Treatment of left ventricular thrombi with a low molecular weight heparin

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Abstract

Background: Once a diagnosis of left ventricular thrombus has been established, the classical attitude consists in the administration of unfractionated heparin relayed by oral anticoagulation therapy. However, the use of unfractionated heparins in this indication was only assessed in an open, non-randomized study with no control group, including 23 patients. On the other hand, although low molecular weight heparins are routinely used in some departments, there are no studies available concerning these agents in this indication. The aim of this study was to evaluate the feasibility of low molecular weight heparin therapy in patients with left ventricular thrombi. Methods: The study was a prospective, non-randomized, open-label trial. All patients with a new left ventricular thrombus diagnosed between September 2000 and September 2003 received enoxaparine 100 IU/kg twice daily for a mean duration of 13 days. A relay treatment with fluindione was initiated on day 5. The left ventricular thrombus outcome was followed for 3 weeks by bi-weekly transthoracic echocardiography. Results: 26 left ventricular thrombi were diagnosed over the 3-year study period: 19 in post-infarct patients with a history of anterior myocardial infarction and 7 in patients with dilated cardiomyopathy. The mean thrombus area decreased from 2.30 ± 0.32 to 0.36 ± 0.11 cm² (p < 0.0001). Nineteen thrombi out of twenty-six (73%) disappeared during the treatment period. No thrombocytopenia or hemorrhagic events were observed. One transient ischemic attack was reported. Conclusion: This preliminary study suggests that low molecular weight heparins are well tolerated and efficient in terms of left ventricular thrombi disappearance or size reduction.

Keywords: Left ventricular thrombus; Low molecular weight heparin

The two main causes of left ventricular (LV) thrombi are dilated cardiomyopathy (DCM) and anterior myocardial infarction (AMI). The generalization of reperfusion techniques used during the acute infarction phase allowed a marked reduction in the frequency of LV thrombi. Until the 1990s, it was estimated that LV thrombi complicated approximately 40% of anterior myocardial infarctions [1,2] and that 10–20% of LV thrombi progressed to arterial embolism [3].

The current estimation is that LV thrombi still complicate 5–10% of anterior myocardial infarctions [4–6]. In patients with dilated cardiomyopathy, the frequency of LV thrombi varies from 10% to 30% in the published series [7,8].

Prophylaxis of LV thrombi has been well studied. It is known that neither aspirin [3] nor ticlopidine [9] administered alone are effective preventive measures, but their combination was never studied in this indication. Conversely, a prospective study carried out in AMI patients demonstrated the efficacy of a low molecular weight heparin (dalteparine), which was administered for 10 days at curative doses and significantly reduced the LV thrombi incidence compared to a placebo (relative risk = 0.63; p = 0.02) [10]. Similarly, in an open randomized study, subcutaneous calcium heparin administered at prophylactic dosage (12500 IU, twice daily for 3 months) reduced the incidence of LV thrombi (17.9% versus 31.6% in the placebo group, p < 0.05) in 204 post-infarct patients with a history of anterior myocardial infarction [11].

The issue addressed here is the curative treatment of newly diagnosed LV thrombi, whose embolic potential is particularly high [1,12]. Although it is known that long-term treatment should be based on oral anticoagulation therapy [3,13], no consensus has been reached regarding the treatment to be used in the short term. Some cases of intravenous thrombolysis have been reported, but bleeding and embo-
lism risks appeared (too) high [1]. Some authors have been advocating a surgical approach (in particular for patients with protruding and mobile thrombi) but such patients are exposed to a high risk of complications of surgery [14]. The mostly used therapeutic approach consists in the administration of intravenous unfractionated heparin relayed by oral anticoagulation therapy. Because of their better pharmacokinetic profile, improved safety and simplicity of action, it appeared useful to evaluate low molecular weight heparins (LMWHs) in this indication.

1. Methods

The study was a prospective, two-centers, non-randomized, open-label trial.

1.1. Patients

From September 2000 to September 2003, 4180 patients had at least one transthoracic cardiac echocardiography examination (TTE) at our cardiac rehabilitation center. Of these patients, 310 had been admitted after an anterior myocardial infarction and 146 for a recently uncompensated dilated cardiomyopathy. Among these 456 patients, five were excluded from the study because they had a known LV thrombus and already received long-term anticoagulation therapy. Among these 456 patients, five were excluded from the study because they had a known LV thrombus and already received long-term anticoagulation therapy. Among the remaining 451 patients, 26 had a recent LV thrombus diagnosed in our center: 19 had an anterior myocardial infarction and 7 had a dilated cardiomyopathy. All these patients were included. They were 26 men with a mean age of 59 ± 2 years, who had been transferred in our center 12 ± 3 days after myocardial infarction or 13 ± 4 days after exacerbation of cardiac failure (Table 1).

