Study of the Efficacy, Safety and Tolerability of Low-Molecular-Weight Heparin vs. Unfractionated Heparin as Bridging Therapy in Patients with Embolic Stroke due to Atrial Fibrillation

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Abstract

Background—Anticoagulation with adjusted dose warfarin is a well-accepted treatment for the prevention of recurrent stroke in patients with atrial fibrillation. Meanwhile, using bridging therapy with heparin or heparinoids before warfarin for initiation of anticoagulation is a matter of debate. We compared safety, efficacy, and tolerability of low-molecular-weight heparin (LMWH) and unfractionated heparin (UFH) as a bridging method in patients with recent ischemic stroke due to atrial fibrillation.

Method—This study was a randomized single-blind controlled trial in patients with acute ischemic stroke due to atrial fibrillation who were eligible for receiving warfarin and were randomly treated with 60 milligrams (mg) of LMWH (enoxaparin) subcutaneously every 12 h, or 1000 units/h of continuous intravenous heparin. The primary efficacy endpoints were recurrence of new ischemic stroke, myocardial infarction and/or death. The primary safety endpoint was central nervous system and/or systemic bleeding.

Results—Seventy-four subjects were recruited. Baseline demographic and clinical characteristics of two groups were matched. Composite endpoint outcome of new ischemic stroke, myocardial infarction, and/or death in follow-up period was seen in 10 subjects (27.03%) in UFH group and in four subjects (10.81%) in LMWH group ($p$ value: 0.136). All hemorrhages and symptomatic central nervous system (CNS) hemorrhages in follow-up period were in 7 (18.9%) and 4 (10.8%) patients in UFH group, in 5 (13.5%), and 3 (8.1%) patients in LMWH group ($p$ values: 0.754 and 0.751), respectively. Drop out and major adverse-effects such as heparin-induced thrombocytopenia and drug hypersensitivity were not seen in any patient.

Conclusion—Enoxaparin can be a safe and efficient alternative for UFH as bridging therapy.

Keywords

Atrial fibrillation; embolic; low-molecular-weight heparin; stroke; unfractionated heparin

INTRODUCTION

Stroke is a major health problem in both developed and developing countries [1]. Patients with atrial fibrillation (AF) are four to five times more likely to have ischemic stroke and have more severe neurologic deficit, compared to patients with other causes of stroke [2]. These patients need to be anticoagulated with adjusted doses of warfarin [3]. There are two treatment strategies to prevent thrombosis in ischemic stroke due to AF. One strategy is to start warfarin without bridging therapy. In this method, antiplatelet drug is administered for two weeks. Then, warfarin is substituted [4]. Another strategy is to start warfarin with bridging therapy. Bridging therapy includes the administration of unfractionated heparin (UFH) and starting warfarin after a few days [5]. War-
farin decreases the plasma level of proteins C and S. Meanwhile, the prevalence rates of protein C and S deficiency are 1/200 to 1/500 person in normal population [6]. Therefore, there is at least a theoretical risk of paradoxical thrombosis with administration of warfarin without bridging therapy. In addition, warfarin administration without bridging has a 5% risk of re-embolism during first two weeks [7]. This can be prevented by bridging therapy [8].

UFH use is limited to in-patient settings where continuous intravenous administration can be carried out. Its anticoagulation effect can be monitored by activated partial thromboplastin time (APTT) level [9]. This policy increases the duration of hospital stay and consequently the risk of complications and nosocomial infections [10]. Low-molecular-weight heparin (LMWH) is administered subcutaneously without any need for laboratory data monitoring and can be injected in outpatient settings.

Therefore, we compared LMWH with UFH as bridging method in patients with recent ischemic stroke due to atrial fibrillation with respect to mortality, recurrence of stroke, hemorrhagic complications and other adverse effects.

METHOD

Trial design

This study was a randomized, single-blind, controlled clinical trial, designed to compare LMWH and UFH in patients with ischemic stroke due to AF. Consolidated standards of reporting trials (CONSORT) 2010 guidelines were used in designing the experiment [11].

Participants

The study was conducted at two neurology centers in Namazi Hospital and Faghighi Hospital (Shiraz Medical University affiliated Hospitals, Shiraz, Iran). All subjects were consecutively recruited in the trial from October 2013 to February 2015. Participants’ follow-up ended on 15 May 2015.

Patients aged between 18 and 75 years, acute ischemic stroke documented by brain computed tomography (CT) or magnetic resonance imaging (MRI), and AF confirmed by electrocardiography (ECG) or 24-h Holter monitoring were included in the study.

