Low-molecular-weight heparins allow selected outpatient treatment for venous thrombosis

The conventional treatment for patients with an acute deep-vein thrombosis (DVT) at present consists of an initial continuous intravenous infusion of unfractionated heparin, administered for a minimum of 5 - 7 days.[1] Oral anticoagulation is started at the same time, while the patient is still in hospital, and is continued for at least 3 months. The initial treatment with heparin, which aims to prevent pulmonary embolism and recurrent thrombosis, has been found to be effective,[2] but the anticoagulant response to unfractionated heparin varies markedly. As a consequence the dosage of unfractionated heparin must be monitored carefully by frequent measurement of activated partial thromboplastin times (aPTTs), necessitating hospitalisation of the patient for the period that the unfractionated heparin is being administered.

Low-molecular-weight heparins (LMWHs), prepared from digestion of heparin by chemical or enzymatic depolymerisation (to produce molecules that are usually less than 18 saccharide units in length), have several advantages over the parent compound.

1. The anticoagulant activity of the heparins resides in a unique pentasaccharide sequence which is randomly distributed along the heparin chains and binds with high affinity to antithrombin. Any heparin (no matter how long the molecule), containing this pentasaccharide sequence, inactivates factor Xa simply by binding to antithrombin and thereby accelerating the interaction between factor Xa and antithrombin. In contrast, the inactivation of thrombin by unfractionated heparin requires heparin to bind to both antithrombin and thrombin. This complex can only be formed if the heparin chains are at least 18 saccharide units long and also include the pentasaccharide sequence (most molecules of unfractionated heparin are at least 18 saccharide units in length). As a result, unfractionated heparin has equivalent inhibitory activity against both factor Xa and thrombin, while LMWHs preferentially inactivate factor Xa.

2. Unlike unfractionated heparin, LMWHs can inactivate platelet-bound factor Xa and can resist inhibition by platelet factor 4, which is released during clotting.

3. LMWHs may also cause fewer haemorrhagic complications as a result of their less pronounced effect on platelet and vascular endothelial function.

These characteristics result in a longer half-life, better bio-availability, and more predictable anticoagulant activity.[3,4] The LMWHs can therefore be administered subcutaneously, without laboratory monitoring, in a dosage determined by the patient's weight alone.

Initially, LMWHs were used in small doses in the prevention of venous thrombosis in high-risk patients.[5] In this setting they are as effective at preventing the development of DVTs as low-dose subcutaneous unfractionated heparin (Kakkar's regimen), if not more so. In addition, bleeding complications appear to be reduced and the drug can generally be administered as a single daily dose when used for this indication.

Subsequently, a number of excellent randomised studies have demonstrated that weight-adjusted fixed-dose LMWH given subcutaneously is as effective as intravenous unfractionated heparin (dose-adjusted to prolong the aPTT) in the initial treatment of hospitalised patients with DVT.[6-14] These studies have recently been summarised in a meta-analysis.[15]

1. The venographically determined thrombus size (5th to 10th day after treatment was started) was reduced in 64% of patients receiving LMWH compared with 50% in those receiving unfractionated heparin ($P < 0.001$.) Similarly, there was an increase in thrombus size in 6% of patients receiving LMWH compared with 12% in those receiving unfractionated heparin ($P < 0.001$).

2. The incidence of major bleeding was 3.2% in the patients receiving unfractionated heparin compared with 0.9% in those receiving LMWH (risk reduction 68%; $P < 0.005$).

3. The recurrence rate of clinically apparent DVT was lower in those patients receiving LMWH (unfractionated heparin 7% v. LMWH = 2.7%; risk reduction 61%; $P < 0.005$), as was mortality (unfractionated heparin 8.1% v. LMWH 4.3%; risk reduction 48%; $P < 0.03$).

As a result of these studies, many centres (particularly in Europe) have used LMWH in an outpatient setting as the initial form of therapy in selected patients presenting with DVT. That this is effective and safe has been shown in two recently published studies.[16,17] In both these studies unfractionated heparin given intravenously to hospitalised patients was compared with LMWH given subcutaneously to patients at home. The use of LMWH in an outpatient setting for the treatment of DVT not only increases patient convenience but also reduces hospital costs dramatically.

The major concern regarding the use of LMWHs in an outpatient setting is the possible complications. The two studies mentioned above revealed that life-threatening pulmonary embolism was exceedingly rare with both modalities of treatment, and when death did occur it was not clear that the outcome would have been improved if the patients had been treated in hospital. On the other hand, bleeding complications are potentially more treatable in hospital. It is therefore prudent to treat patients with a coexisting risk of bleeding in a hospital environment, irrespective of the type of heparin used.

In conclusion, LMWHs given in a fixed dose without laboratory monitoring are at least as effective as carefully monitored standard unfractionated heparin administered by continuous intravenous infusion. As they produce less bleeding for equivalent antithrombotic effects, their use in outpatient treatment of DVT has been studied and been found to be safe in selected patients. The resultant increase in patient convenience and reduction in hospitalisation make this a very attractive alternative to the standard form of initial anticoagulation for DVT in selected patients suitable for this treatment.

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