Rev Clin Esp. 2016;xxx(xx):xxx–xxx

Revista Clínica Española

www.elsevier.es/rce

REVIEW

Low-molecular-weight heparins in patients with atrial fibrillation☆

J.M. Calvo

Servicio de Medicina Interna, Hospital Ciudad de Coria, Coria, Cáceres, Spain

Received 29 April 2016; accepted 15 September 2016

KEYWORDS
Low-molecular-weight heparin;
Atrial fibrillation;
Stroke

Abstract In clinical practice, low-molecular-weight heparins are used relatively frequently in patients with atrial fibrillation to prevent embolic events. In this article, it is revised the available evidence in the following clinical situations: rapid onset of anticoagulation, bridging therapy (replacing long-term oral anticoagulant therapy around an invasive procedure) and transesophageal echocardiography-guided cardioversion.

PALABRAS CLAVE
Heparina de bajo peso molecular;
Fibrilación auricular;
Ictus

Heparinas de bajo peso molecular en pacientes con fibrilación auricular

Resumen En la práctica clínica, las heparinas de bajo peso molecular se utilizan con relativa frecuencia en pacientes con fibrilación auricular con el objetivo de prevenir eventos embólicos. En este artículo se revisa la evidencia disponible en las siguientes situaciones clínicas: inicio rápido de anticoagulación, tratamiento «puente» (en sustitución del tratamiento anticoagulante oral crónico en relación con un procedimiento invasivo) y cardioversión guiada por ecocardiograma transesofágico.

Background

Atrial fibrillation (AF) is estimated to cause approximately 20% of all ischemic strokes.[1] Additionally, the risk of early recurrence of an ischemic stroke is greater in patients with AF.[2] These data give an idea of the importance of proper prevention of embolic events in patients with AF.

In this article, we review the evidence available on low-molecular-weight heparins (LMWHs) in 3 clinical situations: rapid onset of anticoagulation, bridging therapy (replacing long-term oral anticoagulant therapy related to an invasive procedure) and transesophageal echocardiography-guided cardioversion.

☆ Please cite this article as: Calvo J. Heparinas de bajo peso molecular en pacientes con fibrilación auricular. Rev Clin Esp. 2016. http://dx.doi.org/10.1016/j.rce.2016.09.007

E-mail address: Romerojm.calvo@orangemail.es

We conducted a literature search in the PubMed database to March 2016 with the keywords ''low molecular weight heparin'', ''atrial fibrillation'' and ''stroke''. We completed the search in the Cochrane Library database with the same keywords. We manually reviewed the literature references of the selected articles to identify other relevant articles.

Rapid start of anticoagulation

LMWHs are employed relatively frequently in clinical practice to achieve rapid anticoagulation to prevent embolic events in patients diagnosed with AF. A clinical trial conducted on patients with recent-onset AF and a CHADS2 score $\leq$2, who were treated in an emergency department, compared subcutaneous tinzaparin at a dosage of 175 U/kg of body weight every 24 h in 46 patients with intravenous unfractionated heparin (UFH) in 50 patients.[3] None of the participants treated with tinzaparin presented an ischemic stroke or transient ischemic attack in the first 48 h compared with 5 (10%) of those treated with UFH (all of whom had a subtherapeutic activated partial thromboplastin time) ($p = .04$).[3] There were no episodes of major hemorrhage in either of the 2 groups.[3] In a retrospective observational study on hospitalized patients with chronic or recent-onset AF, none of the 78 patients treated with therapeutic dosages of enoxaparin (1 mg/kg of body weight every 12 h or 1.5 mg/kg every 24 h subcutaneously) experienced a stroke during treatment, compared with 5 (3.7%) of the 135 patients treated with lower dosages of enoxaparin. There were no cases of intracranial or fatal hemorrhage.[4] The evidence on the safety and efficacy of LMWHs for achieving a rapid start to anticoagulation in patients with AF, in order to prevent embolic events, is scarce and definitive conclusions cannot be extracted.

