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Should low-molecular-weight heparin be used in the treatment of acute coronary syndromes in rural hospitals?

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Objective: To evaluate the use of low-molecular-weight heparin (LMWH) for acute coronary syndromes (ACS) in a rural setting.

Methods: A review of LMWH effectiveness and a simplified costing exercise that focused on potential differences between rural and urban settings for delivering LMWH versus unfractionated heparin (UFH).

Results: LMWH is as clinically effective as UFH for the treatment of ACS in a rural setting. The estimated drug delivery cost of the dalteparin ($65 per admission) was less than that for UFH ($110). The high cost of after-hours activated partial thromboplastin time monitoring in a rural setting ($86 per admission) more than offset the increased cost of LMWH compared to UFH.

Conclusions: LMWH is the heparin of choice for the treatment of ACS in a rural setting. The method of using an abbreviated effectiveness and costing exercise may be a practical approach for evaluating other health interventions in a rural setting.

Objectif : Évaluer l'utilisation de l'héparine de faible poids moléculaire (HFPM) dans le traitement des syndromes coronariens aigus (SCA) en milieu rural.

Méthodes : Étude d'efficacité de l'HFPM et exercice simplifié d'établissement des coûts visant à rechercher les différences éventuelles entre les milieux rural et urbain dans l'administration de l'HFPM par rapport à l'administration de l'héparine non fractionnée (HNF).

Résultats : Sur le plan clinique, l'HFPM est aussi efficace que l'HNF dans le traitement des SCA en milieu rural. Le coût estimé d'administration de la daltéparine (65 $ par admission) est inférieur à celui de l'HNF (110 $). Le coût élevé de la surveillance, après les heures normales, du temps de céphaline activée en milieu rural (86 $ par admission) compense nettement le coût plus élevé de l'HFPM par rapport à l'HNF.

Conclusions : L'HFPM est l'héparine de choix dans le traitement des SCA en milieu rural. La méthode abrégée d'étude d'efficacité et d'établissement des coûts pourrait être une démarche praticable pour l'évaluation d'autres interventions de santé en milieu rural.

Introduction

Acute coronary syndromes (ACS), which comprise unstable angina, non-Q wave myocardial infarction and ST-

segment elevation myocardial infraction, account for a large percentage of the burden for health care. In Ontario, cardiovascular disease is the second leading cause of hospitalization.1 Angina pectoris and chest pain of non-cardiac origin account for greater than one-third of all cardiac hospital admissions.2 The risk of progression to myocardial infarction or death from non-ST elevated ACS (unstable angina and non-Q wave infarction — referred to as ACS in this study) may be up to 20% in the first 30 days of follow-up.3 Many patients will undergo further in-hospital investigation and treatment, including angiography, angioplasty and coronary artery bypass surgery.

Standard therapy with unfractionated heparin (UFH) and acetylsalicylic acid reduces mortality from ACS.4 Low-molecular-weight heparin (LMWH) is an attractive alternative because it has similar antithrombotic properties compared to intravenous UFH but is easier to administer. LMWH is completely absorbed with less protein binding and it can be given subcutaneously in 1 or 2 standard daily doses without monitoring. More recently, the management of high-risk ACS patients may include the use of glycoprotein IIb/IIIa inhibitors.5

The use of LMWH is gaining acceptance in the treatment of ACS in urban hospitals. Assessments in this setting suggest that LMWH is as effective as UFH with potential cost savings due to a reduction in the number of invasive procedures for patients treated with LMWH.6,7

We hypothesize that in rural hospitals LMWH may be a more appropriate therapy than UFH for the treatment of ACS. For some rural hospitals, monitoring of UFH anticoagulation is likely more unwieldy and costly due to the lack of on-site laboratory facilities. In these settings, there are additional courier costs for transporting blood samples to off-site laboratories, and/or overtime fees for calling in laboratory staff to process samples for anticoagulant monitoring outside regular laboratory hours. In the controlled setting of clinical trials, more than 50% of patients treated with UFH are over- or under-anticoagulated 24 hours after the start of therapy.4 The proportion of patients adequately anticoagulated in rural hospitals may be even lower because resources for anticoagulant monitoring in the rural setting are more limited. If there are fewer patients with therapeutic anticoagulant levels this may result in worse patient outcomes and possibly greater health care utilization from investigations and treatment of those complications. Furthermore, the overburdened rural physician will undoubtedly value the ease of administering LMWH.

