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Fondaparinux is an effective alternative to other non-heparin anticoagulants in the treatment of heparin-induced thrombocytopenia

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ABSTRACT A critical appraisal and clinical application of Kang M, Alahmadi M, Sawh S, Kovacs MJ, Lazo-Langner A. Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia: a propensity score-matched study. *Blood*. 2014;125(6):924-929. doi: 10.1182/blood-2014-09-599498.

Keywords: *Fondaparinux, heparin-induced thrombocytopenia, thrombin inhibitors*

Clinical Context

Luke Sanders (pseudonym), an 87 year-old male with past medical history of castrate resistant prostate cancer and COPD, presented after recently having started on Lovenox treatment the prior week for an acute deep vein thrombus. Other medications he was taking at the time included Xgeva (denosumab), Xtandi (enzalutamide), and Lupron (leuprolide) for his cancer, and lisinopril for hypertension. Mr. Sanders arrived for his routine medication injection and laboratory check-up, where his platelet count had decreased from the 140,000s to 36,000 (the most recent CBC results before and after Lovenox are shown in Table 1) and he was subsequently admitted. His calculated 4T score, a tool utilized to help physicians rule out HIT in cases when it may be suspected, placed him at high risk (64%) of having developed heparin-induced thrombocytopenia (HIT), and a HIT panel was positive. The 4T score evaluates patients based on four areas: degree of thrombocytopenia, timing of decreased platelet counts, thrombosis, and other potential causes of thrombocytopenia. Each area is assigned a score between 0 and 2, and the total score is then accumulated. A score of 3 or less represents a low probability of HIT, a score of 4-5 represents an intermediate probability, and a score of 6-8 equates to a high probability. Mr. Sanders' total score of 6 (2 for degree of thrombocytopenia, 2 for the timing of platelet decline, 0 for thrombosis, and 2 for other potential causes) yielded a high probability of HIT; therefore, Lovenox was discontinued and a discussion about which agent to utilize, argatroban (a direct thrombin inhibitor) or fondaparinux (a synthetic polysaccharide that activates antithrombin III), was undertaken. Mr. Sanders, who acknowledged he had a limited amount of time before the cancer was too extensive to overcome, wanted "to spend happy days with his family" while he still could. He did not want another medication to "cost him" any remaining time with his family by causing severe side effects, as the Lovenox had. Currently, argatroban is a commonly used FDA approved treatment for HIT, followed by bridging to Coumadin treatment, for those with a high probability of HIT or confirmed HIT unless a patient has severe hepatic failure, which Mr. Sanders did not (ALT of 52 IU/L and AST of 26 IU/L). However, argatroban is highly expensive and requires continuous IV infusion with concurrent laboratory monitoring to be utilized in a proper fashion.[1,2] Due to this reason, fondaparinux is often used as an off-label alternative, as clinicians have more experience using the drug and it requires less intensive monitoring upon administration, as well as the ability to

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administer it subcutaneously. However, there have been rare reports of continuation of HIT in those who have been given fondaparinux. [1,2]

Clinical Question

Is fondaparinux an effective alternative to currently used non-heparin anticoagulants in the treatment of heparin-induced thrombocytopenia?

Research Article

Kang M, Alahmadi M, Sawh S, Kovacs MJ, Lazo-Langner A. Fondaparinux for the treatment of suspected heparin-induced thrombocytopenia: a propensity score-matched study. *Blood.* 2014;125(6):924-929. doi: 10.1182/blood-2014-09-599498.