The Heparin in Acute Embolic Stroke Trial (HAEST) study was a randomized, double-blind clinical trial that included 449 patients with acute ischemic stroke and FA.[5] The study compared dalteparin (100 U/kg every 12 h subcutaneously) with acetylsalicylic acid (160 mg every 24 h orally), both of which were started within 30 h of the stroke.[5] There were no significant differences in the recurrence of ischemic stroke (8.5% vs. 7.5%), onset of symptomatic cerebral hemorrhage in the first 14 days (2.7% vs. 1.8%) or functional result or mortality at 14 days and at 3 months.[5] The analysis of the various subgroups found no superiority for the dalteparin treatment in any of the groups.[6] The analysis of the patient subgroup with presumably cardioembolic ischemic stroke of the Tinzaparin in Acute Ischemic Stroke (TAIST) study compared tinzaparin at a dosage of 175 or 100 U/kg every 24 h subcutaneously ($n = 256$) with acetylsalicylic acid at a dosage of 300 mg every 24 h orally ($n = 112$), both of which were started within 48 h of the stroke.[2] There were no differences in the recurrence of stroke in the first 10 days (1.6% vs. 1.8%), but there were more symptomatic cerebral hemorrhages in the group treated with tinzaparin (2.7% vs. 0%).[2] The results of these 2 clinical trials of patients with presumably cardioembolic acute ischemic stroke show that LMWHs at therapeutic dosages within 30–48 h of the stroke do not reduce the risk of recurrence and can increase the risk of symptomatic cerebral hemorrhage when compared with acetylsalicylic acid.[2,5]

Bridging therapy

Bridging therapy consists of substituting long-term oral anticoagulant therapy in patients who will undergo an invasive procedure or surgery. The Bridging Anticoagulation in Patients Who Require Temporary Interruption of Warfarin Therapy for an Elective Invasive Procedure or Surgery (BRIDGE) study was a randomized, double-blind clinical trial that compared bridging therapy with dalteparin against placebo. The study included 1884 patients who underwent anticoagulation for AF.[7] The mean CHADS2 score was 2.3 and only 1.5% of the patients had mitral stenosis. The study excluded, among others, patients with mechanical heart valve prostheses (MHVP) or a creatinine clearance <30 mL/min. Warfarin was discontinued 5 days before the procedure and restarted in the afternoon or the day after the procedure. Dalteparin was administered at a dosage of 100 U/kg every 12 h subcutaneously from 3 days to 24 h before the procedure and subsequently for 5–10 days. There were no significant differences in the rate of arterial thromboembolism at 30 days (0.3% vs. 0.4%), but there were more major hemorrhages in patients treated with dalteparin (3.2% vs. 1.3%, $p = .005$).[7]

In an prospective observational registry of 2280 patients with AF and a mean CHADS2 score of 2.4, in which oral anticoagulation was discontinued due to an invasive procedure, there were no significant differences in the onset of stroke or systemic embolism at 30 days between the patients who underwent bridging therapy (in 74% of the cases with LMWHs) and those who did not undergo the therapy (0.6% vs. 0.3%, $p = .3$).[8] The rate of major hemorrhages was greater among those who were treated with bridging therapy (3.6% vs. 1.2%, $p = .0007$).[8] Only a minority of patients had moderate-severe mitral stenosis or a MHVP.[8] Another prospective series of 176 patients with AF and a mean CHADS2 score of 1.9 undergoing long-term warfarin therapy assessed a strategy consisting of administering enoxaparin (1.5 mg/kg every 24 h subcutaneously) as bridging therapy.[9] There were 4 episodes (2.3%) of cardiac embolism.[9]

Another prospective registry assessed a strategy consisting of the discontinuation of the vitamin K antagonist 4–6 days before the procedure. When the international normalized ratio (INR) was <2, enoxaparin was started at a dosage of 1 mg/kg every 12 h subcutaneously in patients with normal renal function and a moderate-high risk of embolism (e.g., CHADS2 score of 3–6) or at 1 mg/kg every 24 h subcutaneously in the patients with a creatinine clearance <50 mL/min or a low risk of embolism (e.g., CHADS2 score of 0–2). The last dose of enoxaparin was administered at least 24 h before the procedure. The enoxaparin and vitamin K antagonist were restarted in the afternoon of the day of the procedure in cases of low hemorrhagic risk, after 48 h in cases of high hemorrhagic risk and after 72 h in cases of very high hemorrhagic risk.[10] The study assessed 703 patients with AF with a mean age of 76 years, 358 of whom (50.9%) had a high-moderate risk of embolism; 33 (4.7%) patients underwent major surgery.[10] There were no embolic events, but there were 3 cases of major hemorrhage (0.4%) in the 30 days after the procedure.[10]