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PREVENTION OF DEEP VEIN THROMBOSIS IN ORTHOPEDIC SURGERY

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Abstract: In the absence of thromboprophylaxis, venous thromboembolism (VTE) affects about 50 to 80% of the patients after total hip replacement (THR), total knee replacement (TKR), or hip fracture surgery. Since stratification of patients in those who will become symptomatic and those who will not, is not possible, primary high risk thromboprophylaxis should be provided to all patients undergoing major orthopedic surgery of the lower extremity. Various non-pharmacologic and pharmacologic thromboprophylactic measures have been evaluated. With regard to pharmacologic thromboprophylaxis unfractionated heparin has now almost completely been replaced by low molecular weight heparin (LMWH) for VTE prophylaxis. The use of acetylsalicylic acid for thromboprophylaxis in patients undergoing major orthopedic surgery of the lower extremities is not recommended. The optimal beginning of LMWH thromboprophylaxis is either 2 hours preoperatively or 6 to 8 hours postoperatively. Extended thromboprophylaxis (beyond 7 to 10 days after surgery) is recommended for high-risk patients. New antithrombotics, such as fondaparinux or (xi)melagatran, significantly reduce the risk of asymptomatic but not of symptomatic VTE compared to LMWH. In the light of other potential side effects (e.g., an increased bleeding risk) and high costs the role of these new drugs in the prophylaxis of VTE in patients undergoing major orthopedic surgery of the lower extremities remains to be established.

Key words: thromboprophylaxis, orthopedic surgery, low molecular weight heparin

Venous thromboembolism (VTE) is a common problem that – in the absence of prophylaxis - affects about 50 to 80% of the patients after total hip replacement (THR), total knee replacement (TKR), or hip fracture surgery (Table 1). Patients undergoing TKR have a higher risk of deep vein thrombosis (DVT) than those after THR and the risk of pulmonary (PE) is highest after hip fracture surgery (4-7%). Most VTE resolve spontaneously without causing problems. There are, however, certain patients who become symptomatic either because of venous occlusion or embolisation. Some risk factors for symptomatic VTE have been identified (e.g., prolonged immobility, obesity, previous thromboembolism, cancer) [1], but proper stratification of patients in those who will become symptomatic and those who will not, is thus far impossible. Thus, primary thromboprophylaxis should be provided to all patients undergoing major orthopedic surgery of the lower extremity.

Over the years various non-pharmacologic and pharmacologic thromboprophylactic measures have been evaluated. Pharmacologic thromboprophylaxis has been revolutionized by the introduction of heparin. Meanwhile unfractionated heparin (UFH) has now almost completely been replaced by low molecular weight heparin (LMWH) for VTE prophylaxis.

LMWH VERSUS UFH

TOTAL HIP REPLACEMENT

Compared with low-dose UFH (5000 IU s.c. tid) LMWH is more effective and likewise safe in patients undergoing THR [2]. LMWH (enoxaparin 30 mg s.c. bid) has also been compared with 7500 IU UFH s.c. bid starting 12 to 24 hours postoperatively [3]. The overall incidence of DVT was similar between LMWH and UFH (19% vs 23%, respectively; $p > 0.2$), but a lower frequency of bleeding complication was seen in patients receiving LMWH (5.1% vs 9.3% for major and minor bleedings; $p < 0.05$).

Thromboprophylaxis with LMWH is also at least as effective [4] or superior [5] to adjusted-dose UFH in patients after THR.

TOTAL KNEE REPLACEMENT AND HIP FRACTURE SURGERY

In general, the number of studies in which LMWH was evaluated for thromboprophylaxis in patients after TKR or hip fracture surgery is limited.

In patients after TKR, LMWH was significantly more effective than intermittent pneumatic compression [6,7]. In only one study LMWH (enoxaparin) was directly compared to low-dose UFH [8]. The incidence of proximal and distal deep venous thrombosis in the enoxaparin group was 24.6%

Table 1. Risk Categories for Venous Thromboembolism (VTE) [2].