1.2. Echocardiography

All patients initially selected (n = 456) had a first transthoracic cardiac echocardiography examination (TTE1) 2 ± 2 days after admission. The 26 included patients had then 2 TTEs per week throughout the hospitalisation period (21 ± 2 days). All examinations were performed using a VIVID FIVE type echograph (Vingmed GE, 2.5 MHz gauge, second harmonic imaging). Results presented here are those of TTE1 and TTE2 (the latter being the final echography performed 18 ± 2 days after admission, i.e. a mean 16 days after the diagnosis of thrombus).

The diagnosis of LV thrombus was established by two observers who jointly performed the echographic examination. Were considered as LV thrombus all masses whose echogenicity was superior to that of the blood, with well-defined edges distinct from the endocardium, contiguous to an akinetic or dyskinetic myocardium segment and present during the whole cardiac cycle on at least two different views [15].

Left ventricular end diastolic diameter was measured in time movement (TM) on the parasternal long axis view, left ventricular end diastolic volume and ejection fraction being measured using the Simpson method. Thrombus area was measured by planimetry on a four-chamber apical view.

1.3. Treatment (Table 1)

Enoxaparine therapy (100 IU/kg injected subcutaneously twice daily) was initiated as soon as the diagnosis of LV thrombus was established. Relay anticoagulation therapy with fluindione administered at doses adjusted to obtain an International Normalized Ratio between 2 and 3 was started 5 days after the initiation of enoxaparine therapy and maintained indefinitely. Moreover, in all the 19 patients who had a history of anterior myocardial infarction, an angioplasty with coronary stent placement had been performed during the acute infarction phase and all were already treated with a combination of antiplatelet drugs (aspirin + clopidogrel). To elude the concomitant administration of four antithrombotic drugs (fluindione + enoxaparin + aspirin + clopidogrel), treatment with clopidogrel was stopped on day 21 post-angioplasty, and fluindione was started only 5 days after enoxaparin introduction thus avoiding in particular the use of a combination of clopidog-
rel and anti-vitamin K agents (because of the long half-life of these two molecules, we deemed such a combination could be dangerous in case of bleeding).

All seven dilated cardiomyopathy patients had aspirin.

Complete blood count was done twice weekly. Anti-Xa activity was monitored in only four patients aged 75 years or more, and remained consistently within the therapeutic range. None of the patients had renal failure (i.e. creatinine clearance superior to 40 ml/min).

1.4. Statistical analysis

Variables are presented as mean values plus or minus mean standard error. Quantitative variables were compared using non-parametric tests (Mann–Whitney) and qualitative variables were compared using the $\chi^2$ test. $P$ values <0.05 were considered as statistically significant.

2. Results

2.1. Clinical outcome

Neither bleeding events nor thrombocytopenia episodes were observed. One 77 years old patient, with an initial mobile thrombus had a transient ischemic attack (aphasia) 9 days after the start of therapy (after initiation of the relay treatment, when enoxaparin and fluindione were administered concomitantly). On control echography, a small size persistent thrombus was observed (1 cm$^2$); brain CT scan examination was normal. In coronary patients, there were no new ischemic or stent re-occlusion episodes. A phone examination was normal. In coronary patients, there were no new ischemic or stent re-occlusion episodes.

2.2. Left ventricular thrombus echocardiographic outcome

Baseline echographic data are detailed in Table 2.

Table 2

<table>
<thead>
<tr>
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<th>Persistent Thrombus (n=7)</th>
<th>Disappeared Thrombus (n=19)</th>
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<tbody>
<tr>
<td>Duration (d)</td>
<td>13 ± 3</td>
<td>13 ± 1</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>61 ± 4</td>
<td>56 ± 1</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>158 ± 38</td>
<td>148 ± 15</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>34 ± 3</td>
<td>39 ± 2</td>
</tr>
<tr>
<td>Initial Thrombus Area (cm$^2$)</td>
<td>2.85 ± 0.9</td>
<td>2.1 ± 0.3</td>
</tr>
<tr>
<td>Mobile</td>
<td>2/7 (28.5%)</td>
<td>2/19 (10.5%)*</td>
</tr>
<tr>
<td>Protruding</td>
<td>4/7 (57%)</td>
<td>13/19 (68.5%)*</td>
</tr>
</tbody>
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No significant differences for all other parameters. AMI, anterior myocardial infarction; DMC, dilated MyoCardiopathy; LMWH, Low Molecular Weight Heparin; LVEDD, Left Ventricular End Diastolic Diameter; LVEDV, Left Ventricular End Diastolic Volume; LVEF, Left Ventricular Ejection Fraction.

* Statistical analysis was not performed (samples too low).

During the treatment period and in the 26 patients, mean thrombus area regressed from 2.30 ± 0.32 to 0.36 ± 0.11 cm$^2$ ($p < 0.0001$), see Fig. 1. Nineteen thrombi totally disappeared (73%). The area of the seven persisting thrombi significantly decreased from 2.85 ± 0.9 to 1.3 ± 0.3 cm$^2$ ($p < 0.05$). None of the parameters studied, whether clinical (etiology of cardiopathy and age) or echographic (left ventricular diameter and volume, left ventricular ejection fraction, initial thrombus area, mobile or protruding characteristics), allowed to predict the the evolution of the thrombus (Table 3).

