Acute coronary syndromes - low molecular weight heparins or unfractionated heparin

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The Cochrane Collaboration is an international organization of health care professionals, practicing physicians, researchers and consumers which aims to help people make informed decisions about health care and its delivery by preparing, maintaining and promoting the accessibility of systematic reviews (1). It is made up of about 50 collaborative Review Groups (i.e. Heart Group, Airways Group, and Injuries Group - see web site for a complete list http://www.cochrane.org/contact/entities.htm#CRGLIST) that helps coordinate reviews that pertain to their area of expertise. The Collaboration is published in the Cochrane Library which is available on CD-ROM and the internet (http://www.cochrane.org/index0.htm).

The Library contains the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials and other databases. In 1972 Archie Cochrane, a British epidemiologist, recognized that people who want to make informed decisions about health care do not have ready access to reliable reviews of the available evidence (2). This paved the way to the "Cochrane Centre" that was established in 1992 with financial support from the British National Health Service. Six months later, with the help of the New York Academy of Science, the ideas of the Cochrane began to spread which led to the launch of Cochrane Collaboration at the first Colloquium held in Oxford in October 1993. The Cochrane Collaboration's logo illustrates a systematic review of seven randomized controlled trials (RCTs) comparing corticosteroid versus placebo use in women who develop preterm labor. The first study was performed in 1972 and the last in 1980. The diagram summarizes the evidence that would have been revealed a decade earlier if done systematically, which indicates strongly that corticosteroids reduce the risk of babies dying from complications of immaturity (1).

Systematic Review Source

This is a systematic review abstract, which will be a regular feature of the Israeli Journal of Emergency Medicine Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Magee KD, Sevcik W, Moher D, Rowe BH. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. (Cochrane Review). In: The Cochrane Library, Issue 3, 2003. Oxford: Update Software.

Objective:

To compare the effects of low molecular weight heparins (LMWH) with unfractionated heparins (UFH) for the treatment of patients with acute coronary syndromes (ACS).

Data Source:

The primary source was the central data base of the Cochrane Collaboration. A broad search of MEDLINE, EMBASE and CINAHL was conducted (until December 2000) as well as a search of reference lists of articles. Authors of all included studies and pharmaceutical industry representatives were contacted to determine if unpublished studies, which met the inclusion, criteria were available.

Study Selection:

Randomized controlled trials were included that compared subcutaneous LMWH to intravenous UFH in patients with acute coronary syndromes (unstable angina or non-ST segment elevation MI) irrespective of the levels of blinding. Only studies which included adult patients (> 18 years of age) presenting with acute coronary syndrome requiring treatment within 72 hours of presentation were eligible. For this review unstable angina was defined as typical chest pain lasting at least 10 minutes within 72 hours of presentation with either historic, electrocardiographic or angiographic evidence of underlying ischemic heart disease. Non-ST segment elevation MI was defined as chest pain without ST segment elevation and elevation of relative cardiac enzymes. The primary outcomes were death, MI, recurrent angina, revascularization and side effects (major/minor bleeding and thrombocytopenia). The primary side effect was major hemorrhage (fall in hemoglobin level of >20 g/L; requirement for transfusion; intracranial, retroperitoneal, or intraocular bleeding; hemorrhage resulting in death or cessation of the study treatment).

Data Extraction:

Two reviewers independently selected articles for inclusion, evaluated methodological quality of the studies and abstracted the data. Continuous variables were reported as weight mean difference (WMD) and dichotomous variables were reported as relative risk (RR); a fixed-effects or random-effects model was used, based on the study's heterogeneity, both with associated 95% confidence intervals (95% CI).

Main Results:

From a total of 27 abstracts, 7 articles were included in this review involving 11,092 patients and four different LMWHs. Overall, LMWH did not reduce the incidence of death compared to UFH (RR=1.00; 95%CI: 0.69, 1.44). When the data from all follow up periods are combined for MI, LMWH shows a benefit compared to UFH (RR: 0.83; 95% CI: 0.77, 0.99). LMWH was only superior to UFH in preventing MI at 3 to 14 days following treatment. LMWH showed a trend towards preventing recurrent angina which was not statistically significant in the sub-acute phase (n=7218) and overall with RR=0.83 (95% CI: 0.68, 1.02) and RR=0.81 (95% CI: 0.65, 1.00), respectively. Patients treated with LMWH (n=11128) had few revascularization procedures compared to those treated with UFH (RR: 0.80; 95% CI: 0.82. 0.95). The risk of major bleeding was similar between treatment groups (RR: 1.00; 95% CI: 0.8, 1.24). Patients receiving LMWH experienced more minor bleeding compared to UFH, but this effect was not statistically significant (RR: 1.40; 95% CI: 0.68, 2.90). Thrombocytopenia was a rare event occurring in only 1.5% of patients. However, significantly less thrombocytopenia was observed in patients receiving LMWH than UFH (RR: 0.64; 95% CI: 0.44, 0.94).

