ARTICLE

The Cost of Unfractionated and Low-Molecular Weight Heparin in the Management of Acute Coronary Syndromes

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ABSTRACT

Objectives: To determine the direct costs involved in the administration of intravenous (IV) unfractionated heparin (UFH) compared with the projected costs of subcutaneous (SC) low molecular weight heparin (LMWH), dalteparin, in the management of acute coronary syndromes (unstable angina or acute myocardial infarction) from a hospital perspective.

Methods: A 9-week prospective time-motion study was conducted in a 9-bed coronary care unit (CCU) of a Canadian university-affiliated hospital. Direct costs (expressed in 1998 Canadian dollars) including all drug, labour, supply and equipment costs associated with the preparation, administration, and monitoring of IV UFH were calculated. Throughout the duration of therapy, the number and types of heparin-related activities and the time spent completing these activities were self-recorded by 25 CCU nurses for 116 consecutive patients with acute coronary syndromes requiring IV UFH. The final labour cost was determined by multiplying the mean hourly nursing wage by the mean times recorded during the time-motion study. The projected costs from use of SC dalteparin for this indication were also estimated.

Results: IV UFH was associated with a drug cost of $4.19 per day plus nursing time ($7.28 ± 0.32), supplies ($4.13) and laboratory monitoring ($10.09 ± 0.49) for a total daily cost of $25.68 ± 0.81. The projected cost of dalteparin SC was quite similar at $28.82 ± 0.47 per day consisting mainly of drug acquisition ($26.56 ± 0.47) with a small component for administration ($2.26).

Conclusions: The administration of IV UFH for the management of acute coronary syndromes involves a number of activities and consumption of resources beyond the price of drugs alone, and overall the daily costs are similar to using a SC LMWH regimen. The decision to use a LMWH for acute coronary syndromes therefore should be based on the further consideration of clinical outcomes rather than focusing on drug acquisition cost.

Key Words: *acute coronary syndromes, heparin, intravenous therapy, low molecular weight heparin, time-motion*

RÉSUMÉ

Objectifs : Déterminer les coûts directs engagés dans l'administration intraveineuse (I.V.) d'héparine non fractionnée (HNF) comparativement à ceux projetés dans l'administration sous-cutanée (S.-C.) d'héparine de faible poids moléculaire (HFPM), la daltéparine, dans le traitement des syndromes coronariens instables (angine instable ou infarctus du myocarde aigu) d'un point de vue hospitalier.

Méthode : Une étude prospective temps-mouvements de neuf semaines a été menée dans une unité de soins coronariens (USC) de neuf lits d'un centre hospitalier canadien affilié à une université. Les coûts directs (exprimés en dollars canadiens de 1998) comprenant ceux de tous les médicaments, de la main d'oeuvre, des fournitures et des équipements associés à la préparation, à l'administration, et au suivi de l'administration IV HNF ont été calculés. Pendant toute la durée du traitement, le nombre et les types d'activités liées à l'administration d'héparine et le temps passé à accomplir ces activités ont été inscrits par 25 infirmières de l'USC pour 116 patients consécutifs présentant des syndromes coronariens instables nécessitant l'administration IV HNF. Le coût final de la main d'oeuvre a été déterminé en multipliant le salaire horaire moyen d'une infirmière par les temps moyens inscrits au cours de cette étude temps-mouvements. Les coûts projetés de l'utilisation de la daltéparine sous-cutanée dans ces cas ont aussi été évalués.

Résultats : L'administration IV HNF a été associée à un coût de 4,19 $ par jour pour le médicament, plus la main d'oeuvre du personnel infirmier (7,28 ± 0,32 $), les fournitures (4,13 $) et le suivi du laboratoire (10,09 ± 0,49 $), pour un total quotidien de 25,68 ± 0,81 $. Le coût projeté de l'administration de la daltéparine S.-C. était très semblable, soit 28,82 ± 0,47 $ par jour, et consistait principalement en coût d'acquisition du médicament (26,56 ± 0,47 $) avec une faible partie pour l'administration (2,26 $).

Conclusions : L'administration IV HNF dans le traitement des syndromes coronariens instables implique un certain nombre d'activités et la consommation de ressources en-deça du prix du médicament seul, et les coûts globaux quotidiens sont semblables à ceux de l'utilisation du traitement S.-C. HFPM. La décision d'utiliser une HFPM pour les syndromes coronariens instables devrait par conséquent être fondée sur une évaluation plus poussée des résultats cliniques plutôt que sur le coût d'acquisition du médicament.

