

Relationship between urinary prothrombin fragment 1+2 levels and venous thromboembolic or bleeding events following total hip replacement

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Introduction

- ◆ Venous thromboembolism (VTE) and bleeding events occur frequently in patients undergoing major orthopaedic surgery
 - Anticoagulation therapy is recommended in the peri-operative period to reduce the risk of VTE^{1,2}
 - Patients at high risk of bleeding may benefit from initial mechanical prophylaxis, followed by anticoagulation therapy after the bleeding risk has decreased^{3,4}
 - However, the duration of thromboprophylaxis remains a matter of debate⁴
- ◆ Therefore, the management of patients undergoing major orthopaedic surgery would be greatly improved if a simple, non-invasive clinical test was available for clinicians to evaluate the intensity of coagulation activation after surgery⁵
 - This test could help to identify patients at high risk of VTE or bleeding
- ◆ Prothrombin fragment 1+2 is excreted in urine (uF1+2) as a result of thrombin generation and, therefore, may be a useful marker of coagulation status

Objective

- ◆ To assess uF1+2 levels after total hip replacement (THR) in patients with VTE and bleeding events, and in event-free control patients matched to these two patient groups

Methods

Study design

- ◆ This study was conducted in parallel with a prospective, dose-finding study evaluating the efficacy and safety of different doses of rivaroxaban for thromboprophylaxis, relative to enoxaparin⁶
- ◆ Deep vein thrombosis was diagnosed by mandatory bilateral venography performed 5–9 days after THR, or earlier if symptomatic
- ◆ Symptomatic pulmonary embolism was diagnosed by objective testing
- ◆ Bleeding complications were registered and stratified into major bleeding, clinically relevant non-major bleeding, and minor bleeding, using predefined criteria

Laboratory analyses and urine sampling

- ◆ Spot urine samples were collected on the morning of surgery (day 1), on day 3 after THR, on the day of venography (day 5–9), and at follow-up (day 39)
- ◆ Levels of uF1+2 were measured using a commercially available ELISA kit (Enzygnost F1+2, Monoclonal, Dade Behring, Marburg, Germany) and a BEP 2000[®] analyzer (Dade Behring, Marburg, Germany)
 - This kit measures F1+2 in pmol/l, with a proposed cut-off for symptomatic VTE of uF1+2 between 50 and 103 pmol/l

Statistical analyses

- ◆ One sex- and age-matched, event-free patient was randomly selected for each patient in the VTE group and the bleeding group, to comprise the VTE control and bleeding control groups, respectively
- ◆ The non-parametric Wilcoxon rank sum test was used to compare the medians of uF1+2 levels (actual levels) between VTE or bleeding event cases and controls on the different sampling days, assuming that the data were not normally distributed within cases and controls
 - Results were considered statistically significant if the two-sided p -value was <0.05

Results

- ◆ Eighty-four patients had a VTE and 57 patients had a bleeding event
- ◆ Significantly higher median uF1+2 levels were observed in the VTE group on day 3 after THR ($p=0.03$), compared with control (Table 1)

Table 1. Median levels of prothrombin fragment 1+2 excreted in urine in the venous thromboembolism (VTE) group and the matched, event-free, VTE control group on each sampling day

	Median prothrombin fragment 1+2 levels in urine pmol/l (range)		
	VTE group (n=84)	VTE control group (n=84)	p -value ^a
Preoperatively (day 1, or day of surgery) (range)	19 (19–254.8)	19 (19–347.2)	0.58
Day 3 after total hip replacement (range)	127.3 (19–1200)	70.6 (19–1200)	0.03
Day 5–9 (venography) (range)	30.8 (19–560.8)	30.1 (19–699.1)	0.34
Follow-up (day 39) (range)	19 (19–1200)	19 (19–269.2)	0.12

^aWilcoxon test (two-sided).

- ◆ Median uF1+2 levels were lower in the bleeding group on day 3 after THR ($p=0.005$) and on the day of venography ($p=0.36$), compared with control (Table 2)

Table 2. Median levels of prothrombin fragment 1+2 excreted in urine in the bleeding group and the bleeding control group on each sampling day

	Median prothrombin fragment 1+2 levels in urine pmol/l (range)		
	Bleeding group (n=57)	Bleeding control group (n=57)	p -value ^a
Preoperatively (day 1, or day of surgery) (range)	19 (19–83.1)	19 (19–289.9)	0.12
Day 3 after total hip replacement (range)	41.8 (19–964.8)	90.2 (19–1200)	0.005
Days 5–9 (venography) (range)	20.9 (19–149)	23.5 (19–476.0)	0.36
Follow-up (day 39) (range)	19 (19–88.8)	19 (19–233.5)	0.86

^aWilcoxon rank sum test (two-sided).

- ◆ Comparisons between the VTE and bleeding groups showed significantly lower median uF1+2 levels in the bleeding group on day 3 after THR and on the day of venography ($p<0.0001$ and $p=0.005$, respectively) (Table 3)

Table 3. Median levels of prothrombin fragment 1+2 excreted in urine in the venous thromboembolism (VTE) group and the bleeding group on each sampling day

	Median prothrombin fragment 1+2 levels in urine pmol/l (range)		
	Bleeding group (n=55) ^a	VTE group (n=82) ^a	p -value ^b
Preoperatively (day 1, or day of surgery) (range)	19 (19–83.1)	19 (19–254.8)	0.71
Day 3 after total hip replacement (range)	40.5 (19–964.8)	127.3 (19–1200)	<0.0001
Days 5–9 (venography) (range)	20.7 (19–149)	29.2 (19–560.8)	0.005
Follow-up (day 39) (range)	19 (19–88.8)	19 (19–1200)	0.40

^aTwo patients experienced both a VTE and a bleeding event, and were excluded from both groups. ^bWilcoxon rank sum test (two-sided).

Conclusions

- ◆ Differences in uF1+2 levels were observed between the VTE group (high levels) and the bleeding group (low levels) after THR
- ◆ Therefore, measurement of uF1+2 levels may have the potential to document non-invasively the intensity of activation of coagulation in patients who have undergone THR and alert clinicians to abnormalities (VTE or bleeding event)

References and disclosures

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