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Systematic Review

Administration of low molecular weight and unfractionated heparin during percutaneous coronary intervention

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ABSTRACT

This systematic review with meta-analysis sought to determine the efficacy and safety of unfractionated heparin (UFH) and low molecular weight heparin (LMWH) on clinical outcomes following percutaneous coronary intervention. Medline, Embase, Elsevier, and web of knowledge as well as Google scholar literature were used for selecting appropriate studies with randomized controlled design. After screening 445 studies, a total of 23 trials (including a total of 43,912 patients) were identified that reported outcomes. Pooled analysis revealed that LMWH compared to UFH could significantly increase thrombolysis in myocardial infarction grade 3 flow ($p < 0.001$), which was associated with similar target vessel revascularization ($p = 0.6$), similar incidence of stroke ($p = 0.7$), and significantly lower incidence of re-myocardial infarction ($p < 0.001$), major bleeding ($p = 0.02$) and mortality ($p < 0.001$). Overall, LMWH was shown to be a useful type of heparin for patients with MI undergoing PCI, due to its higher efficacy and lower rate of complication compared to UFH. It is also associated with increased myocardial perfusion, decreased major hemorrhage, and mortality.

1. Introduction

Ischemic heart disease is the leading cause of morbidity and mortality worldwide, whereas it is expected to significantly increase the disease burden over the next 10 years.[1] Ischemia-reperfusion injury (IRI) is a well-known phenomenon in thrombolysis, percutaneous coronary intervention, coronary artery bypass grafting, and cardiac transplantation. IRI is clinically manifested as a damage of myocardial cells due to myocardial stunning, microvascular injury, and myocyte necrosis.[2] In patients with ST-segment elevation myocardial infarction (STEMI) or acute coronary syndrome without ST elevation (non-STEMI or unstable angina), early mechanical

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or pharmacological reperfusion, anti-thrombotic therapy with aspirin, thienopyridine, glycoprotein IIb/IIIa inhibitors, and unfractionated heparin (UFH) have become the standard of care and have been widely used for decreasing mortality and myocardial infarction (MI).[3,4] However, due to its structural defects, the utilization of UFH has many limitations, such as short half-life, low bioavailability, and non-specific binding to proteins that lead to variability of dose-anticoagulant effects.[5,6] On the other hand, UFH may activate platelets just a few minutes after administration and may lead to thrombocytopenia.[5,6] UFH has unpredictable pharmacokinetics; thus there is a need to monitor activated clotting time for adjusting the dose of UFH.[7–9] Low molecular weight heparin (LMWH) is an alternative anticoagulant characterized by more predictable and stable anti-coagulation without the need for continuous infusion or tight monitoring of activated clotting time.[7–9] Furthermore, it demonstrates less protein binding, less platelet activation and relatively greater inhibition of the coagulation cascade compared to UFH, as it has a ratio of 4.3:1 in its anti-factor Xa to anti-factor IIb activity.[10] Several previous reports indicated that LMWH was shown to be non-inferior to UFH in terms of reducing the risk of morbidity and mortality at 30 days.[11–14] This systematic review with meta-analysis sought to determine the strength of evidence for evaluating the efficacy and safety of UFH and LMWH in patients with MI undergoing PCI.

2. Methods and materials

2.1. Literature search

A comprehensive literature search was conducted in major electronic databases (Medline/Pubmed, Embase, Elsevier, Web of Knowledge and Google Scholar) from their inception through July 20, 2014 to identify randomized controlled trials (RCTs) reporting on the use of UFH vs. LMWH including clinical outcomes in patients with MI undergoing percutaneous coronary intervention. Predefined search terms included: ''unfractionated heparin'', ''UFH'', ''low molecular weight heparin'', ''LMWH'', ''enoxaparin'', and ''myocardial infarction'', ''MI'', ''ST-segment myocardial infarction'', ''STEMI'', ''acute coronary syndrome'', ''non-STEMI'', and ''percutaneous coronary intervention'', ''PCI'', and ''angioplasty''. No language restrictions were applied. All retrieved references of the included RCT were also reviewed to determine additional studies not indexed in common databases. Studies were included into the analysis when they met the following criteria: (1) RCT, (2) reporting at least one of the outcomes of interest including: thrombolysis in myocardial infarction (TIMI) score, re-MI, stroke, thrombosis, major bleeding, target vessel revascularization (TVR), major adverse cardiovascular events (MACE), and mortality. Abstracts and manuscripts that did not undergo peer-review, duplicate reports and ongoing RCTs were not included.

2.2. Data extraction and outcome measures

Two investigators (S.A.-H.-S. and A.S.) extracted data independently, and discrepancies were resolved via a consensus standardized abstraction check-list used for recording data in each study. Data retrieved from trials included: author's name, country study design, details of therapeutic regimens, clinical scenario, sample size, follow-up duration, mean age and gender, and clinical outcomes of interest. For exploration of heterogeneity among the trials, a subgroup analysis of disparities in the patients' characteristics was performed for[1]: follow-up (≤6 months vs. >6 months),[2] clinical scenario of patients (STEMI vs. ACS and non-STEMI),[3] type of administration (intravenous vs. subcutaneous),[4] and sample size (≤500 vs. >500).

2.3. Definitions of endpoints

TVR was defined as ischemia-driven revascularization of the infarct-related artery with PCI and coronary artery bypass graft. Re-infarction was defined as recurrent symptoms suggestive of ischemia with ST-segment elevation and/or elevation of the levels of cardiac markers. TIMI 0 flow (no perfusion) refers to the absence of any antegrade flow beyond the occlusion; TIMI 1 flow (penetration without perfusion) is a faint antegrade flow beyond the occlusion, with incomplete filling of the distal coronary bed; TIMI 2 flow (partial perfusion) is a delayed or sluggish antegrade flow with complete filling of the distal territory; TIMI 3 flow (complete perfusion) is a normal flow, which fills the distal coronary bed completely. Mortality was considered cardiac, unless a non-cardiac cause of death could be established. MACE were defined as composition of death or MI or major cerebrovascular event.

2.4. Statistical analysis, publication bias and quality assessment

Data were analyzed by using STATA version 11.0 utilizing METAN and METABIAS modules. The effect sizes measured were odds ratio (OR) with 95% confidence interval (CI) for categorical variables. OR <1 favored LMWH and OR >1 favored UFH group. RCTs with no events in the two arms were discarded from pooled analysis. Forest plots were created for each outcome. Values of $p < 0.1$ for Q test or $I^2 > 50\%$ indicated significant heterogeneity among studies. Heterogeneity among the trials was accounted for by applying a random effect model when indicated. The presence of publication bias was evaluated using Begg and Egger tests. Quality assessment of RCTs was performed using the Jadad score. The Jadad score assesses 3 items including randomization (0–2 points), blinding of study (0–2 points) and withdrawals and dropouts (0–1 points). Higher scores indicate better reporting (''high'' quality: 5; ''good'' quality: 3–4; ''poor'' quality: 0–2). Results were considered statistically significant at a p-value <0.05.

3. Results

3.1. Literature search strategy and included trials

Our literature search retrieved a total of 445 studies from screened databases of which 295 (66.2%) were excluded after initial review (Fig. 1). Of 150 primary included studies, 127 were excluded after detailed evaluation due to insufficient information on endpoints of interest. Thus, the final analysis included 23 RCTs.