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Factors Associated with the Types of Heparin used in the Treatment of Unstable Angina at a Brazilian Hospital

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ABSTRACT

Unfractionated heparin (UFH) and low-molecular-weight heparins (LMWHs) are widely used in curative and preventive treatments of thromboembolic disorders. The aim of the study was to investigate factors associated with the choice of these types of heparin to treat patients with unstable angina under real conditions of hospital use. A cross-sectional study was performed in a private general hospital in Belo Horizonte, Brazil, from January 1st to December 31th, 2001. Data were collected from the hospital electronic database. Inpatients with angina who received enoxaparin or UFH were included in the survey. Data for 555 patients were recorded, including 401 treated with enoxaparin and 154 with UFH. Univariate analysis showed that male and elderly people predominated in both groups, with no statistical difference in the proportions (p>0.05). Multivariate analysis showed 4 factors associated with the use of enoxaparin: cardiac revascularization surgery (OR=0.434), arrhythmias (OR=9.343), risk factors for coronary artery disease (OR=1.333) and private health insurance (OR=0.297). Thus, clinical and organizational factors were associated with the type of heparin used by patients with unstable angina at this hospital. Further drug utilization studies are necessary to expand and improve the data available on the use of heparins in the hospital setting.

Keywords: Hospital pharmacy/assessment. Angina pectoris/treatment. Heparin/prescription. Enoxaparin/prescription.

INTRODUCTION

Anticoagulants are used for prophylaxis and treatment of thromboembolic disorders. Unfractionated heparin (UFH) plays a standard part in anticoagulation therapy, though it is associated with unpredictable dose response, narrow therapeutic range and the need for regular laboratory monitoring. These factors have led to the development of newer agents such as low-molecular-weight heparins (LMWHs), which maintain anticoagulant properties while offering a more suitable pharmacokinetic profile (Weitz, 1997; Hirsh et al., 2008). Several meta-analyses have demonstrated that LMWHs are at least as effective as UFH for preventive (Nurmohamed et al., 1992; Koch et al., 2001; Mismetti et al., 2001) and curative (Leizorovicz et al., 1994; Gould et al., 1999; Dolovich et al., 2000) treatment of deep venous thrombosis. LMWHs, in combination with other drugs (Nicolau et al., 2007), are also used in the current treatment of acute coronary syndromes which include unstable angina and non-ST segment elevation myocardial infarction (FRISC, 1996; Eikelboom et al., 2000; Le Nguyen & Spencer, 2001; Malhotra et al., 2001; Magee et al., 2003; Hirsh et al., 2008).

Results from randomized controlled trials are based on drug use under ideal conditions, which may differ significantly from the real world. Drug utilization studies can help us to understand the prescribing patterns of a therapeutic agent after its commercialization (Lee & Bergman, 2005; Melo et al., 2006). Recent studies on the use of LMWHs after commercialization have shown prescribing errors for thromboprophylaxis (Belmin et al., 2001; Tilleul et al., 2006) and other indications (Howard & Burenheide, 1999; Geffroy et al., 2002; Cestac et al., 2003; Fahimi et al., 2008). In Brazil, both the consumption and hospital cost of LMWHs have increased (Crozara, 2001; Farhat, 2001) and their misuse is also an issue of concern (Silva, 2002; Furlanetto, 2005; Deheinzelin et al., 2006; Rocha et al., 2006). The aim of the present study was to investigate factors associated with hospital consumption of enoxaparin, a LMWH, in the treatment of patients with unstable angina, in light of the fact that enoxaparin had been included in the hospital protocols by the time of the study. In a previous study, it was shown that angina was the most prevalent diagnosis among enoxaparin users (Martins, 2003; Martins et al., 2007).

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MATERIAL AND METHODS

This paper reports a drug utilization study with a cross-sectional design. The study was carried out in a 259-bed hospital from January 1st to December 31st, 2001, in a general private hospital located in Belo Horizonte city (Minas Gerais State), southeast Brazil.

