THE CONTRAST BETWEEN VENOGRAPHIC AND CLINICAL ENDPOINTS IN TRIALS OF THROMBOPROPHYLAXIS IN HIP REPLACEMENT

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In clinical medicine we should be interested in clinical outcomes. Much of the research on thromboembolism in orthopaedic surgery has been based upon the venogram.¹ Venography has certain advantages. It is a well-defined technique² which is relatively simple and easy to carry out. It is more sensitive than non-invasive methods such as plethysmography and ultrasound for the diagnosis of asymptomatic thrombosis.^{3,4} It also detects 'silent' thrombosis, which is important because most fatal emboli derive from asymptomatic proximal leg clots. Venography, however, remains a surrogate outcome, used because clinical thromboembolic outcomes, apart from death, are difficult to study. The symptoms and signs of a deep-vein thrombosis (DVT) are non-specific and less than 20% occur during hospitalisation. Those of chronic venous insufficiency are equally so and there is a long lead-time between operation and the outcome of a swollen ulcerated leg. It is only when we understand the frequency at which symptoms occur that we can make a balanced judgement on cost-effectiveness and of the risk of any particular method of prophylaxis. Surrogate outcomes can be misleading in other aspects of medicine⁵ and there are indeed some drawbacks to venography. The procedure has not been fully validated and we have no evidence that the high incidence of DVT detected by venograms reflects a high rate of symptoms. Although the incidence of DVT as detected by venography can be modified by prophylaxis we do not know how it can predict the modification of the symptomatic event rate.

Prevalence rather than incidence. Since it is invasive, uncomfortable and possibly thrombogenic, repeated venography is impractical. A single venogram can only measure prevalence, the rate at the moment when the test is carried out, rather than incidence, the total rate in the postoperative period. This discrepancy is important. First, if the peak onset of DVT is influenced by prophylaxis, then the venogram will not provide a true comparative rate (Fig. 1). Secondly, it will not detect thrombi which have formed and resolved or embolised before the venogram, nor will it

detect those destined to occur afterwards.⁶ To reduce the discrepancy between incidence and prevalence, testing should be repeated on several occasions. Ultrasound has the advantage of being non-invasive, safe and repeatable, although it is expensive and time-consuming, but at present, it is not accepted as being sufficiently accurate to replace venography,⁴ although the accuracy is likely to be improved by the experience of the technician⁷ and better equipment.⁸ As ultrasound improves in accuracy, it will provide the opportunity for the study of the natural history of thrombosis and the relative effects of different methods of prophylaxis. Repeated ultrasound studies would underestimate the rate of occurrence of symptoms, since significant thrombi would be treated when diagnosed and their potential for clinical expression probably suppressed.

Delayed thrombosis. Anticoagulant prophylaxis may delay the onset of DVT as detected by venography and of pulmonary embolism, although it may not reduce the rate.^{6,9,10} If prophylaxis delays the onset of thromboembolism, venography will attribute an inflated benefit to it (Fig. 1).

Late thrombosis. Typically, the venogram is carried out between 7 and 14 days after operation. This choice of timing is not founded on epidemiological or haematological evidence, but rather on convenience, since this period has been, until recently, the typical duration of hospital stay after hip replacement. Although many risk factors which may initiate thromboembolism occur in the perioperative period when the femoral vein is kinked during surgery,¹¹ coagulation is activated and fibrinolysis is suppressed,⁷ thrombi may not appear for a few weeks after surgery. These would not be detected by a venogram on days 7 to 14. In two recent level-1 studies^{12,13} patients were randomised to receive either low-molecular-weight heparin or a placebo after a normal venogram on days 7 to 10 after hip surgery. Of the placebo patients 20% to 25% had evidence of DVT when a further venogram was carried out between days 28 and 35 after surgery, although the number with a symptomatic thromboembolic event was low.^{14,15} This suggests that conclusions based on the traditional studies using a venogram on days 7 to 14 should be regarded with circumspection, and the tendency for very early discharge from hospital makes the carrying out of the investigation at this time increasingly difficult.

