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Debate

Heparin has No Place as an Anticoagulant in PCI – A Protagonist's View

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ABSTRACT
Unfractionated heparin is the standard anticoagulant of choice for patients undergoing percutaneous coronary intervention. However it has significant pharmacologic limitations such as need for frequent laboratory monitoring of anticoagulation status and unpredictable response in acute inflammatory states. Low molecular weight heparin such as enoxaparin has emerged as a feasible alternative with clinical studies of its use in both elective and emergency PCI indicating that it is just as effective, and has higher safety profile. With its more predictable anticoagulant response, greater bioavailability, practical clinical benefits including early sheath removal; and potential cost saving, enoxaparin has made itself a preferred alternative in modern PCI.

Standard unfractionated heparin (UFH) has been the adjunctive anticoagulant of choice during elective percutaneous coronary intervention. It is a heterogeneous mixture of glycosaminoglycans with molecular weights that range from 5000 to 30000 Daltons. It inhibits coagulation and prevents hemostasis by a number of mechanisms that include combining with anti-thrombin III to inactivate activated coagulation factors, and with heparin cofactor-2 to inhibit thrombin directly, and also some degree of inhibition of platelet aggregation. However the past decades of experience has revealed its pharmacokinetic limitations. UFH is hampered by unpredictable levels of heparin binding to plasma proteins and relative ineffectiveness against platelet-rich and clot-bound thrombin, especially in acute coronary syndromes when there is significant rise in acute phase reactant proteins. Its rapid and unpredictable clearance from plasma requires continuous monitoring of the activated partial thromboplastin time (aPTT) to assess its effect. This is particularly relevant in preventing coronary thrombosis during a PCI procedure.

Low-molecular weight heparins (LMWHs), on the other hand, are generated by chemical enzymatic depolymerization of standard heparin, with a mean molecular weight of approximately 4000 to 6000 Daltons. These fractions have pharmacologic characteristics that are different from the parent compound. While they retain the ability to inhibit Factor Xa, they are less effective than UFH in inhibiting thrombin because only 25% to 50% of LMWH molecules are large enough (>6000 Daltons) to bind both thrombin and antithrombin simultaneously.

LMWHs are such that they have better bioavailability, a more predictable anti-thrombotic effect, are less protein-bound and are less likely to cause bleeding. Its use is now preferred in routine clinical practice in patients with acute coronary syndromes of unstable angina/ non ST-segment elevation myocardial infarction (NSTEMI). Below are some reasons why LMWH may also be preferred in patients undergoing PCI.

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Simpler to Use

The antithrombotic effect of heparin is reflected in its ability to prolong clotting time, which is measured by the aPTT. Because of marked variability in the effect of heparin, its anticoagulant activity during coronary angioplasty procedure has to be closely monitored. This is usually carried out by way of monitoring activated clotting time (ACT). The correlation between ACT and aPTT is acceptable at low level of heparin anticoagulation but become unreliable at higher doses of heparin used[1]. In a study by Ferguson et al, complications in PTCA patients occurred in all those with ACT of less than 250 seconds but only in 0.3% of those with ACT[2]. It is therefore recommended that ACT of 300 seconds or greater using the HemoTec monitor be maintained during angioplasty procedure and ACT of 350 seconds or greater be targeted using the Hemochron monitor, as the former tends to be 30 to 50 seconds lower than the latter[3].

More patients achieve target anticoagulation levels when receiving enoxaparin than when given UFH. It has been reported that 93% of patients achieved anti-Xa activity above the lower limit of 0.5 IU/ml[4], whereas 70% of patients administered UFH achieved a target aPTT above 60 seconds[5] when administered in standard dose. In the STEEPLE trial which involved 3528 patients requiring nonurgent PCI who were randomized to one of 3 treatment arms, enoxaparin 0.5mg/kg iv; enoxaparin 0.75mg/kg iv; or iv UFH (70-100 IU without GP IIb/IIIa inhibitors, or 50-70 IU with GP IIb/IIIa inhibitors), 78.8% and 91.7% of patients in the 0.5mg/kg and 0.75mg/kg enoxaparin groups achieved a target anti-Xa activity level of 0.5 to 1.8 IU/ml. A significantly lower percentage of UFH patients, 19.7%, reached their predefined ACT targets of 300 to 350 seconds if no GP IIb/IIIa inhibitor was given, or 200-300 seconds for patients also receiving GP IIb/IIIa therapy ($p<0.001$ for both comparisons). Thus enoxaparin achieves target anticoagulation levels more reliably than UFH[6]. And that is why laboratory monitoring of anticoagulation effects is generally not required for LMWH, which simplifies patient management.

