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Prevention of post-discharge venous thromboembolism in patients with rheumatoid arthritis undergoing knee or hip arthroplasty: a continuing matter of debate

Patients undergoing major hip or knee surgery are particularly prone to postoperative venous thromboembolism (VTE)—that is, deep venous thrombosis (DVT) and pulmonary embolism (PE). Without thromboprophylaxis, the incidence of DVT in such patients is more than 50%, and fatal PE occurs in 1–6%.¹ These data are based on studies in which, predominantly, patients with osteoarthritis (OA) were investigated.

It is not known whether or not there is a significant difference in the risk for developing VTE between patients with rheumatoid arthritis (RA) and those with OA undergoing major orthopaedic surgery as adequate investigations are lacking.²

Thromboprophylaxis during hospitalisation

During the past three decades, numerous investigations documented the efficacy of unfractionated heparin, pneumatic compression, warfarin, and low molecular weight heparin (LMWH) in reducing the incidence of postoperative VTE.

Nowadays, LMWH is the most commonly applied thromboprophylactic agent in most orthopaedic surgery units in Europe. The evidence for the efficacy and safety of LMWH is derived from (large) trials, in which, predominantly, patients with OA were studied. Although these studies encompassed only a limited number of patients with RA, LMWH is also commonly used in patients with RA as thromboprophylaxis.

However, notwithstanding the use of preventive pharmacological thromboprophylaxis, there is still a considerable rate of asymptomatic DVT, approximately 15–20%, at the time of hospital discharge.³

Is post-discharge (venous) thromboprophylaxis needed?

Despite this high residual rate of DVT and laboratory evidence of continuing coagulation activation up to six weeks or longer after the operation,⁴ there is no consensus about whether and for how long thromboprophylaxis should be given after hospital discharge in patients with OA or RA who have undergone major orthopaedic surgery.

An argument used against prolonged thromboprophylaxis is that most DVT occurring in the post-discharge period is symptomless and of unknown clinical significance. However, others argue that some of these asymptomatic thrombi will ultimately lead to potentially fatal thromboembolic complications, and others will lead to the post-thrombotic syndrome (PTS).

Relation between asymptomatic DVT and symptomatic VTE in the post-discharge period

Thus far at least six randomised, double blind, placebo controlled trials have examined the effect of administration of LMWH after discharge in the prevention of VTE in patients undergoing hip or knee replacement.^{5–10} The investigations had a comparable design—patients post-discharge were randomly allocated to receive either additional LMWH or placebo for a period up to six weeks. Venography to detect asymptomatic DVT was used in five of these trials, whereas the remaining trial focused on symptomatic VTE and mortality. Large risk reductions of 40–60% with residual DVT incidences of 4–37% during the post-hospitalisation period were observed. The percentage of symptomatic VTE in the placebo groups varied between 2% and 8%. This large variation in incidence is probably caused by the relatively small sample sizes of the individual investigations.

Two recently published, much larger studies, a case-control study and a prospective investigation, indicate an incidence of approximately 3% in untreated patients.^{11,12} The case-control study was conducted in 21 718 patients who had had hip surgery; symptomatic thromboembolic complications were detected after discharge in 2.1% of the patients.¹¹ The diagnosis was confirmed in 96% of patients, and of the 297 selected patients, 203 had DVT and 94 had a PE. The true incidence of symptomatic VTE—that is, without prolonged thromboprophylaxis, is probably underestimated in this investigation as more than 20% of the patients received warfarin in the post-discharge period. The prospective study was performed in 156 clinical centres, encompassing a total 3015 patients, and found symptomatic VTE in 90 (3.0%) patients.¹²

Together, these two studies demonstrate an incidence of approximately 3% symptomatic VTE in the post-discharge period when no prolonged thromboprophylaxis is given.

One might argue that this incidence is too low to justify prolonged prophylaxis. However, VTE is a potentially fatal complication and this obviously outweighs the (low) major bleeding risk in these patients. Hence, prolonged thromboprophylaxis seems warranted after major orthopaedic surgery in patients with OA.

Post-discharge VTE and RA

However, these results cannot be extrapolated to patients with RA as (a) data on the thromboembolic risk in patients with RA are lacking and (b) most patients with RA continue to receive non-steroidal anti-inflammatory drugs

(NSAIDs) postoperatively, which might lead to a different benefit (that is, reduction of post-discharge thromboembolism) to risk (that is, induction of bleeding complications) ratio as compared with patients with OA.

To date, only one study of the incidence of post-discharge VTE in patients with RA has been published.¹³ In this investigation, van Heereveld *et al* present retrospective data of 103 patients with RA undergoing major orthopaedic surgery procedures and found symptomatic VTE only on the 17th day after surgery (95% CI 0 to 4%). The authors suggest that in patients with RA undergoing major orthopaedic surgery post-discharge thromboprophylaxis might not be necessary. One explanation might be that such patients have a lower post-discharge VTE risk owing to the use of NSAIDs.

