Review article

Thromboprophylaxis in hip arthroplasty

New frontiers and future strategy

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Coagulation-related complications are a frequent cause of death following hip replacement surgery. Venographically-proven deep vein thrombosis (DVT) is found in a high frequency. Most cases have no symptoms. Fatal pulmonary embolism (PE) may develop from subclinical thrombi. In addition, arterial thromboses may induce serious cardiovascular events and an unknown number of patients may develop cardiorespiratory insufficiency, due to non-fatal venous PE. Finally, several patients may develop venous insufficiency.

Recent prospective double-blind studies have shown that the frequency of deep vein thrombosis increased after hospital discharge in patients undergoing hip replacement surgery. Prolonged thromboprophylaxis with low-molecular-weight heparin (dalteparin or enoxaparin) is recommended for at least 5 weeks after the operation.

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Each year more than 100,000 total hip arthroplasties are done in the United States (Woo et al. 1995) and about 15,000 in Norway and Sweden (Havelin et al. 1996, Malchau and Herberts 1996). In addition, many patients with femoral neck fractures are treated primarily with hemiprostheses.

Damage to the vessel wall draining the operation area, enhanced local and systemic activation of coagulation and stagnation of the blood flow during surgery trigger intraoperative and postoperative thromboembolic events (Stewart et al. 1983, Dahl et al. 1988, 1992, 1993, McNally and Molland 1993). Postoperatively, suppression of the fibrinolytic system followed by reactivation of the coagulation system and concomitantly reduced blood flow in the lower limbs favor thrombosis formation for at least 5 weeks (McNally and Molland 1993, Dahl et al. 1995). This may lead to rehospitalization of many patients owing to late thromboembolism (Johnson et al. 1977, Seagroatt et al. 1991).

Following hip replacement, DVT is mostly asymptomatic and may cause fatal PE without warning (Sandler and Martin 1989). Postmortem studies have shown that PE continues to be an important cause of death. In England, the National Confidential Enquiry into Peri-operative Deaths (NCEPOD) has stated that "pulmonary embolism is still the most common cause of death following hip replacement surgery" (Campling et al. 1993, 1994). In Norway, Karwinski (1995) found in a general autopsy material that "pulmonary embolism as the main and sole cause of death had increased over the last decade", indicating that although not apparent to the clinicians, it remains a serious threat to the patients.

Usually, thromboprophylaxis has been given for approximately 1 week, i.e., during hospitalization. However, the thromboembolic risk seems to persist after hospitalization (Dahl 1995). Recently, 4 European prospective placebo-controlled studies have been performed to clarify the late frequency of thromboembolism after hip replacement surgery and to find out whether thromboprophylaxis should be continued after discharge from hospital (Lassen et al. 1995, Bergqvist et al. 1996, Planes et al. 1996, Dahl et al. 1997).

In three studies, low-molecular-weight heparin (LMWH) (dalteparin 5000 IE/d or enoxaparin 40 mg/d) was given prophylactically during the first postoperative week (dextran-70 and graded elastic stockings were added in one study). The patients were then randomized to placebo or LMWH for a further 3 and 4 weeks (Lassen et al. 1995, Bergqvist et al. 1996, Dahl et al. 1997). The prevalence of DVT was found to be more than 30% in two studies (Bergqvist et al. 1996,

Dahl et al. 1997) and 12% in one study (Lassen et al. 1995), until 5 weeks after the operation.

The incidence of DVT between 1 respectively 2 and 5 weeks after hip replacement was assessed in two studies (Planes et al. 1996, Dahl et al. 1997). In patients with no venographic signs of DVT before discharge, 25% developed DVT after 1 week on thromboprophylaxis and 19% after 2 weeks on prophylaxis.

The frequency of DVT was reduced by about 50% in patients receiving LMWH prophylaxis in the double-blind period, compared with placebo.

The clinical diagnosis of thromboembolism was inadequate, compared with objective diagnostic methods (Lassen et al. 1995, Bergqvist et al. 1996, Planes et al. 1996, Dahl et al. 1997). This is in harmony with other reports (Wells et al. 1995, Andreassen and Dahl 1997). During hospitalization, none of the patients had signs and symptoms of DVT, reflecting that the initial posttraumatic leg-pain and swelling effectively masked concomitant symptoms of DVT (Bergqvist et al. 1996, Dahl et al. 1997). However, in the posthospitalization period, readmission due to suspected DVT was found in nearly 6% (12/218) in one study (Dahl et al. 1997) and was venographically verified in about half of the cases.

Clinically, PE was found in approximately 1% (10/878) of the patients (Lassen et al. 1995: 4 patients (personal communication), Planes et al. 1996: 1 patient, Bergqvist et al. 1996: 2 patients, Dahl et al. 1997: 3 patients). 1 patient died suddenly 3 weeks after surgery in a recreation center. Autopsy showed a massive bilateral pulmonary embolism. This patient had a small DVT in a calf vein on venograms taken on day 7 (Dahl et al. 1997).

In one study, pulmonary embolism was systematically investigated (Dahl et al. 1997). Mandatory chest radiographs and ventilation perfusion lung scan (V/Q scan) were performed on days 7 and 35 after the operation. The overall occurrences of symptomatic and asymptomatic PE (high and intermediate probabilities of PE according to Biello) in this interval were found to be approximately 7% in the placebo group (including 1 death) and 4% in the prolonged prophylaxis group.

