ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Low-molecular-weight heparin for anti-coagulation after left ventricular assist device implantation

Sigrid E. Sandner, MD,[a] Julia Riebandt, MD,[a] Thomas Haberl, MD,[a] Stephane Mahr, MD,[a] Angela Rajek, MD,[b] Heinrich Schima, PhD,[a] George M. Wieselthaler, MD,[c] Guenther Laufer, MD,[a] and Daniel Zimpfer, MD[a]

From the Divisions of [a]Cardiac Surgery and [b]Cardiothoracic and Vascular Anesthesia and Critical Care Medicine, Medical University of Vienna, Vienna, Austria; and [c]Division of Adult Cardiothoracic Surgery, University of California, San Francisco School of Medicine, San Francisco, California.

KEYWORDS:
anti-coagulation;
low-molecular-weight;
ventricular assist device;
heart failure

BACKGROUND: Anti-coagulation is required in patients with left ventricular assist devices (LVADs). We evaluated the feasibility of low-molecular-weight heparin (LMWH) for initiation of anti-coagulation and transitioning to oral anti-coagulation after LVAD implantation.

METHODS: This single-center study included 78 consecutive patients who underwent either Thoratec HeartMate II LVAD ($n = 27$) or HeartWare ventricular assist device (HVAD, $n = 51$) implantation. The LMWHs enoxaparin ($n = 50$) and dalteparin ($n = 28$) were used. LMWH was started within 24 hours post-operatively in 79.5% of patients. No anti-coagulation was given before starting LMWH therapy. LMWH activity was monitored by determination of anti–factor Xa levels in plasma.

RESULTS: The majority of patients (80.7%) had peak anti-Xa activity within the defined range of efficacy of 0.2 to 0.4 IU/ml by the second day of treatment. Mean effective peak anti-Xa activity was 0.28 ± 0.06 IU/ml. Mean duration of anti-coagulation with LMWH was 25.8 ± 18 days. Ischemic strokes were observed in 3 patients (3.8%), with a total of 4 events. Three events occurred while on LMWH, and 1 event occurred during follow-up on oral anti-coagulation. There was 1 fatal stroke. No pump thrombus was observed. Major bleeding was observed in 5 patients (6.4%), with a total of 6 events. Gastrointestinal bleeding was the most common complication ($n = 3$). There were no fatal bleeding events.

CONCLUSIONS: LMWH in the setting of LVAD shows rapid and constant biologic efficacy. Anti-coagulation with LMWH appears feasible after LVAD implantation. These findings support further evaluation of LMWH as an alternative to unfractionated heparin in this patient cohort.

J Heart Lung Transplant 2014;33:88–93

Low-molecular-weight heparin (LMWH) has been successfully applied in multiple settings, including prevention and treatment of deep vein thrombosis and pulmonary embolism,[1,2] and in acute coronary syndromes.[3–5] LMWH has been shown to be as safe and effective or superior to unfractionated heparin (UFH) in these settings and is now considered standard therapy.[6,7] More recently, LMWH has been evaluated as an alternative to UFH in atrial fibrillation[8,9] and mechanical heart valve replacement.[10–12] LMWH in these settings also appears to offer effective and stable anti-coagulation.

No guidelines exist concerning optimal anti-coagulation after left ventricular assist device (LVAD) implantation, particularly in the immediate post-operative period. In the pivotal HeartMate II clinical trials,[13–15] as well as the recently published HeartWare Ventricular Assist Device (HVAD) Bridge to Transplant ADVANCE Trial,[16] recommendations

Reprint requests: Sigrid E. Sandner, MD, Division of Cardiac Surgery, Medical University of Vienna, Wahringer Gurtel 18-20, A 1090 Vienna, Austria. Telephone: +43-1404006969. Fax: +43-1404005640.

E-mail address: sigrid.sandner@meduniwien.ac.at

1053-2498/$ - see front matter
http://dx.doi.org/10.1016/j.healun.2013.10.009

were made for intravenous UFH to be initiated post-operatively as a transition to warfarin and aspirin therapy, and this reflects the prevailing current clinical practice. Bleeding and thromboembolism remain among the most common and serious adverse events associated with the use of LVADs. Slaughter et al[17] recently showed that patients who do not receive early post-operative intravenous UFH are not at an increased risk for thrombotic events and their risk of post-operative bleeding is reduced. Small observational series using LMWH after VAD implantation have shown favorable results[18–20]; however, its use has not yet been examined in larger series.

The aim of this study was to evaluate the feasibility of LMWH for initiation of post-operative anti-coagulation and transitioning to fully effective oral anti-coagulation in consecutive patients undergoing LVAD implantation.