Low risk	
Minor surgery, patients < 40 yrs, no additional risk factors*	
Risk of calf DVT	2%
Risk of proximal DVT	0.4%
Risk of clinical PE	0.2%
Moderate risk	
Minor surgery + additional risk factors*, or	
Nonmajor, patients 40-60 yrs, no additional risk factors*, or	
major surgery, patients 40-60 yrs, no additional risk factors*	
Risk of calf DVT	10-20%
Risk of proximal DVT	2-4%
Risk of clinical PE	1-2%
High risk	
Nonmajor surgery, patients 40-60 yrs + additional risk factors*, or	
major surgery, patients > 40 yrs or additional risk factors*	
Risk of calf DVT	20-40%
Risk of proximal DVT	4-8%
Risk of clinical PE	2-4%
Very high risk	
major surgery, patients > 40 yrs + additional risk factors*, or	
total hip or knee replacement, hip fracture surgery, or	
major trauma, spinal cord injury	
Risk of calf DVT	40-80%
Risk of proximal DVT	10-20%
Risk of clinical PE	4-10%

* including advanced age, previous VTE, obesity, heart failure, paralysis, thrombophilia (e.g., antithrombin deficiency)

Table 2. LMWH in comparison to Vitamin K-antagonists (INR 2.0-3.0) in patients undergoing THR or TKR

	LMWH vs Vit. K-antagonists	**All DVT n/n (%)**	**Proximal DVT n/n (%)**	**Major Bleeding n/n (%)**
Total Hip Replacement				
Hull 1993 [13]	tinzaparin 75 IU/kg sc od vs warfarin (INR 2.0-3.0)	69/332 (21) 79/340 (23)	16/332 (5) 13/340 (4)	11/398 (2.8) 6/397 (1.5)
RD Heparin Arthroplasty Group 1994 [14]	ardeparin 50 IU/kg sc bid vs ardeparin 90 IU/kg sc od warfarin (INR 2.0-3.0)	12/178 (7) 22/171 (13) 20/174 (11)	5/178 (3) 12/178 (7) 11/178 (6)	not reported not reported not reported
Hull 2000 [15]	dalteparin 2500/IU pre/postop. surgery, then 5000 IU od vs dalteparin 2500 IU post-surgery, then 5000 IU od vs warfarin (INR 2.0-3.0) begun post-surgery	37/337 (11) 44/336 (13) 81/338 (24)	3/354 (0.8) 3/358 (0.8) 11/363 (3)	10/496 (2) 5/487 (1) 8/489 (1.6)
Hamulyak 1995 [16]	nadroparin 60 IU/kg sc od vs acenocoumarol (INR 2.0-3.0)	27/195 (14) 27/196 (14)	12/195 (6) 9/196 (5)	3/195 (1) 7/196 (3.6)
Total Knee Replacement				
Hull 1993 [13]	tinzaparin in 75 IU/kg sc od vs warfarin (INR 2.0-3.0)	116/258 (45) 152/277 (55)	20/258 (8) 34/277 (12)	9/317 (2.8) 3/324 (0.9)
RD Heparin Arthroplasty Group 1994 [14]	ardeparin 50 IU/kg sc bid vs ardeparin 90 IU/kg sc od vs warfarin (INR 2.0-3.0)	37/150 (25) 41/149 (28) 60/147 (41)	9/150 (6) 7/149 (5) 15/147 (10)	25(381 (7) 20/389 (5) 21/403 (5)
Hamulyak 1995 [16]	nadroparin 60 IU/kg sc od vs acenocoumarol (INR 2.0-3.0)	16/65 (25) 23/61 (38)	5/65 (8) 6/61 (10)	2/65 (3) 1/61 (1)
Leclerc 1996 [17]	enoxaparin 30 mg sc bid vs warfarin (INR 2.0-3.0)	76/206 (37) 109/211 (52)	24/206 (12) 22/211 810)	7/336 (2) 6/334 (2)

(56/228), and in the heparin group 34.2% (77/225). In another study [9] in which low-dose UFH alone was evaluated for thromboprophylaxis in TKR, risk reductions for DVT (25% relative risk reduction for proximal DVT) were also relatively small and, thus, low-dose UFH is not recommended for thromboprophylaxis in patients after TKR.

Low-dose UFH was studied in two small trials for thromboprophylaxis in patients after hip fracture surgery, but in only one study LMWH was directly compared to low-dose UFH [10]. The results of these studies demonstrated an overall 44% relative risk reduction of DVT after surgery for hip fracture compared to control [10, 11]. Compared to low-dose UFH no significant difference in bleeding rates was seen [10]. In one study in which two different dosing regimens of LMWH (enoxaparin 20 mg s.c. od vs 40 mg s.c. od) were evaluated in patients undergoing surgery for hip fracture, distal and proximal DVTs occurred in 18.3% of patients receiving enoxaparin 20 mg and in 10.4% in the enoxaparin 40 mg group. No major hemorrhagic complication was observed, except for two hematomas in each group [12]. This trial suggests that a total daily dose of 40 mg of enoxaparin can be effective in the prevention of DVT in patients after hi fracture surgery without a major risk of bleeding.

