COMMENTARY

Mortality from pulmonary embolism after acute stroke: can we do better?

Anticoagulants are highly effective in preventing morbidity and mortality from venous thromboembolism, yet pulmonary emboli have accounted for one eighth to a quarter of early deaths after stroke over the last few years [1, 2]. The explanation for this apparent paradox lies in the current approach to prophylaxis and diagnosis of venous thromboembolism in these patients.

Thromboprophylaxis after stroke

In the International Stroke Trial (IST) [3], low-dose unfractionated heparin significantly reduced the risk of recurrent stroke and death at 2 weeks, though mortality and disability at 6 months were unaffected. Based on this absence of a sustained benefit, routine prophylaxis with low-dose heparin is no longer recommended. Consequently, the primary strategy of thromboprophylaxis is now combined early use of aspirin and graded compression elasticated stockings (GCS), but how effective are these interventions?

Aspirin failed to reduce the risk of pulmonary emboli significantly in the IST [3], though a modest 29% reduction emerged when the results of this trial were pooled with data from 7 others, containing over 20,000 additional stroke patients [4]. GCS help prevent deep vein thromboses in surgical patients, though their effect on pulmonary emboli is less clear [5], and while it seems reasonable to suppose they will also benefit stroke patients, this has yet to be demonstrated. It is now the subject of a multi-centre study (http://www.dcn.ed.ac.uk/CLOTS). Furthermore, administration of aspirin may be delayed in dysphagic patients in some units, and GCS are inconsistently used. The overall effectiveness of these combined measures as commonly practised is therefore uncertain.

By contrast, high-risk surgical patients routinely receive heparin (usually in addition to GCS) which reduces fatal pulmonary emboli by two thirds and is the only form of prophylaxis proven to lower overall mortality [6].

Diagnosis of clinical venous thromboembolism post-stroke

When symptomatic venous thromboembolism occurs after a stroke, factors such as dysphasia, cognitive impairment and obtundation compound diagnostic difficulties. Subtle signs such as small increases in calf circumference, mild tachypnoea and minor arterial oxygen desaturations are often overlooked and when symptoms are recognized, they are frequently misattributed (for example, to hemiplegic oedema or pneumonia). More importantly, half of clinically-evident pulmonary emboli’s after stroke present as sudden death [7] and most of these patients will not have exhibited clinical evidence of deep vein thromboses [8], symptomatic events representing merely the tip of the venous thromboembolism iceberg.

How can venous thromboembolism-related morbidity and mortality be reduced?

Despite the fact that the incidence of deep vein thromboses after stroke exceeds that following general surgery and is equivalent to that after hip or knee arthroplasty, thromboprophylaxis in these patients is less effective. Indeed, recent interest in the concept that venous thromboembolism might be further reduced by extended out-of-hospital prophylaxis following orthopaedic surgery, on a background of optimal in-patient prophylaxis, illustrates the generally more proactive thromboprophylactic paradigm in these patients. Furthermore, improved vigilance for clinically-evident venous thromboembolism will have only a limited impact on outcome because of the frequency of unheralded pulmonary emboli presenting as sudden death. Arguably, then, the current approach to venous thromboembolism after stroke may be insufficiently aggressive.

The situation could be improved either by introducing more effective prophylactic measures or diagnosing deep vein thromboses at the pre-symptomatic stage, with initiation of anticoagulation in selected cases.

Better prophylaxis

Although it is now clear that intermediate and high dose heparin have no role in the routine management of acute ischaemic stroke [3, 9], unanswered questions about the role of prophylactic low-dose heparin remain since the publication of the IST [3]. For example, given that most fatal pulmonary embolis occur between the second and fourth weeks after stroke [10], and that patients will remain relatively immobile after the 14 day treatment period in the study, would a more prolonged course of heparin have resulted in sustained benefit? And would use of low molecular weight heparin (LMWH), with its more favourable risk-to-benefit ratio, have improved outcome? A further trial of low-dose LMWH in combination with aspirin for a longer period and with a more
systematic ascertainment of venous thromboembolism seems justified, but it might be necessary to enrol several tens of thousands of patients [4] to demonstrate improved clinical end-points. Furthermore, several novel classes of antithrombotic agents have been developed in recent years. The most promising thromboprophylactic agents are the synthetic pentasaccharide fondaparinux (a more selective indirect inhibitor of factor Xa than LMWH) and the direct thrombin inhibitors desirudin (recombinant hirudin) and melagatran, early data showing that these agents may be more effective in preventing venographically-demonstrated deep vein thromboses in high-risk orthopaedic surgery patients than LMWH [11, 12]. Further studies are needed to evaluate the clinical and cost-effectiveness of these agents, but it seems possible that heparin may be superceded as the thromboprophylactic of choice. Moreover, intermittent pneumatic compression devices are effective post-stroke, but are not well tolerated in this population and consequently are rarely used [13].