Patients

All patients admitted to hospital in 2001 with angina and treated with UFH or enoxaparin were included. When the same patient was readmitted, data from all his/her admissions were combined, despite the gaps in the treatment. The exclusion criteria were: use of both types of heparin during hospital stay, use of heparins in the out-patient setting and beginning of hospitalization in 2000 or its prolongation until 2002.

Data collection

Data related to patients and drug consumption were collected manually by the researcher from an electronic database available at the hospital. A pilot study was first performed to test the proposed questionnaire on data from 50 users of both types of heparin. Given that the questionnaires were not then modified, the patients analyzed in the pilot study were included in the main survey that followed.

For patients enrolled in the study, the following data were recorded:

- *Demographic characteristics*: gender and age;
- *Clinical conditions*: number of risk factors for coronary artery disease which were represented by previous cardiac revascularization procedures and myocardial infarction, smoking, systemic arterial hypertension, diabetes mellitus, dyslipidemia and familiar history plus coronary disease, concomitantly (Braunwald et al., 2001). Any general complications registered (cardiogenic pulmonary edema, prolonged mechanical ventilation, cardiogenic shock, dialysis, pneumonia and other infections, respiratory failure, other pulmonary complications, cardiorespiratory stroke, tamponade, myocardial infarction, cerebral vascular accident, reoperation, arrhythmia, cognitive alteration/delusion, other cardiovascular complications, other neurological complications, congestive heart failure) and complications associated with heparin use (bleeding episodes, thrombocytopenia, osteoporosis) (Hirsh et al., 2008) were recorded separately. Clinical evolution (discharge or death) was also recorded;
- *Care characteristics*: type of coverage for health care (Public Health System or private health insurance), length of hospital stay, readmission(s) and specific invasive cardiologic interventions (revascularization surgery or angioplasty);
- *Heparin therapy*: length of treatment (days), clinical specialty of prescriber;

Statistical analysis

For the analysis, variables were classified as follows:

- *Response variable*: prescription of enoxaparin;
- *Explanatory variables*: patients´ demographic and clinical conditions, care characteristics, including treatment with heparins.

The program Epi-Info version 2002 (Dean & Arner, 2002) was used to build the research database and the data were analyzed with SPSS-11 (SPSS, 2001). Firstly, a univariate analysis was performed and the association between enoxaparin use and the explanatory variables was investigated with a *t* test for independent samples. Qualitative data were compared with a Pearson χ^2 test or the exact Fischer test, when appropriate. A logistic regression model was constructed to withdraw potential confounding variables. The strength of association between the response variable and each explanatory variable was assessed by calculating the odds ratio (OR) and its respective 95% confidence interval. Explanatory variables shown to be significant predictors ($p< 0.25$) in the univariate analysis were included in the logistic regression model. The logistic model was chosen as described by Hosmer & Lemeshow (2000). Non-significant variables ($p>0.05$) were excluded from the final model.

Ethical aspects

The investigation was approved by the Research Ethics Committee at the Federal University of Minas Gerais (ETIC 203/02 code).

RESULTS

Data for 555 patients with angina were recorded. Among these, 401 (72.3%) patients were treated with enoxaparin and 154 (27.7%) with UFH. There were no statistically significant differences with respect to gender or age ($p>0.05$). In both groups, men were more numerous, with 233 (58.1%) in the enoxaparin group and 100 (64.9%) in the UFH group ($p=0.140$). Mean age was 63.5 (±12.21) and 61.4 (±10.74) years old for enoxaparin and UHF users, respectively ($p=0.068$). Table 1 summarizes the characteristics of the patients.

