Regular Review

Can we really prevent postoperative pulmonary emboli?

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An important difference between patients and their doctors is that the former are concerned only with the outcome of their illness, whereas it is all too easy for doctors to become distracted by intermediate issues such as naming the illness or the results of tests done to diagnose it and to monitor its progress. This divergence of interests is very clearly shown by the confusion currently surrounding the prevention of postoperative venous thromboembolism.

When a patient enters hospital for an operation his prime concern is to come out again alive and well. He wants to reduce to the minimum any chance of death or disability. One hazard is leg-vein thrombosis and pulmonary embolism. No valid long-term studies have yet been reported on the ability of prophylactic measures to reduce subsequent disability from the all-too-common post-thrombotic swelling and ulceration or the rarer event of heart failure from thromboembolic pulmonary hypertension. Until such studies are reported, survival is the only valid end-point, so a shrewd patient would listen carefully to the arguments put forward by his doctors and would then ask just one telling question.

He would be told that most deep-vein thrombi are symptomless, so that special tests (^{125}I -scanning and phlebography) are needed to identify them. These tests have shown that thrombi can be found in 70% of elderly patients operated on for hip fractures, 50% of patients who undergo hip replacement, 50% of patients after prostatectomy, 35% of general surgical patients over the age of 40, and 15% of women who have a hysterectomy for benign conditions.¹ He would be told that though only a few of these detectable thrombi will ever produce pulmonary embolism a fatal embolus can occur in any patient with deep-vein thrombosis, especially when the thrombus is in the proximal iliofemoral segments.² So the chain of reasoning put to him would be that operation increases his chance of developing leg-vein thrombosis, which in turn increases his chance of pulmonary embolism, which in turn decreases his chance of survival. Effective prophylaxis should minimise all the steps in the chain—but the only one which is of interest to the patient is the final one: his chance of dying of pulmonary embolism. All the other steps, crucial though they may appear to his attendants, are merely means to this end and are not an end in themselves.

The shrewd question which the patient would therefore put to his doctors would be, "If fatal pulmonary embolism is common after operation then it should have been easy to show that your treatments are really effective because they will have kept more people alive. Have your prophylactic regimens improved survival? If not, why not? Is it because they do not work or because pulmonary embolism is not so important as you think?" He would brush aside attempts to offer him other answers relating to intermediate end points such as leg scans, phlebography, and lung scans and might suggest that the best way to prevent the results of these tests from becoming

abnormal and worrying the doctors is to stop doing them. An ideal postoperative prophylactic regimen is one which is simple to administer and to control, free from ill effects (such as a tendency to increase operative bleeding), and effective as judged by a reduction in total deaths. The current candidates are conventional anticoagulants, low-dose heparin, platelet-modifying agents, dextran, and mechanical methods such as the use of stockings or gaiters, or calf stimulation. There is little doubt that anticoagulation with warfarin is effective,^{3,4} but the complex control measures needed and fears of bleeding have meant that only 3% of British surgeons looking after the highest-risk group are using them⁵—and yet it was in this group of elderly patients with femoral neck fractures that Sevitt and Gallagher³ showed that the regimen saved lives. Platelet-modifying agents such as aspirin and dipyridamole are currently under active scrutiny,⁶ and though they fulfil our requirements for ease of administration and safety none of them have so far been shown to reduce total mortality. The need to remain alert to the existence of diverse subgroups within the total is highlighted by the ability of aspirin to prevent phlebographically identified thrombosis in men but not in women.⁷ If this also applies to fatal pulmonary embolism, then studies will need enormous numbers of patients if they are to show a significant reduction in mortality after stratification to take account of this and other crucial variables such as age, severity of operation, the presence of malignant disease, and a previous history of venous thromboembolism.⁸

Though large-scale studies on dextran have been mounted they have shown no favourable effect on total mortality. The results of the trials have been conflicting; some have reported a reduction in pulmonary embolism without any apparent effect on leg-vein thrombosis,⁹ and others have indicated a reduction in clinically or isotopically detected venous thrombosis.¹⁰ Similarly, mechanical methods have been tested for their effect on intermediate or doctor-based end points, but none of the trials have included enough patients to fulfil our patient-based criterion of survival.