**Earlier diagnosis**

In the absence of further data on improved methods of prophylaxis, the concept of screening stroke patients for subclinical deep vein thromboses warrants appraisal. Studies using $^{125}$I fibrinogen scanning have revealed evidence of deep vein thromboses in about half of patients within a fortnight of onset, one third of which are proximal [14]. But given the small but significant risk of intra- and extracranial bleeding evident in the IST with intermediate-dose unfractionated heparin (12,500 units bd) [3], what would be the balance of risks and benefits of treatment?

Data from general surgical patients suggest that asymptomatic proximal deep vein thromboses are associated with a risk of fatal pulmonary emboli of 12–13% [15]. By contrast, pooled data from 21 studies of unselected patients presenting with symptomatic deep vein thromboses (which, in contradistinction to asymptomatic deep vein thromboses, are mostly proximal) revealed a risk of fatal pulmonary emboli during a 3-month period of anticoagulation of only 0.4% [16]. Intermediate-dose unfractionated heparin was associated with an excess risk of death and recurrent stroke, and non-fatal extracranial bleeding of 0.5% and 1.5% respectively in the IST [3], while the incremental risk of major haemorrhage in patients with a history of stroke treated with warfarin for 3 months is about 1% [17]. In practice, use of LMWH and initiation of treatment for proven deep vein thromboses a few days after stroke onset (as patients would probably not be screened before about one week) might diminish these early risks. Although this issue has not been studied prospectively, these data suggest that patients with subclinical proximal deep vein thromboses after acute ischaemic stroke would benefit from treatment. The ratio of risk-to-benefit is less clear with below-knee deep vein thromboses, which rarely give rise to fatal pulmonary embolism when isolated [18] but propagate proximally in 20% of cases. An observational brief might be reasonable in this subgroup, with repeat screening to identify the subgroup in whom proximal propagation occurs. The balance of risks might, however, favour treatment in patients with inadequate cardiorespiratory reserve, in whom even a small pulmonary embolism can prove fatal.

**Screening for subclinical deep vein thrombosis**

The identification of proximal deep vein thromboses would therefore be the essence of such a strategy, but the choice of screening tool presents difficulties. Use of contrast venography is undesirable in asymptomatic individuals as it is invasive, and $^{125}$I fibrinogen scanning is no longer used. While highly sensitive for the diagnosis of symptomatic proximal deep vein thromboses, a meta-analysis of studies comparing various ultrasound techniques to contrast venography for the diagnosis of asymptomatic proximal deep vein thromboses in orthopaedic patients found a sensitivity of only 62%, though the specificity remained high [19]. However, false negative examinations tended to occur with smaller, non-occlusive clots [19] which might theoretically be associated with a lower risk of pulmonary emboli. Certainly, ultrasound is known to be a powerful tool for predicting recurrence in patients with actual or suspected pulmonary emboli—despite the fact that some deep vein thromboses are probably overlooked [20]. It is therefore possible that serially negative ultrasound examinations may yet be a useful marker of a subsequent low risk of clinical venous thromboembolism when used in screening, though this is uncertain.

Direct thrombus imaging [21] using magnetic resonance technology is an attractive option as it is non-invasive, highly accurate and allows simultaneous imaging of the lower limbs and thorax, potentially facilitating a more titrated approach to treatment. Availability is currently limited, but this technique is likely to assume increasing importance. Plasma D-dimers might also be of interest as part of a two-step process as their high sensitivity for the diagnosis of venous thromboembolism might allow targeted imaging in a considerably diminished subgroup, though this measure would not be useful in isolation because of its relatively low specificity.

**Conclusion**

Given the present state of knowledge on thromboprophylaxis after stroke, future research might profitably be directed towards investigating the concept of screening for asymptomatic deep vein thromboses. Two strategies, in particular, warrant evaluation. First, a clinical management study comparing ultrasound surveillance (and treatment of proximal deep vein thromboses where identified) to usual care on the incidence
of clinical venous thromboembolism and overall mortality. Secondly, a pilot study investigating the utility of D-dimers as a screening tool for venous thromboembolism in acute stroke. If this demonstrated a D-dimer threshold which allowed identification of a subgroup with a high prevalence of underlying proximal deep vein thromboses who could be selectively imaged, a management study comparing this strategy to standard care on clinical end-points would be justified.

Pulmonary embolism may sometimes be the coup de grace in a profoundly disabled patient with co-morbidity and a poor prognosis for functional recovery, in whom a temperate approach to the prevention and diagnosis of venous thromboembolism may be appropriate. However, a previously fit patient with a good prognosis for recovery succumbing to an unheralded pulmonary embolism is tragic and is an experience not easily forgotten. Such cases will continue to occur with a perpetuation of current practice.

JAMES KELLY  
TONY RUDD  
ROGER R. LEWIS  
BEVERLEY J. HUNT

Elderly Care Department, Alexandra Ward, North Wing, 9th Floor, St Thomas' Hospital, London SE1 7EH, UK  
Fax: (+44) 207 928 2339  
Email: jameskelly@northbrookfm.fsnet.co.uk

References