Mots clés : *maladies cardiovasculaires, héparine, intraveinothérapie, héparine de faible poids moléculaire, temps-mouvements*

INTRODUCTION

Several prospective clinical trials have demonstrated the effectiveness of intravenous (IV) unfractionated heparin (UFH) in the treatment of acute coronary syndromes, including unstable angina (UA) and acute myocardial infarction (MI).[1] Unfortunately, UFH is associated with a number of limitations including: a short half-life necessitating an intravenous route of administration, unpredictable bioavailability following subcutaneous (SC) administration, variable pharmacokinetics and pharmacodynamics, requirement for regular anticoagulation monitoring, and adverse-effects such as heparin-induced thrombocytopenia.

In the acute and chronic management of acute coronary syndromes, LMWHs may be preferred over UFH due to the excellent bioavailability following SC administration, longer half-life permitting administration on a once or twice daily basis, predictable anticoagulant response, fewer laboratory monitoring requirements, lower incidence of adverse-effects, and demonstrated efficacy in reducing MI, death, or recurrent angina.[2–4] Unfortunately, the acquisition cost of LMWHs is significantly higher compared to UFH, prohibiting its widespread use.

The objective of this study was to determine the direct costs involved in the administration of IV UFH compared with the projected cost of SC LMWH (dalteparin) in the management of acute coronary syndromes from a hospital perspective.

METHODS

A prospective time-motion study was completed (from April 1, 1998 to July 1, 1998) in a 9-bed coronary care unit (CCU) of a Canadian university-affiliated hospital to determine the nursing labour required to prepare, administer, and monitor an IV UFH continuous infusion. Throughout the duration of therapy, the number and types of heparin-related activities and the time spent completing these activities (estimated to the nearest second) were self-reported by 25 CCU nurses for 116 consecutive patients with acute coronary syndromes requiring IV UFH. Heparin sodium 25,000 U in 500 mL 5% dextrose in water was administered by means of an infusion delivery pump (IMED Volumetric Pump) and the infusion-rate was adjusted according to a weight-adjusted heparin nomogram, previously validated at our hospital.[5] A standard data collection form was used to record the following patient information: age, sex, indication for heparin therapy, duration of heparin therapy, heparin-related activities and the respective time required to complete these activities. The Institutional Research Ethics Board did not require informed consent.

Heparin-Related Activities

Nursing activities related to IV UFH, defined *a priori*, included the preparation, administration, and monitoring of IV UFH.

Preparation time included the time required to establish the intravenous site, prime the IMED system, prepare the main line and connect the infusion to the patient's venous catheter.

Administration time included the time required to process orders, prepare and administer the heparin bolus, change infusion rates according to the activated partial thromboplastin time (aPTT), change the heparin bag, and discontinue the infusion.

Monitoring time included the time required to draw and check the aPTT, and physician consults.

Labour Costs

Nursing hourly wages (including benefits) for a CCU nurse was obtained from the human resources department at our hospital. To facilitate generalizability of results, a wage rate of $25 per hour was applied to the calculations. The *final labour cost* was determined by multiplying the mean hourly nursing wage by the mean times recorded during the time-motion study.

Laboratory and Supply Costs

Acquisition costs of the Accuset® tubing for the IMED delivery pump was obtained from the hospital central supply. The aPTT cost was obtained from our hospital's cost-accounting system (Transition Systems Incorporated®) that assigns costs to each resource unit consumed in the hospital based on workload measurement and consideration of facility overhead.

Equipment Costs

The total cost and average lifespan of an IMED delivery pump was obtained from the hospital biomedical engineering department. The daily cost of the IMED pump was estimated by dividing the acquisition cost ($3,000) by the average lifespan (15 years).

Drug Costs

Wholesale drug acquisition costs were obtained from the PPS® PHARMA Publication (July 1998) for dalteparin sodium 25,000 IU/mL multi-dose vial (Fragmin®, Pharmacia & Upjohn) and heparin pre-mixed 25,000

U/500 mL premixed bag (Abbott). The costs of UFH and LMWH were compared assuming equal efficacy and side-effects based on the FRIC study.[4]

Statistical Analysis

Descriptive statistics were used for analysis of the time needed to prepare, administer, and monitor a continuous IV UFH infusion (SPSS for Windows, Release 6.0, SPSS Inc., Illinois). Data are presented as means ± SEM.

RESULTS

Patients

A total of 116 patients were enrolled in the study. There were 38 women (33%) and 78 men (67%) with a mean age of 65 ± 1 years and weight of 74 ± 1 kg. The majority (77%) of patients were treated with heparin for UA, while 23% were being managed post-MI. Adverse events were not observed in any patients.