What, then, would our patient make of the current vogue for low-dose heparin, a regimen which satisfies most of our requirements for the ideal prophylactic? In a multicentre international trial¹² 4121 patients over the age of 40 undergoing elective surgery were randomly allocated to no prophylaxis or to 5000 units of calcium heparin given subcutaneously two hours before operation and eight-hourly thereafter for seven days. The doctor-based end points were appreciably affected (16 deaths in the control group were attributed to pulmonary embolism but only two in the heparin group, while leg-vein thrombosis as detected by radioactive iodine was found in 24.6% and 7.7% of the groups respectively). But in answer to our patient's crucial question, we would have to admit that total deaths, though following the same pattern (100 in the

control and 80 in the heparin group) did not differ significantly. We would thus have to tell him that, despite the vast investment of effort required to recruit and document over 4000 patients at risk, no statistically significant effect on mortality had been shown. He might then assert that the trial had been stopped too soon—before a valid end point had been reached—and many would support him. The harsh fact is that while pathologists can decide what patients die with they cannot decide, on any objective basis, what patients die of.¹³ The claim that the trial indicated benefit from heparin by reducing deaths attributed to pulmonary embolism is based on subjective opinion and is no substitute for a reduction in total deaths. Moreover, subsequent discussions about the results from one of the participating centres^{14 15} have cast doubt on the criteria for assessing the way in which deaths were attributed to pulmonary embolism.

Last week (p 1447) in the *BMJ* Immelman *et al* described the first phases of a study intended to reopen the controversy which many had wrongly regarded as having been resolved by the international trial. They have entered white patients aged over 40 undergoing intraperitoneal procedures, under general anaesthesia lasting over 30 minutes, into a randomised comparison of no prophylaxis and of subcutaneous sodium heparin (5000 units eight-hourly). Another group is receiving calcium heparin as used in the international trial, but these results are not yet available. The trial end points, with the small numbers recruited, are inevitably intermediate and doctor-based and so cannot answer our critical patient's question, "Will I live or will I die?" Of interest, however, is their preliminary finding that calf-vein thrombosis was reduced by heparin, but that proximal-vein thrombosis and pulmonary emboli (as detected by radiographs, lung function tests, and perfusion scanning) were not. The failure to reduce proximal thrombosis is at variance with the outcome of previous work¹⁸; nevertheless, this preliminary result must reopen the whole question of the relevance of calf-vein thrombosis to pulmonary embolism. Browse *et al*¹⁶ showed that there was a relation, but that only 18% of patients with isotopically detected leg thrombi went on to develop lung-scan abnormalities. Do the 200 patients reported by the Cape Town group allow us to draw conclusions about infrequent events such as pulmonary emboli with the same degree of confidence with which we can form a view about the more frequent calf-vein lesions? All concerned will urge that this study should not be stopped before it produces convincing results.

Even when we have eventually clarified the place of low-dose heparin in general surgical patients, this cannot be a universal panacea; its mode of action is to prevent operative trauma from activating the clotting mechanism and it therefore functions best when given before the trauma. In patients with fractures the first dose can only follow the trauma, when activation has already occurred. In the highest-risk patients of all, elderly patients with femoral neck fractures, low-dose heparin does not significantly reduce the frequency of isotopically detected venous thrombosis.¹⁷ Patients undergoing total hip replacement are a specially crucial group. They are at high risk because of the direct trauma to the femoral vein¹⁹—and yet are so highly selected for their fitness in other respects that death from pulmonary embolism would be untimely. The evidence on the effect of low-dose heparin on intermediate end points is conflicting^{20–22} and there is no evidence that it alters mortality.

To our questioning patient, therefore, we would have to say that conventional anticoagulation remains the only

regimen for which a significant effect on total mortality has been claimed, but that it can never make a contribution to large-scale prophylaxis because of the problems of control, dosage, and acceptance by surgeons. In respect of low-dose heparin we can only echo Sherry²³ and say, "One is forced to the conclusion that there is a very high probability that the difference in fatal pulmonary embolism between the two groups is real," but that because of the premature cessation of the international trial and the failure of any other group to mount a similar, large-scale trial we are left with a probability, and not a certainty. Thus if the patient asks, "Will low-dose heparin increase my chances of surviving an operation?" we can only give the answer dreaded by pollsters—"Don't know."

The conflict between doctor-valued intermediate end points, which are easy to collect, and crucial patient-based end points such as total mortality, which are difficult to amass, exemplifies a common dilemma in medical research: what we have is not what we want; what we want is not what we need; what we need is not what we can obtain.

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