Patients younger than 18 or more than 75 years, any hemorrhage at the time of recruitment, National Institute of Health Stroke Scale (NIHSS) more than 20, several lobes infarction, hypersensitivity to UFH or LMWH, pregnancy, breast feeding, uncontrolled hypertension (blood pressure more than 220/120 mmHg), renal, hepatic, respiratory or cardiac failure, infectious endocarditis, dissection of vertebral or carotid arteries, the presence of other cardioembolic causes rather than AF (recent myocardial infarction [MI], left ventricular thrombus, valvular heart disease, ejection fraction (EF) less than 28%, atrial myxoma, patent foramen ovale, aneurysm of inter atrial septum, mobile thrombus in ascending aorta or aortic arch, and/or grade 4 atheroma in ascending aorta & aortic arch were excluded from the study.

Interventions

Having collected written informed consent, subjects were randomly assigned to receive LMWH (arm 1) or UFH (arm 2).

Starting anticoagulation was carried out with respect to the 3–6–12 day rule: after three days for subjects with small, nondisabling infarct, after six days for moderate strokes; and after 12 days for large infarcts involving large parts of the arterial territory [12].

First group received enoxaparin (Clexane, Sanofi, Paris) 1 mg/kg for ideal body weight subcutaneously every 12 h and warfarin sodium (Coumadin, Bristol-Myers Squibb Company, New York) 2.5 mg daily started on the same day. Enoxaparin administration was alternated between the left and right anterolateral or posterolateral abdominal wall, using a different site for each injection.

International normalized ratio (INR) was the only laboratory data, which were monitored in this group to evaluate the anticoagulation effect of warfarin. Both enoxaparin and warfarin continued until the target INR level (2.5) was achieved [13]. Then, the administration of enoxaparin was stopped.

Second group received continuous intravenous infusion of UFH (heparin sodium, Alborz Darou, Tehran) 1000 units/h. APTT was checked on admission to determine the baseline level. Then, it was checked every day. UFH dose was adjusted according to the level of APTT to maintain a therapeutic level (two times the baseline level) [14]. Then, 2.5–5 mg/day of warfarin sodium (Coumadin, Bristol-Myers Squibb Company, New York) started and both drugs continued to be administered. APTT and INR levels were monitored to attain the target level of INR (2.5). Then, the administration of UFH was stopped.
Clinical condition at the time of admission was evaluated with respect to the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (MRS). All patients were clinically observed for seven days. Brain CT scans were taken on day 7. However, in case of any clinical deterioration, it was taken during the first seven days. NIHSS score was assessed on day 7. Next follow-up study was conducted three months later through telephone interview in order to assess new MRS score.

Lesion size in brain CTs were measured qualitatively as small, nondisabling infarct, moderate infarcts and large infarcts involving large parts of the arterial territory.

Outcomes
The primary efficacy endpoint was any occurrence of new ischemic stroke, myocardial infarction and/or death. The primary safety endpoints were symptomatic or asymptomatic central nervous system (CNS) hemorrhage and non-CNS hemorrhage (major or minor bleedings). The secondary efficacy endpoint was the time to reach INR ratio which was assessed from the starting date of rapid anticoagulants until the time that INR level reached between 2 to 3 (target 2.5). Secondary safety endpoints were other drug adverse events such as heparin induced thrombocytopenia and drug hypersensitivity. Tolerability of drugs was assessed by the number of patients for whom administration of anticoagulants was stopped due to inability to tolerate the route of administration.

Stroke was defined as a neurological deficit attributed to an acute vascular caused focal injury to the CNS and was divided into two categories: ischemic and hemorrhagic. CNS-hemorrhage was defined as the presence or addition of blood in intraparenchymal, intraventricular, subdural, subarachnoid, or epidural spaces in sequential brain CT scans. Symptomatic CNS-hemorrhage was defined as an increase in NIHS score by 4 or more points from baseline score. Major bleeding was defined as hemoglobin level drop of 20 g/l and/or transfusion of at least two units of blood packed cells. Other types of bleeding were considered as minor.

AF is considered paroxysmal if a first detected episode stops spontaneously in less than 7 days. If the episode lasts for more than 7 days, then it is known as persistent AF. In this case, the episode might continue for a long time (more than one year), and then, it is considered permanent AF. Another classification of AF is according to the heart rate (HR). AF with rapid ventricular rhythm (RVR) is defined when the HR is more than 100 beats/min and non-RVR AF is defined when the HR is less than 100 beats/min.

The Ethical Committee of Shiraz University of Medical Sciences approved the study under the approval number of 92-01-01-5667. All patients who were included in the trial filled out informed consent forms. The study was submitted in ClinicalTrials.gov under the approval number NCT02159287 and in IRCT.ir under registration number: IRCT2014020213698N1.

Randomization
Equal randomization was performed using random block size of 4 (1: 1 for two groups). Randomization table was prepared by an investigator with no clinical involvement in the trial. Patients who met the inclusion criteria were enrolled in the trial according to the allocation list. Principal investigator and data analyst were blinded to the allocations. Patients also were not aware which treatment strategy included the new drug.