Possible differences in outcomes, resource implications and values between rural and urban settings suggest that LMWH (and other therapies) should be assessed considering the unique attributes of a rural setting. However, the infrequent assessment of technology outside the urban/teaching hospital setting suggests that there may be barriers in this setting. In this study, we attempted to perform a simplified review of LMWH effectiveness and cost analysis by focussing on important differences between urban and rural practice that may influence the decision to incorporate LMWH in a rural hospital.

Methods

There were 2 parts to the study. In the first part, the evidence of effectiveness of LMWH and UFH for the treatment of ACS was compared. A systematic review was performed by reviewing all randomized controlled trials (RCTs) of LMWH for outcomes applicable to a rural hospital setting. Appropriate articles were identified through a MEDLINE search using the key words "heparin" and "acute coronary syndromes" or "unstable angina" and "randomised controlled study." All articles comparing LMWH to UFH were reviewed. All-cause and cardiovascular deaths were considered pertinent outcomes. We did not evaluate the use of invasive cardiovascualr procedures such as angioplasty or cardiac surgery, although these are relevant outcomes, because these procedures are not performed at rural hospitals.

In the second part of the study, we assessed the practice of UFH treatment and performed a simplified cost analysis by estimating the actual costs of UFH treatment in a sample of patients admitted to the Chesley Site of the South Grey Bruce Health Centre, Chesley, Ont., compared to an estimated cost of LMWH treatment. For this analysis we considered only the difference in costs associated with drug treatment. We assumed all other direct and indirect costs such as nursing care, length of hospital stay, complication rates, hospital investigations, and hospital transfers remained the same regardless of type of heparin treatment. At the time of the study LMWH was not used at the hospital for the treatment of ACS patients.

All patients who were admitted during 1999 with laboratory records who had 2 or more activated partial thromboplastin time (aPTT) determinations during the hospital admission and a diagnosis of angina, non-Q wave myocardial infraction or ACS were selected for this part of the study. Hospital charts for these patients were

extracted to identify the timing, number and result of aPTT determinations as well as risk factors for ACS. Cost estimates for aPTT determination of both regular hour and after-hour testing (including laboratory technician call-in) were obtained from the hospital laboratory manager. Drug costs for UFH and LMWH were obtained from the hospital pharmacist.

Results

Effectiveness of LMWH compared with UFH

Three randomized controlled trials of LMWH for the treatment of ACS were identified and reviewed.8-10 The results from these trials are summarized in Table 1. All studies had meaningful outcomes for rural hospitals; the most common outcome measure was a composite outcome of death, myocardial infarction, recurrent angina and urgent revascularization. Although we did not formally compare type of patient in our study with that of the RCT studies, it appeared that the inclusion criteria of the RCTs selected patients with similar disease severity compared to our study (see next section for our study patient characteristics); in fact, if there were differences, our study patients had more severe disease.

The FRISC study of dalteparin8 showed a non-significant increase in the main composite endpoint with a marginal increase in death at day 6. The 2 enoxaparin studies9,10 showed a relative risk reduction in outcome measures varying from 16% to 37.5%; most of these outcomes were statistically significant at $p < 0.05$. All studies showed no difference in major bleeding complications between the study groups.

ACS patients and UFH treatment

We reviewed the charts of all 38 patients admitted with a diagnosis of ACS in 1999. The characteristics of these patients (Table 2) were similar to the RCT trials of LMWH; differences were not statistically tested. The median age of patients was 68 years compared with RCT median age range 63 to 69 years; 50% were male (RCT 65%-71%).

Patients often were at high risk; 42% had ST-segment depression or T-wave inversion — two leads $\geq$ 0.1 mV — (RCT 46%-57%), and there was a high mortality risk (30 day post discharge mortality of 17%, approximately twice as high as RCTs).

