienced bleeds to those who did not

Results

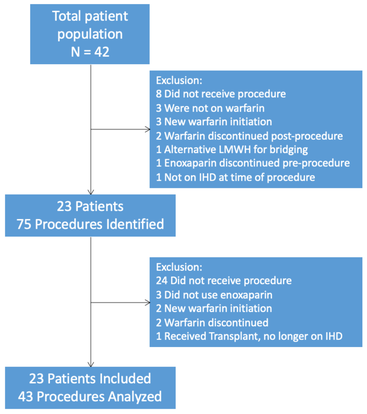

Table 1: Baseline Characteristics

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

Figure 1: Summary of Primary & Secondary Outcomes (N = 43)

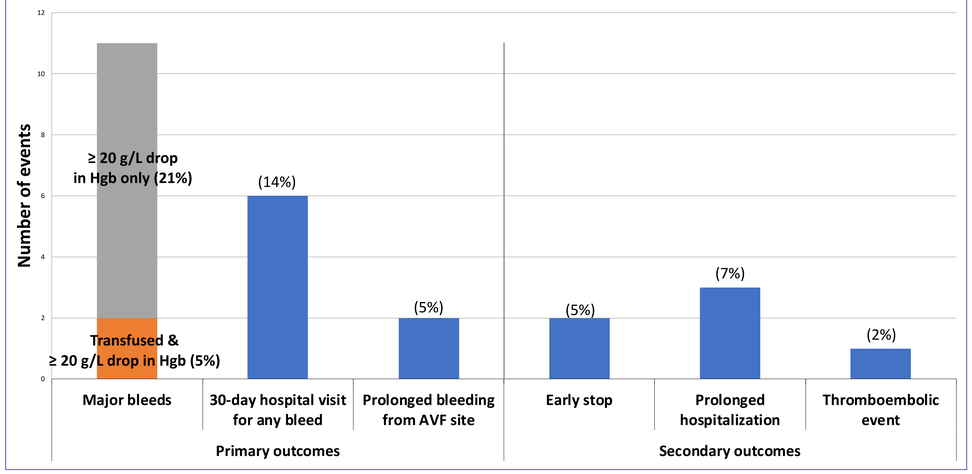

Table 2: Univariate Analysis Summary

Variable of Interest	Total observations (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
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 3: Multivariate Analysis Summary

	Logistic (no clustering)		Logistic (clustering)	
Exposure of interest:	OR (95% CI)	p-value	OR (95% CI)	p-value
Dose mg/kg	12.6 (0.0, 7071.1)	0.43	6.9 (0, 12047.5)	0.62
Number Enoxaparin doses	1.1 (0.9, 1.3)	0.39	1.1 (0.9, 1.3)	0.34

Results Continued

- 11 major bleeding events with a drop in Hgb ≥ 20 g/L – 2 required blood transfusions
- 6 patients visited the hospital for bleed within 30 days of last dose of enoxaparin; 4 patients met the criteria for major bleed
- No 30-day mortality observed
- 37% enoxaparin doses were > 1mg/kg
- 1 symptomatic thromboembolic episode (PE) was observed during the bridging period

Conclusion

- Bleeding rates from this study are higher than reported in the literature (26% vs 6%); the difference may be dose related (1 mg/kg vs 0.7 mg/kg)[2]
- Thromboembolic rate is higher than reported in literature (2% vs 0%)[2] and expected rate (< 1%)[3,4]; may be due to the small sample size
- This study did not find statistically significant risk factors to explain bleeding events in IHD population during perioperative bridging with enoxaparin

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