Time to achieving therapeutic international normalized ratio increases hospital length of stay after heart valve replacement surgery

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Background Achieving a therapeutic international normalized ratio (INR) before hospital discharge is an important inpatient goal for patients undergoing mechanical cardiac valve replacement (MCVR). The use of clinical algorithms has reduced the time to achieve therapeutic INR (TTI) with warfarin therapy. Whether TTI prolongs length of stay (LOS) is unknown.

Methods Patients who underwent MCVR over a consecutive 42-month period were included. Clinical data were obtained from the Society of Thoracic Surgeons Adult Cardiac Surgery database and electronic medical records. Therapeutic INR was defined as per standard guidelines. Warfarin dose was prescribed using an inpatient pharmacy-managed algorithm and computer-based dosing tool. International normalized ratio trajectory, procedural needs, and drug interactions were included in warfarin dose determination.

Results There were 708 patients who underwent MCVR, of which 159 were excluded for reasons that would preclude or interrupt warfarin use. Among the remainder of 549 patients, the average LOS was 6.4 days and mean TTI was 3.5 days. Landmark analysis showed that subjects in hospital on day 4 (n = 542) who achieved therapeutic INR were more likely to be discharged by day 6 compared with those who did not achieve therapeutic INR (75% vs 59%, $P < .001$). Multivariable proportional hazards regression with TTI as a time-dependent effect showed a strong association with discharge ($P = .0096$, hazard ratio 1.3) after adjustment for other significant clinical covariates.

Conclusions Time to achieve therapeutic INR is an independent predictor of LOS in patients requiring anticoagulation with warfarin after MCVR surgery. Alternative dosing and anticoagulation strategies will need to be adopted to reduce LOS in these patients. (Am Heart J 2017;187:70-77.)

Mechanical valve replacement surgery can be complicated by valve-related thromboembolism, with a 24% incidence in the first year and an incidence between the second and fourth years of 15%, decreasing thereafter.[1,2] Thrombi can be detected as early as 9 days by transesophageal echocardiography after mechanical valve replacement, and it is usually these early thrombi that are associated with greater morbidity and thromboembolic complications.[3] In one study involving 2,982 patients who underwent mechanical aortic valve replacement (AVR), transient ischemic attacks occurred in 42 patients, permanent strokes in 42 patients, and peripheral thromboembolic events in 15 patients before discharge.[4] To minimize thromboembolic complications, initiating anticoagulation therapy with warfarin immediately after mechanical cardiac valve replacement surgery is standard practice at most medical centers. The warfarin dosage is titrated based on international normalized ratio (INR) levels[5,6] using warfarin dosing algorithms, with a goal of reaching therapeutic INR targets before hospital discharge.

Current inpatient algorithms for warfarin dosing adjust for multiple clinical variables. However, despite this protocol-driven approach, clinical experience suggests that time to therapeutic INR (TTI) can vary widely, potentially protracting hospital length of stay (LOS). However, there has been no study performed examining

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the impact of TTI on LOS after mechanical cardiac valve replacement. Length of stay plays an important role in determining the cost of treating patients after elective surgery, and hospitals have a significant economic incentive to expedite discharge of patients especially in the era of capitated reimbursements.[7]

There are many factors that contribute to prolonged LOS after cardiac surgery, and some of these include prolonged intensive care unit (ICU) stay, postoperative atrial fibrillation, congestive heart failure, and age. Whether TTI is a determinant in prolonging LOS in patients undergoing mechanical cardiac valve replacement and who receive warfarin is unknown. Although patient-related risk factors may not necessarily be modifiable, algorithms can be designed and used to safely but effectively prescribe warfarin in the postoperative setting to minimize LOS if TTI indeed plays an important role in prolonging LOS. Such an intervention could result in significant cost savings. In this study, we reviewed and analyzed data from electronic medical records and the Society of Thoracic Surgeons Adult Cardiac Surgery Database to investigate whether TTI is an independent predictor for increased hospital LOS after mechanical cardiac valve replacement surgery.

