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Enoxaparin versus Heparin

The SYNERGY Trial from an Emergency Medicine Perspective

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Abstract

The SYNERGY (Superior Yield of the New strategy of Enoxaparin, Revascularisation, and GlYcoprotein inhibitors) trial, involving almost 10 000 patients, is a landmark cardiology study published in 2004. The study compared two anticoagulants used as part of a modern early invasive strategy involving angiographic triage of high-risk non-ST-elevation acute coronary syndrome patients. The trial as a whole showed similar efficacy between unfractionated heparin and enoxaparin. Regarding safety, two of the three in-hospital bleeding endpoints reported were similar between the two anticoagulants. Importantly, because of the high rate of pre-enrolment anticoagulant administration, many study participants required an anticoagulant change after randomisation. Thus, close attention is warranted to a prespecified subanalysis of >6000 patients who received 'consistent therapy'; that is, the same anticoagulant was administered pre- and post-enrolment based on intention to treat. In this large 'consistent therapy' cohort, the efficacy endpoint favoured enoxaparin and, as in the overall study population, two of the three reported bleeding endpoints were similar between the two anticoagulants. Finally, the rate of peri-procedural thrombotic complications that occurred during percutaneous coronary intervention was equal for both anticoagulants. Thus, since both anticoagulants have a similar efficacy and safety profile, then the simplicity of the enoxaparin regimen (i.e. no monitoring of activated partial thromboplastin time and easy dose calculation of 1 mg/kg subcutaneously) provides an important and desirable feature relevant to a busy emergency medicine practitioner.

The practice of cardiology continues to evolve rapidly and provides the practising emergency physician (EP) with new tools for treating acute coronary syndromes (ACS). The recently published SYNERGY (Superior Yield of the New strategy of Enoxaparin, Revascularisation, and GlYcoprotein inhibitors) study[1] is an important trial involving approximately 10 000 patients, which provides the EP with new evidence to guide their choice of anticoagulant for use as part of an early invasive treatment strategy in high-risk ACS patients.

In the past, the EP only had to identify patients with acute ST-elevation myocardial infarction (STEMI). Now, the EP must also identify high-risk ACS patients with either non-STEMI (NSTEMI) or high-risk unstable angina pectoris (HR-UA) from a cohort of undifferentiated 'chest pain' patients. A patient with positive cardiac markers (troponin or creatine kinase-MB isoenzyme) is diagnosed with a

NSTEMI, whereas a patient with new ST-depression or deep T-wave inversion is diagnosed with HR-UA. According to the 2002 American College of Cardiology/American Heart Association guidelines,[2] therapy for either NSTEMI or HR-UA should start with the use of anticoagulant, antiischaemic and antiplatelet medications. Ideally, this is followed by a coronary angiogram within 48 hours. On the basis of this angiogram, a decision is made to proceed with either a percutaneous coronary intervention (PCI), such as angioplasty or stenting, coronary artery bypass surgery (CABG) or medical management only.

1. The SYNERGY Trial

The SYNERGY trial compared two anticoagulants in the modern setting of an early invasive strategy for high-risk ACS patients. Patients with angina pectoris who fulfilled at least two of the following criteria were included: age ≥60 years, positive cardiac markers or an ECG showing signs of ischaemia (usually ST-depression). This open-label randomised study assigned 4993 patients to receive enoxaparin (1 mg/kg subcutaneously every 12 hours). If PCI was performed >8 hours after the last dose of enoxaparin, an additional 0.3 mg/kg was given intravenously. Another 4985 patients were randomised to receive unfractionated heparin (UFH; 60 U/kg bolus and 12 U/kg/hour infusion), titrated to achieve an activated partial thromboplastin time (aPTT) of 50–70 seconds. Both assigned study drugs were usually discontinued after completion of revascularisation.

