

BALANCING BLEEDING AND THROMBOSIS: SAFETY OF LOW-MOLECULAR-WEIGHT HEPARIN THROMBOPROPHYLAXIS IN PATIENTS WITH HEMOPHILIA UNDERGOING MAJOR SURGERY

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Background and Aims. In patients with hemophilia, the risk of venous thromboembolism (VTE) has historically been considered low. However, in the setting of major surgery, particularly orthopedic and oncologic procedures, this risk may become clinically relevant. Available evidence is limited and sometimes conflicting. The World Federation of Hemophilia guidelines (WFH, 3rd edition) recommend an individualized assessment of both thrombotic and bleeding risk, favoring mechanical thromboprophylaxis and reserving pharmacological prophylaxis for selected cases under adequate factor replacement and in patients without inhibitors. Similarly, the International Society on Thrombosis and Haemostasis (ISTH) highlights the low quality of available evidence and the need for a personalized approach. A recent systematic review reported a low incidence of VTE after major orthopedic surgery, but considerable heterogeneity in thromboprophylaxis use, reflecting the lack of consensus. In this context, we aimed to retrospectively evaluate the safety of pharmacological thromboprophylaxis with low-molecular-weight heparin (LMWH) in patients with hemophilia undergoing major surgery.

Methods. Medical records of 105 patients with moderate/severe hemophilia A or B followed at our center were retrospectively reviewed. Among these, 12 patients undergoing a total of 18 major surgical procedures received postoperative LMWH thromboprophylaxis. Data were verified and integrated through comparison with the rare diseases registry.

Results. All included patients had severe hemophilia A and received perioperative factor replacement therapy. Trough factor levels during the first three postoperative days were $\geq 14\%$, and $\geq 11\%$ thereafter. Patient characteristics, type of surgery, and trough levels are reported in *Table 1*. A single

bleeding event occurred in a patient undergoing intestinal reanastomosis for previous rectal adenocarcinoma (previously treated with LMWH prophylaxis without complications), who presented on postoperative day 4 with hematemesis and rectal bleeding, requiring LMWH discontinuation and transfusion support. No other major or minor bleeding events were observed. One patient developed a clinically evident VTE on postoperative day 8 despite LMWH thromboprophylaxis, in the presence of multiple risk factors (high-risk inherited thrombophilia and smoking). No additional clinically evident thromboembolic events were observed.

Conclusions. In a setting of limited and conflicting evidence, all patients underwent individualized assessment of thrombotic and bleeding risk. They received adequate factor replacement therapy and were monitored through factor levels. In this context, LMWH thromboprophylaxis appeared safe in the vast majority of cases. These findings support the feasibility of a personalized approach to pharmacological thromboprophylaxis in patients with hemophilia undergoing major surgery, although prospective studies are warranted to confirm its safety.

Pt	Age at surgery	Preoperative prophylaxis	Additional VTE risk factors	Surgery	VTE	Bleeding	Trough FVIII POD 1-3 (%)	Trough FVIII >POD3 (%)
1.1	60	Replacement	Heterozygous factor V Leiden + homozygous prothrombin polymorphism + smoking	Laparoscopic cholecystectomy + endoscopic bile duct clearance	NO	NO	44	80
1.2	63	Replacement	Heterozygous factor V Leiden + homozygous prothrombin polymorphism + smoking	TKA	YES	NO	59	88
2	65	Replacement	Obesity	TKA	NO	NO	100	50
3	50	Replacement	History of PICC-related VTE	Infected TKA removal + debridement + knee arthrodesis with external fixation	NO	NO	55	16
4.1	66	Non replacement (Emicizumab)	Rectal adenocarcinoma + smoking	Thoracoscopic lung biopsy	NO	NO	45	NA
4.2	60	Replacement	Rectal adenocarcinoma + smoking	Rectal resection for adenocarcinoma with ileostomy	NO	NO	47	20
4.3	61	Replacement	Rectal adenocarcinoma + smoking	Surgical revision for anastomotic leak after rectal resection	NO	NO	24	17
4.4	61	Replacement	Rectal adenocarcinoma + smoking	Intestinal reanastomosis	NO	YES	35	21
5.1	54	Replacement	Klinefelter syndrome	TKA	NO	NO	49	95
5.2	50	Replacement	Klinefelter syndrome	TKA	NO	NO	106	50
6	36	Replacement	NO	TKA	NO	NO	152	160
7	62	Replacement	NO	TKA revision for periprosthetic fracture	NO	NO	58	40
8	41	Replacement	NO	TKA	NO	NO	63	11
9	67	Non replacement (Emicizumab)	NO	TKA	NO	NO	39	49
10.1	54	Replacement	NO	Patellar tendon repair	NO	NO	14	14
10.2	51	Replacement	NO	TKA	NO	NO	84	104
11	28	Replacement	NO	Ischial tuberosity exostosis resection (osteoma)	NO	NO	60	45
12	67	Replacement	NO	TKA	NO	NO	63	40

Abbreviations: Pt, patient; VTE, venous thromboembolism; POD, postoperative day; TKA, Total knee arthroplasty; THA, Total hip arthroplasty; NA, not available.