

Cost reduction associated with heparin-induced thrombocytopenia panel ordering for enoxaparin versus heparin for prophylactic and therapeutic use: A retrospective analysis in a community hospital setting

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ABSTRACT

Background: Most hospitals still use unfractionated heparin (UFH) as the primary agent for venous thromboembolism (VTE) prophylaxis in the hospital setting due to ease of use and insignificant cost. However, the risk of heparin-induced thrombocytopenia (HIT) has led some groups to favor other options for therapeutic and prophylactic anticoagulation. This is particularly relevant in light of recent data demonstrating a lower rate of HIT in patients receiving enoxaparin compared with UFH. This study examines the cost-effectiveness of enoxaparin, compared to UFH for prophylactic and therapeutic usage in hospitals. **Methods:** We conducted a retrospective chart review of patients who underwent HIT panel testing at the Inspira Health Network, Vineland campus (an approximately 262-bedded community hospital located in southern New Jersey that services a population of approximately 61,050) from the period of April 1, 2015 through December 31, 2016. The starting date represents the time from which enoxaparin became the primary alternative anticoagulant available at this hospital. Records of the total usage and cost of UFH and enoxaparin for the specified time period were collected from the hospital pharmacy database for evaluation, as were records of HIT panels. The information was analyzed to determine the frequency of HIT panel testing orders for patients receiving UFH versus those receiving enoxaparin. Annual cost-savings for the hospital were extrapolated using the comparative incidence of HIT panels and associated costs, including increased length of stay, hematology/oncology consultation, use of an alternative anticoagulant, critical bleeding requiring transfusion, and complications of HIT-associated thrombosis. These variables were multiplied by the incidence rate for each specified drug and usage to determine the daily cost for each drug. **Results:** The use of enoxaparin did not result in a significant decrease in the ordering of HIT panels in the hospital, with a relative rate ratio of 0.948 (95% confidence interval: 0.336, 2.21). When the data were stratified to examine prophylactic and therapeutic anticoagulation, there was a marked difference in the frequency of HIT testing. The rate ratio of HIT panel orders for patients receiving therapeutic enoxaparin rather than intravenous (IV) UFH

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was 0.118 (0.006, 0.625). These numbers were used to extrapolate the total daily cost of enoxaparin compared with IV UFH; therapeutic enoxaparin cost \$30.66, while IV UFH cost \$162.30. IV UFH use was associated with a higher incidence rate of HIT panel orders, and consequently a higher daily cost due to the likelihood of increased length of stay, use of alternative anticoagulation, bleeding requiring transfusion, and request for expert consultation. **Conclusion:** In this study, the use of enoxaparin was associated with a significant cost-saving over IV UFH when used for therapeutic anticoagulation, but this cost saving was not observed for prophylactic anticoagulation.

Key words: Anticoagulation, heparin-induced thrombocytopenia, low molecular weight heparin

INTRODUCTION

Venous thromboembolisms (VTEs) contribute to considerable morbidity and mortality and substantially increase cost for hospitalized internal medicine patients. Reductions in VTE incidence in hospitalized patients have therefore become a major goal. In the past decade, the most effective and patient-friendly approach to VTE prophylaxis has become a matter of concern, with some groups arguing for the use of low molecular weight heparins (LMWHs) and others remaining faithful to unfractionated heparin (UFH) due to lower costs. The role of the most frequently used LMWH, enoxaparin, for prophylaxis and therapeutic use has been studied extensively over the past 10 years, with data showing that enoxaparin was an option for prophylaxis for venous thromboembolism (VTE) compared to no prophylaxis.^[1]

Most hospitals still use UFH as the primary agent for VTE prophylaxis in the hospital setting due to the ease of use and insignificant cost. However, the risk for development of heparin-induced thrombocytopenia (HIT) has led to questions about whether other options for prophylaxis and therapeutic anticoagulation might be more appropriate for use in the hospital.^[1,2] HIT is a major event in terms of morbidity, mortality, and cost for the patient. Moreover, HIT-associated thrombosis (HITT) is a dreaded complication for most hospitals.^[3,4]

Recent data have shown that enoxaparin is safer in terms of incidence of HIT when compared to UFH.^[2,5] The question of cost reduction has also been explored and previous studies have shown a cost reduction with LMWH from both a payer and societal perspective over UFH.^[2] A study published by McGowan *et al.* reported on an “Avoid heparin” protocol. This approach was instituted in 2006 at the Sunnybrook Health Sciences Centre in Toronto and replaced UFH with enoxaparin for prophylactic and therapeutic use in all instances except for during hemodialysis, intraoperative use for cardiovascular surgery, and for some patients with acute coronary syndrome. This study showed a significant cost-saving from an institutional perspective as well.^[5] The

study evaluated the frequency of HIT and HITT before (2003–2006) and after the implementation (2006–2012) of protocol therapy. These investigators found a significant reduction in HIT, HITT, and cost associated with testing and treatment for the above using enoxaparin instead of heparin.^[5]