The course of DVT development between days 7 and 35 was also assessed in one study (Dahl et al. 1997). Progression of DVT was found to be twice as frequent (about 50% of the DVTs) in the placebo group as in the treatment group (about 25% of the DVTs), while thrombolysis was twice as frequent in the treatment group (about 50% of the DVTs) as in the placebo group (about 25% of the DVTs).

Thrombocytopenia, defined as a platelet counts below $100/10^9$/L), was reported in 1 case on day 21 (87×10^9/L) in one study (Planes et al. 1996).

Self-injection of LMWH was taught to the patients by the nurses during the hospitalization period and was successfully performed by most patients following discharge (Lassen et al. 1995, Planes et al. 1996, Dahl et al. 1997).

Comments

Four European studies from four different populations have shown that the frequency of deep vein thrombosis increased for about 1 month after the prophylaxis was postponed in patients who had undergone hip replacement surgery (Lassen et al. 1995, Bergqvist et al. 1996, Planes et al. 1996, Dahl et al. 1997). The emergency readmission rate due to clinically suspected thromboembolism was high (15/218, 7%) (Dahl et al. 1997), which is in accordance with the results of other studies (Seagroatt et al. 1991). Pulmonary embolism (clinical and subclinical, verified with V/Q scan), including one death, was about twice as frequent in patients who received LMWH prophylaxis for only 1 week as in those who had protection for 5 weeks (about 7% versus 4%) (Dahl et al. 1997).

Although overwhelming information shows the value of using thromboprophylaxis to prevent DVT following major orthopedic surgery, some surgeons still question the efficacy of chemical prophylaxis, in view of findings from open non-randomized studies (Clarke et al. 1997, Fender et al. 1997, Warwick and Whitehouse 1997). In a paper recently published, the patients were venographically screened for DVT within the first postoperative week and those having proximal DVT were treated with anticoagulants (Clarke et al. 1997). A similar approach with ultrasonography has also been proposed by Agnelli et al. (1995). However, such an approach, which aims to treat patients with subclinical DVT before hospital discharge, does not take into account that the incidence of DVT seems to increase after discharge (Planes et al. 1996, Dahl et al. 1997). In spite of LMWH prophylaxis up till 2 weeks after the operation (Planes et al. 1996) and continuing daily physical training at recreation centers for a further 3 weeks (Dahl et al. 1997), 20%–25% of the patients had developed DVT after discharge.

These findings may help to explain the high readmission rate due to clinically suspected DVT (Seagroatt et al. 1991) and that fatal PE caused by subclinical DVT still seems to be a leading cause of death, following major surgery (Campling et al. 1993, 1994).

It has been claimed that there is a discrepancy between the high frequency of subclinical thromboem-

bolism and the low frequency of clinical thromboembolism and that clinical thromboembolism is the most important endpoint (Murray et al. 1996, Warwick and Whitehouse 1997). Therefore, some authors have claimed that prophylaxis is not needed (Clarke et al. 1997, Fender et al. 1997). First, inadequate clinical study design help to obscure the real frequency of fatal thromboembolism. Secondly, subclinical DVT is a potential threat to these patients' life. Autopsy studies have repeatedly shown that the clinical diagnosis has been missed (Havig 1977, Sandler and Martin 1989, Karwinski 1995). Thirdly, the patients that die are from the majority of the patients with untreated asymptomatic DVT.

The occurrence of thromboembolism is a consequence of an unbalanced posttraumatic coagulation-dependent healing process. Prevention of subclinical DVT by controlling thrombin generation certainly prevents fatal pulmonary embolism, since it is the same pathophysiological process independently of clinical symptoms. However, short-term neutralization of the thrombin activity seems insufficient to prevent late thromboembolism. Prophylaxis should probably be continued until the healing process has come to an end and the increased thrombin generation has normalized.

Studies on myocardial infarction and unstable angina have shown that discontinuation of heparin, hirudin and argatroban caused a secondary increase in activation of coagulation and thrombotic events (Gallino et al. 1986, Gold et al. 1993, Granger et al. 1995, Merlini and Ardissino 1997). Prolonged anticoagulation seems to reduce this risk (Wallentin et al. 1996, Cohen et al. 1997). This is like the findings following hip replacement surgery (Dahl et al. 1995). Interruption of LMWH prophylaxis 1 week after surgery immediately increased activation of coagulation and the incidence of DVT (Dahl et al. 1995, 1997). In addition, reduced blood flow for several weeks (McNally and Molland 1993) may help to prolong this hypercoagulable period. Although calf muscle movements have been shown to increase blood flow (McNally et al. 1997), daily exercise did not prevent DVT formation after hip replacement surgery (Dahl et al. 1997). Thus, at present we have good evidence for recommending thromboprophylaxis with LMWH (dalteparin or enoxaparin) for at least 5 weeks after hip replacement surgery.

Further strategy

Thrombin generation caused by bone traumatization is significantly more severe in arterial than in venous blood during hip replacement surgery (Dahl et al. 1988, 1992, 1993, Dahl 1997b). This is reflected by a high rate of coagulation-related deaths after major orthopedic surgery (Schöning et al. 1980, Dahl 1997a). Consequently, we have to reconsider our view of thromboprophylaxis. It should prevent both venous and arterial thromboembolic events. Control of thrombin generation may prevent intraoperative coagulation-related cardiorespiratory and vascular collapse (Dahl 1997), postoperative myocardial infarction, embolic stroke and venous thromboembolism.

Future studies should focus on the optimal duration of thromboprophylaxis, preferably on an individual basis. Thromboprophylaxis should probably continue until thrombin generation has normalized, to avoid late venous and arterial thrombus formation.

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