LMWH versus Vitamin K-Antagonists

Total Hip Replacement

The efficacy and safety of LMWH (tinzaparin, ardeparin, dalteparin) compared with warfarin (target INR 2.0-3.0) or acenocoumarol (vs nadroparin) in patients having THR has been evaluated in four randomized trials [13-16]. LMWH begun postoperatively and given either once or twice daily was as effective as vitamin K-antagonists (Table 2). Major bleeding complications were low in both groups.

LMWH (dalteparin) starting in close proximity to surgery (6 to 8 hours postoperatively) was more effective than warfarin started the evening after surgery and had a low frequency of bleeding complications [15].

The incidence of symptomatic DVT was lower with LMWH started preoperatively than with warfarin the evening after surgery (1.5% vs 4.4%, $p = 0.02$) [15].

In a meta-analysis of five studies in which LMWH was compared with vitamin K-antagonists, the rates of DVT were 20.7% in the vitamin K-antagonist groups and 13.7% in the LMWH groups. The proximal DVT rates were 4.8% and 3.4%, respectively. Major bleeding rates were 3.3% for vitamin K-antagonists and 5.3% for LMWH (mainly bleedings from surgical sites), respectively [2].

Total Knee Replacement

Four randomized trials have shown that LMWH (ardeparin, tinzaprin, enoxaparin or nadroparin) is more effective than warfarin or acenocoumarol [13,14,16,17]. In a pooled analysis of six trials directly comparing LMWH with vitamin K-antagonists, DVT rates were 31.5% in the patients who received LMWH and 46.2% in the vitamin K-antagonist group. Proximal DVT rates were 10.2% and 6.7%, respectively. Four studies showed an increase either in major bleeding (0.9% vs. 2.8%) or in blood loss and transfusion requirement among patients receiving LMWH [2].

Hip Fracture Surgery

There are no trials that directly compare LMWH and vitamin K-antagonists in patients after hip fracture surgery. One study with a low molecular weight heparinoid (Orgaran®) demonstrated less efficacy of warfarin in comparison with the heparinoid (incidence of DVT 21% vs 7%) in patients with hip fracture surgery [18].

Despite an early start of vitamin K-antagonist (the evening before surgery or postoperatively as soon as possible), the INR usual does not reach the target INR until at least the third postoperative day. In addition, the INR monitoring as well as food- and drug-interactions are considerable drawbacks of the drug.

LMWH versus Fondaparinux

Fondaparinux sodium (Arixtra®) is a pentasaccharide that selectively and reversibly inhibits factor Xa by inducing a conformational change in antithrombin thereby increasing its anti-factor Xa activity [19]. A meta-analysis of four multicenter, randomized, double-blind trials (Pentamaks, Penthifra, Pentathlon 2000, Ephesus) in 7344 patients undergoing THR, TKR or hip fracture surgery [20-23] demonstrated a 55.2% relative risk reduction of postoperative asymptomatic VTE with fondaparinux (2.5 mg s.c. od) started 6 hours after surgery as compared to enoxaparin [24]. The cumulative incidence of VTE in patients assigned to fondaparinux or enoxaparin was 6.8% and 13.7%, respectively. The incidence of symptomatic VTE by day 11 was low and did not differ between patients with fondaparinux (0.6%) compared with those receiving enoxaparin (0.4%, $p = 0.2$). Compared with enoxaparin, fondaparinux was more frequently associated with major bleedings (1.7% vs 2.7%, $p = 0.008$). Fondaparinux has been approved for the prevention of VTE in patients undergoing THR, TKR and hip fracture surgery in Europe and in the USA.

LMWH versus Ximelagatran

Melagatran (Exanta®) is a direct thrombin-inhibitor with a favorable and predictable pharmacokinetic and pharmacodynamic profile after intravenous or subcutaneous application [25]. Ximelagatran (Exanta®) is a prodrug of melagatran with a reproducible oral bioavailability of around 20%. Ximelagatran is rapidly absorbed and bioconvert-

