

Role of Heparin in the Antithrombotic Treatment of Valvulopathies

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Heparin is indicated to replace warfarin in patients with valve disease requiring antithrombotic treatment. Its use is thus necessary for short periods during which warfarin is contraindicated, but the thromboembolic risk persists. These circumstances, which are common in patients with mechanical prostheses, include: hemorrhagic risk or event complicating an existing thromboembolic risk (heart or extracardiac surgery, severe hemorrhage, end of pregnancy); when an unstable situation develops and imposes the rapid diminution or interruption of anticoagulants (stroke, infectious endocarditis); when immediate efficacy is required, rather than the delayed action of warfarin (onset of atrial fibrillation); and when warfarin is contraindicated (early pregnancy). Regardless of whether

Antithrombotic treatment for valvulopathies usually consists of oral anticoagulant therapy (OAT), which has been clearly defined by national and international guidelines (1-6) published over the past decade. OAT achieves anticoagulation over the long term, but has several drawbacks linked to its delayed action and its potential side effects which contraindicate its use in certain situations. When the thromboembolic risk necessitates the continuation of anticoagulation, a transient recourse to heparin is required, but its duration is defined by the period during which OAT is contraindicated added to the time needed for delayed OAT action to take effect and be confirmed by repeated INR determinations of therapeutic efficacy.

Heparin therapy raises three questions. First, which

unfractionated or low molecular-weight heparin (LMWH) is used, therapeutic doses must be prescribed: continuously perfused intravenous and subcutaneous injections (t.i.d.) with repeated biological monitoring for the former, or subcutaneous injections (b.i.d.) with initial biological controls preferred and repeated in elderly subjects or those suffering from renal insufficiency. International guidelines have specified the respective roles of heparin in general, and each preparation individually with an ever-increasing use of LMWH, the efficacy of which has been proven in the majority of common thromboembolic pathologies and in pregnant women.

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heparin should be used; second, in which precise situations should it be used; and third, how should it be administered and monitored?

Which heparin should be used?

Unfractionated heparin

Unfractionated heparin (UFH) has been used as an anticoagulant for many years, during which time its simple intravenous or subcutaneous administration has made it the reference therapy. When injected intravenously, heparin retains the advantage of rapid action, being easily modified and a logical choice for any patient with an intravenous line maintained during the acute phase of a disease. Moreover, its high molecular weight prevents it from crossing the placental barrier. In addition to these advantages, however, UFH has several disadvantages associated with its mediocre bioavailability, its short half-life (which varies as a function of the dose administered), and the need for repeated biological monitoring of the activated partial thrombin time (APTT). It can also induce thrombocytopenia and, when its use extends beyond one month, there is a risk of osteoporosis.

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Low-molecular-weight heparin

Low-molecular-weight heparin (LMWH) was developed more recently than UFH, and has been recommended for use in all international guidelines, as its efficacy has been proven in pregnant women and the majority of venous and arterial thromboembolic pathologies. LMWH has numerous advantages over UFH, including better bioavailability, facility of administration, and a lack of any need for biological monitoring (once established), except in elderly individuals or those with renal insufficiency. In addition, the risks of thrombocytopenia and osteoporosis are lower. In 1998, despite the recognition of these advantages supporting its use, the ACC/AHA guidelines (2) did not recommend LMWH for use in patients with prosthetic mechanical valves, because no data were available to guide such use. In contrast, the 2001 ACCP guidelines (6) authorized LMWH for this indication as an alternative to UFH.

In what situations should heparin be used?

Recourse to heparin treatment is transiently indicated in all situations in which antithrombotic treatment is indispensable but OAT must be stopped because an enhanced hemorrhagic risk requires more flexible treatment (cardiac or extracardiac perioperative period, severe hemorrhage), or because OAT side effects dictate its discontinuation (pregnancy).

Early postoperative period

During this period, the thromboembolic risk of cardiac origin is increased about 10-fold (7), and systematic transesophageal echocardiography (TEE) (8,9) has proved valuable in thrombus detection, particularly after mitral valve replacement (9). The early postoperative period is also the time during which the risk of bleeding can lead to surgical reintervention. The first hours and days after surgery are when thromboembolic and hemorrhagic risks are at their highest, thus indicating heparin use. No particular recommendations have been established in this setting, and therapeutic practices vary from one surgical team to another. Usually, intravenous heparin is started 6 h after the end of surgery, OAT is prescribed between the second and fourth postoperative days, and heparin is stopped when two successive daily determinations yield INR values within the therapeutic range.

