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A Brief Literature Review on Heparin: To Bolus Or Not To Bolus, That Is The Question

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Abstract:

Heparin is an anticoagulant medication, used to inhibit the formation of thrombi that pose arteriolar and vein-occlusive risk. The choice between starting a heparin infusion with or without an initial bolus is case dependent based on whether a patient is already anticoagulated and if so, foregoing an initial bolus. In contrast, both anticoagulated and non-anticoagulated patients share the same goal when receiving Heparin for various thromboembolic syndromes, and that is to be within aPTT target range of 1.5-2.5 or 45 to 75 seconds. Falling below goal range leads to a 20-25% recurrence of VTE, and aPTT above goal range has been shown to increase the probability of major bleeding by roughly 7% for every 10 second increase in aPTT[1,5]. The bolus dose has been shown to achieve therapeutic range faster than without the bolus, however this is often accompanied by overshooting the therapeutic range and necessity of titrating down on the subsequent infusion.

Introduction:

Heparin WITH or WITHOUT bolus, that is the question. Whether it is TIA, ACS, DVT, or a PE, treatment management often includes a heparin infusion. In managing these scenarios physicians commonly come to a fork in the road when deciding between initiating a heparin infusion with an initial bolus or withholding the bolus. The choice of going left or right at this fork, is often difficult to make, and the wrong choices can lead to poor clinical outcomes. Approximately 500,000 to 600,000 hospital admissions each year are due to PE alone, most commonly caused by venous thromboembolism (VTE), and lead to roughly 12% increase in mortality in hospitalized patients[10, 11]. Whether a patient is admitted to the hospital for PE, or develops a PE during their hospitalized stay, PEs are responsible for 200,000-300,000 deaths annually in the US[11]. These statistics show the significance of physician knowledge on the pharmacokinetics of heparin and how to utilize heparin appropriately. In this literature review, the choice between adding a heparin bolus or withholding will be discussed, as well as what repercussions there may be with making the incorrect management choice. A large collection of surveys, reviews, as well as prospective studies have analyzed the effects of heparin with and without bolus, as well as monitoring adequate heparin infusion levels with activated partial thromboplastin time (aPTT) to maintain therapeutic range. Based on the reports, the following questions will be addressed in this literature review:

1. What is the function of a heparin bolus and the goals to maintain doses in Therapeutic Range?
2. What is the risk of subtherapeutic aPTT
3. What is the risk of supratherapeutic aPTT

Methods:

PubMed [Pubmed.com] searches were performed to identify research publications pertinent to the following questions:

1. What is the function of a heparin bolus and the goals to maintain doses in Therapeutic Range?
2. What is the risk of subtherapeutic aPTT
3. What is the risk of supratherapeutic aPTT

The following broad keyword searches were entered to focus on each of these questions: “heparin with or without bolus” “heparin MOA” “therapeutic range heparin”. Of these searches, results were classified into which question or questions they best addressed. Over 150,000 publications resulted, of which multiple were used to compile pertinent information to guide clinical practice of heparin dosing. Each paper was read and organized into its respective area(s) in the results section.

Results:

Both heparin dosing with and without a bolus utilize aPTT for monitoring therapeutic range. Patients who are found to have thromboembolic syndromes and are already anticoagulated should not receive an initial heparin bolus, as their initial anticoagulation acts as the bolus itself. Patient who are not anticoagulated should receive a bolus, and can be dosed utilizing various guidelines. Providing 80 units/kg IV bolus, THEN continuous infusion of 18 units/kg/hr is one way to reach therapeutic range as rapidly as possible. Another option is to provide 5000 units IV bolus, THEN continuous infusion of 1300 units/hr. Additionally subcutaneous heparin can be used, providing 250 units/kg or 17,500 units, followed by 250 units/kg SC q12hr[6]. Heparin dosing is monitored and adjust accordingly to avoid subtherapeutic or supratherapeutic dosages, via aPTT ranges. The American College of Cardiology and the American Heart Association, ACC/AHA recommend an aPTT range of 1.5 to 2.5 times the control value or 45 to 75 seconds[1]. This range has been used for many studies addressing the utilization and effects of heparin on anticoagulation. Reaching therapeutic range in the fastest manner possible to hinder the coagulopathic condition is what the bolus dose is geared towards. In one clinical trial by Cory Toth, 206 patients were studied, in which 33 received heparin with a bolus and in 173 the bolus was withheld. The group receiving a bolus achieved higher aPTT at the first time mark 6 hours after initiation of therapy, with bolus group aPTT 87.6 +/- 36.3 versus 61.0 +/- 8.1. It was also found that patients receiving bolus achieved an initial aPTT above minimum threshold for therapeutic range more than 60 seconds sooner than patients without an initial bolus (9.6 +/- 7.3 versus 14.5 +/- 10.8 h), however, neither groups had a significantly greater chance of achieving or maintaining therapeutic range[3]. The reason for this is not entirely clear however, pharmacokinetic properties are likely the root cause. These kinetics were examined in “The Pharmacokinetics of heparin II, studies of time dependance in rats,”. Here, heparin activity in plasma at the end of the infusions were roughly twice as high as predicted on the basis of the total clearance of the bolus dose. It was found that a bolus dose increases the half-life of which heparin circulates in the body [4]. This property of heparin, notably with the bolus, yields insight to not only reaching therapeutic range quickly, but why often patients achieve an elevated aPTT out of the therapeutic window and need to titrate down. The risk of this overshoot has been analyzed in multiple studies, and to the contrary, forgoing the bolus and subsequently not reaching therapeutic levels promptly.

In the Prospective Study of “The Value of Monitoring Heparin Treatment with the Activated Partial Thromboplastin Time,” both subtherapeutic levels of heparin as well as supratherapeutic level were examined. It was shown that at subtherapeutic levels, ie APTT less than 1.5-2.5, recurrence of VTE increases. In this study 162 patients out of 234, were treated for VTE. The five patients with venous thromboembolism in whom recurrence developed had a significantly lower APTT than patients without recurrence even though they received similar amounts of heparin. No recurrence developed in any patient with a mean APTT within the therapeutic range[2].

The necessity to fall within therapeutic range is bolstered when examining The OASIS-2 Trial. Here the relationship between APTT and recurrent cardiovascular events as well as bleeding were studied. 5058 patients having ACS without ST elevation who received intravenous heparin were examined. The increase in relative risk of recurrent CV events was 1.54 (95% CI 1.10 to 2.15; P0.01) among patients with APTT values <60 seconds compared with patients with APTT values >60 seconds[7]. Other studies have shown similar finings such as patients with proximal deep vein thrombosis who receive inadequate anticoagulation. These patients were found to have a risk of recurrent VTE at a rate approaching 20% to 25%[5]. The risk of falling in subtherapeutic range of heparin for more than 48 hours, yields a relative risk of 1.84 (95% CI 1.25 to 2.70) for recurrent CV events. In contrast, supratherapeutic APTT values were associated with bleeding, showing for each 10 second increase in APTT, the probability of major bleeding was increased by 7% (95% CI 3% to 11%; P0.0004)[1].

Discussion:

Through this literature review, the effects of heparin with and without an initial bolus were reviewed. The therapeutic range monitored by aPTT of 1.5-2.5 or 45-75 seconds was examined as a tool to guide optimal therapeutic dosages to avoid the consequences of bleed risk when supratherapeutic, and recurrent VTEs when subtherapeutic. It was determined that an initial bolus of heparin in patients not already anticoagulated will achieve therapeutic aPTT sooner than those without a bolus by more than 60 seconds sooner, however, neither groups have a significantly greater chance of achieving or maintaining therapeutic range over the other. This may be due to a variety of reasons, however, it is likely due to the pharmacokinetics of heparin itself that makes reaching and maintaining therapeutic range difficult. This difficulty bolsters the necessity of tight control of therapeutic range to avoid bleed risks at one end and recurrence of coagulopathies at the other. Through the use of aPTT goals, these risks can be minimized.

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