3. Discussion

Unfractionated heparin (UH) has many disadvantages comparatively to LMWH: the time required to obtain an activated partial thromboplastin time (APTT) in the therapeutic range (1.5–2.5 fold the control values) is often longer (more than 72 h), the efficient dose is close to the toxic dose (narrow therapeutic window), bioavailability is low and the marked interaction with plasma proteins makes it impossible to predict the level of anticoagulation effect of a given dose in a given patient. In addition, the high sensitivity of UH to platelet factor 4 and its platelet aggregation promoting effect still limit its anti-thrombotic efficacy [16]. Finally, the risk of hemorrhage and the risk of thrombocytopenia are higher than with LMWH. The benefit/risk ratio of UH is thus sub-optimal, and when UH is compared to LMWHs in the treatment of arterial diseases (e.g. in the treatment of unstable angina in the ESSENCE study [17]), it is concluded that LMWHs are equivalent or even superior to UH in terms of both efficacy and tolerance. Nevertheless, UH is considered as the reference treatment in three indications (atrial fibrillation, mechanical valve prostheses, LV thrombus) even though its evaluation has been
limited and no direct comparison with LMWH is available. Ethical reasons (inclusion of a placebo group is impossible) and small sample sizes (at least for LV thrombus and for mechanical valve prostheses series) make it difficult to carry out double-blind, prospective, randomized studies in these indications. It should be noted, however, that a French group demonstrated in a non-randomized study including 208 mechanical valve prosthesis recipients that anticoagulation was quicker and more efficient with LMWH than with UH [18]. Moreover, in a preliminary series of patients with complete arrhythmia, LMWH seemed to prevent efficiently the occurrence of thromboembolic complications [19]. To our knowledge, unfractionated heparin in the treatment of LV thrombus was only assessed in 23 patients treated for 14 ± 4 days. The study, which was open, non-randomized and had no control group was published in 1994 [20]. The follow-up of LV thrombus was more difficult than today because second-harmonic imaging did not exist when that study was done. Mean thrombus area decreased from 3.9 ± 2.6 cm² to 0.76 ± 0.38 cm² and 83% of thrombi disappeared.

LMWH therapy for left ventricular thrombi was never evaluated; only one clinical case was reported [21].

Because of the decrease in the incidence of LV thrombus during the recent years, it seems even more difficult today to perform a study involving an important population of patients to make a double-blind comparison of UH and LMWH in this indication. Our open study therefore reproduces with a LMWH the imperfect methodology of the reference study of UH in this indication.

Our results suggest that the proposed therapeutic regimen is efficient and safe, since 73% of thrombi totally disappeared after a mean treatment duration of 13 days and the mean thrombus area significantly regressed. These results are similar to those reported with unfractionated heparin in the study quoted above [20]. Neither the etiology of the cardiopathy (anterior myocardial infarction or dilated cardiomyopathy), nor the different concomitant antiagregant treatments appeared to influence the progression of thrombi on LMWH therapy, which confirms the literature data [1,9,13]. Moreover, neither the age of the patients, nor the echographic parameters (left ventricular diameter and volume, left ventricular ejection fraction and initial thrombus area) allowed to predict the evolution of left ventricular thrombi. Our study confirms the current low incidence of LV thrombus following anterior myocardial infarction (20/310 = 6.4% versus about 40% before general acceptance of reperfusion techniques during the acute phase). Among the 146 dilated cardiomyopathy patients, 7.5% (n = 11) had a LV thrombus (including the 5 already known thrombi excluded) (see Table 2).

The question of the duration of vitamin K antagonist treatment can be raised. It is advised to maintain this treatment for a long time because, although most systemic emboli occur within the first weeks following the discovery of the thrombus, a 13% incidence of systemic embolism throughout a 4-year period among patients with poor left ventricular function has been reported [22].

4. Limitations of the study

Our study had an open methodology. Comparisons were not made with unfractionated heparin or with other low molecular weight heparins; also, it did not seem ethically reasonable to consider the inclusion of a placebo group. LV thrombus diagnosis is difficult; trans-thoracic echography remains the reference technique and the use of second-harmonic imaging, the joint performance of examinations by two echographists and the non-inclusion of patients in whom the presence of a thrombus was considered uncertain allowed to reduce the incidence of false positive echography results. MRI seems also to be a good technic to identify LV thrombus [23] but it is not routinely used yet. Finally, the fact that no link could be established between the initial thrombus area and thrombus disappearance with treatment might have been due to the low number of thrombi with an area of more than 5 cm² included (n = 3).

5. Conclusions

This pilot study suggests that enoxaparin may be efficiently and safely used in the treatment of newly diagnosed left ventricular thrombi before initiation of a relay oral anticoagulation therapy. Only a randomized study comparing enoxaparin and unfractionated heparin might confirm the role of enoxaparin in this indication. However, the currently low incidence of LV thrombi renders the performance of such a study difficult.

References


