



Enoxaparin for Early Anticoagulation after Mitral Valve Repair

Younes Moutakiallah^{1*}, Roland Henaine², Mehdi Bamous¹, Jacques Robin²,
Jean Ninet² and Jean-François Obadia²

¹Faculty of Medicine and Pharmacy of Rabat, Department of Cardiac surgery, Mohammed V University, Mohammed V Military Hospital, Rabat, Morocco.

²Faculty of Medicine Lyon Est, University of Claude Bernard Lyon 1, Hospices Civils de Lyon, Groupement Hospitalier Est, Hôpital Cardiologique Louis Pradel, Cardiac Surgery Unit, Lyon, France.

Authors' contributions

This work was carried out in collaboration between all authors. Authors YM, RH and J-FO designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors MB and YM managed the literature searches. Authors YM, JR and JN collected, analyzed and interpreted data. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Despite recent progress and technological advances, heart valve surgery remains associated with a high rate of thromboembolic complications requiring anticoagulation, which must be both safe and effective to prevent any thromboembolic or bleeding events.

Objectives: The objective of this study was to verify the efficacy and the safety of Low Molecular Weight Heparin followed by vitamin K antagonists for the early anticoagulation after mitral valve repair.

Patients and Methods: This work was conducted as a prospective study. We selected 120 consecutive patients who underwent mitral valve repair and received enoxaparin as bridge between continuous unfractionated heparin and fully effective vitamin K antagonist therapy. The mean age was 63.6±13.5 years (15-84 years).

*Corresponding author: E-mail: dryouns@hotmail.com;

Results: There was no in-hospital mortality. One bleeding event (0.8%) was described: a right haemothorax drained percutaneously with transfusion and no thrombo-embolic events.

Conclusion: Low molecular weight heparin enoxaparin as bridging therapy between immediate postoperative unfractionated heparin and complete efficacy of oral anticoagulants may be considered as an option for the prevention of thromboembolic events in patients recently undergoing mitral valve repair.

Keywords: Early anticoagulation; mitral valve repair; low molecular weight heparin.

ABBREVIATIONS

TE: Thromboembolic; MVRp: Mitral valve repair; LMWH: Low molecular weight heparin; UFH: Unfractionated heparin; VKA: Vitamin K antagonist; AF: Atrial fibrillation; DVT: Deep venous thrombosis; TTE: Transthoracic echocardiography; INR: International ratio; PAI: Platelet aggregations inhibitors; CABG: Coronary artery bypass graft; APTT: Activated partial thromboplastin time; MVHR: Mechanical valve heart replacement.

1. INTRODUCTION

Despite recent progress and technological advances, heart valve surgery remains associated with a high rate of thromboembolic (TE) complications requiring anticoagulation, which must be both safe and effective to prevent any TE or bleeding events. This balance is all the more difficult to achieve during the early postoperative phase, associated with maximum TE and bleeding risks [1-4]. The optimal early anticoagulation strategy after mitral valve repair (MVRp) remains controversial requiring randomized double-blind studies.

2. OBJECTIVES

The aim of the study was to evaluate the efficacy and the safety of Low molecular weight heparin (LMWH) therapy as a bridge between immediate postsurgical unfractionated heparin (UFH) and effective oral anticoagulation by vitamin K antagonist (VKA), using the rate of TE and bleeding events during the early postoperative phase as primary endpoint in patients who recently underwent MVRp.

3. PATIENTS

This prospective study was conducted over one year period in the department of cardiac surgery and concerned 120 consecutive patients with a mean age of 63.6±13.5years (15-84 years) during the early postoperative phase after MVRp treated according to the same anticoagulant protocol (Table 1). This study was approved by our institution's Ethics Committee. All patients who underwent MVRp were included in the

study. Patients with the following characteristics were excluded: previous or simultaneous valve heart replacement, renal failure (creatinine clearance < 30ml/mn) and previous heparin-induced thrombocytopenia.