Methods

Patients

Consecutive patients who underwent either mechanical aortic (AVR) or mitral valve replacement (MVR) or both at Mayo Clinic, Rochester, MN, were included. Warfarin dose was prescribed using an inpatient pharmacy-managed algorithm and computer-based dosing tool for all patients in the analysis as described in detail below. Patients who were on warfarin before surgery or patients who could not continue the algorithm-based warfarin therapy for clinical reasons were excluded from the analysis. Blood samples for INR were taken every morning, collected in 3.2% sodium citrate and evaluated using the STA-R Evolution (Stago, Parsippany, NJ) fully automated electromechanical viscosity detection system using RecombiPlasTin 2G reagents (Instrumentation Laboratory, Milan, Italy). Therapeutic INR was defined as per standard guidelines to a target[8-12] INR 2.0 or greater but less than 4 (goal INR 2.5) in patients with AVR, and target INR 2.5 or greater but less than 4 (goal INR 3.0) in patients with MVR.[5] Definition of therapeutic INR in patients with both AVR and MVR was the same as that of MVR. No extramural funding was used to support this work.

The initial warfarin dose was according to expected patient response adjusted for sensitivity and risk factors[13] but not exceeding 5 mg daily per the algorithm. Loading doses were avoided due to risks associated with initial excessive suppression of coagulation factor activity (factors VII and IX, proteins S and C), and hemorrhagic complications.[14] Very high-sensitivity risk factors included profound liver dysfunction[15] or malnutrition as indicated by a baseline INR value 1.7 or greater. High-sensitivity risk factors were identified as hepatic disease[15] or hepatic malignancy, hepatic congestion secondary to right heart failure (post-cardiac valve surgery),[16,17] acute heart failure, age 80 years or greater,[18] concomitant strong medication potentiators of warfarin, serum albumin <2.5, baseline INR 1.4-1.6, actual body weight <50 kg,[13] poor nutritional state, or malabsorptive states. Moderate-sensitivity risk factors were defined as age 70-79 years,[18] acute hyperthyroidism,[19] serum albumin 2.6 to 3, heart failure diagnosis,[17] (stable) concomitant medications that lower warfarin potentiation effects: (1-3 medications in lower potentiator risk account for 1 risk factor, >3 medications in lower potentiator risk list count for 2 risk factors).

Similar to the nomogram model of warfarin dosing by Kovacs et al,[20] a fixed warfarin dose was used for the first 2 days and subsequent dose adjustment was made according to a change in INR values. Initial dose was started based on sensitivity risk factors. For individuals with 1 very high-sensitivity risk factor, a warfarin dose of 1 mg was administered on days 1 and 2. For persons with 1 high-sensitivity risk factor, 3 mg warfarin on days 1 and 2 was initiated; however, if the person has 2 or more high-sensitivity risk factors, a lower dose of 2 mg on days 1 and 2 was started. For persons with 2 or more moderate-sensitivity risk factors, 3 mg was initiated on days 1 and 2, and for those with only 1 moderate-sensitivity risk factor or no risk factors, the initial warfarin dose was 5 mg on days 1 and 2. By the third day of warfarin therapy, dose adjustments of 10% to 50% were made in response to INR results. If at any time the INR increased by more than 1.2 on any single day, an overshoot avoidance protocol was initiated, using low-dose oral phytonadione 0.25 mg given once,[21] and holding that days warfarin dose, with a resumption of warfarin the following day at a reduced dose. Daily INR laboratory results, clinical evaluation of potential interacting medications, nutrition and drug elimination considerations, and INR trajectory, along with computer nomogram–generated dose adjustment recommendations, allowed the pharmacist to adjust the warfarin dose in response to multiple variables each day. Intravenous unfractionated heparin originally initiated 12 to 24 hours after surgery according to thromboembolic risk and early bleeding and dosed to achieve and activated partial thromboplastin time 1.5 to 2 times the norm using a heparin nomogram system was stopped once the INR achieved the target goal. Concomitant aspirin therapy was continued according to comorbid risk factors and standard guidelines.

Statistical analysis

The descriptive characteristics of patients at the time of surgery were summarized using mean and SD for continuous variables and number and percentage for categorical variables. To investigate the timing of achieving INR target goals, Cox proportional hazards