ed to its active form melagatran. The half-life of melagatran is about 3 hours mandating twice daily oral administration of ximelagatran without the need for coagulation monitoring. In a study from North America in 1838 patients undergoing THR, the cumulative incidence of VTE among patients receiving LMWH (enoxaparin s.c. 30 mg bid) was significantly lower than in patients receiving melagatran (24 mg p.o. bid) (4.6% vs 7.9%) [26]. In contrast, in three European studies (Methro II, Methro III, Express) (xi)melagatran was at least as effective or superior to LMWH in major orthopedic surgery of the lower extremities [27-29]. Differences in the study design may explain the different results. In contrast to the North American trial a combination of subcutaneous melagatran given preoperatively followed by oral ximelagatran (24 mg p.o. bid) as well as a lower dose of LMWH (enoxaparin 40 mg s.c. od) was used in the European trials. A meta-analysis of the European trials suggests that the treatment regimen of the Express trial (2764 patients undergoing THR or TKR) was most favorable [29]. In this trial, melagatran 2 mg was started immediately before surgery, 3 mg was then administered postoperatively, followed by 24 mg of oral ximelagatran b.i.d. beginning the next day. Compared to enoxaparin (40 mg s.c. od) initiated 12 hours preoperatively there was a significant reduction in the overall rate of VTE in the (xi)melagatran group (20.3% vs 26.6%, $p < 0.0001$) leading to a 24% relative risk reduction. Bleeding events were more common in the (xi)melagatran group (3.1% vs 1.2%, $p < 0.001$), although the frequency of bleeding in critical organs or fatal bleedings was similar in both groups.

Timing of Anticoagulation

European trials usually evaluated thromboprophylactic regimens starting preoperatively (e.g., LMWH ~5000 IU s.c. od), while in North American trials the postoperative beginning of prophylaxis is favored (e.g., LMWH ~3000 IU s.c. bid). There is only one trial (in hip arthroplasty patients) in which three prophylactic regimens were compared in a randomized double-blind design: dalteparin 2500 IU begun within 2 hours preoperatively, then 2500 IU at 4 to 6 hours postoperatively followed by 5000 IU od beginning the next day, if neuroaxial anesthesia was used, the preoperative dose was administered after the spinal puncture and only if the procedure was uncomplicated; dalteparin 2500 IU begun 4 to 6 hours postoperatively, followed by 5000 IU od beginning the next day; warfarin begun postoperatively the evening after surgery, target INR 2.0-3.0 [15]. Prophylaxis was continued in average for 6 days. Overall DVT rates for the preoperative dalteparin, the postoperative dalteparin and warfarin regimens were 11%, 13% and 24%, respectively. The rates for proximal DVT were 0.8%, 0.8% and 3%, respectively. The rates for major bleeding were 8.9%, 6.6% and 4.5%, respectively. These results demonstrate that a postoperative regimen of LMWH (dalteparin) begun early postoperatively is more effective than warfarin for preventing DVT including proximal DVT without increasing clinically important bleeding complications. The preoperative regimen did not produce a clinically important improvement in the effectiveness compared to the early postoperative regimen, but did increase the rate of major bleeding. In a meta-analysis in patients with elective hip surgery, perioperative regimens of LMWH administered either 2 hours preoperatively or 4 to 6 hours postoperatively were associated with a decreased incidence of proximal DVT compared to regimens begun 12 to 48 hours postoperatively [30]. Another systematic review of the timing of initial administration has also shown that the optimal interval for beginning LMWH thromboprophylaxis seems to be between 2 hours preoperatively and 6 to 8 hours postoperatively [31].

Duration of Anticoagulation

Anticoagulation is usually given for the duration of the hospital stay which generally ranges from 7 to 14 days. Recently, the duration of the hospital stay is often less than 5 days. Thus, debate about the optimal duration of anticoagulation is ongoing.

In patients after THR, a number of randomized double-blind trials have shown that extended LMWH prophylaxis through postoperative day 27 to 35 significantly reduced the incidence of total DVT, and support the need for continued prophylaxis with LMWH for 28 to 42 days after surgery [15,32-35]. Two meta-analyses demonstrated that a significant decrease in the incidence of VTE compared with placebo is achieved without an increase in major bleeding episodes [36, 37]. Importantly, these meta-analyses also showed that extended-duration prophylaxis also significantly reduced the frequency of symptomatic VTE.

In order to determine the optimal duration of prophylaxis with fondaparinux a placebo-controlled trial (Penthifra-Plus) has been conducted in 656 patients undergoing hip fracture surgery [38]. Compared to patients receiving thromboprophylaxis for one week after surgery, the incidence of venographically detected VTE was significantly lower among patients treated for 28 days postoperatively (35% vs 1.4%). Moreover, a significant reduction also in the rate of symptomatic VTE with prolonged prophylaxis (2.7% vs 0.3%, $p = 0.02$) without an increase in clinically relevant bleeding complications was seen. Fondaparinux is now licensed for prolonged thromboprophylaxis in patients after hip fracture surgery.

Evidence for extended prophylaxis beyond 10 days for patients undergoing total knee replacement is weak. Prolonging therapy for an additional three to six weeks does not appear to provide further benefit [36].