Accuracy. There is no absolute method to confirm the accuracy of venography and therefore kappa analysis of interobserver and intraobserver reproducibility is used. The diagnosis of venographic DVT is only modestly reproducible¹⁶⁻¹⁸ and this interobserver variability influences the

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Fig. 1

Prevalence or incidence? The number of clots seen on venograms, compared with the day after operation.

reliability of meta-analyses based on venographic data.

Generalisability. Each thromboprophylactic study reports a different overall rate of DVT and a different pattern of thrombosis. This may reflect the regimen of prophylaxis, the day chosen for venography, the vulnerability of the study sample to thrombi, the interpretation of venograms and confounding prophylactic methods such as stockings, regional anaesthesia, mobility and surgical technique, which may influence one arm of the study differently from the other. A variability in the incidence of DVT among different centres is well recognised. Thus, there is a need for caution when generalising the results of any one venographic study to another population.

Treatment effects. In venographic studies, patients with a large thrombus, even if asymptomatic, have usually been treated. This alters the natural history and masks the potential for clinical expression of the thrombus as thrombophlebitis or a pulmonary embolism. Patients in such studies may therefore have a better clinical outcome than those to whom the results of the study would be generalised, since the latter would not have had routine venography.

Feasibility. Contrast media and facilities for radiology are expensive, contributing to a large proportion of the cost of clinical trials. Venography is also uncomfortable for the patient. This reduces compliance in trials which require assessment of both legs or repeated investigation. To detect all thrombi bilateral venography is necessary since about 20% occur in the unoperated leg.

Is a venographic study needed? Before investigating a new regimen of thromboprophylaxis two questions should be asked:

- 1) Is there a problem with the existing method such as unacceptable rates of symptomatic thromboembolism, cost or complications?
- 2) Does the new regimen have a realistic prospect of reducing further the rate of symptomatic events without introducing unacceptable complications or expense?

Clinical audit may provide the answer to the first question. This needs a large number of patients to produce

usefully narrow confidence intervals and to detect rare, but important complications, particularly death. Patients should be followed for at least three months.¹⁹ The outcome measures must be clearly defined and objectively recorded. This can be difficult, since most clinical outcomes, apart from death, are varied and non-specific in presentation. Nevertheless, it is only after answering the first question that the second should be considered. This second question should also be answered with clinical outcome measures.

Clinical outcome measures. If audit has suggested the need for better prophylaxis, the most appropriate outcome measure for a subsequent randomised control trial would be the total clinical event rate. Studies on the death rate are limited because they ignore expensive and clinically-relevant events such as symptomatic thromboembolism, chronic venous insufficiency and the side-effects of the drug. A very large sample size is needed. Death is, however, an objective outcome although autopsy rates have greatly decreased and so the cause of death may not be known. If clinically-relevant endpoints are to be used in trials, then their objectivity must be optimised. They can be defined as 'symptomatic events which lead to objective radiological confirmation and subsequent treatment'. A similar definition is already used as the primary outcome in trials of treatment for established thromboembolism.²⁰ Wound haematomata could be defined as those confirmed by ultrasound or requiring intervention. The lead-time of two to five years for the development of chronic venous insufficiency and the poor specificity of clinical diagnosis mean that it is unlikely that this could be a primary outcome measure for a clinical trial.

Screening. Because of the difficulties with studies on the rate of symptomatic events, surrogate radiological tests are likely to continue on the assumption that major DVTs correlate with death and chronic venous insufficiency. This is most suitable for phase-II studies in which investigators are trying to compare, objectively, new methods of prophylaxis with reasonably small sample sizes.

Conclusion. Venography has demonstrated a high rate of DVT after hip replacement, and has allowed objective comparison of different methods of prophylaxis. It may be difficult, however, with existing venographic data to draw clinically relevant conclusions on the most effective form of prophylaxis, its appropriate duration or the most cost- or risk-effective method. Future studies should consider the symptomatic relevance of conclusions based on a radiological surrogate, with a balanced assessment of risk- and cost-benefit. This will require large sample sizes with close definitions of clinical events, or studies with repeated use of a valid surrogate marker.

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