In this study, most cases of HIT and HITT were associated with cardiovascular surgery patients. By comparison, there were much less significant events associated with other surgical services, cardiology, and medical services. As a hospital that does not offer cardiac surgical services currently, the question arises whether or not there would truly be a cost-benefit to implementing the use of enoxaparin primarily for VTE prophylaxis and most therapeutic uses. Taking the results of the “Avoid heparin” study and evaluating our hospital usage of enoxaparin and UFH, the cost difference in the medications and the ordering of HIT panels with subsequent costs may reveal an opportunity for significant cost-savings for the hospital.

METHODS

After Institutional Review Board approval, the investigators conducted a retrospective chart review of patients that had HIT panels ordered at the Inspira Health Network, Vineland campus, from April 1, 2015 to December 31, 2016. The starting date represents the time from which enoxaparin became the primary alternative anticoagulant available at this hospital.

Inclusion and exclusion criteria

Inclusion criteria for the study included any patient admitted to the hospital who had an exposure to either enoxaparin or UFH for either prophylactic or therapeutic treatment during that hospitalization. Patients were excluded if they did not have any exposure to either enoxaparin or UFH for either prophylactic or therapeutic treatment of a VTE during hospitalization, or if they were prisoners (for HIPAA compliance). The dosing of enoxaparin was defined for therapeutic use as 1 mg/kg subcutaneous (SQ) every 12 hours. The dosing of enoxaparin for prophylaxis

was 40 mg SQ daily. The dosing of UFH for prophylaxis was 5000 units SQ every 8 hours; dose adjustments were made for patients with renal impairments according to pharmacy recommendations.

Data collection

Records of the total usage of UFH and enoxaparin for the specified time period were collected from the hospital pharmacy database for evaluation. The total cost associated with these usages was also evaluated, using pharmacy information regarding the cost of each drug. The usages of enoxaparin and SQ UFH were evaluated by total dosages administered. The usage of intravenous (IV) UFH was evaluated by total bags of UFH used. Therefore, even if the entire bag of UFH was not used (for instance, if the IV UFH was discontinued for a patient), it was counted as a single usage dose. Once these totals were calculated, records of HIT panels were obtained from the same pharmacy database for the same time period. A chart review was then performed of individuals who had a HIT panel ordered to ascertain the following characteristics: primary diagnosis, age, sex, anticoagulant exposure, total length of stay, length of stay after ordering of the HIT panel, ordering of a hematology/oncology consultation specifically to address the possibility of HIT, ordering of an alternative anticoagulant, ordering of packed red blood cells (pRBCs) for bleeding after ordering a HIT panel, positivity of the HIT panel, and incidence of HITT.

Data analysis

After the data were collected, the information was analyzed to determine the rate of HIT orders for patients receiving enoxaparin versus UFH. These were compared using a Continuous Maximum Likelihood Estimation rate-ratio mid-P exact test [Table 1]. Significance was determined by comparing enoxaparin to UFH for total usage, prophylactic usage alone, and therapeutic usage alone. Using these numbers, annual cost-savings for the hospital were extrapolated using the comparative incidence of HIT panels and associated costs, including increased length of stay, hematology/oncology consultation, use of an alternative anticoagulant, cost of pRBC transfusion,

and complications of HITT. This was done by taking the current costs of enoxaparin and UFH and calculating the total cost of each drug for the hospital during the specified time period [Table 2].

The cost of HIT panel testing as provided by the hospital laboratory was \$153.86 per panel. The average length of stay per case of HIT in the hospital was calculated from the chart review and multiplied by the average cost of a hospital stay on a general medical floor. The cost of an alternative anticoagulant was calculated per case based on a hospital expenditure of \$90,000 for the given time period.^[6,7] The alternative anticoagulant used for patients who had HIT panels ordered was argatroban. When a HIT panel was ordered for a patient, the anticoagulant was immediately switched to weight-based argatroban. At the time, the use of direct oral anticoagulants for off-label use was not a common practice, especially in our hospital. Fondaparinux was not used in the hospital for off-label use for suspected HIT, though it is noted that for a 70 kg individual with suspected HIT, the dose of 7.5 mg once daily cost \$29.29/day. Argatroban pricing for a 2 mcg/kg/min dosing for a 70 kg individual was \$495.73/day, given that a 50 mg/50 ml bottle of argatroban cost the hospital \$122.95.

