Low Molecular Weight Heparin as an Alternative to Unfractionated Heparin in the Immediate Postoperative Period After Left Ventricular Assist Device Implantation

*Sigrid E. Sandner, *Daniel Zimpfer, *Philipp Zrunek, †Barbara Steinlechner, †Angela Rajek, *Heinrich Schima, *Ernst Wolner, and *Georg M. Wieselthaler

*Department of Cardiothoracic Surgery, Medical University of Vienna and †Department of Cardiothoracic Anesthesia, Medical University of Vienna, Vienna, Austria

Abstract: We present a regimen for anticoagulation in the immediate postoperative period after left ventricular assist device (LVAD) implantation using low molecular weight heparin (LMWH) as an alternative to unfractionated heparin. Between May and September 2007, eight consecutive patients undergoing LVAD implantation for advanced heart failure received the LMWH nadroparin. Nadroparin was given twice daily to achieve anti-Factor Xa activity target peak levels of 0.4 ± 0.1 U/mL. The antiplatelet therapy consisted of aspirin (100 mg/day) and dipyridamole (3 × 75 mg/day). One patient underwent heart transplantation, three patients died, and four patients continued to receive device support. The median duration of support was 78 days (range, 46 to 174). No major bleeding was observed; minor bleeding occurred in three patients. In two patients, pump thrombosis was suspected. There were two ischemic and no hemorrhagic strokes. The use of LMWH may provide a new anticoagulation treatment option in the immediate postoperative period after LVAD implantation. **Key Words:** Anticoagulation—Bridge to transplantation—Left ventricular assist device—Low molecular weight heparin—Unfractionated heparin.

Adequate anticoagulation remains a key issue with the use of left ventricular assist devices (LVAD). Conventional anticoagulation management has

doi:10.1111/j.1525-1594.2008.00634.x

Received November 2007; revised June 2008.

Address correspondence and reprint requests to Sigrid E. Sandner, MD, Department of Cardiothoracic Surgery, Medical University of Vienna, Waehringer Guertel 18-20, A 1090 Vienna, Austria. E-mail: sigrid.sandner@meduniwien.ac.at

Presented in part at the 15th Congress of the International Society for Rotary Blood Pumps held November 2–4, 2007, in Sydney, Australia.

included unfractionated heparin (UFH) in the postoperative period, oral anticoagulants in the outpatient setting, and adjunctive antiplatelet therapy. In addition to its well-known bleeding complications, UFH has several limitations (1), including immune-mediated platelet activation leading to heparin-induced thrombocytopenia, a variable anticoagulant response requiring continuous anticoagulant monitoring, and the need for venous access that puts patients at risk for infection. Clinical experience with the use of LMWH in mechanical circulatory support is limited (2–4). Here, we evaluated the use of LMWH (nadroparin) as an alternative to UFH in the immediate postoperative period after LVAD implantation.

PATIENTS AND METHODS

Patients

The retrospective analysis included eight consecutive patients with end-stage heart failure undergoing LVAD implantation as bridge to transplant therapy ($n = 7$) or destination therapy ($n = 1$) between May and September 2007. Devices included the MicroMed DeBakey ($n = 5$; MicroMed, Houston, TX, USA), HeartWare ($n = 2$; HeartWare, Miramar, FL, USA), and Incor ($n = 1$; Berlin Heart AG, Berlin, Germany) LVADs. Mean patient age was 63.5 ± 7.2 years. All patients were male. Ischemic heart disease was the cause of heart failure in five patients, and idiopathic dilated cardiomyopathy in three patients. All patients had symptoms of New York Heart Association class IV heart failure at implant. Patients had moderately impaired end-organ function as indicated by mean Modification of Diet in Renal Disease-derived glomerular filtration rate of 58.0 ± 7.8 mL/min/1.73 m^2, mean serum albumin of 39.9 ± 3.1 g/dL, and mean serum total bilirubin of 1.6 ± 0.8 mg/dL. None of the patients had received other mechanical circulatory support including intra-aortic balloon pump prior to LVAD implantation, and none were ventilated. Concomitant anticoagulant medications before LVAD implantation included phenprocoumon ($n = 7$), aspirin ($n = 2$), and clopidogrel ($n = 1$); none had received heparin. Mean international normalized ratio (INR) at implant was 2.5 ± 0.3. In two patients, LVAD implantation was a redo procedure; both patients had undergone previous coronary revascularization. In two patients, tricuspid valve repair was performed at LVAD implantation.