Table 1. Gender, age, type of health care and risk factors for patients with angina treated with heparins, Belo Horizonte, MG. 2001

Characteristic	enoxaparin (N = 401)	UFH (N = 154)	*p* value
Gender – n (%)			
Female	168 (41.9)	54 (35.1)	
Male	233 (58.1)	100 (64.9)	0.140
Age – years ± SD	63.47 ± 12.	2161.42 ± 10.74	0.068
Health care coverage – n (%)			
Health Insurance	347 (86.5)	101 (65.6)	
Public Health System	54 (13.5)	53 (34.4)	0.000
Number of risk factors – n (%)			
0	58 (14.5)	44 (28.6)	
1	114 (28.4)	31 (20.1)	
2	105 (26.2)	41 (26.6)	
3	78 (19.5)	24 (15.6)	
4	37 (9.2)	12 (7.8)	
5	9 (2.2)	2 (1.3)	0.005

Statistical analysis showed significant differences between the two heparin treatment groups in the type of health care coverage and the number of coronary disease

risk factors ($p<0.05$). Enoxaparin was more frequently prescribed for health insurance patients than UFH (86.5% versus 65.6%; $p=0.000$). Among UFH users, 28.6% of patients had no risk factors, against 14.5% of the patients treated with enoxaparin, and the difference was statistically significant ($p=0.005$).

Data related to the course of hospitalization is shown in Table 2. Percentage of group readmitted ($p=0.015$) and time of heparin therapy ($p=0.000$) were higher for patients treated with enoxaparin. Considering invasive procedures, cardiac revascularization surgery occurred more frequently in the UFH group ($p=0.001$) whereas angioplasty was more prevalent in the enoxaparin group ($p=0.049$). Statistical analysis showed no significant differences for clinical specialty of the prescriber ($p=0.268$) or the evolution to discharge or death ($p=0.440$). A total of 4.7% and 3.2% patients died in the enoxaparin and UFH groups, respectively. Most patients were attended by cardiologists (>90%). The period of stay was significantly longer for enoxaparin users ($p=0.000$).

Table 2. Characteristics of hospitalization for patients with angina treated with enoxaparin or UFH, Belo Horizonte, MG. 2001

Characteristic	enoxaparin (N = 401)	UFH (N = 154)	*p* value
Readmission – n (%)			
Yes	15 (3.7)	0 (0)	
No	386 (96.3)	154 (100)	0.015
Cardiac revascularization surgery – n (%)			
Yes	105 (26.2)	63 (40.9)	
No	296 (73.8)	91 (59.1)	0.001
Angioplasty – n (%)			
Yes	125 (31.3)	35 (22.7)	
No	276 (68.7)	119 (77.3)	0.049
Length of hospital stay (days ±SD)	11.88 ± 7.75	7.30 ± 5.48	0.000
End of stay – n (%)			
Discharge	382 (95.3)	149 (96.8)	
Death	19 (4.7)	5 (3.2)	0.440
Time of heparin therapy (days ±SD)	5.94 ± 22.12	4.20 ± 20.67	0.000
Clinical specialty of the prescriber – n (%)			
Cardiology	362 (90.3)	140 (90.9)	
Hematology	1 (0.2)	0 (0)	
Chest Surgery	0 (0)	1 (0.6)	
Internal Medicine	0 (0)	1 (0.6)	
Intensive care	34 (8.5)	10 (6.5)	
Missing data	4 (1)	2 (1.3)	0.268

Considering the total number of general clinical complications, patients treated with enoxaparin had complications more frequently than those treated with UFH ($p=0.027$). On the other hand, complications due to heparin use showed no significant difference between the groups ($p=0.547$) (Table 3). Arrhythmias were the only clinical condition that contributed to the significant difference observed in the total number of general complications ($p=0.006$) and they occurred more frequently among enoxaparin users (7.2%) (Table 4).

Table 3. Complications presented by patients with angina treated with enoxaparin or UFH, Belo Horizonte, MG. 2001

Characteristic	enoxaparin (N = 401)	UFH (N = 154)	p value
Complications - n (%)			
Yes	85 (21.2)	20 (13.0)	
No	316 (78.8)	134 (87.0)	0.027
Complications due to heparin use – n (%)			
Yes	9 (2.2)	5 (3.2)	
No	392 (97.8)	149 (96.8)	0.547

Table 4. Frequency of general clinical complications of patients with angina treated with enoxaparin or UFH, Belo Horizonte, MG. 2001