Costs of IV UFH Administration

The mean period of observation for heparin treatment was 51.6 ± 2.9 hours. The nursing-related activities during this period are shown in Table 1 and included initiating and maintaining the heparin infusion and aPTT monitoring. A total of 21.41 ± 1.66 minutes of nursing time was spent on these activities on average per patient. By applying a wage rate of $25 per hour, this yielded a cost of $15.65 ± 0.69 per patient over the period of observation, or $7.28 ± 0.32 per patient per day. Physician input into the anticoagulation process was minimal since our hospital had pre-established protocols for heparin administration. The laboratory costs associated with aPTT measurement totaled $21.69 ± 1.05 while the actual heparin infusion, tubing and pump accounted for another $17.88 per patient over the 2.15 days. The mean total cost per patient per day was therefore $25.68 ± 0.81.

Projected Costs of SC Dalteparin Administration

The costs for administration of a LMWH such as dalteparin involve mainly the drug acquisition cost as well as a small component of nursing time and a syringe (Table 2). There is no need for aPTT monitoring, use of other laboratory resources or equipment. A 3.8 mL multidose vial of dalteparin 25,000 IU (anti-Xa)/mL has a manufacturer's wholesale price of $142.50 (PPS® PHARMA, July 1998), or $0.0015 per IU. The recommended dalteparin dose for management of

TABLE 1: Costs of IV UFH Administration

Task	Time per task (mins) or Unit Cost	Frequency	Cost per observation period (at $25/hour)	Cost per day
Nursing-Related Activities				
Prepare / administer heparin bolus	2.24 ± 0.16	1.00	$0.93 ± 0.07	
Establish IV site	4.20 ± 0.41	1.00	$1.75 ± 0.17	
Prepare main line	4.13 ± 0.33	1.00	$1.72 ± 0.14	
Draw PTT	2.14 ± 0.15	3.72 ± 0.18	$3.32 ± 0.23	
Check PTT	1.49 ± 0.10	3.72 ± 0.18	$2.31 ± 0.15	
Change infusion rate	1.74 ± 0.01	2.25 ± 0.16	$1.63 ± 0.01	
Change IV UFH bag	1.82 ± 0.17	1.51 ± 0.13	$1.15 ± 0.11	
Process orders	1.65 ± 0.25	2.62 ± 0.23	$1.80 ± 0.27	
MD consult	2.00	1.25 ± 0.25	$1.04 ± 0.10	
SUBTOTAL	*21.41 ± 1.66*		*$15.65 ± 0.69*	*$7.28 ± 0.32*
Laboratory and Supply Costs				
APTT	$5.83	3.72 ± 0.18	$21.69 ± 1.05	$10.09 ± 0.49
Accuset® tubing	$7.70	1.00	$7.70	$3.58
Equipment Cost				
IMED pump	$0.55	Duration of 2.15 days	$1.18	$0.55
Drug Costs				
UFH pre-mixed bag	$4.50	2.00	$9.00	$4.19
TOTAL				**$25.68 ± 0.81**

unstable angina based on the FRIC trial is 120 IU/kg bid translating to 17,709 ± 313 IU ($26.56 ± 0.47) per day, using the average weight of our patient population (74 ± 1 kg).[4] Based on our time-motion study above, the nursing cost for preparation and administration of a single heparin injection was $0.93 and a syringe was $0.15. The projected total daily cost for SC dalteparin for our patient population therefore would be $28.82 ± 0.47 per day.

DISCUSSION

The LMWHs are being used for a growing number of thromboembolic indications and the results of more recent trials are generating interest in the management of acute coronary syndromes.[2–4,6,7] Given the increasing fiscal pressures on controlling drug expenditures in the hospital sector, drug acquisition costs have become a major concern around the approval of new medications. Specifically in the case of LMWHs, drug expenditures can have a significant impact on budgets due to the current usage in the prophylaxis and treatment of deep venous thrombosis and pulmonary embolism, and expansion to the management of acute coronary syndromes. Focusing on drug costs alone, however, can be quite misleading and inappropriate, as there are many other inputs into the real costs of drug administration. It is also crucial to examine the positive and negative cost and clinical outcomes that arise from therapy in a comprehensive economic evaluation of a product. In this analysis we have attempted to clarify the amount of resources that are consumed during treatment with IV UFH. This allows for a more realistic comparison of daily treatment costs.

