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Can we use a low molecular weight heparin after mechanical prosthetic heart valve surgery?

Philippe Meurin, Jean Yves Tabet

The risk of thromboembolism is high during the first month after mechanical prosthetic heart valve (MPHV) surgery,[1 2] particularly during the lag time before oral anticoagulant (OAC) treatment reaches effective levels. Indeed, vitamin K antagonists (VKAs) take at least 5 days theoretically—and about 2 weeks in practice[3]—to achieve a therapeutic international normalised ratio.

A "bridging" anticoagulant is usually prescribed to cover this period. Traditionally, the bridging agent has been unfractionated heparin (UH),[4] but low molecular weight heparin (LMWH) has been used more recently.[3 5 6] As there are few studies to validate the efficacy and safety of either UH or LMWH in this setting, the need for heparin remains controversial and practice guidelines are not very clear cut.[1] Thus, in some centres, OAC starts with VKA monotreatment, so that bridging does not become necessary unless there is an unusual delay in achieving a therapeutic international normalised ratio.[4 7 8] However, a recent survey[4] confirms that, after MPHV surgery, UH and LMWH are routinely administered by about 65% and 22% of surgeons, respectively.

In most centres UH is rarely introduced immediately in a therapeutic dose, because of the fear of bleeding,[8] and it often takes several days to obtain a therapeutic activated partial thromboplastin time (APTT).

The use of UH raises several other concerns. First, the bioavailability and predictability of intravenous UH anticoagulation are poor (reviewed by Meurin *et al*[5]), especially in patients treated subcutaneously. Montalescot *et al* reported that only 9% and 27% of patients had an APTT value within the therapeutic range (1.5–2.5 times control) after respectively 2 and 13 days of subcutaneous UH treatment,[3] implying that subcutaneous UH administration should be reserved for lower-risk patients, such as those with venous thromboembolism.[9] Therefore, unlike LMWH, UH is generally given as a continuous intravenous infusion, which reduces the patient's mobility, delays hospital discharge and can be a source of local and general infections. Finally, heparin thrombocytopenia is less common with LMWH than with UH.

LMWH too has certain disadvantages, however. First, if bleeding occurs, anticoagulation is more rapidly and completely reversible with UH than with LMWH. Second, in the very early postoperative period the systemic bioavailability of subcutaneous LMWH may be inadequate because of peripheral vasoconstriction due to haemodynamic instability or vasoactive drug administration, or both.[10] Finally, cases of thrombosis, mostly in pregnant women treated with LMWH, have raised tricky medicolegal issues. The product labelling for one LMWH states that "the use of Lovenox (enoxaparin) injection has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves". It is beyond the scope of this short editorial to discuss this fully, so I would refer the reader to the very thorough review published in the *American Heart Journal* in 2005.[11] The recent ACC/AHA guidelines for the management of patients with heart valve disease[1] state that "for pregnant patients with mechanical prosthetic valves, up to 36 weeks of gestation, the therapeutic choice of continuous intravenous or dose-adjusted subcutaneous UH, dose-adjusted LMWH, or warfarin should be discussed fully" (class I, level C). Most patients are not pregnant, however, and the appropriateness of extrapolating these cases of thrombosis to larger subsets of patients is questionable.

Because there is no preferred method, the use of LMWH instead of UH as a bridge pending full VKA efficacy warrants further study. Only a few observational studies have been conducted[3 5 6]; none were randomised and all were small: only about 400 patients having received LMWH in this setting have been reported. All these studies showed a low rate of thromboembolic complications (1%) and few major haemorrhagic complications (1–3%). It is unlikely, unfortunately, that prospective studies with sufficient numbers of patients will ever be conducted to compare LMWH with UH after heart valve replacement, not only because they would be difficult to perform (small, high-risk populations; difficulties in blinding adjusted UH treatment) but also, perhaps, because this indication is not financially rewarding for the companies concerned.

Clinical data are therefore highly valued. The prospective study by Rivas-Gándara and colleagues[12] published in this issue of *Heart* (***see article on page 205***), was a survey which included 140 patients who underwent cardiac surgery (mostly MPHV surgery). It provides some very useful new information. First, it presents data on preoperative anticoagulation. Second, enoxaparin was introduced very early (1 day) after surgery, whereas in other studies it was started after bridging with intravenous or subcutaneous UH for 5[3] to 16[5] days. Finally, Rivas and colleagues used a standardised periprocedural (pre- and postoperative) anticoagulation regimen, consisting of OAC interruption 5–7 days before surgery and substitutive treatment with enoxaparin as a bridge. It must be emphasised that, among the 51 patients receiving long-term OAC before the operation, 16 (29%) had an international normalised ratio >1.5 the day before surgery and therefore received a vitamin K analogue to normalise it before the operation.

Major bleeding events were uncommon (2.1% during treatment with enoxaparin), in keeping with the results of most other published studies. In contrast, the rate of thromboembolisms (TE) was higher than reported elsewhere (4.3%; n = 6), and this must be discussed. Two of these TE occurred in the immediate postoperative period, before the resumption of anticoagulation treatment. This could rule out LMWH as the cause and suggests that vitamin K analogues should not be given routinely in the preoperative period as they may create a hypercoagulable state.[1] Indeed, these two early TE occurred in patients who had received vitamin K (2/16, 12.5%). In addition, Rivas counted all TE, starting immediately after the end of the operation, whereas, on average, Montalescot[3] and our team[5] began their studies on postoperative days 5 and 16, respectively, and at least three of the six TE in Rivas' study[12] would not have been

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taken into account by these other authors because they occurred between postoperative days 0 and 2. Finally, follow-up lasted 3 months in Rivas' study, and two of the six TE occurred more than 2 months after the end of LMWH treatment.

This study still leaves certain questions outstanding. First, in which patients should anti-Xa activity be measured? There is little correlation between adverse events and anti-Xa activity[8]; the current informal consensus seems to be that anti-factor Xa levels do not need to be measured routinely in non-pregnant patients if they have normal renal function and are not obese.[11]

Is such early LMWH administration, starting 1 day after surgery, really useful? These patients have an intravenous line for about the first 3 postoperative days, and UH can therefore be given intravenously during this period, LMWH being started after removal of the intravenous line.

The main problem raised by the use of LMWH in this setting is the risk of misuse, as these products are so convenient. It must not be forgotten that the platelet count must be regularly checked, that LMWH is contraindicated in patients with renal failure, and that in all the studies conducted after MHPV surgery, LMWH was administered *twice* (not once) daily, and at a high dose (100 IU/kg twice daily).

In summary, LMWH appears to be safe and effective in this high-risk setting but has not yet been tested in randomised studies. Thus, the different heparins can be used indiscriminately as long as the treatment is correctly prescribed and monitored. Let us hope that forthcoming antithrombotic drugs will be evaluated systematically in patients with an MPHV.

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