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EDITORIAL

Thromboembolism and thromboprophylaxis in high risk surgery: facts and assumptions – a topic for emotions?

Major orthopaedic surgery is associated with serious coagulation related complications. Perioperative cardio-respiratory and vascular dysfunction have regularly been reported in connection with hip replacement surgery and account for a mortality up to 0.5% [1,2]. Organ failure syndromes, myocardial insufficiency and infarction, brain stroke and clinical venous thromboembolism may occur from the time of the trauma and until many weeks after and account for additionally 3–4% [1,3–7].

Inherited thrombophilic disorders

Some patients seem predisposed to arterial and/or venous thromboembolic events. This may be due to abnormalities in the blood proteins regulating pro- and anticoagulant activities and several hereditary and acquired deficiencies have been described.

Since the frequency of thromboembolism increases with age and patients undergoing major joint surgery are predominantly in the older age groups, thrombophilic disorders could theoretically set these patients at a particularly high risk of postoperative thromboembolic complications. The prevalence of some of these thrombophilic defects could therefore be expected to increase. However, in patients over 85 years of age, the same prevalence of the Leiden V mutation was found as in young people and without any association with mortality [8,9]. In another study in patients over 65 years, Factor V Leiden was not found to be a risk factor for arterial thrombosis [10]. Another possibility is that the plasma levels of the coagulation inhibitors could increase with age. Sakkinen and co-workers [11], however, failed to find any association between age and the plasma levels of antithrombin, protein C, protein S and tissue factor pathway inhibitor. Neither the coexistence of factor V Leiden genotype nor methylentetra-hydrofolate reductase (MTHFR) which is associated with thrombophilia, have been shown to increase the risk of thrombosis following high risk orthopaedic surgery whether assuming a recessive or a dominant allele model [12–14]. One recent study showed that women heterozygous for factor V had an increased risk for late venous thrombosis after hip replacement surgery [15]. This result could not be confirmed in a similarly designed study [16]. Recently, an association between the genotype for angiotensin I-converting enzyme (involved in regulation of vascular tone) and the risk of postoperative thrombosis has been reported to increase the risk of DVT in patients undergoing joint arthroplasty [14]. It would appear, from the few and conflicting studies currently available, that underlying inherited diseases do not play an important role in the post-traumatic procoagulant process.

Hypercoagulability

For many years, we have focused on postoperative venous thromboembolism as an important cause of death. Recent research has shown that post-traumatic hypercoagulability affects both the venous and arterial circulation following major orthopaedic surgery. Trauma to the large bones causes extravasation of bone marrow cells [17]. These cells have a high content of tissue factor (TF) [18] and high blood concentrations have been measured by Giercksky and his coworkers [19]. This triggers activation of coagulation locally in

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veins draining the operative area [20]. Blood-borne procoagulant debris from the traumatized area is brought to the lungs where it triggers an additional substantial activation of coagulation and thrombin generation as the blood passes through the lungs. Significantly higher activation of coagulation has been found in arterial blood leaving the lungs as opposed to mixed venous blood entering the lungs during hip replacement surgery [21–23]. Thus, the lung capillaries seem to play a key role in the thrombin-generating process during major bone surgery.

Impaction of bone cement, which is frequently used to fix implanted prostheses, adds both a mechanical and a chemical component. This contributes to the coagulation process and to the formation of deep venous thrombosis [20,24,25]. In addition there is haemodynamic instability and a higher perioperative mortality when compared to non-cement prosthesis implantation [26].

Following the operation, reactivation of the coagulation process occurs when prophylaxis is stopped. This phenomenon has also been observed following cardiac disease and has resulted in an increase in angina pectoris and myocardial infarction [27–29]. Hypercoagulability seems to last for 6 weeks or more following hip arthroplasty particularly if prophylaxis is discontinued. This parallels reduced venous blood flow and an increased formation of late deep vein thrombosis [30,31].

Thromboprophylaxis

Many believe that mobilization is the best way to avoid venous thromboembolic complications, as stated in the Consumers Guide to Total Joint Replacement from the American Association of Hip and Knee Surgeons 1999. Although venous blood flow may be increased by more than 20% above the resting level [32], mobilization alone is often not enough to overcome the considerable pro-coagulant activity that has been found following major orthopaedic surgery (*vide supra*).