Characteristic	enoxaparin (N = 401)	UFH (N = 154)	*p* value
Cardiogenic Pulmonary Edema – n (%)			
Yes	10 (2.5)	0 (0)	
No	391 (97.5)	154 (100)	0.069
Prolonged Mechanical Ventilation (>24 hours) – n (%)			
Yes	8 (2)	2 (1.3)	
No	393 (98)	152 (98.7)	0.730
Cardiogenic Shock – n (%)			
Yes	10 (2.5)	3 (1.9)	
No	391 (97.5)	151 (98.1)	1.000
Dialysis – n (%)			
Yes	5 (1.2)	0 (0)	
No	396 (98.8)	154 (100)	0.329
Pneumonia – n (%)			
Yes	10 (2.5)	2 (1.3)	
No	391 (97.5)	152 (98.7)	0.525
Other infections – n (%)			
Yes	5 (1.2)	0 (0)	
No	396 (98.8)	154 (100)	0.329
Respiratory failure – n (%)			
Yes	1 (0.2)	0 (0)	
No	400 (99.8)	154 (100)	1.000
Other pulmonary complications – n (%)			
Yes	12 (3)	6 (3.9)	
No	389 (97)	148 (98.1)	0.596
Cardiorespiratory stroke – n (%)			
Yes	15 (3.7)	3 (11.9)	
No	386 (96.3)	151 (98.1)	0.423
Tamponade – n (%)			
Yes	0 (0)	1 (0.6)	
No	401 (100)	153 (99.4)	0.277
Myocardial infartion – n (%)			
Yes	4 (1)	2 (1.3)	
No	397 (99)	152 (98.7)	0.670
Cerebral Vascular Accident – n (%)			
Yes	5 (1.2)	2 (1.3)	
No	396 (98.8)	152 (98.7)	1.000
Reoperation – n (%)			
Yes	1 (0.2)	3 (1.9)	
No	400 (99.8)	151 (98.1)	0.067
Arrythmias – n (%)			
Yes	29 (7.2)	2 (1.3)	
No	372 (92.8)	152 (98.7)	0.006
Cognitive alterations/delusion – n (%)			
Yes	8 (2)	1 (0.6)	
No	393 (98)	153 (99.4)	0.456
Other cardiovascular complications – n (%)			
Yes	16 (4)	3 (1.9)	
No	385 (96)	151 (98.1)	0.236
Other neurological complications – n (%)			
Yes	6 (1.5)	0 (0)	
No	395 (98.5)	154 (100)	0.194
Congestive Heart Failure – n (%)			
Yes	6 (1.5)	3 (1.9)	
No	395 (98.5)	151 (98.1)	0.713

Multivariate analysis was performed to identify which associations would maintain the statistical significance found in the univariate analysis. The final logistic model is presented in Table 5. Covariates statistically associated with enoxaparin consumption were: cardiac revascularization surgery, arrhythmias, number of risk factors for coronary artery disease and type of coverage for health care ($p<0.05$). The final logistic model fitted the data well, according to the Hosmer & Lemeshow test ($p=0.115$). The odds ratio showed that patients previously subjected to revascularization surgery had a lower chance of being an enoxaparin user than others (OR=0.434; 95% CI: 0.279-0.675). Arrhythmias were strongly and positively associated with the use of enoxaparin (OR=9.343; 95% CI: 2.084-41.885). The number of risk factors for coronary artery disease was positively associated with enoxaparin use. For

each additional risk factor there was an increase of 0.333 in the chance of being an enoxaparin user (OR=1.333; 95% CI: 1.128-1.576). A patient covered by the Public Health System alone had a significantly lower chance of being an enoxaparin user than those covered by health insurance (OR=0.297; 95% CI: 0.186-0.473).