Montalescot et al. (10) included 208 patients who underwent monovalvular replacement (157 aortic, 51 mitral), and compared 106 patients who received UFH with 102 given LMWH. On the second postoperative day, 87% of the LMWH patients were within the therapeutic range, defined as an anti-Xa level between 0.5 and 1 U/ml. By contrast, this was the case in only 9% of the UFH-treated patients, whose APTT was between

1.5- and 2.5-fold the control value ($p < 0.0001$). At 14 days after surgery, 81% of the LMWH patients were within the therapeutic range, and 19% were above it. The distribution differed for patients receiving UFH, with only 27% being within the therapeutic range, 62% above it, and 11% below it. Very few patients (2%) in each group hemorrhaged, and one UFH-treated patient had a stroke. These observations led the authors to conclude that LMWH can be used during the immediate postoperative period, with satisfactory biological efficacy and safety comparable to that of UFH.

Percutaneous mitral commissurotomy

In this setting, heparin use is limited to the short period of the procedure and the following 24-h period, provided that oral anticoagulation has been effective for at least two months and TEE has confirmed the absence of any left intra-atrial thrombus. OAT is reintroduced thereafter, in agreement with its indication for mitral valvulopathies (1).

Extracardiac surgery

Heparin is not always necessary, especially for minor interventions when bleeding is minimal, for example tooth extraction (11), dermatological or ophthalmological surgery, for which a slight lowering of the dose to obtain an INR of ~2 suffices. Nevertheless, recourse to heparin is justified when the INR is < 2.5 for patients with a high thromboembolic risk (12) and a history of thromboemboli, atrial fibrillation and/or mitral prosthesis. If the hemorrhagic risk is elevated (orthopedic or abdominal surgery, digestive or urological endoscopy with biopsy), OAT must be stopped at least three days before the intervention (and sometimes even earlier), depending on the anticoagulant used, and replaced by heparin, UFH or LMWH (13) at therapeutic doses, that will be interrupted 8 h before the onset of surgery and reintroduced 6 h after its termination. OAT can be reintroduced on the second postoperative day (sometimes later), depending on the hemorrhagic risk.

Atrial fibrillation

Heparin use is justified only in patients who are not receiving OAT at the onset of their first episode of atrial fibrillation. Heparin treatment is started at the same time as OAT, and stopped when the INR reaches the therapeutic range. Heparin may be the only anticoagulant administered before and after electrical cardioversion, performed a few days after starting heparin, and when TEE has confirmed the absence of any left intra-atrial thrombosis. Using LMWH in this setting has not yet been evaluated in a randomized study, but published results based on several series have been encouraging (14,15).

Prosthesis thromboses

Heparin treatment of thromboses of valvular prostheses is limited to small-sized (as assessed by TEE), non-obstructive thrombi revealed by a stroke. In this context, heparin anticoagulation can be modified more easily as a function of the thromboembolic and hemorrhagic risks associated with recent strokes. Heparin is given by continuous intravenous infusion at a dose adapted to the results of repeated APTT determinations.

For obstructive thrombi with heart failure, treatment is essentially surgical. When the surgical center is far, or surgery is contraindicated by the patient's condition, intravenous thrombolysis can be administered.

Major hemorrhage

Severe bleeding - for example cerebral or digestive tract hemorrhage - under OAT compromises the patient's survival and requires the interruption of treatment, sometimes in combination with prothrombin complex concentrate (PPSB) or vitamin K which can control the dangerous bleeding but may lead to resistance towards OAT at the time of its reintroduction. Certain examinations (e.g. digestive endoscopy) which seek the origin of the hemorrhage are made possible by using intravenous heparin (16).

Endocarditis of the prosthetic valve

Despite indications for early reintervention and appropriate antibiotic therapy, endocarditis on a prosthetic heart valve carries a 30% mortality rate. In this context, relaying OAT with heparin is highly recommended to manage the prosthesis bearer's delicate situation and the sometimes urgent decision to operate. UFH is given in an IV perfusion with the dose adapted to the APTT results.

Pregnancy

Even though the pregnancy of a woman with a biological prosthesis is similar to that of a normal woman - except for the risk of accelerated structural valve fail-

ure (17) - the need to pursue anticoagulant therapy complicates the course for mechanical prosthesis bearers. Pregnancy induces a hypercoagulability state that has little or no effect on the course of a normal pregnancy, during which the risk of thromboembolism, particularly venous, is elevated only very slightly. This is not the case for women with a mechanical prosthesis, particularly when implanted in the mitral position, and is concomitant with atrial fibrillation whereby the thromboembolic risk is greatly increased.

Historically, recommendations in this field have evolved with successive publications emphasizing the respective disadvantages of OAT and heparin. At a very early stage, OAT was reported to induce embryopathies (18), especially during the first trimester, and this led to a preference for heparin use at the time. Unfortunately, although heparin improves the fetal prognosis, it aggravates that of the mother because of the enhanced thromboembolic risk (19,20). These two risks are far from negligible (Tables I and II).