Another reported advantage of iv enoxaparin over iv UFH is that the use of the former at a dose of 0.5mg/kg allows for immediate removal (or at least within an hour) sheath removal after PCI[6,7]. When iv UFH is used as an anticoagulant therapy in PCI, sheath removal must be delayed until such time as the ACT reaches a maximum of 150-180 seconds to avoid high bleeding risks[8]. This requires ongoing assessment of ACT and means that, generally, femoral sheaths remain in place for 4 to 6 hours after PCI with UFH. The ability to remove sheaths immediately after PCI both simplifies the practicalities of the procedure and has clinical benefits such as reduced bleeding risk and improved patient's comfort.

Enoxaparin activity, as measured by anti-Xa levels, achieves peak effect within 10 minutes of an iv injection, regardless of whether patients received additional medications such as GP IIb/IIIa inhibitor and clopidogrel[7]. However subcutaneous administration of enoxaparin achieved maximum anti-Xa activity levels only at 3 to 5 hours after. Clinical data from SYNERGY trial suggested that there may be an increased risk of death or MI associated with PCI performed within the first few hours after a single enoxaparin does (1mg/kg sc)[9]. Thus a booster dose of 0.3mg/kg iv enoxaparin is recommended when such patients need to undergo PCI, and also in patients who received their last enoxaparin dose 8 to 12 hours before PCI[9].

Cheaper

With the obviated need for frequent ACT measurement in the catheterization laboratory, there is significant cost saving when using enoxaparin as an anticoagulant. In my local context of subsidized public patients, the total cost of administering intravenous enoxaparin to an average 65kg weight patient is significantly lower than UFH, when cost of ACT measurement is factored in (S$4 vs S$21).

Safer

The patients undergoing nonurgent PCI is typically at the lower end of the spectrum for risk of ischemic events, which makes bleeding events in such patients relatively more important. Minimising bleeding complication rate is increasingly being seen as a major objective of antithrombotic therapy during PCI especially when it is now been identified as a predictor of future adverse major

cardiovascular outcomes[6]. Early meta-analysis of small-scale studies suggested that enoxaparin was associated with reduced rates of major bleeding (0.6% vs 1.8%, respectively; p=0.0001)[10]. The STEEPLE trial demonstrated that enoxaparin reduced the relative risk of major bleeds by 57% compared with UFH, with comparable reductions in ischemic events between the 2 drugs[6]. The primary endpoint of protocol-defined non-CABG related major or minor bleeding at 48 hours occurred less frequently with enoxaparin 0.5mg/kg than with UFH (5.9% vs 8.5%, respectively; p=0.01), but the difference did not reach statistical significance at a dose of 0.75mg/kg (6.5% vs 8.5%, respectively; p=0.051). Major bleeding rates were lower in both the enoxaparin groups (0.5mg/kg and 0.75mg/kg) when compared with UFH (1.2% and 1.2% vs 2.8% respectively; p=0.004 and p=0.007). The reduction in major bleeding events was achieved without any increase in ischemic events.

A more recent meta-analysis of 13 trials including 7318 patients showed that the use of LMWH during PCI was associated with a significant reduction in major bleeding events compared with UFH, but this did not impact on the hard ischemic endpoints. Intravenous LMWH was associated with a significant reduction in the risk of major bleeding compared with UFH (OR 0.57; 95% CI 0.40-0.82). A trend towards a reduction in minor bleeding was also observed among LMWH-treated patients (OR 0.75; 95% CI 0.47-1.2).