Related Literature

A PubMed search using the terms “fondaparinux,” “heparin induced thrombocytopenia,” and “effectiveness” was performed. The same search terms were also applied in the Research and Practice in Thrombosis and Hemostasis online library. Citations associated with systemic reviews of the topic were examined. Furthermore, references from UpToDate articles related to HIT and its treatment options were also reviewed and analyzed, with an emphasis on evaluating the most current treatment regimens. In addition, several articles were found after searching for HIT in cancer patients. However, only one is presented as part of the appraisal, as the others focused mainly on cancer as the cause of thromboembolism or as a potential exacerbating factor of HIT rather than the use of non-heparin anticoagulants in cancer patients with HIT. This article by Lobo was found following reading the Aljabari article and subsequently searching “cancer and heparin induced thrombocytopenia,” and scrolling to page two of the search.[3,4] As stated, no papers were identified that directly compared different non-heparin anticoagulants in the cancer and HIT population in terms of safety and efficacy. Therefore, discussion of how cancer may alter Mr. Sanders’ individual case and research relating to medication choices is detailed in the clinical application section. The Chan article was found following the Lobo article after entering the key words “fondaparinux and heparin-induced thrombocytopenia”, while the Baghdarsarian article was found using the terms “argatroban and heparin-induced thrombocytopenia.”[5,6] The Short article was identified following a PubMed search utilizing key terms of “anticoagulants,” “cancer,” and direct thrombin inhibitors, while the Wahby article was found on PubMed using the terms “fondaparinux,” “anticoagulation,” and “ill.”[7,8] After excluding the articles that were not directly relevant to the clinical question at hand based on title and abstract, the search yielded 7 remaining results.

Due to the nature of HIT and the fact that laboratory testing (serotonin release assay) is often not utilized in confirming its diagnosis, as well as a lack of interest in pharmaceutical companies in seeking FDA-approval for such an application, randomized control studies relating to the clinical question posed have not been conducted. Randomized control studies are preferred as they are best able to detect a cause and effect relationship between treatments and outcomes. This is because they randomly allocate participants to groups, are double-blinded, and manage all groups equally except for the treatment being analyzed, allowing the researchers to minimize any potential bias. Nonetheless, a comprehensive propensity score-matched study, which has been demonstrated to be almost as useful in certain scenarios where a randomized controlled study is infeasible or has never been conducted, has been performed.[9]

The Al-Eidan paper compared argatroban and fondaparinux in the treatment of HIT via retrospective cohort study.[10] Only 95 participants were involved in the study, which limits the ability to draw a significant conclusion from the study. Further, one of the authors had received funding from a pharmaceutical company and has engaged in medicolegal activities related to certain anticoagulant medications.

The Aljabari article analyzed the cost-effectiveness of utilizing fondaparinux instead of argatroban or bivalirudin.[3] While it effectively demonstrated the cost-effectiveness of using fondaparinux, it focused little on efficacy. As this research focused mostly on cost-effectiveness and simply relied on the Kang article to support its secondary point of increased efficacy instead of conducting primary research, it was not chosen.

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The Warkentin article discusses the diagnosis and management of HIT.[2] While the article indicates fondaparinux to be an intriguing option for HIT, it does not demonstrate any primary research to support its findings. Further, the author has received research funding from pharmaceutical companies.

The Schindewolf paper is a prospective study focusing on the rate of allergic reactions and development of HIT in those administered fondaparinux. The article states that fondaparinux is a quality choice, both financially and medically, for HIT.[11] However, It does not specifically address the development/worsening of HIT in patients with suspected HIT who are then treated with fondaparinux. Additionally, the research was funded by a pharmaceutical company, which may introduce bias into the study.

The paper by Linkins attempts to perform a comprehensive literature review to best evaluate the efficacy of fondaparinux in HIT without there being any randomized controlled trials of the subject.[12] The article aptly summarizes a multitude of research articles, forming an opinion that supports the use of fondaparinux in HIT. Nonetheless, since the authors are analyzing the research instead of conducting it and also place a large focus on the Kang literature, it was not chosen.

The Lobo paper utilized a prospective clinical trial while comparing patients with HIT who were treated with fondaparinux versus a direct thrombin inhibitor, such as argatroban. The article comes to the conclusion that, although more evidence is needed, fondaparinux seems to be a reasonable choice in the treatment of HIT.[4] However, due to the small sample size of patients in the study (17 in total), the lack of a confirmatory serotonin-release assay in the trial, and different starting times of medications between the two groups, this paper was not chosen.