The results of the main studies published over the past 20 years (19-26) indicated mean risks of 3.9% for embryopathy, 7.6% for prosthesis thrombosis and 2.4% for maternal death. Recommendations in this setting are in agreement, for the most part, to limit heparin use to only those periods during which OAT is really contraindicated: the first trimester of pregnancy, because of the elevated risk of embryopathy, and the last two weeks, because of the enhanced risk of hemorrhage for the newborn infant and for the mother at delivery. Some authors consider that heparin use should be even more restricted. It can be limited to the second half of the first trimester (weeks 6 to 12), which is the selective period for embryopathies. For others, the first trimester can proceed under OAT (27) to avoid multiple OAT-heparin interchanges, which favor the occurrence of thromboembolic events.

The lower the OAT dose required to maintain the INR between 2 and 3 (<5 mg warfarin), the fewer the embryopathies that would result primarily in miscarriage at this stage of pregnancy (28).

Table I: Pregnancies and thromboses of prostheses.

Reference	Pregnancies (n)	Thromboses (%)	Deaths (%)
Larrea et al. 1983 (21)	47	6.8	2.1
Iturbe-Alessio et al. 1986 (23)	72	4.2	2.7
Vitali et al. 1986 (24)	98	9	2
Born et al. 1992 (26)	35	8.6	5.7
Sbarouni and Oakley 1994 (19)	151	8.6	2.6
Hanania et al. 1995 (20)	108	9.2	2.8
Vitale et al. 1999 (28)	58	3.5	0
Total	569	7.6	2.4

Table II: Pregnancies and embryopathies.

Reference	Pregnancies (n)	Embryopathies (%)
Larrea et al. 1983 (21)	47	5.5
Salazar et al. 1984 (22)	38	7.9
Iturbe-Alessio et al. 1986 (23)	72	14
Sareli et al. 1989 (25)	50	4
Sbarouni and Oakley 1994 (19)	151	0
Hanania et al. 1995 (20)	108	1
Vitale et al. 1999 (28)	58	4
Total	524	3.9

First trimester

None of these therapeutic strategies is totally exempt from risk for the mother and/or child. The choice will be made only after informing the future parents. Thus, should heparin be chosen, its unfractionated form will be administered intravenously when the thromboembolic risk is high (history of thromboemboli, ball or tilting-disc prosthesis, mitral prosthesis) with an APTT between two- and three-fold control levels.

When the thromboembolic risk is moderate (no prior thromboembolic event, bileaflet or pivoting-disc prosthesis, aortic prosthesis), UFH is injected subcutaneously three times daily at therapeutic doses (2), associated with regular and frequent biological monitoring, or LMWH is injected twice daily (6), with biological monitoring at the onset, and perhaps repeated at longer intervals. Should OAT be chosen exclusively for the first trimester, the INR should be maintained between 2 and 3. Heparin is not a valid means of anticoagulation for pregnant women during their second trimester and most of the third trimester, which can proceed entirely under OAT.

End of pregnancy

Heparin should be reintroduced only as of the 36th week of gestation because of the peripartum risks of fetal and maternal hemorrhage. It is administered subcutaneously and then intravenously as the delivery date nears, and is stopped at the onset of labor. Some authors (29) even propose allowing the entire pregnancy to proceed under OAT, stopping it only 48 h before a scheduled cesarean section.

All of these regimens, dictated by the frequency of debilitating or even fatal maternal thromboembolic events, are associated with the prolonged use of UFH, which only rarely achieves perfectly stabilized anticoagulation. The possibility of using LMWH (6) will perhaps change this therapeutic strategy in the context of less thrombogenic bileaflet prostheses in the aortic position.

European (1) and North American (2) guidelines are very similar for the end of pregnancy, differing only by

the more-or-less precocious reintroduction of anticoagulants: respectively, starting heparin between the sixth and 12th hours or between the fourth and sixth hours, and OAT between the third and sixth days or as of the first day in the absence of hemorrhage. Neither heparin nor OAT is a contraindication for breastfeeding.

How should this treatment be given and monitored?

In all cases, UFH or LMWH must be prescribed at therapeutic doses. UFH in its intravenous formulation is given as a continuous perfusion, whereas its subcutaneous formulation is injected three times a day, and adjusted to obtain an APTT twice the normal level. LMWH is injected subcutaneously twice daily with a therapeutic dose able to control the anti-Xa level at 0.5 to 1 U/ml at the onset of therapy. The heparin-OAT interchange transpires over several days with monitoring of INR stabilization in the therapeutic range for two consecutive days.

Conclusion

The use of heparin for patients with a valvulopathy or a mechanical prosthesis should be restricted to short periods during which immediate efficacy is required because of the thromboembolic risk, or when OAT is contraindicated either because of a risk of hemorrhage (cardiac or extracardiac surgery, stroke) or of malformation (pregnancy). Despite the lack of prospective randomized trials with large populations, LMWH is in the process of progressively supplanting UFH in these indications because of its safety and ease of use, and excellent results in all deep venous or arterial thromboembolic diseases and in pregnant women.

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