■ ASPECTS OF CURRENT MANAGEMENT

New concepts in orthopaedic thromboprophylaxis

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Thromboprophylaxis is a controversial and changing topic. Some have questioned its very need. Various objections have been raised as to its use including the relatively low incidence of symptomatic thromboembolic events, the risk of bleeding, the possibility of late infection, the reliance on surrogate end-points such as venography and finally 'no evidence of effect', when the beta error has been misinterpreted as 'evidence of no effect'. However, in our current environment of risk management, it would be wise to remember that the weight of evidence supports the view that thromboembolism is a potentially serious complication and that on the balance of probability the risk can be diminished.¹⁻³ There is no evidence that careful prophylaxis causes major wound bleeding, infection, loosening of the implant or death.

Why thromboembolism is important

The rate of fatal pulmonary embolism (PE) without prophylaxis after hip and knee replacement is probably in the region of 0.4%. It may be said that this figure constitutes a rare and unimportant incidence. However, with 1.25 million hip and knee replacements in Europe each year, 0.4% represents 5000 fatalities annually. Even very low death rates are important. Around 4% of patients suffer symptomatic venous thromboembolism (VTE) after arthroplasty. It is the most common complication, more than dislocation and infection combined. Every orthopaedic surgeon accepts the need for antibiotic prophylaxis to avoid infection and a meticulous surgical approach to avoid dislocation. Why not accept the need for safe and effective thromboprophylaxis?

Thromboprophylaxis really does work

Fatal PE. Crawford, Hillman and Charnley⁴ showed that by comparing the use of phenindione with a control group in a randomised trial of 900 patients, extreme anticoagulation merely exchanged a reduction in fatal PE for an increase in fatal bleeding. However, more

judicious anticoagulation can probably reduce the number of deaths. Fatal PE is very rare indeed in patients taking prophylactic warfarin at adequate levels. Amstutz et al⁵ had no fatalities in 3000 consecutive hip replacements using this drug. There is fairly good evidence that death rates can be reduced by heparin. A meta-analysis⁶ of all the early randomised trials of heparin in orthopaedic surgery showed that the rate of fatal PE was reduced by 66% in patients receiving heparin rather than a placebo or nothing. The overall death rate, as well as the rate of fatal PE, was reduced by heparin. However, there was an increase in bleeding of two-thirds in those taking heparin (2% absolute increase). Death rates are now so low even without prophylaxis that a randomised study would require about 90 000 patients to study death as an end point.⁷ Hence we have to rely upon surrogate end-points.

Symptomatic VTE. Although it has been argued that the evidence for thromboprophylaxis is based upon a surrogate outcome (usually venography) rather than a clinical end-point,⁸ there is good evidence to show that reduced rates of deep-vein thrombosis (DVT) correspond to reduced levels of symptoms.

A meta-analysis of the use of heparin⁶ showed a similar reduction in risk for both asymptomatic DVT as assessed by scintigraphy or venography of 67% and of fatal PE of 68% (Fig. 1). However, this paper was weakened because it was based upon a heterogeneous group of small studies of various orthopaedic patients in whom the presence of thrombi was diagnosed primarily by iodinated fibrinogen.

More robust data are now available. A further meta-analysis⁹ showed that extending the duration of use of low-molecular-weight heparin (LMWH) to about five weeks after hip replacement reduced the rate of DVT as diagnosed by venography from 21% to 8.2%, a risk reduction of 61%. These studies were large enough to show that the frequency of symptomatic VTE was reduced by the same proportion from 4.5% to 1.7%, a risk reduc-

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Fig. 1

Graph showing that reduction in asymptomatic DVT in orthopaedic surgery correlated with the reduction in fatal PE.⁶

Fig. 2

Graph showing the reduction of risk with extended prophylaxis. Venographic DVT correlates with symptomatic VTE.¹⁶

Fig. 3

Graph showing the effect of Arixtra extended for five weeks after fracture of the hip.¹⁰

tion of 62% (Fig. 2). Similarly, when a placebo was compared with pentasaccharide in a double-blind randomised controlled trial for four weeks after operations for hip fracture, the venographic demonstration of DVT was reduced by 95.9% and the symptomatic event rate by 88.8% (Fig. 3).¹⁰

We can now be confident that venographic surrogates do reflect clinical reality.

Chronic venous insufficiency. Whether joint replacement predisposes to chronic venous insufficiency, and whether this risk can be reduced by prophylaxis, is not yet known.

Extended prophylaxis

Until recently, most clinical trials studied the use of prophylaxis in arthroplasty for only seven to ten days while the patient was in hospital. With this strategy LMWH would

reduce the rate of DVT detected by venography by 60%. However, there is consistent evidence to show that half of symptomatic venous thrombi after knee replacement and two-thirds after hip replacement occur after the second week, usually when the patient has been discharged from hospital.¹¹⁻¹³ The total hip replacement outcome study¹⁴ showed that venous thromboembolism was the commonest cause of readmission after hip replacement. As noted above, several recent randomised trials have demonstrated that the risk of both venographic and symptomatic thrombosis after discharge from hospital after hip surgery can be reduced by two-thirds if LMWH or pentasaccharide are continued for at least four weeks after operation (Fig. 3).^{9,10,15,16} The benefits of extended prophylaxis in knee replacement are not clear.