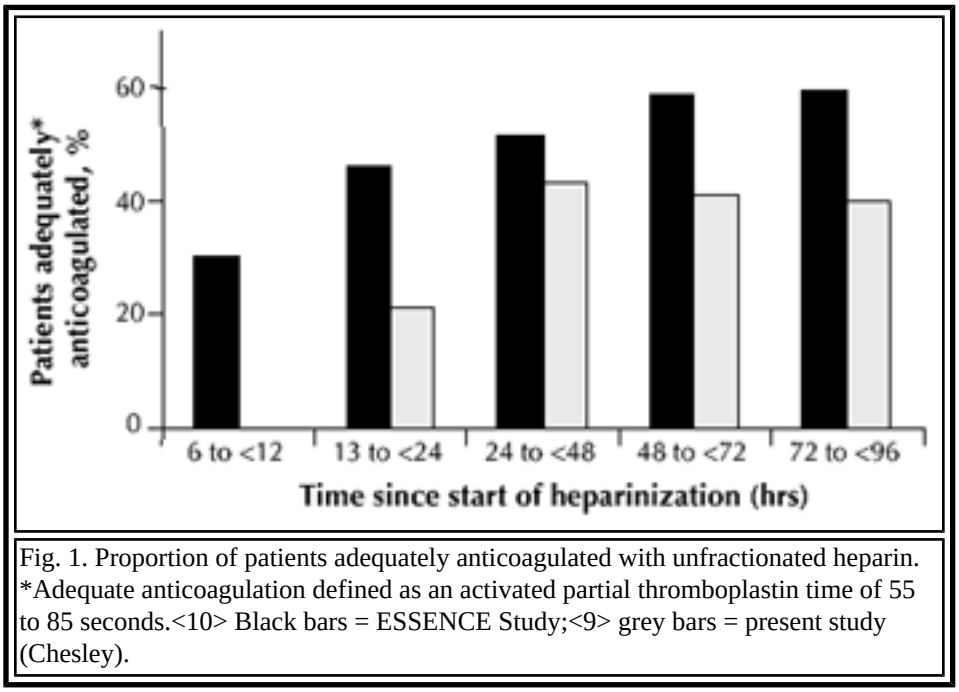

Fig. 1. Proportion of patients adequately anticoagulated with unfractionated heparin. *Adequate anticoagulation defined as an activated partial thromboplastin time of 55 to 85 seconds.<10> Black bars = ESSENCE Study;<9> grey bars = present study (Chesley).

All patients received UFH. The average patient weight was 76 kg. The mean duration of treatment was 3 days (median length of hospital stay was 4 days). There was an average of 1.4 aPTT measurements per day of UFH treatment. There was no on-site laboratory at the study hospital site; all aPTT determinations were performed at a hospital site approximately 40 minutes away. The laboratory performed aPTT determinations for 3 hospital sites of

similar size to the study site. Non-scheduled tests were couriered to that hospital (21% of all aPTT determinations). Fourteen percent of aPTT determinations were performed on evenings or weekends, necessitating a lab technician call-back. Generally, the proportion of patients in therapeutic anticoagulation range was lower than most trials of LMWH versus UFH. Figure 1 shows the therapeutic range in our study compared to the ESSENCE Study.9

LMWH treatment cost compared with UFH

The drug and monitoring cost for UFH and LMWH are shown in Table 3. The cost of UFH drug and monitoring was calculated based on the average number of aPTT determinations and the proportion of tests that required a courier and/or after-hours laboratory technician call-back (Table 2). To simplify the costs analysis, we did not include the cost of infusion equipment (intravenous pumps and tubing) or nursing costs. Other costing studies have suggested that most of these cost savings are not recoverable (there is not a reduction in nursing costs if UFH IV infusion is not performed) and therefore they should not be included;6 regardless, these costs would increase the cost of UFH therapy, thereby further favouring LMWH over UFH. The total cost of UFH therapy per hospital admission was $110 compared with $91 for enoxaparin and $65 for dalteparin.