The Kang paper utilized a propensity-matched scoring analysis in order to reduce selection bias as much as possible. It also performed subgroup analysis and matched participants based on equal measures into control groups receiving argatroban or danaparoid (60 patients) and those receiving fondaparinux (133 patients).[13] This article is currently the closest one available to a randomized controlled study; as such, it was the chosen publication to be analyzed.

Critical Appraisal

This article conducted a retrospective cohort study to compare the efficacy and complication rate of fondaparinux to argatroban and danaparoid for treatment of HIT. The study used an associated propensity-score matched analysis in an attempt to reduce selection bias. The authors had no conflicting financial interests related to this research. The study enrolled patients within the London (Ontario) Health Sciences Center who were given a non-heparin anticoagulant for suspected HIT. The non-heparin anticoagulants were argatroban, danaparoid, or fondaparinux. Patients who had received one of these medications as well as a HIT-ELISA test performed were identified via retrospective chart review and were anonymously enrolled as participants in the study. Those patients who received more than one of the above anticoagulants were excluded. This allowed for the avoidance of any crossover effects that would not be able to be pinpointed to one particular drug as the source.

A diagnosis of HIT was established if a hematologist made the decision or if a patient had a positive serotonin release assay. However, as not all patients had a serotonin release assay performed, there is the potential for misdiagnosis.[1,14] All information was analyzed by two investigators who were blinded to the medication the participants were given. If a consensus decision was not reached, a third reviewer was consulted. Through this blinding and consensus process, any potential investigator bias towards one medication was eliminated.

Between the period of February 2005 and June 2011, there were 337 patients who were initially identified. Of these, 28 patient charts were unavailable for further review; this left 309 patient charts to be reviewed. After thorough analysis of these remaining records, 70 additional patients were excluded from the study for receiving more than one non-heparin anticoagulant, not receiving the HIT-ELISA test that was ordered, or for other reasons (these reasons are not specified in the article). These eliminations left 239 patients in the final study.

With these patients established, the participants were matched and divided into two cohorts: those who received fondaparinux and those who received argatroban or danaparoid. Using propensity-matched scoring based on categories such as age, gender, 4T score, creatinine, and the Charlson comorbidity index (which is a weighted index that incorporates 17 comorbidities, such as age, MI, diabetes mellitus, and malignancy, in an attempt to estimate a patient's 1-year mortality risk), participants were matched to the

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controls to account for observed covariates. However, unlike in a randomized control study, this process cannot account for covariates that are not directly observed. This process resulted in 133 patients in the cohort who received fondaparinux and 60 patients in the cohort who received argatroban or danaparoid (the control group). The groups were not statistically different, although the possibility for a type II error does exist as the authors, due to the low prevalence of HIT, were unable to perform a power calculation based on theoretical data rather than observation. However, a post-study calculation yielded a power of 74% to detect a difference of 10% in thrombotic events in the groups.

The average age of participants in the control group was 67 and in the fondaparinux group was 68. No participants in either group were 87 years of age as Mr. Sanders was, and there was no documentation if any participants had cancer like he did. Additionally, other than including creatinine, there is little reporting of the overall health status of the participants. Other than being diagnosed with HIT and monitoring their creatinine levels, it is unclear whether or not other factors could have been contributing to a patient's health. The authors utilized Fisher's Exact test, the Mantel-Haenzel common odds ratio, and the Kaplan-Meier method for various statistical analyses. The statistical analysis performed in the article is thorough and includes data relating to both the unmatched and matched cohorts. Sub-analysis of the three non-heparin anticoagulants used was also conducted and demonstrated no statistically significant difference amongst them in terms of safety or efficacy. This comparison is important as it ensures no participants received statistically different treatment if they received argatroban instead of danaparoid, for example.