This conclusion appears premature as their data are still compatible with those found in patients with OA—that is, a clinically relevant VTE risk. Moreover, the hypothesis that NSAIDs have an (venous) antithrombotic effect is controversial and has never been investigated in properly conducted trials.

In addition, the recently marketed COX-2 inhibitors might replace conventional NSAIDs in the future because they have a more favourable benefit to risk profile. However, these compounds seem to have a much lower antithrombotic efficacy, which might lead to a somewhat higher postoperative VTE risk than with conventional NSAIDs.¹⁴ In other words if conventional NSAIDs do have any antithrombotic effect, this will disappear when they are replaced by the COX-2 inhibitors.¹⁵

Orthopaedic surgery and the PTS

Up to now two important, albeit retrospective, studies have investigated this subject.^{16, 17} Siragusa and Serafini evaluated 152 patients who had had major orthopaedic surgery, and who had undergone venography at hospital discharge, two to four years after the operation for the existence of PTS.¹⁶

The patients received full dose anticoagulation in the case of venographically proved DVT, which were all asymptomatic. The incidence of PTS was 24% in the patients who had a DVT, compared with 4% in the control group. Moreover, proximal DVT led far more often to PTS than to isolated calf DVT. Obviously, this study demonstrates a possible relationship between asymptomatic (treated) DVT and the occurrence of PTS.

The results of this study are in striking contrast with the findings of Ginsberg and coworkers.¹⁷ Their study had a similar design, and they investigated 255 subjects who had undergone major hip or knee arthroplasty. The rates of PTS were low and not significantly different among the three subgroups (that is, proximal DVT, isolated calf DVT, and no DVT). The discrepancy between the results of the two studies might be explained by methodology—for example, different patient groups or different outcome assessment.

At present, the only valid conclusion that can be drawn is that more prospective, sufficiently powered, investigations are required before we know whether or not PTS is a serious problem after major orthopaedic surgery and if it can be prevented by post-discharge thromboprophylaxis.

Post-discharge thromboprophylaxis and bleeding

ORAL ANTICOAGULANTS

Bleeding risks caused by prolonged (post-discharge) anticoagulation with oral anticoagulants have never been examined properly for patients who have undergone major orthopaedic surgery. Investigations in other patient categories (for example, treatment of VTE) indicate a major

bleeding risk (requiring admission to hospital) of 1–8% and a fatal bleeding rate of 0.5–4.8% for each patient treated.^{18–22} An important point to be considered, is the additional bleeding risk if an NSAID is used in combination with oral anticoagulants.²³ For instance, the relative risk for a gastrointestinal bleeding or perforation has been shown to be increased by more than six times when an NSAID is used in addition to oral anticoagulants.²⁴ These bleeding risks also favour withholding prolonged thromboprophylaxis with oral anticoagulants.

LMWH HEPARIN

The trials investigating post-discharge thromboprophylaxis showed no major bleeding episodes in almost 1500 patients treated with LMWH. In most of these trials the use of NSAIDs was not prohibited and hence, a clinically relevant major bleeding risk caused by the concurrent administration of LMWH and NSAIDs seems implausible.

Current clinical practice

Reduction of post-discharge VTE by anticoagulants should be carefully weighed against risk of bleeding and the concomitant costs. To date, no conclusive evidence, particularly for patients with RA, is available and, presently, many orthopaedic surgeons in the Netherlands continue thromboprophylaxis after hospital discharge for six weeks up to three months, for which oral anticoagulants, mostly acenocoumarol, are used. Thus far, the routine use of post-discharge anticoagulation with oral anticoagulants and the length of time for which it is used have never been validated adequately and, consequently, post-discharge anticoagulation is not applied by all orthopaedic surgeons.

At present, LMWH is not commonly used for post-discharge anticoagulation, but in view of the low risk of bleeding its use is expected to increase in the near future.

Throughout the years there has been a clear trend towards shorter hospital stays—for example, five instead of 10 days, after major orthopaedic surgery, which means that the length of thromboprophylaxis becomes shorter. As it is generally believed that patients should get at least seven days' thromboprophylaxis, this means that some patients are inadequately protected at the time of a hospital discharge which favours post-discharge anticoagulation.

Conclusions

Post-discharge venous thromboembolism is a clinically relevant complication after major orthopaedic surgery. Presently, we do not know whether the risk for developing post-discharge VTE is different between patients with OA and those with RA. Obviously, this problem can only be solved by an appropriate placebo controlled trial, preferably with LMWH, in view of the negligible bleeding risk. Such a trial should focus on clinically relevant end points—that is, symptomatic objectively confirmed, DVT and PE, instead of surrogate end points. Moreover, patients should be followed up yearly (for at least four years) for the occurrence of the PTS.

Recently, a phase two study with a synthetic pentasaccharide demonstrated an improved benefit to risk ratio for the prevention of VTE during the hospitalisation period as compared with LMWH in patients undergoing major hip replacement.²⁵ It remains to be shown by phase three trials that at the time of hospital discharge there is indeed a negligible incidence of VTE, making post-discharge anticoagulation unnecessary, without an enhanced bleeding risk. Until then post-discharge thromboprophylaxis remains a matter of continuing debate.

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