Upon analysing data for all 9978 enrolled patients, the authors of the SYNERGY study concluded that "enoxaparin was not superior to UFH, but was non-inferior for the treatment of high-risk patients with non-ST-elevation ACS".[1] Re-stated in simpler terms, efficacy for both drugs can be considered essentially equal from a clinical standpoint, since neither drug was statistically superior or inferior. The composite efficacy endpoint of 30-day death or nonfatal myocardial infarction (MI) occurred in 14.0% of enoxaparin-treated patients and 14.5% of UFH patients (odds ratio [OR] = 0.96; 95% CI 0.86, 1.06). The prespecified statistical non-inferiority of enoxaparin was established because the upper boundary for the 95% confidence interval did not exceed 1.1. With regard to safety, two of the three major bleeding endpoints were statistically similar. TIMI (Thrombolysis In Myocardial Infarction) major haemorrhage events (intracranial haemorrhage [ICH] or a drop in haemoglobin of >5 g/dL during the index hospitalisation) occurred more commonly with enoxaparin than UFH (9.1% vs 7.6%; p = 0.008). However, the rate of GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) severe bleeds (ICH or bleeding that causes haemodynamic compromise) was similar (2.7% enoxaparin vs 2.2% UFH; p = 0.08) between treatments. Of note, isolated ICH was rare (<0.1% incidence for either drug). The third endpoint of blood transfusion (arguably the most relevant safety endpoint from a clinical perspective) was similar for both drugs (17.0% for enoxaparin vs 16.0% for UFH; p = 0.16).

Upon initial inspection, the efficacy and safety of enoxaparin and UFH are quite similar based on data from the full SYNERGY cohort. However, both the efficiency of getting high-risk ACS patients to the catheterisation laboratory and the frequency of anticoagulant crossover greatly hampered the trial's ability to find any difference between the two drugs.

- The median time from randomisation to PCI was <23 hours.
- Within 6 hours of randomisation, 24% of patients underwent PCI.[3] Thus, some enoxaparin-treated patients received only one dose of medication during the entire study.
- A median of approximately 10 hours elapsed between hospital arrival and SYNERGY enrolment.
- During this pre-enrolment phase, 75% of patients were started on an anticoagulant according to physician preference (allowed by the protocol).
- An additional crossover occurred post-randomisation in another 8% of patients at the time of PCI, probably because of interventionalist preference (protocol violation).

These issues provide a rationale for further examination of the pre-specified analysis of study patients receiving only one anticoagulant. About 25% of all SYNERGY study patients received no anticoagulant pre-randomisation, and another 37% received an anticoagulant pre-randomisation that happened to be the same as that assigned post-randomisation. The primary efficacy endpoint in these 6138 'consistent therapy' patients clearly favours enoxaparin (13.3% enoxaparin vs 15.9% UFH; p = 0.004). This difference translates into a number-needed-to-treat of 39 to prevent one death or recurrent MI when enoxaparin is used consistently, instead of UFH. Furthermore, since drug crossover was so common in the SYNERGY trial, it is unlikely that selection bias changed the baseline characteristics of the 6138 study patients who were eligible for inclusion in this 'consistent therapy' subanalysis. The safety analysis of these 6138 'consistent therapy' patients again shows bleeding events with either enoxaparin or UFH to be similar. Most importantly, the requirements for blood transfusion were nearly identical (16.9% of enoxaparin recipients vs 17% UFH; p = not significant). Interestingly, the rate of the TIMI major bleeding endpoint was now similar between treatments in the 'consistent therapy' cohort, while the rates of the GUSTO bleeding endpoint were statistically different.

Overall, the results of SYNERGY showed similar efficacy and safety between enoxaparin and UFH when the entire 9978 patient study cohort was analysed, and greater efficacy with enoxaparin for the subanalysis of the 6138 patient 'consistent therapy' cohort.

2. Enoxaparin Use in the Emergency Department

At this point, a few practical issues regarding enoxaparin use in the emergency department (ED) also warrant review.

2.1 Safety

Is it safe to use enoxaparin with all of the other antiplatelet and anti-ischaemic agents commonly started in the ED for NSTEMI or HR-UA?