Statistical analysis
Baseline characteristics of subjects and the incidence of primary and secondary outcomes were calculated by t-test, Pearson Chi-squared test and Fisher's exact test. Also, 95% confidence interval (CI) and relative risk (RR) were calculated in the study. In order to evaluate the normality of MRS scores, we examined this quantitative variable by Kolmogorov–Smirnov and Shapiro tests. The results suggested that this variable was not normally distributed, so instead of t-test, we decided to use the equivalent nonparametric one that is Mann–Whitney test. For all statistical calculations in the study, SPSS version 22.0 (Chicago, Ill) for Windows was used.

RESULTS
Seventy-four subjects were recruited. Figure 1 shows flow diagram of the subject recruitment and randomization according to CONSORT guidelines. Baseline demographic and clinical characteristics of two groups were matched (Table 1). The median duration between the onset of symptoms and initiation of anticoagulants in both groups were also similar (4.7 ± 3.52 days in LMWH group vs. 4.3 ± 3.78 days in UFH group, p value: 0.240). Baseline MRS and NIHSS score in two groups were not statistically different (p values: 0.057 and 0.067, respectively). Figure 2 compares the baseline and follow-up MRS scores in UFH- and LMWH-treated groups. MRS was 2.59 ± 2.02 for three months follow-up in LMWH group, while it was 2.92 ± 1.93 in UFH group (p-value: 0.483). NIHSS calculated on day 7 was...
4.4 ± 3.7 in LMWH group, while it was 6.2 ± 4.1 in UFH group (p-value: 0.055). The difference between NIHSS on admission and day 7 of follow-up was 3.19 ± 2.5 in LMWH group, while it was 2.82 ± 2.2 in UFH group (p-value: 0.513).

* These patients received standard treatment

**Figure 1. Participants' flow diagram**
Table 1. Baseline demographics and clinical characteristics of patients

<table>
<thead>
<tr>
<th>Risk factors for stroke:</th>
<th>LMWH group (n=37)</th>
<th>UFH group (n=37)</th>
<th>Total (n=74)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.9 ± 7.61</td>
<td>64.8 ± 11.57</td>
<td>66.4 ± 9.8</td>
<td>0.180</td>
</tr>
<tr>
<td>Range</td>
<td>45–75</td>
<td>35–75</td>
<td>35–75</td>
<td></td>
</tr>
<tr>
<td>Sex: Male</td>
<td>12 (32.4%)</td>
<td>16 (43.2%)</td>
<td>28 (37.8%)</td>
<td>0.472</td>
</tr>
<tr>
<td></td>
<td>25 (67.6%)</td>
<td>21 (56.8%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior history of warfarin consumption</td>
<td>14 (37.8%)</td>
<td>15 (40.5%)</td>
<td>29 (39.2%)</td>
<td>1.000</td>
</tr>
<tr>
<td>NIHSS on admission</td>
<td>7.8 ± 4.56</td>
<td>9.9 ± 4.83</td>
<td>8.8 ± 4.77</td>
<td>0.067</td>
</tr>
<tr>
<td>MRS on admission</td>
<td>3.5 ± 1.3</td>
<td>4.1 ± 1.07</td>
<td>3.8 ± 1.22</td>
<td>0.057</td>
</tr>
<tr>
<td>Size of infarction:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>4 (10.8%)</td>
<td>7 (18.9%)</td>
<td>11 (14.9%)</td>
<td>0.515</td>
</tr>
<tr>
<td>Medium</td>
<td>28 (75.7%)</td>
<td>22 (59.5%)</td>
<td>50 (67.5%)</td>
<td></td>
</tr>
<tr>
<td>Large</td>
<td>5 (13.5%)</td>
<td>8 (21.6%)</td>
<td>13 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>AF:</td>
<td>6 (16.2%)</td>
<td>11 (29.7%)</td>
<td>17 (23%)</td>
<td>0.269</td>
</tr>
<tr>
<td>RVR</td>
<td>31 (83.8%)</td>
<td>26 (70.3%)</td>
<td>57 (77%)</td>
<td>0.269</td>
</tr>
<tr>
<td>Non-RVR</td>
<td>13 (55.1%)</td>
<td>13 (55.1%)</td>
<td>26 (35.1%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>24 (64.9%)</td>
<td>24 (64.9%)</td>
<td>48 (64.9%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

1 Data are means (mean ± standard deviation [SD]) or numbers (%).
2 dx: disease

Table 2 demonstrates the primary and secondary outcomes. Composite endpoint outcome of new ischemic stroke, MI and/or death in follow-up period were seen in 10 patients (27.03%) in UFH group and in four patients (10.81%) in LMWH group (p-value: 0.136, 95% CI: 0.092–1.161). The occurrence of new ischemic stroke in follow-up period was seen in two patients (5.4%) in UFH group and 0 in LMWH group (p-value: 0.493). MI