Anticoagulation protocol

The Factor Xa inhibitor nadroparin was given subcutaneously twice daily with the first dose given 24 h after implant at 0.075 mL/10 kg. Anticoagulation was monitored by anti-Factor Xa activity trough and peak levels. Nadroparin dose was adjusted to achieve target peak levels of 0.4 ± 0.1 U/mL. A protocol exception was made for Patient no. 5, in whom the start of anticoagulation was postponed to postoperative day (POD) 8 due to insufficient hemostasis. In this patient, anti-Factor Xa activity target peak level was defined as 0.2–0.3 U/mL as the patient remained prone to bleeding due to an unstable clinical course (described below). Nadroparin was given for a median duration of 26 days (range, 10 to 77). Patients were switched to oral anticoagulants (phenprocoumon) for long-term anticoagulation. Antiplatelet therapy was started on POD 3 and consisted of aspirin 100 mg once daily in combination with dipyridamole 75 mg three times daily ($n = 5$) or aspirin 100 mg once daily only ($n = 3$).

RESULTS

Overall outcomes

One patient underwent heart transplantation (time to transplantation 63 days). Of the four patients who continued to receive device support, all were eligible for heart transplantation and on the active waiting list for heart transplantation. Causes of death among the three patients who died on support were sepsis ($n = 1$, time to death 84 days), and ischemic stroke ($n = 1$, time to death 46 days); in one patient, the cause of death (after 72 days) remained unknown. The median duration of support was 78 days (range, 46 to 174), with a mean of 95 ± 47 days during a cumulative follow up of 2.1 patient-years.

Adverse events

Adverse events are shown in Table 1. There were no episodes of major bleeding that required surgery.

TABLE 1. *Adverse events in the eight study patients*

Event	Duration of nadroparin treatment	
	Patients with event	No. of events
Bleeding		
Requiring surgery	0	0
Requiring ≥2 units of packed red cells only*	3	8
Stroke		
Ischemic	2	2
Hemorrhagic	0	0
Transient ischemic attack	0	0
Peripheral non-neurologic thromboembolic event	0	0
Suspected pump thrombosis*	2	2
Hemolysis	0	0

* Detailed description of event in text.

One patient required transfusion of ≥2 units of packed red blood cells (PRBCs) following drainage of a jugular hematoma (POD 16). A second patient required PRBC transfusion following drainage of a pleural effusion (POD 40). The third patient required multiple transfusions due to a highly unstable postoperative course that included postimplant respiratory failure and consecutive right heart failure. In this patient, chest closure could not be achieved without hemodynamic compromise and he was treated with a sternal VAC system. Although this patient was maintained on nadroparin with lower anti-Factor Xa activity target peak levels (0.2–0.3), he did not develop hemolysis or pump thrombus formation throughout his stay in the ICU and he died of sepsis and multiorgan failure after 84 days. Two events of suspected pump thrombosis were observed. One patient (on a MicroMed DeBakey device) experienced increased device power uptake without signs of hemolysis (POD 24). He underwent a single course of r-TPA lysis (5 mg bolus followed by 10 mg as continuous infusion over 1 h), after which device power uptake returned to normal and the patient remained event-free. The second patient (on an Incor device) disconnected his driveline; subsequently, lowering of the pressure gradient across the pump indicative of pump thrombus formation was observed and this patient went on to have an ischemic stroke. Ischemic stroke was observed in one other patient for a total of two ischemic strokes observed under nadroparin treatment.