These studies show that the number-needed-to-treat to prevent one case of symptomatic DVT or PE after hip replacement is 37. From this figure, the cost-effectiveness can be calculated. Because the cost of LMWH is relatively low, and that of investigation or treatment of thromboembolism relatively high, this is likely to be a cost-effective approach.^{17,18} Even if these statistics are not thought to be compelling enough to extend prophylaxis for five weeks, it should be remembered that hospital stays after arthroplasty are falling. Discharge four days after operation is not uncommon and minimally-invasive day-case hip surgery is on the horizon. Even the most sceptical of us may realise that prophylaxis for only one day is too short. Thus, the practical issue of administering prophylaxis after discharge is real. When should it be stopped? Who should administer it and who should pay for it?

The use of aspirin

The use of aspirin is superficially attractive. It is a cheap, readily available, familiar tablet. Initial meta-analysis suggested that aspirin might reduce the frequency of DVT and PE.¹⁹ However, a recent study²⁰ has shown that aspirin is

Fig. 4

Graph showing the incidence of DVT and PE with aspirin.²⁰

Fig. 5

Graph showing the effect of pentasaccharide versus LMWH. VTE rates after 11 days.²²

not as helpful as might have been hoped. Over 13 000 patients with fracture of the hip were randomised to have either aspirin or a placebo. The death rate was identical in each group. The risk reduction for symptomatic VTE from 2.5% to 1.6% was only about 30%, half that which would be expected from using LMWH and one-third from using pentasaccharide (Fig. 4). The reduced risk of VTE was matched by an increased incidence of transfusion, gastrointestinal bleeding and bleeding from the wound.²¹ In the supplementary group of 4000 patients with hip and knee replacement, there was an insignificant difference in symptomatic VTE. Thus, aspirin has a relatively weak thromboprophylactic effect, carries an alternative complication rate and its use may deprive patients of safer or more effective

prophylaxis. It is not recommended by the two largest evidence-based consensus groups,^{2,3} and is not licensed for thromboprophylaxis in the UK.

Is warfarin more trouble than it is worth?

Warfarin has been widely used in North America and the UK for prophylaxis. If used carefully, death is exceedingly rare and it is almost as effective as LMWH in reducing venographic DVT. Its use is supported by the main consensus groups. It can be delivered beyond hospital discharge to protect against the risk of late-onset VTE. However, it has many drawbacks. It requires regular monitoring, which is expensive and time-consuming. If started too close to surgery or at too high a dose, there will be a risk of bleeding. If started later, and at a lower dose, there is an interval of several days in which the patient is unprotected during their most thrombogenic time. Warfarin interacts with many drugs and alcohol. It is difficult to see an advantage for warfarin over LMWH or pentasaccharide, except that it is perhaps more convenient to continue it beyond discharge.

Pentasaccharide

Fondaparinux (Arixtra, Sanofi-Synthelabo, Guildford, UK) is a pentasaccharide which offers a new, effective and relatively safe pharmacological approach. It precisely inhibits factor Xa, which is a key component of coagulation. It has been meticulously compared with LMWH in over 7300 patients having hip and knee replacements and after fractures of the hip.²² The overall rate of VTE at 11 days after surgery was reduced from 13.7% with Enoxaparin to 6.8% with Arixtra (odds reduction 55.3%; 95% confidence interval 45.8 to 63.2, p < 0.001); (Fig. 5). Some of the advantage in reduction of VTE, but a disadvantage as regards bleeding, may be explained by the fact that it is given nearer to surgery than LMWH. Fondaparinux appears to induce some increased bleeding, the bleeding index, but no major bleeding in comparison with LMWH. It is given at least six hours after surgery and at least 12 hours after removal of the spinal/epidural catheter in order to avoid the risk of surgical or neuraxial bleeding. The case for pentasaccharide has been critically analysed²³ with some discussion about cost, the choice of end-point, the relevance of the bleeding and the means of reversal. Nevertheless, the reduction of risk for DVT is attractive.

Chemical prophylaxis with neuraxial anaesthesia

Neuraxial (i.e. spinal or epidural) anaesthesia conveys many benefits to orthopaedic patients.²⁴ The mortality after surgery is reduced by 30%, post-operative analgesia is enhanced and it is weakly thromboprophylactic.²⁵ The initial European experience suggested that neuraxial anaesthesia could be used safely in the presence of prophylactic anticoagulants.²⁶ However, more recently the American Food and Drug Administration has raised concerns that on occasions a spinal haematoma may develop. It is therefore prudent to avoid giving neuraxial anaesthesia and chemical

prophylaxis together and individual guidelines should be followed.²⁷

Oral thrombin inhibitors

The ideal chemical agent would be taken orally. This would overcome the difficulty of reconciling the clear need for extended prophylaxis with the pragmatic issue of who will administer it. Aspirin, which is antiplatelet rather than anticoagulant, may fulfil this, but its efficacy is weak and there is no good evidence for its extended use. Warfarin has many disadvantages, as already described. Melagatran (Astra-Zeneca, Luton, UK) is a recently-developed direct oral thrombin inhibitor which has a number of important advantages over warfarin. There is a wide therapeutic and safety window, no monitoring is needed and it is not known to interact with other drugs. Recent trials have shown equivalence with LMWH in prophylaxis after arthroplasty.²⁸⁻³⁰ Future trials may show its efficacy for extended prophylaxis in which case a pragmatic solution to this important problem would be available.