Methods

Study population

This single-center study included 78 consecutive patients with end-stage heart failure who underwent either HeartMate II LVAD (Thoratec Corp., Pleasanton, CA) or HVAD (HeartWare International, Inc., Framingham, MA) implantation between August 2008 and December 2012 at the Medical University of Vienna and who received either enoxaparin (Lovenox; Sanofi-Aventis) or dalteparin (Fragmin; Pfizer) post-operatively as a bridging anti-coagulant to fully effective oral anti-coagulation. We excluded patients who underwent HeartMate II LVAD or HVAD implantation during this period, but who received UFH or any non-LMWH anti-coagulant, and patients with confirmed or suspected heparin-induced thrombocytopenia or previously diagnosed coagulopathy ($n = 33$). Follow-up consisted of daily monitoring of in-patients, weekly follow-up visits in the VAD outpatient clinic in the first 3 months after discharge, and once-monthly visits thereafter. All data were prospectively entered into the Vienna Mechanical Circulatory Support database.

Anti-coagulation protocol

LMWH was started within 24 hours post-operatively. Start of LMWH could be delayed due to prolonged post-operative bleeding or in patients on temporary post-operative extracorporeal membrane oxygenation (ECMO) support. Of note, no anti-coagulation was given in these patients before starting with LMWH. Enoxaparin was given at an initial dose of 0.5 mg/kg rounded to 40, 60 or 80 mg, and dalteparin was given at an initial dose of 60 anti-Xa IU/kg rounded to 2,500, 5,000 or 7,500 IU. Doses could be adjusted downward in patients with impaired renal function and if patients were perceived to be at risk of bleeding. LMWH was administered subcutaneously at 12-hour intervals, and LMWH activity was monitored by determination of anti-factor Xa levels in plasma at 3 to 4 hours post-injection. Peak anti-Xa activity of 0.2 to 0.4 IU/ml was considered therapeutic. LMWH dose was adjusted accordingly when anti-Xa levels were not within the target range. Titration of LMWH doses to the effective range was performed at the physician's discretion taking into consideration the patient's clinical course. LMWH was continued until a target international normalized ratio (INR) of 2 to 2.5 was achieved under oral anti-coagulation. Oral anti-coagulation in VAD patients was started after removal of all chest tubes and in-dwelling catheters, when no further interventions (such as drainage of pleural effusions) were anticipated, and oral intake of medication was satisfactory. In case of post-operative renal replacement therapy oral anti-coagulation was started after discontinuation of continuous veno-venous hemofiltration. Anti-platelet therapy was started on Day 3 post-operatively. Standard anti-platelet therapy consisted of aspirin 100 mg/day. Depending on the patient's risk profile a second anti-platelet agent was added, or a different anti-platelet agent was used as first-line therapy. In the case of a history of bleeding related to anti-platelet drugs, anti-platelet therapy could be omitted.

Outcome measures

The end-point for efficacy was the occurrence of a symptomatic arterial thromboembolic event, defined as ischemic stroke, transient ischemic attack, any arterial non–central nervous system thromboembolism, or occurrence of pump thrombus from the first day of LMWH until Day 90 post-operatively. The end-point for safety was major bleeding during LMWH treatment, defined as any non-surgical bleeding from the first day of LMWH to initiation of oral anti-coagulation. This included thoracic, retroperitoneal and gastrointestinal bleeding; intracerebral bleeding (hemorrhagic stroke); and any bleeding of unknown source associated with a drop in hemoglobin of >2 g/dl in a 24-hour period and transfusion of ≥ 2 U of packed red blood cells.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation.

Results

Patients' characteristics

Seventy-eight patients with end-stage heart failure who underwent either HeartMate II LVAD ($n = 27$) or HVAD ($n = 51$) implantation were studied (Table 1). Patients were mostly male (87.1%), with a mean age of 56.0 $\pm$ 10.0 years. The majority of patients were either INTERMACS Profile 3 (33.3%) or Profile 4 to 7 (24.4%), whereas 19.2% of patients were Profile 1. This included 3 patients on pre-operative ECMO support, and 2 patients with an intra-aortic balloon pump. A considerable proportion of patients had risk factors for arterial thromboembolism, including history of high blood pressure (41.0%), diabetes (38.4%), previous stroke (10.2%), atrial fibrillation (30.7%) and intracardiac thrombus (2.5%). Overall, patients also had moderately impaired renal function, with a mean Modification of Diet in Renal Disease–derived glomerular filtration rate of 57.4 $\pm$ 24.3 ml/min/1.73 m^2. In 14% of patients, LVAD implantation was performed without standard cardiopulmonary bypass. This included 9 patients in whom LVAD implantation was performed on ECMO, and 2 patients in whom no extracorporeal circulation was used. A thoracotomy approach avoiding full median sternotomy was used in 18% of patients.