Other Thromboprophylactic Measures

Non-pharmacologic thromboprophylaxis, such as elastic stockings, intermittent pneumatic compres-

sion and early ambulation have been shown to reduce the risk of DVT by 6% to 60%, mainly by preventing distal thrombosis but with little effect on proximal DVT.

Compared to general anesthesia, spinal or epidural anesthesia significantly reduces the incidence of postoperative DVT in THR surgery and hip fracture [39-41]. However, the risk of VTE still remains high so that additional primary thromboprophylaxis is needed.

With regard to pharmacologic thromboprophylaxis in patients undergoing major orthopedic surgery of the lower extremities, low-dose UFH or acetylsalicylic acid are more effective than no prophylaxis but are less effective than other treatment regimens. In the Pulmonary Embolism Prevention (PEP) Trial, patients with hip fracture surgery (n = 13 356) were randomized to acetylsalicylic acid 160 mg or placebo [42]. 18%, 26% and 30% of the patients received additional thromboprophylaxis with low-dose UFH, LMWH or elastic stockings. A significant reduction of both fatal PE and DVT was seen in the patients who received acetylsalicylic acid. However, bleeding from surgical wounds and gastrointestinal bleeding were also significantly more common in the acetylsalicylic acid group.

Hirudin inhibits thrombin by directly binding to the fibrinogen recognition and catalytic sites of heparin. In one single multicenter study 2079 patients undergoing THR were randomized to DVT prophylaxis with either subcutaneous recombinant hirudin (desirudin) started 30 minutes before surgery or LMWH (enoxaparin) started on the evening before surgery [43]. The recombinant hirudin group had a significantly lower rate of total DVT (18.4% vs 25.5%) and also of proximal DVT (4.5% vs 7.5%). The superior results with hirudin could be due to a more efficient mode of action of this agent or to the timing of the first dose (within 30 minutes before surgery). No difference in bleeding complications between the two treatment groups was observed.

In patients having surgery for hip fracture, the heparinoid danaparoid is more effective than acetylsalicylic acid and is associated with a low risk (2%) of bleeding [44]. However, the relative effectiveness of danaparoid compared with warfarin in hip fracture patients remains uncertain.

The efficacy and safety of inferior vena cava filters have not been evaluated in comparison or addition to other recommended thromboprophylactic regimens. In patients with acute DVT, the short-term incidence of PE but not mortality was significantly reduced in the filter group [45]. During follow-up, filter patients had significantly more recurrent DVTs. Thus, extrapolation of these data leads to discouraging the use of vena cava filters in major orthopedic surgery.

SUMMARY

- Patients undergoing major orthopedic surgery of the lower extremities belong to a very high risk group for VTE and are candidates for high risk thromboprophylaxis.
- Thromboprophylaxis with LMWH (~ 5000 IU s.c. daily) is recommended for patients with THR. Alternatively, vitamin K-antagonists (target INR 2.0 -3.0) can be given.
- Patients undergoing TKR should receive LMWH thromboprophylaxis (~ 5000 IU s.c. daily). In general, prophylactic interventions are less effective in these patients, and DVT rates remain high despite primary thromboprophylaxis.
- After hip fracture surgery, LMWH thromboprophylaxis (~ 5000 IU s.c. daily) should be given to all patients. Alternatively, vitamin K-antagonists (target INR 2.0 -3.0) can be given.
- Thromboprophylaxis should be started 2 hours preoperatively or 6 to 8 hours postoperatively.
- The use of acetylsalicylic acid for thromboprophylaxis in patients undergoing major orthopedic surgery of the lower extremities is not recommended, as other measures are more efficacious.
- Adjuvant prophylaxis with elastic stockings or intermittent pneumatic compression may have additional benefit.
- The optimal duration of anticoagulation in patients after THR or TKR is uncertain. Extended thromboprophylaxis (beyond 7 to 10 days after surgery) is recommended for high-risk patients.

  In patients with hip fracture, thromboprophylaxis should be continued until the patient is ambulatory.
- Fondaparinux or (xi)melagatran is associated with a significantly reduced relative risk of asymptomatic VTE compared to LMWH (enoxaparin). The incidence of symptomatic VTE is not reduced by these new antithrombotics compared with LMWH. In addition, an increased bleeding risk during fondaparinux or (xi)melagatran prophylaxis is observed. In the light of other potential side effects [e.g., elevation of transaminases in case of (xi)melagatran] and high costs the role of these new antithrombotics in the prophylaxis of VTE in patients undergoing major orthopedic surgery of the lower extremities remains to be established.

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