Just-in-time prophylaxis

There is a dilemma with chemical prophylaxis in that the closer to surgery that it is administered, the better is the thromboprophylaxis, but the greater is the chance of bleeding complications. If LMWH is given before surgery, as recommended in Europe, because of a relatively short half life, the serum levels are too low for any prophylactic effect. If LMWH is delayed until after surgery, as is recommended in North America, the thrombi may have already begun to form during the very thrombogenic operation. Prophylaxis needs to be given close, but not too close, to surgery; so-called "just in time prophylaxis".³¹ The optimum moment to administer LMWH or Fondaparinux is probably around six to eight hours after surgery.

Combined mechanical and chemical prophylaxis

The Art, rather than Science, of clinical medicine is to apply knowledge in a balanced way, tailored to the needs of the individual patient.

Thromboprophylaxis has been often regarded as a dichotomy; either chemical or mechanical. The advantages of drugs, namely their ease of use, relative cheapness and efficacy, must be weighed against the potential for bleeding both into the surgical wound and into the spinal cord after neuraxial anaesthesia. The advantages of mechanical prophylaxis such as the foot pump, with no bleeding, no drug interactions and reasonable efficacy must be taken into account against the disadvantages of compliance, refitting when mobilising and the impracticality of extended use. A sensible approach would be to use the foot pump as soon as possible after injury or surgery and then to switch to chemical prophylaxis once the risk of bleeding has subsided and for as long as the risk of thromboembolism persists. For patients with a particular risk of thrombosis, the two can be combined in the hope of a synergistic effect.

There are no clinical trials which have directly addressed this approach.

Can we design a sensible, safe, evidence-based approach?

Care pathways and guidelines are becoming endemic. They should ensure the routine and automatic provision of important care, yet allow flexibility when the circumstances of the individual patient require. This should give the patient the benefit of best practice and give the hospital protection against risk.

Each orthopaedic department should publish guidelines for thromboprophylaxis which combine common sense with available evidence. These can then be incorporated into care pathways. The following scheme may be considered.

Risk assessment. All patients should have a risk assessment to determine previous VTE, a family history, malignancy, the likelihood of prolonged immobility or poor mobilisation.

Hip replacement. Regional anaesthesia and early mobilisation should be encouraged. For those surgeons who are comfortable with chemical prophylaxis LMWH or pentasaccharide should be started not less than six to eight hours after surgery and regional block but at least 12 hours after any indwelling epidural catheter has been removed. For those surgeons who are concerned about perioperative bleeding, a mechanical device such as a foot pump should be fitted in the recovery room. It should be continued for the entire hospital stay for those thought to have a particularly high risk of VTE. Otherwise, it could be stopped once the patient begins to mobilise. If possible chemical prophylaxis should be continued for five weeks.

Hip fracture. In some patients, medical and social comorbidity may occasionally suggest a more holistic approach. Otherwise, a mechanical device should be applied as soon after injury as possible in the Emergency Department. The device should be used, and chemical prophylaxis instigated in the same way and for the same duration as hip replacement.

Knee replacement. The risk of side-effects on soft tissues is higher in knee replacement, yet VTE is more resistant to prophylaxis. Regional anaesthesia should be encouraged. A mechanical device should be started in recovery and continued, if tolerated, for as long as the patient is in hospital. Chemical prophylaxis should be started as soon after surgery as the surgeon feels is safe and continued for the entire stay in hospital. For those being discharged in less than ten days or with other risk factors, chemical prophylaxis should be considered beyond discharge.

Other orthopaedic operations. There are few data available on both epidemiology and prophylaxis in other orthopaedic procedures. If the risk assessment suggests a minimal risk of VTE then the cost and potential side-effects of perioperative chemical prophylaxis may not be justified. However, if there is a potential risk, then a sensibly-timed combination of mechanical and chemical prophylaxis should be

devised. Major trauma of the lower limb and spinal surgery carry a risk of symptomatic thromboembolism but have a greater threat of bleeding. A longer period of mechanical prophylaxis, followed by extended chemical prophylaxis when safe, seems sensible. Day-case arthroscopy causes very occasional problems with VTE yet practical prophylaxis is difficult since the patient will have gone home before it is safe to give the drugs. The best course is to carry out a careful risk assessment and provide those with a higher risk with an injection before discharge and follow with home prophylaxis until the patient is fully mobile.

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