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Figure 2.
Mortality in follow-up period occurred in eight patients in UFH group (21.6%) and in four patients (10.8%) in LMWH group (p-value: 0.345, 95%CI: 0.601–8.107). All hemorrhages during the follow-up period were observed in seven patients (18.9%) in UFH group and in five patients (13.5%) in LMWH group (p-value: 0.754, 95%CI: 0.192–2.340). Symptomatic CNS hemorrhage in follow-up period was observed in four patients (10.8%) in UFH group and in three patients (8.1%) in LMWH group (p-value: 0.751, 95%CI: 0.151–3.505). Asymptomatic CNS hemorrhage in follow-up period was witnessed in one patient (2.7%) in UFH group and was not seen in LMWH group (p-value: 0.751). Non-CNS hemorrhage (major or minor bleeding) in follow-up period was seen in two patients (5.4%) in UFH group and in two patients (5.4%) in LMWH group (p-value: 1.000, RR: 1), which included one case of minor lower gastrointestinal bleeding and one case of gross hematuria in UFH group, and one case of epistaxis and one case of gross hematuria in LMWH group.

Regarding tolerability, drop out in follow-up period did not occur to any patient.

Heparin-induced thrombocytopenia and drug hypersensitivity were not seen in any patient.

Patients receiving LMWH achieved INR ratio after 5.32 days (SD=2.64) compared with 6.11 days (SD=2.35) in patients receiving UFH (p-value: 0.182, 95%CI: 0.122–0.310).

### DISCUSSION

Our study showed that 60 mg of subcutaneous LMWH twice daily, compared with intravenous infusion of UFH, has the same efficacy and safety outcomes including new stroke, MI, death, CNS and non-CNS hemorrhages. New ischemic stroke, CNS-hemorrhage and death were slightly higher in UFH group, but the difference was not statistically significant, compared to LMWH group. Non-CNS hemorrhage and MI were similar in both groups.

Time to achieve INR ratio was longer in patients treated with UFH, which prolonged the duration of hospitalization. Moreover, the risk of complications and nosocomial infection, which depend on hospital stay, might increase [10]. In LMWH group, enoxaparin and warfarin were initiated on the same day. Therefore, the time to reach INR level decreased. In addition, subcutaneous administration of enoxaparin may enable patients to use LMWH at home. This will reduce the duration of hospital stay significantly.

LMWHs present several advantages over UFH in terms of convenience route of administration, longer bioavailability and plasma half-life [15], reduced heparin-induced osteopenia and heparin-induced thrombocytopenia [16]. They exhibit a smaller interindividual variability of the anticoagulation effect and they do not require anticoagulation effect monitoring. The findings of other studies suggested that LMWHs reduces hospital stay and total cost of care with transition to warfarin therapy in an outpatient setting. Earlier studies suggested that LMWH was equally effective as UFH in minimizing the risk of recurrent embolism in patients with deep vein thrombosis and acute MI and pulmonary thromboembolism [17,18,19].

One of the limitations of our study was its small sample size which was mainly on the basis of limited budget allocation. Moreover, the single-blind design of the study and the impracticability to carry out double-blind trial was another limitation. Single-blind design was employed on the grounds that physicians were supposed to follow the laboratory data in both groups, to perform physical examination and to evaluate the probable side effects of drugs in patients. Although the physicians in the study did not state a preference for either of drugs, we ensure bias was limited in the evaluation of patients.

In a pilot cohort study conducted by Mary A. Kalafut et al, enoxaparin, 1 mg/kg twice daily was used as bridging
therapy in 24 patients. Patients included in the study had embolic stroke due to any of the embolic reasons (AF, cardiac emboli, dissection, and hypercoagulable state). Administering LMWH was associated with a net savings of $2197 per patient. Furthermore, it appeared to be safer than bridging UFH and was associated with reduced duration of hospital stay and total cost of care [20].

Earlier similar studies had limitations in terms of restricted number of participants, cohort design of the studies and patients with causes other than AF were also included.

To our knowledge, this is the first randomized clinical trial performed to compare the efficacy, safety and tolerability of LMWH and UFH, in which patients with ischemic stroke purely due to AF were included. This study demonstrated that 60 mg of subcutaneous LMWH twice daily has the same efficacy and safety compared with intravenous UFH in this group of patients. More importantly, it can be used with more convenient route of administration and may enable patients to use LMWH at home, which consequently reduces the duration of hospital admission and total cost of hospitalization. It is noteworthy that these data should be confirmed in future investigations with a larger study population and if possible, a double-blind design.

REFERENCES