There was 82 men (68.3%) and 38 women (31.7%). The patients had a mean 0.8±0.9 (0-3) cardiovascular risk factors. 40 patients (33.3%) was receiving VKA therapy before surgery for atrial fibrillation (AF) in 38 cases (31.7%) and deep venous thrombosis (DVT) in 2 cases (1.7%). In transthoracic echocardiography (TTE), 62 patients (51.7%) had a left atrium diameter superior than 45mm and 10 patients had left ventricular ejection fraction less than 45%. In the immediate postoperative period, UFH therapy was started on the 6th postoperative hour in the surgical intensive care unit. Patients were included in the study from their admission to the ward after transfer from the surgical intensive care unit and UFH was replaced by LMWH. They received enoxaparin 2000, 4000 or 6000IU/12hour respectively if the weight is under 51 Kg, between 51 and 80Kg or more than 80 Kg. The VKA therapy was started after chest drain removal usually at day 2. LMWH was continued until VKA therapy achieved the target international ratio (INR) that must be over 2.

4. METHODS

All surgical procedures were performed under cardiopulmonary bypass (CPB) and aortic clamping with intermittent antegrade crystalloid cardioplegia and usually moderate hypothermia at 32°C. The surgical approach was a full median sternotomy for 38 patients (31.7%) and minimally invasive right thoracotomy with video-assistance

for 82 patients (68.3%) (Table 2). VKA therapy (fluidione) in combination with heparin was started after removal of the chest drain and LMWH was continued until the target INR was superior than 2. Platelet aggregations inhibitors (PAI) were not used systematically, but reserved to 10 patients (8.3%) who had a combined coronary artery bypass graft (CABG). 28 patients (23.3%) had Epicor® (St Jude, Minnesota, USA) for AF ablation and 8 patients (6.7%) tricuspid annuloplasty.

5. RESULTS

As per the guidelines for reporting morbidity and mortality after cardiac valvular operations, thromboembolism was defined as an embolic event that occurred in the absence of infection, after the immediate operative period, and a bleeding event was defined as an episode of major internal or external bleeding that caused death, permanent injury, or required transfusion [1,2]. Results are expressed as mean±SD.

There was no in-hospital mortality. There was no in-hospital TE event. However, we report one bleeding event (0.8%): right haemothorax at day 2 after surgery drained percutaneously with transfusion of 2 units of red packed cell, with a favorable outcome. This patient was a 62 year-old woman followed for more than 5 years for idiopathic thrombocytopenia with normal platelet

counts diagnosed during minor hemorrhagic syndrome (recurrent epistaxis) and in whom severe mitral regurgitation was discovered six months before surgery.

The return of patients to ward was on average of 2.3±2.5day (1–14 day) and 78.3% of patients returned between the 1st and the 2nd day. The bridging therapy with both VKA and enoxaparin lasted on average of 2.7±0.9day (2–5 day) and in 86.7% of cases the bridge lasted before the 3rd day. The anti Xa activity was measured for all patients 4 hours after the first and the third injection of enoxaparin, it was on average 0.3±0.1UI/ml (0.1–0.5UI/ml) and all patients were in the therapeutic range. Follow-up TTE showed 1 case of non compressive and resolving pericardial effusion (0.8%) (Table 3).

6. DISCUSSION

Heart valve surgery is still associated with high morbidity and mortality related to TE and haemorrhagic complications, despite the trend towards valve repair techniques and technological improvements of biological and mechanical valve prostheses. This TE risk is particularly high during the 1st month following heart valve surgery [3,4]. The ideal early postoperative anticoagulation strategy (with both high antithrombotic efficacy and low bleeding risk) has yet to be found [2].

Table 1. Clinical and paraclinical characteristics of the population

Parameter	Number of patient	percentage
Age:	63.58±13.46 year	
Gender		
Male:	82	68.3%
Female:	38	31.7%
Cardiovascular risk factors:	0.85±0.89 (0 – 3)	
Arterial hypertension:	20	16.7%
Diabetes:	10	8.3%
Smoking:	30	25%
Dyslipidaemia:	30	25%
Obesity:	14	11.7%
Preoperative VKA therapy:	40	33.3%
Atrial fibrillation:	38	31.7%
Deep venous thrombosis:	2	1.7
Risk factors of thromboembolism		
Age > 60 years	76	63.3%
Enlarged LA (LAD> 45mm)	62	51.7%
LVEF < 45%	20	16.7%
Euroscore	2.9±0.9	

VKA: Vitamin K Antagonist; LVEF: Left ventricular ejection fraction; LA: left atrium; LAD: left atrium diameter