Major bleeding and thrombosis were identified as the major safety and efficacy outcomes, respectively, being analyzed in the study. Bleeding was detected in 12 of 60 patients (20%) in the control group and in 28 of 133 patients in the fondaparinux group (21.1%). Thrombotic episodes occurred in 13 of 60 control group patients (21.4%) and 22 of 133 fondaparinux group patients (16.5%). Survival analysis of the matched cohorts in relation to efficacy demonstrated a log-rank P value of 0.415 and survival analysis in relation to safety yielded a log-rank P value of 0.779. These results imply no statistically significant difference between the medications utilized. While the median 4T scores and the percentage of those diagnosed with HIT across both groups were statistically the same, it is noteworthy that among those in the control group, there were a larger proportion of participants with a 4T score placing them in the high probability category. This could have had an effect on the results, as there were more patients in the control group with potentially more severe HIT. Overall, these results indicate that the fondaparinux group received at least non-inferior medical care compared to the control group in terms of both safety and efficacy.

Clinical Application

The results of the Kang paper suggest that fondaparinux is non-inferior to argatroban and danaparoid for the treatment of HIT. Upon initial discussion, the medical team strongly considered fondaparinux for Mr. Sanders due to its cost effectiveness and relative ease of use as a subcutaneous injection versus argatroban, which requires IV access and routine blood monitoring. Furthermore, after evaluating his medication list, there were no interactions found between his current regimen and either fondaparinux or argatroban, allowing the team to select from both options.[15] However, after further discussion with Mr. Sanders and taking into consideration his stated goals of having as much time with his family as possible without further complications he expressed a preference for a medication specifically approved for HIT. Hhe was given argatroban, as it is the FDA-approved medication that met his goals.

Had Mr. Sanders had only thromboembolism secondary to his cancer and not HIT, fondaparinux would have been a better option, as there is no current data supporting the use of argatroban in that specific situation, unlike fondaparinux.[16] Furthermore, a study evaluating the use of argatroban in critically ill patients, who were without significant liver disease and were diagnosed with HIT, recommended reconsidering the current dosing regimen, and suggested that a lower dosage of the medication may be more appropriate in such a scenario.[6] The idea that other factors may be involved in the metabolism of argatroban in critically ill patients lends some credence to using fondaparinux in Mr. Sanders' case. A study relating to the use of fondaparinux in critically ill patients with severe renal disease was also identified. Evaluating peak and trough anti-factor Xa levels, it found no significant difference between the ill patients and non-ill patients with normal renal function, and suggests that fondaparinux may be an effective alternative to heparin agents in those specific cases.[8] The Chan paper employs a retrospective study of 21 cancer patients who were given fondaparinux for confirmed HIT. The study found that 15 of the 21 had a successful return to normal of their platelet count. Nonetheless, with the small sample size and lack of

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comparison to argatroban use in similar situations, it is difficult to extrapolate these results.[5] As no study exists directly comparing the use of fondaparinux and argatroban for Mr. Sanders' individual case and since argatroban is FDA-approved for HIT, a direct comparison yielding a clear answer cannot be made.

Additionally, a fully complete analysis on the choice of medication cannot be made in the case of Mr. Sanders, as no current papers exist directly comparing the safety and efficacy of these two medications in both the HIT and cancer population or in cancer patients alone for argatroban (no phase three trials have been conducted).[7] His cancer diagnosis undoubtedly worsens his prognosis and clearly increases his risk of thromboembolism. Compared to many people in the study, his cancer surely lowers his health status and makes him less likely to recover fully with either medication. Nevertheless, based on current data, it appears that fondaparinux is becoming an increasingly employed treatment option with a good deal of success.

Overall, the current available evidence points towards the use of fondaparinux as a viable treatment option for HIT. Although current studies have not necessarily demonstrated its superiority to current options in terms of efficacy, it appears to at least be non-inferior in that regard as well as in terms of safety, and is simpler and less costly to utilize. Nonetheless, randomized control studies analyzing this topic that could potentially provide even more compelling data have still yet to be conducted.

Learning points:

1. Fondaparinux is a practical option to employ in the treatment of HIT, especially considering its simpler use and cost savings in comparison to current treatments.

2. Further investigation with randomized controlled studies would be of benefit in firmly establishing fondaparinux as a thoroughly vetted treatment option.

3. Decisions regarding the treatment of HIT should be individually based on safety and patient goals.

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