DISCUSSION

Several advantages of LMWH over UFH have been reported. Recently published data have shown that LMWH was associated with superior efficacy among patients with acute coronary syndromes when compared with UFH (5). In addition, consistent evidence demonstrates that LMWH is superior to UFH for the initial treatment of deep venous thrombosis, particularly for reducing mortality and risk for major bleeding during initial therapy (6). Many centers have adopted the use of LMWH within 24 h after mechanical heart valve replacement without use of UFH, with continuation of LMWH until a therapeutic INR for long-term management with oral warfarin has been achieved (7,8). LMWH has many potential advantages for patients with mechanical heart valves that may also be relevant for patients with assist devices. LMWH has a better safety profile with less bleeding, a more predictable and rapidly reached anticoagulant effect, the possibility of self-administration without laboratory monitoring, and shorter hospital stays and lower costs associated with patient management (9). Fanikos et al. (8) performed a comparative case-control study of perioperative anticoagulation after mechanical valve implantation with the LMWH enoxaparin (29 patients) versus intravenous UFH (34 patients). There were no thromboembolic events in the LMWH group compared with two (6%) in the UFH group, and no difference in major hemorrhagic events was reported. The use of LMWH reduced the length of hospital stay after surgery and reduced the cost per patient. Similar outcomes were demonstrated in a randomized trial comparing the LMWH nadroparin to intravenous UFH after mechanical heart valve replacement (9). Clinical experience with the use of LMWH in mechanical circulatory support is limited. It has recently been shown that the combination of enoxaparin and antiplatelet therapy can be used as an alternative to oral anticoagulants in the long-term management of LVAD patients (4). Similarly, satisfactory anticoagulation could be achieved in infants on VAD (3). Nadroparin is routinely used at our department for venous thrombosis prophylaxis and initial anticoagulation of patients after heart valve replacement. Here, we evaluated the use of LMWH as an alternative to UFH in the immediate postoperative period after LVAD implantation. Early mortality before 30 days after LVAD implantation in our study patients was 0%. The greatest risk for patients in the immediate postoperative period is bleeding. Using nadroparin at the described target levels, we did not observe any major bleeding that required reoperation. Two events of bleeding that required transfusion of PRBC occurred at later time points and followed elective interventions. We did observe two thromboembolic events that warrant further studies to determine optimal LMWH dosing in this selected cohort of patients. Limitations of the study include a small sample size. In addition, we did not perform a direct, randomized comparison of nadroparin with other LMWH or UFH, and thus we cannot describe the comparative benefits and safety of this therapy. In conclusion, our outcomes show that anticoagulation with LMWH after LVAD placement appears feasible and provides adequate anticoagulation. The use of LMWH may prove a promising new anticoagulation treatment option for LVAD patients.

REFERENCES

1. Hirsh J, O'Donnell M, Eikelboom JW. Beyond unfractionated heparin and warfarin: current and future advances. *Circulation* 2007;116:552–60.
2. Vermes E, Kirsch M, Farrokhi T, et al. Management of intracranial hemorrhage in patients with mechanical circulatory

support: a role for low-molecular-weight heparins? *ASAIO J* 2005;51:485–6.
3. Ghez O, Liesner R, Karimova A, Ng C, Goldman A, van Doorn C. Subcutaneous low molecular weight heparin for management of anticoagulation in infants on Excor ventricular assist device. *ASAIO J* 2006;52:705–7.
4. Meuris B, Arnout J, Vlasselaers D, Schetz M, Meyns B. Long-term management of an implantable left ventricular assist device using low molecular weight heparin and antiplatelet therapy: a possible alternative to oral anticoagulants. *Artif Organs* 2007;31:402–5.
5. Murphy SA, Gibson CM, Morrow DA, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. *Eur Heart J* 2007;28:2077–86.
6. Snow V, Qaseem A, Barry P, et al. Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. *Ann Intern Med* 2007;146:204–10.
7. Montalescot G, Polle V, Collet JP, et al. Low molecular weight heparin after mechanical heart valve replacement. *Circulation* 2000;101:1083–6.
8. Fanikos J, Tsilimingras K, Kucher N, Rosen AB, Hieblinger MD, Goldhaber SZ. Comparison of efficacy, safety, and cost of low-molecular-weight heparin with continuous-infusion unfractionated heparin for initiation of anticoagulation after mechanical prosthetic valve implantation. *Am J Cardiol* 2004;93:247–50.
9. Kulik A, Rubens FD, Wells PS, et al. Early postoperative anticoagulation after mechanical valve replacement: a systematic review. *Ann Thorac Surg* 2006;81:770–81.