Patients may still be at risk from thromboembolic complications for many weeks after surgery [3–5,33]. Rapid and systematic mobilization did not seem to significantly influence thrombus formation in these patients. In a 4-week period after discharge, DVT progression was found to be approximately twice as frequent as DVT regression in spite of daily training under direct supervision by physiotherapists. About 20–25% of patients developed a DVT during the 3- to 4-week postdischarge period. Prolonged thromboprophylaxis with low molecular weight heparin (LMWH) (enoxaparin, dalteparin) reduced the frequency of thromboembolism to about half and is therefore highly recommended [7,34–37]. Whether other groups of patients should receive prophylaxis beyond discharge is at present unknown. It is tempting to speculate that patients having undergone surgery or major trauma to tissues with high pro-coagulant activity, for example the brain, should also receive longterm prophylaxis. The healing process can be prolonged in these patients and a high frequency of thrombembolic events has also been found [38].

Neuraxial complications

Attention has recently been paid to neurological deficits after surgery which have been assumed to be caused by an intravertebral haematoma induced by the combination of spinal nerve block and chemical thromboprophylaxis. Such complications have mainly been reported in North America and have mostly been associated with the use of LMWH. A 50% higher dose than that used in Europe has traditionally been administered postoperatively. The risk of inducing a spinal haematoma has been calculated to be in the order of 1 in 250 000 after spinal puncture and 1 in 150 000 after the use of an epidural catheter [39]. The Food and Drug Administration in the USA issued a 'black box warning' (1997) of this risk which all manufacturers of LMWH had to include in their drug information. The American Society of Regional Anesthesia also recommended in 1998 that concomitant use of NSAIDS should be avoided prior to surgery if spinal or epidural analgesia was planned. Many local recommendations based on these guidelines have appeared. At some hospitals these guidelines have almost been practised as rules with potential legal implications.

In placebo-controlled studies, the preoperative injection of LMWH carried no clinically significant increased risk of bleeding [40–43]. In an abstracted North American study, comparing LMWH administered at the time of the surgical procedure with postoperative LMWH, a nonsignificant, slightly increased bleeding tendency was found in the first group [37]. In

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a prospective controlled trial, perioperative administration of NSAIDs together with LMWH were found not to increase bleeding when compared to LMWH alone [44].

The validity of statistics

Official death rates for patients dying from pulmonary embolism have been questioned. In general, the autopsy rate is low (about 15%) in Western countries. In addition, routine autopsies may overlook a number of cases of pulmonary embolism both as a contributing cause of death and as the main cause of death [45] This contributes further to the under-reporting of the number of patients with pulmonary embolism.

Retrospective descriptive studies of a population of interest may give a rough overview of the magnitude of the problem and an hypothesis may be provided. To test the hypothesis, prospective more rigorously designed studies have to be performed. The most powerful study design we have is the prospective double-blind randomized study. This study design is commonly used to compare the efficacy and safety of two anticoagulants. To reach an objective figure for the number of confirmed deep vein thromboses, venography is necessary since the clinical diagnosis of thromboembolism is unreliable after surgery. However, interpretation of data from such studies may be open to question. Selection of study patients and exclusion of patients from the final statistical analysis will automatically lower the estimates of actual events. In addition, treatment of patients who have reached the surrogate endpoint, i.e. DVT, and the fact that pulmonary embolism often is a secondary endpoint, will further contribute to an underestimate of the actual number of thromboembolic events in the basic population. Finally, focusing only on venous complications without including arterial thromboembolic events will also help to obscure the clinical reality of such complications. Meta-analysis based on 'super-studies' is likely to underestimate the real number of patients with postoperative coagulation-related complications. Figures concerning the number of venous thromboembolic events in a specific population is often wrongly extracted from such studies.

New avenues

It has repeatedly been shown that pulmonary embolism is mostly a postmortem diagnosis missed by the clinicians. This strongly indicates that subclinical DVT is the main source of these fatalities [46–49]. Since post-traumatic hypercoagulability is a systemic phenomenon, future studies should include both venous and arterial vascular complications. Such an approach may show a more realistic picture of post-traumatic vascular morbidity and mortality than has been apparent to date due to studies focusing only on deep vein thrombosis as primary outcome measure. However, as previously noted, surrogate endpoints are of great value and should also be included as an endpoint measurement. To optimize the duration of prophylaxis on an individual basis, studies on haemostatic markers may also be of value [50].

It is possible that we have reached an efficacy/safety optimum at least in surgery with moderate prothrombotic risk using recommended doses of available LMWHs [51]. On the threshold of a new millennium, potent new anticoagulants are imminent. The question of whether preoperative or postoperative administration is preferable with these new drugs will hopefully be determined on the basis of well-designed studies and not on the emotional feelings of physicians.

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