Thrombosis Guidelines Group

EXTENDED PROPHYLAXIS OF VENOUS THROMBOEMBOLISM IN MAJOR SURGERY

1) Postoperative venous thromboembolism: a continuing problem after discharge?

Studies from the late 80's and early 90's pointed to the problem of postoperative venous thromboembolism (VTE) occurring at home after discharge from the hospital, despite thromboprophylaxis during the hospital stay:

- Scurr et al.(1) followed 57 patients after discharge from the hospital where they had major surgery. They used ultrasonography and the radiolabeled fibrinogenscan to screen for venous thromboembolism and venography to confirm the diagnosis: during the 6 week follow-up,13 out of 51 who had no DVT at discharge developed deep vein thrombosis.

- Huber et al.(2) screened almost 29000 patient charts from a digestive surgery clinic and found a 0.31% rate of pulmonary embolism (PE) before discharge and a 0.10% rate of readmission because of PE within 30 days after discharge.

- Kakkar et al.(3) reported an incidence of post-discharge PE of 0.41% in a trial which compared two types of heparin in 3809 patients who underwent major abdominal surgery. They suggested that a separate trial was needed to answer the question whether prophylaxis should be continued at home in high risk patients but doubted whether the cost-benefit ratio would justify prolonged prophylaxis given a post-discharge fatal PE rate of 0.09%.

Studies comparing a short course of prophylaxis in the hospital with extended prophylaxis out of the hospital started in the mid 90's and selected initially patients undergoing hip surgery. Later patients having knee replacement surgery and cancer surgery were added (see further). However, there may be differences between these clinical conditions with respect to postoperative VTE. For instance, recent studies concluded to a difference in time course and location of VTE after hip arthroplasty versus knee arthroplasty. In patients having elective hip arthroplasty, the median time of symptomatic VTE was postoperative day 17, whereas in knee arthroplasty it was day 7 . Ninety percent of all VTE events after knee arthroplasty occur within 21 days of the operation but events after hip arthroplasty continue to develop as long as 60 days postoperatively (4, 5, 6). In addition, the location is different, with more proximal thrombosis occurring after hip surgery and more calf thrombosis after knee surgery (7). Thus, the risk of VTE after major surgery may not be alike for all patients. Furthermore, attempts were made to identify factors that would predict high risk. Age > 85 years,a previous history of VTE and a body mass index above 25 were the best predictors of rehospitalization for symptomatic VTE after hip arthroplasty in a case-control study (8)

2) The incidence of symptomatic VTE in orthopedic surgery with common post-operative in-hospital prophylactic regimens.

Data on symptomatic thromboembolism during the first 3 months after hip or knee replacement surgery are available from several recent large (North American) studies which used in-hospital prophylaxis with either warfarin of low molecular weight heparin (LMWH). They are summarized in table 1.

Table 1: Effect of in-hospital prophylaxis on symptomatic VTE at 90 days after joint replacement surgery.

author (ref 9,10,6)	**prophylaxis (days)**	**n**	**all VTE (%)**	**fatal PE (%)**
Robinson, 1997	warfarin (9.8)	506	1.0	0
Leclerc,1998	enoxaparin (9)	1984	4.1	0.15
Colwell, 1999	warfarin (7.3)	1495	3.7	0.1
	enoxaparin(7.3)	1516	3.6	0.1

The pooled average rate of symptomatic VTE at 90 days using in hospital prophylaxis only (started postoperatively) was 3.6% and the rate of fatal PE 0.13%.

3) Effect of continuing prophylaxis on asymptomatic (venographic) deep vein thrombosis (DVT) after hip replacement surgery.

Six studies using venographic DVT as efficacy outcome measure compared in-hospital prophylaxis with extended out-of-hospital prophylaxis with LMWH. They are summarized in table 2.

Table 2: Effect of post-discharge LMWH following in-hospital prophylaxis on venographic DVT after total hip replacement surgery

		all DVT (%)		proximal DVT (%)	
author (ref 11-16)	n	short prophylaxis	extended prophylaxis	short prophylaxis	extended prophylaxis
Bergqvist,1996	223	37	18	24	7
Planes, 1996	173	19	7	8	6
Dahl, 1997	218	32	19	13	9
Lassen, 1998	215	12	4	5	1
Hull, 2000	533	37	20	9	3
Comb, 2001	435	23	8	13	3
pooled average	1797	27	14	12	4

(adapted from Geerts et al, 2001) (17)

In each of these trials in-hospital prophylaxis with LMWH or warfarin was followed by post-discharge placebo or LMWH. All of these studies found the rate of asymptomatic DVT to be substantially reduced by extended out-of-hospital prophylaxis with LMWH. Per 100 patients treated, the reduction ranges from 8 to 19 thromboses when all DVT are considered and from 4 to 17 for proximal deep vein thrombosis.

4) Effect of continuing prophylaxis on symptomatic VTE after orthopedic surgery.

The trials which compared short in-hospital prophylaxis to extended out-of-hospital prophylaxis individually failed to demonstrate a significant reduction in symptomatic VTE because of their too small size. However, 3 meta-analyses indicated that extended prophylaxis reduced symptomatic VTE in parallel with asymptomatic DVT (table 3)

Table 3. Meta-analyses of symptomatic VTE in trials comparing short versus extended out-of-hospital prophylaxis after major orthopedic surgery.

			% VTE		
meta-analysis (ref 18-20)	trials (n)	patients (n)	short pophylaxis	extended prophylaxis	odds reduction
Cohen, 2001	6	2568	3.3	1.6	0.5 (0.3-0.83)
Eikelboom, 2001	9	3708	3.3	1.3	0.38 (0.24-0.61)
Hull, 2001	6	1953	4.2	1.4	0.36 (0.2-0.67)

The recently presented, as yet unpublished, Penthifra-plus trial randomized 656 patients operated for hip fracture after a one-week course of fondaparinux to placebo or further fondaparinux for an additional 3 weeks : symptomatic VTE was reduced from 2.7% (9/330) to 0.3% (1/326), a relative reduction of 89% (p=0.021).

5) Effect of continuing prophylaxis on VTE in other high risk patients.

The Enoxacan II study compared a four-week to a one-week regimen of enoxaparin prophylaxis in patients undergoing elective surgery for abdominal or pelvic cancer. Four-week prophylaxis significantly reduced the incidence of venographically demonstrated thrombosis as compared to one-week prophylaxis (from 12.0 to 4.8%, p= 0.02). The trial had insufficient power to demonstrate a significant reduction in clinical end points (21).

Conclusions:

a) clinical trials comparing extended prophylaxis to short in-hospital prophylaxis demonstrate consistently a significant reduction in venographically demonstrated deep vein thrombosis in high risk patients (hip or knee replacement, hip fracture, abdominal or pelvic cancer surgery)
b) currently available trials are not powered to demonstrate significant differences in symptomatic thromboembolism (one exception in hip fracture surgery). Meta-analysis of randomized trials in hip replacement surgery points to a similar reduction in symptomatic and asymptomatic (venographic) thrombosis
c) since the rate of the 90-day symptomatic VTE after high risk surgery is 3 to 4% (and of fatal PE 0.1 to 0.15%) with currently used short in-hospital prophylactic regimens, cost-effectiveness becomes an important issue if extended prophylaxis is to be recommended to all patients undergoing high-risk surgery. An open question is to what extent it might be possible to identify subgroups with the highest risk which would benefit most from extended prophylaxis.

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