Table 5. Variables statistically associated with enoxaparin treatment for patients with angina, Belo Horizonte, MG. 2001

Variables	Odds ratio (95% CI)	*p* value
Cardiac revascularization surgery	0.434 (0.279-0.675)	0.000
Arrhythmias	9.343 (2.084-41.885)	0.004
Number of risk factors for coronary artery disease	1.333 (1.128-1.576)	0.001
Public Health System	0.297 (0.186-0.473)	0.000

DISCUSSION

The decision to prescribe one drug instead of another for the same indication may be made for a variety of reasons. In the current study, factors associated with enoxaparin use revealed by the multivariate analysis were cardiac revascularization surgery, arrhythmias, number of risk factors for coronary artery disease and type of coverage for health care. Prescription of enoxaparin proved to be preferred for clinical patients and UFH for surgical patients. This result can be seen as appropriate, since it is harder to manage the dose adjustment of enoxaparin during surgical procedures than that of UFH, because of its longer half-life and the absence of a dose-dependent antidote (Weitz, 1997; Hirsh et al., 2008).

Enoxaparin use was associated with a higher prevalence of complications, especially arrhythmias, than UFH use. This finding was also observed by Howard & Burenheide (1999). The prescription of enoxaparin to treat patients with arrhythmias or risk factors for coronary artery disease could arise from physicians' concern about preventing acute events, since enoxaparin showed favorable results for short-term treatment of acute coronary syndromes (Cohen et al., 1997; Antman et al., 1999). The lack of association between the types of heparin and complications due to their use (Table 3) should be analyzed with caution, considering the cross-sectional design of the study and limitations in the available variables (concomitant use of other drugs and comorbidities) encountered in the hospital database.

Despite the evidence available for the superior efficacy of enoxaparin, compared to UFH, in the treatment of acute coronary syndromes in remarkable trials, such as ESSENCE (Cohen et al., 1997) and TIMI-11B (Antman et al., 1999), meta-analyses (Eikelboom et al., 2000; Malhotra et al., 2001) have demonstrated that both drugs have the same efficacy. In addition, a considerable percentage of the "real world" population with angina does not fit the inclusion criteria of the randomized controlled trials performed with enoxaparin. In a study carried out to examine the anticoagulation levels and safety of enoxaparin in unstable angina, Collet et al. (2003) found that patients who did not meet the enrollment criteria of those trials had a higher risk of both bleeding and ischemic events. The safety profile of enoxaparin for special populations, such as patients with renal impairment (Lim et al., 2006) and obese patients (George-Phillips & Bungard, 2006), remains an issue of concern (Gouin-Thibault et al., 2005; Fahimi et al., 2008). In a cohort study, LaPointe et al. (2007) found that 18.7% of patients treated with enoxaparin received an excessive dose which was independently and statistically associated with an increased risk of major bleeding and death.

Patients whose care was covered by health insurance received enoxaparin more frequently than UFH. This result was similar to the findings of a study by Rocha et al. (2006), involving two private and two public hospitals in Brazil, in which enoxaparin was prescribed more frequently than UFH in the private hospitals. Those authors pointed out that lack of awareness among public hospital staff of the cost-effectiveness of LMWHs for thromboprophylaxis could explain their less frequent use of enoxaparin. This hypothesis does not seem to explain the result in the present study, in which the medical staff was the same for both private and public hospital care.

LMWHs seem to be gradually replacing UFH for several indications, as found in the current study in which most patients with unstable angina were treated with enoxaparin (72.3%) rather than UFH (27.7%). Despite the potential advantages that LMWHs have over UFH (Weitz, 1997; Hirsh et al., 2008), they are an expensive therapeutic choice. In Brazil, enoxaparin can cost up to seven times more than UFH. At the hospital under study, the annual expenditure on enoxaparin reached 7.4% of the total amount spent on standard drugs in 2001, against just 1.5% on UFH, according to Martins (2003), who performed a study at the same hospital in Belo Horizonte. The rising consumption of LMWHs at hospitals in the state of São Paulo, Brazil, has already been discussed by other authors (Crozara, 2001; Farhat, 2001; Caiafa & Bastos, 2002).

