



Extended prophylaxis of venous thromboembolism in major orthopaedic surgery

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The risk of postoperative venous thromboembolism continues after discharge from the hospital. Studies in patients undergoing hip replacement or hip fracture surgery consistently found the rate of asymptomatic deep vein thrombosis to be substantially reduced by extended out-of-hospital prophylaxis and meta-analyses demonstrate symptomatic deep vein thrombosis to be reduced in parallel with asymptomatic. On the basis of these data, extended prophylaxis is recommended in hip replacement and hip fractures. The recommendation is particularly strong for patients with additional personal risk factors.

al (10) screened almost 29,000 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* (13) reported an incidence of post-discharge PE of 0.41% in a trial which compared two types of heparin in 3,809 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%.

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* (21) followed 57 patients after discharge from the hospital where they had major surgery. They used ultrasonography and the radiolabeled fibrinogen scan 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*

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

Author (4, 15, 19)	Prophylaxis (days)	n	All VTE (%)	Fatal PE (%)
Robinson, 1997	warfarin (9.8)	1024	0.9	0.1
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

Studies comparing a short course of prophylaxis in the hospital with extended prophylaxis out of the hospital started in the mid 90's and initially selected 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, 22, 25). In addition, the location is different, with more proximal thrombosis occurring after hip surgery and more calf thrombosis after knee surgery (24). 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 rehospitalisation for symptomatic VTE after hip arthroplasty in a case-control study (23).

THE INCIDENCE OF SYMPTOMATIC VTE IN ORTHOPAEDIC 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 large North-

American studies which used in-hospital prophylaxis with either warfarin or low molecular weight heparin (LMWH). They are summarised in table I.

The pooled average rate of symptomatic VTE at 90 days using in-hospital prophylaxis only (started postoperatively) was 3.4% and the rate of fatal PE 0.13%. The majority of these events occurred after discharge from the hospital.

EFFECT OF EXTENDED 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 summarised in table II.

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.

EFFECT OF EXTENDED PROPHYLAXIS ON SYMPTOMATIC VTE AFTER ORTHOPAEDIC 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, meta-analyses (some of

Table II. — Effect of post-discharge LMWH following in-hospital prophylaxis on venographic DVT after total hip replacement surgery

Author (2, 5, 6, 11, 14, 17)	n	All DVT (%)		Proximal DVT (%)	
		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

* patients with total knee replacement omitted (adapted from Geerts *et al*, 2001) (9)

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

Meta-analysis (3, 7, 12)	% VTE				
	Trials (n)	Patients (n)	Short prophylaxis	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)

* analysed only patients with total hip replacement.

which included patients with total knee replacement as well) indicated that extended prophylaxis reduced symptomatic VTE in parallel with asymptomatic DVT (table III).

Another systematic review estimated the frequency of symptomatic pulmonary embolism to be reduced from 0.36% to 0% and of fatal pulmonary embolism from 0.09% to 0% (16). The number needed to treat to prevent one episode of symptomatic pulmonary embolism was calculated to be 278 and to prevent one episode of fatal pulmonary embolism 1,093.

The recently published Penthifra-plus trial randomised 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% ($p = 0.021$) (8).

Extended prophylaxis with oral anticoagulants for a few weeks beyond the hospital stay appears better than short in-hospital prophylaxis (18) but LMWHs cause less bleeding problems (20).

EFFECT OF EXTENDED 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 (1).

CONCLUSIONS

1. Clinical trials comparing extended prophylaxis to short in-hospital prophylaxis consistently demonstrate a significant reduction in venographically demonstrated deep vein thrombosis in high-risk patients (hip or knee replacement, hip fracture, abdominal or pelvic cancer surgery).
2. Currently available trials are not powered to demonstrate significant differences in symptomatic thromboembolism (one exception in hip fracture surgery with fondaparinux). Meta-analysis of randomised trials in hip replacement surgery points to a similar reduction in symptomatic and asymptomatic (venographic) thrombosis.
3. 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-duration 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.

RECOMMENDATIONS

- a. Extended prophylaxis (up to 28-35 days after surgery) is recommended in patients with hip replacement and hip fracture surgery.
- b. The recommendation is particularly strong for patients with additional personal risk factors such as advanced age, obesity, a previous history of venous thromboembolism and prolonged immobilisation. In younger patients without additional risk factors and undergoing high-risk surgery, a 10-14 days period of prophylaxis may suffice if they are fully mobilised at the end of this period. The latter recommendation places a relative high value on cost considerations.

- c. For total knee replacement and for abdominal or pelvic cancer surgery, the evidence is still less convincing and purely venographic. Thus a 10-14 days period of prophylaxis is still acceptable. Extended prophylaxis may be considered in the presence of additional personal risk factors.

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