Table 2. Operative parameters

Parameter	Number of patients	Percentage
Surgical incision:		
Median full sternotomy:	38	31.7%
Minithoracotomy with Video-assistance:	82	68.3%
Associated procedures		
Epicor:	28	23.3%
Tricuspid plasty:	8	6.7%
Coronary artery bypass graft:	10	8.3%
Time of cardio-pulmonary bypass	58.5±37.7 minutes	
Time of aortic clamping	43.8±11.7 minutes	

Table 3. Postoperative parameters

Parameter	Number of patients	Percentage
Day of return to ward:		
Mean (day):	2.28 ± 2.54 day (1 – 14)	
Day1 – Day2:	94	78.3%
Postoperative AF:	26	21.7%
Time to initiation of VKA		
Mean (day):	2.7 ± 0.9 day (2 – 5)	
2 – 3 days:	104	86.7%
Complications		
Non compressive pericardial effusion:	1	0.8%
Haemothorax:	1	0.8%
Death:	0	0%

According to the EACTS guidelines published in 2012, Oral anticoagulation should be considered for the first three months after mitral valve repair (classe IIa) and should be started during the first postoperative days [5].

LMWH has many potential advantages: a better safety profile with less thrombocytopenias [6], less bleeding, a more predictable and rapidly reached anticoagulant effect [7], the possibility of self-administration without laboratory monitoring, and shorter hospital stays and lower costs associated with outpatient administration [8]. However, unlike UFH, LMWH is not fully reversible by protamine, and may carry an increased bleeding risk in the immediate postoperative period [2,9].

LMWH has been successfully used in the treatment and prevention of DVT and pulmonary embolism, unstable angina, acute coronary syndrome, acute myocardial infarction and AF [7,10-12]. The benefit-risk balance of LMWH is at least as good as UFH, which the bioavailability and anticoagulation predictability are poor. Indeed, in the ESSENCE study [13,14] and the TIMI 9B study, [13,15] in about 50% of patients receiving intravenous UFH, effective anticoagulation was achieved on day 3. Hull, [16]

using subcutaneous UFH, observed that only in 37% of patients with recent DVT, the target activated partial thromboplastin time (APTT) was achieved on day 2, despite an additional intravenous bolus of 5000IU. Finally, Montalescot [17] reported that only 9% and 27% of patients treated by subcutaneous UFH for early mechanical valve heart replacement (MVHR), had an APTT value within the therapeutic range (1.5-2.5 times control) respectively after 2 and 13 days. UFH has not been shown to be superior (or even non-inferior) to other anticoagulant regimens pending achievement of the target INR in patients who recently underwent MHVR [13,18]. In the Fanikos study, LMWH were given early after MVHR [19], the number of events (deaths, TE events and bleeding events) was slightly but not significantly lower in the LMWH group (n=29) than in the control group who were given UFH (n=34). The authors concluded that patients who received LMWH had a shorter hospital stay and lower postoperative costs than patients receiving UFH. Luca, in his therapeutic trial about the use of LMWH as bridging therapy to oral anticoagulation in patients undergoing electrical cardioversion for AF, confirmed that enoxaparin was safer and more effective than UFH and the therapeutic zone was reached more rapidly. After successful cardioversion, no cases

of intracardiac thrombosis or TE events were reported in the enoxaparin group [20]. Similar findings were published by C. Schmidt-Lucke, indicating that pharmacological and clinical studies have demonstrated that the therapeutic range of anti-Xa activity ensuring effective anticoagulation was reached during the first 24 hours after the 1st injection in 90% of patients treated with LMWH [21]. In our study, the therapeutic range of anti Xa activity was reached in all patients after the 3rd injection of enoxaparin and no in hospital case of TE event was reported. The only patient who presented a bleeding event (right haemothorax) had an idiopathic thrombocytopeny.

7. STUDY LIMITATIONS

Our work is not randomized study and did not include a control group, we cannot comment on the efficacy or safety of the use of LMWH early after MVRp. However, no study evaluating UFH itself or LMWH and no randomized double-blinded studies comparing LMWH and UFH after MVRp have been conducted; more than 20 years of use of LMWH.

8. CONCLUSION

LMWH as bridging therapy between immediate postoperative UFH and complete efficacy of oral anticoagulants may be considered as an option for the prevention of TE events in patients recently undergoing MVRp. These results need to be confirmed by a randomized double-blind study comparing LMWH and UFH for this indication.

DISCLOSURE

All authors declare that written informed consent was obtained from the patient for publication of this article.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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