Conclusion:

The use of LMWH instead of UFH in unstable angina and non-ST segment elevation MI (ACS) will decrease the risk of recurrent MI, recurrent angina, lower the number of revascularization procedures done and reduce the incidence of thrombocytopenia. At the same time the risk and incidence of major or minor bleeding will remain the same.

Commentary: Clinical Implication

Ischemic heart disease is the leading cause of death among adults in the United States (US) and most western industrialized nations (3). There are about 4-5 million visits annually to the ED for acute chest pain syndromes. Coronary artery disease results in approximately 500,000 deaths annually in the US with an economic burden of about $100 billion (4). Acute coronary syndrome represents a spectrum of disease from unstable angina to acute myocardial infarction (5). Unstable angina (U/A) and non-ST segment elevation MI (NSTEMI) are within this spectrum and chest pain is an exceedingly common reason for visits to the emergency department. In non-ST MI, cardiac enzymes are elevated. However, the treatments for U/A and NSTEMI are virtually identical. Current treatment includes oxygen, ASA, beta-blockers, procedural intervention and some form of anticoagulation (UFH or LMWH).

The use of UFH in acute coronary syndromes is now considered an accepted treatment standard for non-ST segment elevation MI and unstable angina (6,7).The combination therapy of aspirin and heparin reduces the short term risk of death or myocardial infraction by 56 percent, compared with aspirin alone (3). Even with aspirin treatment in combination with UFH combination therapy, there is still a 20% failure rate (death, MI or recurrent angina) at three months (8).

While most emergency physicians are familiar with the use of UFH in ACS, the use of LMWH is more commonly seen in venous thromboembolism. LMWH is a form of heparin that exhibits better bioavailability, lower protein binding, a longer half life and achieves reliable anticoagulation without monitoring coagulation makers compared to UFH. This translates clinically into a drug that can be given once or twice a day and at the same time achieves stable therapeutic response.

The review summarizes a number of comparisons, and space does not permit a full discussion of all of these. The main question for emergency physicians is the effectiveness of LMWH and UFH for ACS. This review included 11092 patients and the overall results indicate no differences in mortality or recurrent angina between those patients treated with UFH or LMWH. The overall incidence of MI was 4.2% for patients treated with LMWH, and 5.0% for patients treated with UFH. The summary analysis presented here, however, suggests that LMWH reduces MI, the need for revascularization procedures and for thrombocytopenia more effectively than UFH. Given a risk difference for MI of 0.008 between LMWH and UFH 125 patients would require treatment to prevent one MI. In the LMWH group, 14.2% experienced revascularization procedures compared to 16.1% in the UFH group with a risk difference of 0.02. 50 patients would need to be treated with LMWH to prevent 1 additional revascularization procedure. Using a combined end point of death, MI, recurrent angina and revascularization LMWH was found to be superior to UFH. The incidence of multiple end points in the LMWH group was 12.5% compared to 14.1% in the UFH group. Given the risk difference of 0.02, the number needed to treat with LMWH is 50 to prevent one event.

With regards to side effects there was no statistically significant difference between LMWH and UFH when comparing both major and minor side effects. One of the more serous minor side effects, thrombocytopenia was reported in 4 trials. In the LMWH group, 1.0% of patients developed thrombocytopenia compared to 1.8% in the UFH group. This represents a risk difference of 0.008; 125 patients would have to be treated with LMWH to prevent 1 additional case of thrombocytopenia.

There was no subgroup analysis performed comparing outcomes in patients with U/A to NSTEMI since these data were not available from most of the studies. Insufficient data also existed to compare the different types of LMWH. However, the majority of patients in this review were treated with enoxaparin which accounted for 63% (7045 patients) of all patients. Parenthetically, enoxaparin was the only LMWH to demonstrate statistically significant benefit over UFH.

Take Home Message:

LMWH should be used to treat U/A and NSTEMI. They are more effective and safer than UFH and are simpler for ED staff to use. LMWHs reduce the risk of the MI, recurrence of angina, and revascularization procedures. Despite these positive results, mortality remains the same regardless of the type of anticoagulation being used. Overall, the minor and major side effects are the same except for thrombocytopenia, which is statistically decreased with the use of LMWH.

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