Through this time-motion study, we were able to determine that the daily costs of IV UFH consisted of relatively large components of nursing time ($7.28), supplies ($4.13) and laboratory monitoring ($10.09) that considerably exceeded the drug acquisition cost ($4.19). For the LMWH dalteparin, the situation was basically reversed with drug costs accounting for 92% of the total daily cost with little requirement for additional resources. Despite the difference in drug acquisition price, the overall daily total costs of IV UFH and SC dalteparin were quite similar ($25.68 vs. $28.82 respectively). The direct cost of therapy should therefore be less of an issue in choosing between these treatment regimens and the focus should instead be on the relative efficacy and safety of these products. The agent with the superior clinical profile (e.g., fewer MIs or hemorrhagic epsiodes) will therefore be "dominant", i.e., better outcomes at the same or lower cost. If this is true for the LMWHs, a policy change around acute coronary syndromes might be considered, but it must be realized that an investment in the pharmacy budget will be required to effect such a change.

Interestingly, a prospective economic analysis of the ESSENCE trial in the United States reported that enoxaparin saved $1172 (U.S.) per patient over 30 days compared to standard treatment of IV UFH and ASA. The cost-savings associated with enoxaparin therapy resulted from a shorter hospital stay and a reduction in invasive cardiac procedures (such as diagnostic catheterization and coronary angioplasty).[6] A Canadian economic analysis of the ESSENCE trial is expected to be published in the near future.

An analogous situation might be the case of LMWHs for the treatment of deep venous thrombosis. LMWHs provided similar or superior safety and efficacy compared to IV UFH, and our institution routinely treats such patients with these agents.[7] However, we have experienced a significant rise in drug expenditures with this class of drugs despite early discharge of patients from hospital. The decision to accept a LMWH in this situation speaks to the willingness of prescribers and administrators to invest in a pharmaceutical product to improve patient outcomes in order to achieve savings elsewhere in the health system (e.g., reduced hospitalization).

Ongoing studies (such as TIMI 11B and FRISC II) will further define the role of LMWHs in unstable coronary syndromes.[8,9] Questions addressed in these studies include the optimal dose and duration of LMWH therapy in this patient population. In the FRIC study, the duration of weight-adjusted dalteparin in the acute management of unstable coronary syndromes ranged from 1 to 6 days. Thus, although the daily costs of dalteparin are very similar to IV UFH in our time-motion study, the costs associated with a complete treatment course may be significantly higher with

TABLE 2: Projected Cost of LMWH Administration

Drug Cost		
Patient Weight 74 ± 1 kg	Dalteparin Dose per day 17,709 ± 313 IU	Cost per day $26.56 ± 0.47
Other costs		
Nursing	2 injections @ $0.93	$1.96
Syringes	2 syringes @ $0.15	$0.30
TOTAL		**$28.82 ± 0.47**

dalteparin. Formal and comprehensive economic evaluations of these studies as the results emerge would be welcome.

This study has a few limitations. In the comparison of IV UFH with SC dalteparin, it would have been ideal to directly observe treatment with both agents on similar patients concurrently. At present however, LMWHs are not used for this indication in our hospital. The sample of patients was drawn from a single unit in one hospital. However, the nursing and lab activities are quite representative of medical care in other hospitals and there was a fair degree of homogeneity in the results. A previous audit of IV UFH therapy at our hospital also yielded very similar findings.[5] One point that may differ in other hospitals is the role of physicians in heparin monitoring and adjustment. Our CCU has used a standardized protocol and nomogram for IV UFH administration for a number of years and thus physician input is minimal. If physicians were actually consulted specifically for a "minor assessment" such as heparin adjustment, then it is possible that billable labour costs in the order of $17 per day (based on the current Ontario Health Insurance Plan fee schedule) may be incurred. However, it is unlikely that responding to a PTT result would account for any incremental charge over the usual daily fees for ongoing patient care. There is one further issue regarding the cost "offsets" with these treatments. A contentious point in the economic literature revolves around real versus theoretical savings, and nursing time provides a good example. The use of a LMWH reduces the time spent on adjustments of IVs and pumps but certainly does not eliminate the need for a nurse. Reduction in laboratory testing is a more tangible benefit, but again one may argue that the only real savings relate to use of consumables (e.g., reagents and supplies). Nonetheless, the use of a LMWH for anticoagulation clearly does reduce the number of tasks involved in administering a therapy that is at least equally efficacious to IV UFH.

CONCLUSIONS

The administration of IV UFH for the management of acute coronary syndromes involves a number of activities and consumption of resources beyond the price of drugs alone. Overall, the daily costs of UFH are similar to using a SC LMWH regimen. The decision to use a LMWH for acute coronary syndromes therefore should be based on the further consideration of clinical outcomes rather than focusing on drug acquisition cost.

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