SYNERGY provides an excellent answer to this first question since few trials have addressed the safety and efficacy of combining multiple different cardiac medications for high-risk ACS patients. Of note, SYNERGY excluded patients with advanced renal insufficiency, defined as a creatinine clearance of <30 mL/min. Concomitant use of other cardiac medications during the index hospitalisation is listed in descending frequency: aspirin (acetylsalicylic acid) [95%], β-adrenoceptor antagonists (β-blockers) [86%], HMG-CoA reductase inhibitors (statins) [70%], nitrates (69%) clopidogrel (63%) and platelet glycoprotein IIb/IIIa inhibitors (57%). Interestingly, the timing of glycoprotein-inhibitor initiation was equally divided between pre-randomisation, post-randomisation and peri-PCI. The timing of clopidogrel initiation was not reported, but should not be started until the need for CABG has been excluded by coronary angiography.

2.2 Continued Care

Will your hospital's interventional cardiologists feel comfortable continuing the enoxaparin that was started in the ED?

The ED physician is at the beginning of a continuum of cardiac care that extends to the interventional cardiologist and, possibly, the cardiothoracic surgeon. Since our actions and drug choices affect these 'downstream' clinicians, many ED physicians hesitate to use enoxaparin if the interventional cardiologist is not comfortable with this agent. The SYNERGY trial clearly shows that peri-procedural thrombotic complications (unsuccessful PCI, abrupt closure or emergency CABG) were similar, regardless of which antithrombotic agent was used, for the 4685 patients who underwent PCI. Furthermore, the rate of 30-day death or MI was clinically similar for this PCI cohort (enoxaparin 13.1% vs UFH 14.2%; OR 0.92; 95% CI 0.79, 1.08).[3]

2.3 Switching Treatment

Is there any advantage to switching from the initial anticoagulant to the other anticoagulant at the time of PCI?

The answer is 'no' and the evidence clearly demonstrates that this switching should be avoided. Of the total study cohort, 798 patients (8%) were switched to the opposite anticoagulant (a protocol violation) at the time of PCI (probably because of interventional cardiologist preference), and this led to a worsening efficacy and safety profile. For patients initially assigned to enoxaparin, the rate of 30-day death or MI went from 13.5% (no crossover) to 17.4% (crossover) [n = 593]. Blood transfusion rates dramatically increased from 15.3% (no crossover) to 30.2% (crossover). Similarly, for patients initially assigned to UFH, the rates of 30-day death or MI went from 14.2% (no crossover) to 22.0% (crossover) [n = 205]; transfusion rates increased dramatically from 15.1% (no crossover) to 35.1% (crossover).

2.4 Costs/Risks

What about dollar costs, time efficiency costs and risk of medical error with either drug when used in ACS patients in a busy and overcrowded ED?

Although the acquisition costs of UFH are minimal, there are the hidden dollar costs and time-efficiency costs of obtaining aPTT values in order to administer the correct dosage heparin infusion. This becomes especially problematic when ACS patients are being held in the ED for extended periods as a result of inpatient bed unavailability. Furthermore, ED staff are usually focused on dealing with other critically ill patients arriving in the ED and have little time to adjust heparin infusions. Thus, although the acquisition costs of enoxaparin are somewhat higher ($US30–50 per dose), there are no hidden dollar or time-efficiency costs. The next dose is simply administered 12 hours after the first dose. Finally, dose calculation for enoxaparin is simple (1 mg/kg) and is theoretically less likely than the calculation of weight-based heparin dosages to lead to a dose administration error in a busy ED.

3. Conclusion

In summary, given the continually increasing complexity of patient care in the ED, a drug that provides simplicity (i.e. enoxaparin) is certainly desirable if the drug can be safely used and is effective. The large SYNERGY trial clearly shows equal efficacy between enoxaparin and UFH, with a prespecified subanalysis of >6000 'consistent therapy' patients showing efficacy in favour of enoxaparin. The safety results have led to significant debate regarding the relative merit of the various bleeding scores. However, the actual blood transfusion rates appear to be the most clinically relevant to both the clinician and the patient, and these rates were not statistically different between treatments regardless of the cohort analysed. The SYNERGY trial provides strong evidence that enoxaparin can satisfy the needs of both EPs and cardiologists as they work together in providing the highest quality of cardiac care. Enoxaparin is simple to use in the ED, provides effective anticoagulation and procedural success for the cardiologist, and, provided crossover to UFH is avoided, can be safely used with multiple other cardiac medications.

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