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Short-Term Therapy with Enoxaparin or Unfractionated Heparin for Venous Thromboembolism in Hospitalized Patients: Utilization Study and Cost-Minimization Analysis

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A B S T R A C T

Objectives: To evaluate the direct costs of venous thromboembolism (VTE) treatment with unfractionated heparin (UFH) and low-molecular weight heparin, from the institutional perspective. **Methods:** This is a real-world cohort study that included inpatients treated with UFH or enoxaparin for deep venous thromboembolism or pulmonary embolism in a tertiary public hospital. To estimate medical costs we computed the acquisition costs of drugs, supplies for administration, laboratory tests, and hospitalization cost according to the patient ward. **Results:** One hundred sixty-seven patients aged 18 to 92 years were studied (50 treated with UFH and 117 with enoxaparin). The median of days in use of heparin was the same in both groups. Activated partial thromboplastin time was monitored in 98% of patients using UFH and 56.4% using enoxaparin. Nonstatistically significant differences were observed between groups in the number of bleeding events (10.0% and 9.4%; $P = 1.00$); blood transfusion (2.0% and 2.6%; $P = 1.00$); death (8.0% and 3.4%; $P = 0.24$); and recurrent VTE, bleeding, or death (20.0% and 14.5%; $P = 0.38$). Daily mean cost per patient was US$12.63 ± $4.01 for UFH and US$9.87 ± $2.44 for enoxaparin ($P < 0.001$). The total costs considering the mean time of use were US$88.39 and US$69.11. **Conclusion:** The treatment of VTE with enoxaparin provided cost savings in a large teaching hospital located in southern Brazil.

Keywords: heparin, deep venous thrombosis, utilization study, cost analysis.

Introduction

Deep venous thrombosis (DVT) in the lower extremities is the most frequent manifestation of venous thromboembolism (VTE), with an incidence of 0.48 to 1.6 cases/1000 persons-year among community residents [1–3]. It is a common condition affecting mainly inpatients and rates increase with age. The most life-threatening manifestation is pulmonary embolism (PE), affecting 0.23 to 0.69 cases/1000 person-years [4]. The treatment of VTE recommended by the American College of Chest Physicians [5] involves short-term low-molecular-weight-heparin (LMWH) or unfractionated heparin (UFH) therapy plus long-term oral warfarin therapy. Anticoagulant therapy with UFH followed by warfarin prevents thrombus extension, reduces the risk of recurrent thrombosis, and prevents death in patients with VTE [6,7]. Subcutaneous LMWH is as effective and safe as conventional UFH therapy, but does not require laboratory monitoring and is less likely to cause bleeding, immune thrombocytopenia, and osteoporosis [8–10]. LMWH prepararions differ considerably in composition, which could result in different antithrombotic effects, but there is no evidence that any LMWH preparation is better or worse than another in terms of efficacy or safety outcomes [11].

Enoxaparin is among the most widely studied treatments for VTE [12,13]. Despite LMWH having a greater acquisition cost, previous pharmacoeconomic analyses have shown that LMWH is more cost-effective than UFH [14–16]. It has been calculated that outpatient treatment with LMWH may save $1641 per patient in comparison to UFH hospital treatment [17]. This economic benefit of outpatient treatment of VTE seems to be present in different health systems of developed countries, although the same can not be extrapolated to developing nations. Economic evaluations in developing countries are desirable to estimate VTE hospital treatment cost with UFH and LMWH, because people with low income do not have access to outpatient treatment with LMWH. We conducted a cohort study to evaluate the direct costs of short-term heparin anticoagulation treatment for VTE in a large teaching hospital located in southern Brazil, from the institutional perspective.

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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1098-3015/$36.00 – see front matter

doi:10.1016/j.jval.2011.05.017

Methods

This was a cohort study that prospectively included patients hospitalized from March 2005 through January 2007 in a university-affiliated, general tertiary teaching hospital with 749 beds in southern Brazil. These patients had been treated with intravenous UFH or subcutaneous LWMH for suspected or confirmed DVT or PE. The study was approved by the institutional review board.

Patients receiving UFH or LWMH were identified through the institution's computerized prescription system and had their clinical records revised to be included in the study. All patients receiving an anticoagulation dose of heparin to treat VTE were potentially eligible. The LMWH included on the hospital formulary was enoxaparin, based in the lowest price acquisition policy of the institution. Patients identified with DVT or PE were prospectively followed-up until the end of the heparin anticoagulation period. The only exclusion criterion was age younger than 18 years. Data about diagnosis confirmation, anticoagulation regimen, duration of treatment, laboratory monitoring with activated partial thromboplastin time (aPTT), bleeding, thrombocytopenia, blood transfusion, and protamine prescription were recorded for all included patients. Adverse events potentially related to DVT or its treatment were defined as combined endpoint and included in-hospital death, bleeding, or recurrent VTE.

Costs were assessed directly from the hospital's records on prices paid for each one of the elements involved in patients' assistance, considering the prices during their period of hospitalization. This information was provided directly by the hospital, so retrospective costs did not have to be estimated based on any other indirect information. Total medication costs were calculated for each patient, considering the prospectively collected data on medicines, supplies, and laboratory tests. To estimate direct medical costs we computed the acquisition costs of drugs and supplies associated with UFH treatment, laboratory tests, and hospitalization cost according to the patient ward. The cost of use of automatic pump for UFH administration was not computed because they were not hospital property and its charge was covered by the cost of pump-specific infusion equipment required. The costs were converted into US dollars considering the mean exchange rate from April to May 2007.