If UFH and LMWHs were considered to be therapeutically equivalent (Eikelboom et al., 2000; Malhotra et al., 2001), then one would not expect certain clinical and organizational factors to be influential in the decision to prescribe one or the other. Notwithstanding this, the present results suggest that these factors are indeed important in this decision. It appears that establishing a less costly heparin (UFH) as the first choice in the public health system would maintain quality of care and be associated with a better use of resources. In developing countries, economic restrictions that make health care affordable have to be considered. In Brazil, besides the scarce resources, there are huge regional differences and health care organization is very complex. These characteristics would justify efforts to rationalize the adoption of new technologies, including drugs. Therapeutic guidelines, policies to restrict drug use and institutional protocols would be useful for the improvement of prescribing practices (Vats et al., 2007).

In this study, the number of patients was greater and the period of time longer than in other heparin utilization studies (Howard & Burenheide, 1999; Malhotra et al., 2000; Belmin et al., 2001; Silva, 2002; Cestac et al., 2003), although still far short of those in the study by Caiafa & Bastos (2002), who surveyed 18690 patients over a four-year period. No observational study was identified, in the scientific literature, with a specific design to compare the use of enoxaparin and UFH for treatment of patients with unstable angina.

Some limitations of the present study should be addressed. Although this cross-sectional study design

allowed preliminary factors associated with the prescription of enoxaparin for patients with angina to be identified, it is not suitable for producing cause-effect inferences. The performance of other observational studies with stronger analytical power (cohort and case-control studies), would help in elucidating the relations between the variables involved (Gordis, 1996). Gaps in the data were minimal and related entirely to 1.1% of missing clinical specialty. Nevertheless, the use of secondary data may not have allowed other important variables associated with heparin use to be identified. The results cannot be extended to the whole Brazilian population, but they can be relevant, considering the fact that few studies have been performed to evaluate heparin consumption in real hospital conditions in Brazil (Silva, 2002; Furlanetto, 2005; Deheinzelin et al., 2006; Rocha et al., 2006) and around the world (Howard & Burenheide, 1999; Belmin et al., 2001; Geffroy et al., 2002; Cestac et al., 2003; Tilleul et al., 2006; Fahimi et al., 2008).

Clinical choices should be based on the best clinical evidence, taking into account factors related to efficacy, safety and cost. In the current study, clinical and organizational factors were associated with the choice of heparin for patients with unstable angina at this hospital. Further drug utilization studies are needed to increase our knowledge of the use of heparins in hospitals; these would help to improve prescribing practice and promote their rational use.

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RESUMO

Fatores associados com os tipos de heparina usados no tratamento da angina instável em um hospital brasileiro

A heparina não-fracionada (HNF) e heparinas de baixo peso molecular (HBPM) são amplamente utilizadas em tratamentoscurativosepreventivosdetromboembolismo. O objetivo do estudo foi investigar os fatores associados com a escolha desses tipos de heparinas para tratar pacientes com angina instável sob as condições reais de uso hospitalar. Trata-se de um estudo transversal realizado em hospital geral privado, na cidade de Belo Horizonte,MG Brasil, no período de Janeiro a Dezembro de 2001. Para a coleta de dados, utilizou-se o banco de dados informatizado do referido hospital. Pacientes internados com angina que receberam enoxaparina ou HNF foram incluídos no estudo. Registrou-se dados de 555 pacientes, incluindo 401 tratados com enoxaparina e 154 com HNF. Na análise univariada, observou-se que o gênero masculino e pacientes idosos foram predominantes em ambos os grupos, sem diferença estatística entre as proporções (*p*>0,05). A análise multivariada revelou quatro fatores associados ao uso de enoxaparina: cirurgia de revascularização cardíaca (OR=0,434), arritmias (OR=9,343), fatores de risco para doença coronariana (OR=1,333) e atendimento por plano de saúde (OR=0,297). Assim, fatores clínicos e organizacionais estão associados com o tipo de heparina usado por pacientes com angina instável, neste hospital. A realização de mais estudos de utilização de medicamentos é necessária para aprimorar o conhecimento sobre o uso de heparinas, em hospitais.

Palavras-chave: Farmácia hospitalar/avaliação. Angina pectoris/tratamento. Heparina/consumo. Enoxaparina/consumo.

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