Most costing exercises include a sensitivity analysis to examine the effect of modifying assumptions to the final cost estimates. We did not formally perform such analysis, in part because our model is simple and therefore the effect of the assumptions is quite apparent or easy to calculate. For instance, many rural hospitals, unlike ours, have in-hospital lab facilities and therefore do not have courier costs. For these hospitals the average cost of UFH treatment would decrease by the courier costs equal to $18 per hospital stay ($20/courier × 21% of non-scheduled aPTT tests requiring a courier × 1.4 aPTT tests/day × 3 days of UFH/admission). Changing this assumption does not change the conclusion that LMWH is an attractive cost alternative to UFH. Similarly, the only 2 factors in the cost of LMWH treatment were the unit cost of LMWH and the weight of the patient. If the average patient weight were higher the cost of LMWH would increase in proportion to this increased average weight — up to a maximum dose depending on the type of LMWH. Again, reasonable increases in patient weight would not have an important influence on the cost difference between LMWH and UFH.

Discussion

Similar to other effectiveness reviews of LMWH at the time, we found evidence in the literature that enoxaparin is more effective in improving important outcomes than UFH.5,11-13 Because the outcomes (death and myocardial infarction) are as meaningful in a rural setting as they are in an urban setting and because patient characteristics are likely similar, we expect that these findings are relevant and generalizable to a rural practice. Unlike urban hospitals, LMWH drug costs of using enoxaparin in the treatment of ACS are lower than for UFH.6,7 Cost savings are achieved because the high cost of after-hours aPTT monitoring in rural hospitals without 24-hour or on-site laboratory services are not needed for LMWH, off-setting the higher cost of LMWH compared to UFH. Based on these findings — along with the ease of use, potential for fewer major bleeding complications, the potential for poor therapeutic treatment with UFH, and additional cost savings from fewer invasive procedures and hospital transfers — LMWH is the heparin of choice for rural hospitals for ACS treatment. We were able to demonstrate these cost savings in a simple costing exercise.

We learned several lessons from this exercise that may be useful when assessing other therapies in rural settings. First, it would have been reasonable to use a review of LMWH effectiveness as opposed to examining each RTC trial as we did in our analysis.5,11-13 We would have arrived at the same conclusions with less effort. Of note, several meta-analyses of LMWH for ACS and the final Cochrane review were published after this study was performed.14-16 These studies conclude that LMWH has equal efficacy as UFH. We reviewed the individual LMWH trials because of the long-standing concern that close attention should be given to potential differences in effectiveness of therapies between populations.17 The authors that popularized this concern have recently de-emphasized the approach because increasing evidence indicates that the relative benefit of therapies is constant across different populations. If, as we suspect from the chart reviews, our patients are at a somewhat higher baseline risk of developing adverse outcomes, there would be a greater absolute benefit of heparin treatment, with a lower number needed to treat (NNT).18 The finding that patients in RCTs are at lower risk than in clinical settings is a common finding that results from the design of clinical trials.19 We were also concerned that effectiveness reviews would not consider outcomes that are important to rural patients and/or physicians. In reality, most outcomes in effectiveness reviews — mortality and morbidity — are universally the most important outcomes.

EFFECTIVENESS	COST		
	Cheaper	Same cost	More expensive
Better	Do	Do	Consider
Same outcomes	Do	Consider	Don't do
Worse	Consider	Don't do	Don't do

Fig. 2. Decision table for a new therapy based on cost and effectiveness. In the simplified decision table, the task is to identify whether the new intervention is more or less effective and more or less costly. For therapies where there are equivocal differences other factors such as physician and patient values should be considered

Second, we demonstrated that a simple cost analysis can easily sort out whether a new therapy is potentially useful in a rural setting. In our approach, we envisioned a 3×3 table where the rows represent whether the cost of the new therapy is more, less or the same cost as the standard therapy. The columns indicate whether the new therapy is more, less or similarly effective (Fig. 2). The task of overburdened decision-makers is not to precisely define the cost or effectiveness of competing therapies, as is the common practice in costing analysis, but to simply and confidently decide into which box the new therapy best fits. If a therapy is more effective and cheaper, then clearly it should be adopted, regardless of the magnitude of the benefit or savings. When there are equivocal results (the same cost and effectiveness), other value factors such as patient or staff preferences should play a larger role in decision-making.20 In this study, transportation and after-hours staffing issues resulted in higher costs in the rural setting. In rural settings there may be other therapies or processes of care that potentially reduce similar costs. Identifying these may yield opportunities for quick and similar cost evaluations that identify cost savings and/or improve care.

This article has been peer reviewed.

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