Data were analyzed with PASW Statistics version 18.0 (2009, SPSS Inc., Chicago, IL) and a level of significance of 0.05 was set. Chi-square statistics were used in the comparison of categorical variables and Student *t* or Mann-Whitney tests were applied to compare continuous variables. Although costs and time of treatment had small skewness deviation, *t* test and Mann-Whitney results were similar and *t* test value was provided to compare means. Logistic regression modeling was applied to analyze the association of heparin form and composite clinical outcomes, to take into account potential confounders identified in crude analyses. Sensitivity analyses were performed during June 2010, considering the actual cost of drugs to account for acquisition prices variation. Propensity score for LWMH prescription was computed to adjust for indication bias.

Results

From the 200 patients included, 33 were excluded because they had been treated for arterial thrombosis. Twelve patients received both heparins and were classified in the group of UFH (n = 7) or LMWH (n = 5) according to the first drug prescribed. The change from the first prescribed drug to the other was more frequent in the UFH group (14.0% vs. 4.3% $P = 0.044$). The characteristics of the groups are similar when excluding the 12 patients that received both heparins (Table 1 in Supplemental Materials found at: doi:10.1016/j.jval.2011.05.017). Patients were 18 to 92 years old; UFH was first prescribed for 50 (29.9%) patients and LMWH for 117 (70.1%) patients. DVT was treated in 107 cases, PE in 43 cases, and both conditions in 17 cases. Diabetes, surgery, infectious disease, and renal failure were significantly more frequent in the group that began anticoagulation with UFH. Previous PE was more frequent in LMWH group ($P = 0.015$). Only general surgery had crude association with combined endpoint (death, bleeding, or recurrent VTE). Among nine critically ill patients, six were treated with UFH (12%) and three with LMWH (2,6%) (chi-square $P = 0.036$). The DVT and PE diagnoses were confirmed in 93.0% and in 51.7% of patients, respectively. The median of days in use of heparin was the same in both groups and warfarin was initiated at the first day in 28.1% of 32 patients on the UFH group and in 24.2% of 89 patients on LMWH group treated with oral anticoagulant. aPTT was monitored in 98% of patients receiving UFH and in 56.4% of patients receiving LWMH. Half of the UFH group had aPTT measured less than once a day (Table 2 in Supplemental Materials found at: doi: 10.1016/j.jval.2011.05.017). Nonstatistically significant differences were observed in the number of bleeding events (10.0% in UFH and 9.4% in LMWH; chi-square $P = 1.00$), blood transfusion (2.0% and 2.6%; chi-square $P = 1.00$), and death (8.0% and 3.4%; chi-square $P = 0.242$). Only one patient in the UFH group evolved to PE. Combined endpoint consisting of recurrent VTE, bleeding, or in-hospital death occurred in 20.0% and 14.5% of patients in the UFH and LMWH groups, respectively (chi-square $P = 0.379$). In a logistic regression model, adjusted for propensity score to receive UFH and for the hospital ward (clinical or obstetric unit, surgery unit, or intensive care unit), LMWH group members showed no significant risk reduction of combined outcome (odds ratio 0.87; 95% confidence interval 0.32–2.41; $P = 0.79$).

We calculated the drug cost per day of treatment taking into account the actual price for the institution (Table 3 in Supplemental Materials found at: doi:10.1016/j.jval.2011.05.017). We excluded patients who were treated initially with one form of heparin and then changed to other on the follow-up (12 individuals). Daily mean cost per patient was US\$12.63 ± \$4.01 for UFH and US\$9.87 ± \$2.44 for LWMH (*t* test $P < 0{,}001$). The total cost of short-term heparin treatment considering the mean length of use was US\$88.39 and US\$69.11, respectively, representing a cost saving of US\$19.28 per heparin treatment. The medication itself is the main component of the LMWH group costs (92.88%), whereas it represents only 5.25% of costs in the UFH group (Fig. 1 in Supplemental Materials found at: doi:10.1016/j.jval.2011.05.017). Sensitivity analysis was performed changing the drug cost according to the actual price of acquisition in 2010 converted to US dollars (exchange rate in June 26, 2010). The daily mean cost became US\$81.48 ± \$55.52 for UFH and US\$14.23 ± \$8.42 for LWMH (*t* test $P < 0{,}001$), and the total unadjusted cost of short-term heparin anticoagulation was respectively US\$757.31 ± \$359.64 and US\$570.94 ± \$201.76 (*t* test $P = 0.002$), representing a cost saving of US\$186.37 per heparin treatment.

Discussion

This was a pharmacoeconomic analysis of heparin use to treat VTE conducted in a developing country, through cost analysis from a public health perspective. This kind of analysis is justified based on the therapeutic equivalence between initial treatment of DVT and PE with UFH and LMWH [5]. One characteristic that distinguishes our study is the evaluation of a real cohort rather then a hypothetical one, concomitantly including groups of patients receiving different treatments. This reflects the usual care of these patients and makes it possible to estimate the actual costs of treatment in a defined setting.