Better in Efficacy

Previous meta-analysis of small-scale feasibility and randomized studies suggested that LMWH may be more effective than UFH in reducing combined ischemic endpoints of death, MI or urgent revascularization (5.8% vs 7.6% respectively; p=0.03) in patients undergoing elective PCI[10]. However this was not demonstrated in the randomized STEEPLE trial which showed that there was no difference in the rate of death, nonfatal MI, or urgent revascularization between the LMWH (0.5mg/kg and 0.75mg/kg) and UFH in patients undergoing elective PCI (6.25 and 6.8% vs 5.8%, respectively; p=0.51 and p=0.30).

The attention among investigators then shifted to the use of intravenous LMWH in patients at the highest risk spectrum of acute coronary syndromes, namely those with ST-segment elevation myocardial infarction (STEMI). In an early retrospective analysis study of 6299 patients conducted by Zeymer U et al with STEMI treated with either no reperfusion, fibrinolysis or primary PCI, 609(10%) patients who received concurrent enoxaparin had lower combined endpoint of death and non-fatal reMI (OR 0.59; 95% CI 0.43-0.80) when compared with the rest who received UFH [11]. Mortality was significantly reduced in the LMWH group when compared to the UFH group (10% vs 7.2%, p<0.05).

In the prospective enoxaparin substudy nested in the large FINESSE study, 2452 patients with STEMI received intravenously either 0.5mg/kg enoxaparin or 40U/kg UFH according to the centres' prespecified regimen. Enoxaparin reduced the composite ischemic endpoint of death, reinfarction, urgent revascularisation, or refractory ischemia by 53%, the triple endpoint of death, reinfarction, or urgent revascularization by 37% and mortality by 41% [12].

In the largest randomized, open-label, ATOLL trial of iv enoxaparin versus UFH in patients with STEMI, 910 patients were randomised to receive iv bolus dose of 0.5mg/kg enoxaparin, or UFH at 70 to 100 IU/kg with no concurrent glycoprotein IIb/IIIa inhibitors (GPI), or 50 to 70 IU/kg with GPI[13]. The results were somewhat disappointing for iv LMWH in that there was no difference in the primary endpoint of 30-day incidence of death, complications of MI, procedure failure or major bleeding (28% vs 34%, RR 0.83 (95% CI 0.68-1.01), p=0.063) between the 2 groups. There was however significant reduction in some of the main secondary endpoints which provide an overall improvement in net clinical benefit with enoxaparin.

Current guidelines

Both the European[14] and American[15] guidelines on PCI have accorded UFH Class 1 recommendations for use during elective PCI. The ACCF/AHA/SCAI guidelines have accorded LMWH Class IIb recommendation for use in patients who have

either been treated with 'upstream' subcutaneous enoxaparin or have not received prior antithrombin therapy. The ESC has given a Class IIa recommendation for LMWH use on the evidence that STEEPLE trial showed reduced bleeding hazard but comparable efficacy with UFH. Both guidelines do cautioned against crossover use between UFH and LMWH before and during PCI.

Table 1
LMWH vs UFH In PCI

	No.	Primary Endpoints
Elective PCI STEEPLE	3528	Reduced non-CABG related bleeding with enoxaparin 0.5 mg/kg (5.9% vs 8.5%, p = 0.01)[6]
Primary PCI ATOLL	910	Non-significant reduction of death, complications of MI, procedure failure or major bleeding (28% vs 34%, p=0.06)[13]
Facilitated PCI FINESSE	2452	Reduced composite endpoints of death, re-MI, urgent revascularization, or refractory ischemia with enoxaparin 0.5 mg/kg (5.3% vs 8.0%, p=0.005)[12]

Conclusion

There is sufficient evidence (Table 1) to support the use of intravenous enoxaparin in elective and emergency PCI as an effective antithombin therapy with high safety profile. The pharmacologic advantages of LMWH over UFH in terms of its more predictable anticoagulant response, greater bioavailability, practical clinical benefits including early sheath removal; and potential cost saving, makes it a preferred alternative. Appropriate dosing and use of enoxaparin have been shown to reduce bleeding risk in clinical trials while being as effective as iv UFH in reducing ischemic complications.

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