We also ascertained the risk of clinically-significant bleeding attributable to anticoagulation after a HIT panel was ordered, based on chart review. Clinically-significant bleeding was defined as bleeding that required transfusion of at least 1 unit of pRBCs. The average amount of pRBCs transfused into a patient after a HIT panel was ordered was multiplied by the hospital cost of a single unit of pRBCs (including the cost of a type and screen), which was found to be \$227.30. The patients may also have undergone additional testing (such as endoscopy) due to this bleeding. However, it was difficult to determine which tests were performed specifically due to bleeding. Therefore, these costs were not included in the cost analysis.

These variables were multiplied by the incidence rate for each specified drug and usage [Formula 1], to calculate the daily cost for each drug [Table 3].

Table 1: Incidence of heparin-induced thrombocytopenia panel ordering by drug

Drug	Enoxaparin (prophylaxis)	UFH (prophylaxis)	Enoxaparin (therapeutic)	UFH (therapeutic)	Enoxaparin (total)	UFH (total)
Total usage (doses administered)	8399	103,117	1880	5999	10,279	109,116
HIT panels ordered	4	29	1	27	5	56
Incidence rate (per 10,000 dose-years)	2.72	1.61	3.04	25.72	2.78	2.99
Rate-ratio (CI)*	1.69 (0.508-4.472)		0.118 (0.006-0.625)		0.948 (0.336-2.21)	
P*	0.33		0.005		0.96	
HITT	0	0	0	3	0	3

*Rate-ratio and P value compares enoxaparin to UFH for prophylaxis, therapy, and total usage. HIT: Heparin-induced thrombocytopenia, UFH: Unfractionated heparin, CI: Confidence interval, HITT: HIT-associated thrombosis

Table 2: Total use and drug-specific cost of enoxaparin and unfractionated heparin

Drug (quantified unit)	Cost (per unit)	Total usage (quantified unit)	Total cost
Enoxaparin (mg)	\$0.0913	485,629	\$44,337.93
SQ UFH (units)	\$0.000195	522,297,868	\$101,848.08
IV UFH (25,000 U/250 cc D5W)	\$0.00031	149,975,000	\$46,492.25

UFH: Unfractionated heparin

Table 3: Daily cost of enoxaparin and unfractionated heparin for prophylactic and therapeutic use

Drug (Usage)	Daily Cost
Enoxaparin (prophylactic)*	\$19.64
SQ UFH (prophylactic)	\$12.39
Enoxaparin (therapeutic)*^A	\$30.66
IV UFH (therapeutic)*^A	\$162.30

*For a 70 kg man with normal renal function, ^AFor venous thromboembolism.

UFH: Unfractionated heparin

Formula 1: Daily cost of enoxaparin and unfractionated heparin for prophylactic and therapeutic use (70 kg male patient). Daily drug cost (Cost per unit \times total units in 24 h period) + heparin-induced thrombocytopenia panel factor ($\$153.86 \times$ Incidence rate for drug) + Expert opinion factor ($\$250.00 \times$ Incidence rate for drug) + Length of Stay factor ($\$56,578.52 \times$ Incidence rate for drug) + Argatroban alternative anticoagulation cost ($\$1,475.41 \times$ Incidence rate for drug) + Critical bleeding factor ($\$138.65 \times$ Incidence rate for drug) = Total daily cost of drug.

RESULTS

We identified 61 cases in which a HIT panel was ordered over the specified time period. After chart review, these cases were stratified according to the exposure to either enoxaparin or UFH, in a prophylactic or therapeutic setting [Table 1]. There were 5 cases which were removed from consideration; 4 of these cases identified UFH exposure only during renal replacement therapy and could not be accurately quantified, while 1 case had no identifiable exposure to any heparin product.

In general, the use of enoxaparin did not result in a significant decrease in the ordering of HIT panels in the hospital, with a relative rate ratio of 0.948 (confidence interval [CI] = 0.336, 2.21). When stratified by indication for the use of anticoagulation, however, the data demonstrated a substantial difference between IV UFH and therapeutic enoxaparin. The use of IV UFH was found in this hospital system to correlate significantly with the incidence of HIT panel ordering. The rate ratio of HIT panel orders for patients treated with therapeutic enoxaparin compared with IV UFH

was 0.118 (CI = 0.006, 0.625), representing a statistically significant reduction in orders of HIT panels [Table 1]. In contrast, there was no significant difference in the frequency of HIT testing among patients receiving prophylactic enoxaparin rather than SQ UFH, as demonstrated by a rate ratio of 1.69 (0.508, 4.472).

The costs of evaluation for HIT and associated treatment adjustments were factored into the analysis based on the data obtained from chart reviews. The increase in length of stay due to the ordering of a HIT panel was found to be, on average, 9.34 days. The increased cost associated with this length of stay, given an average daily cost of $\$6,078/\text{day}$ on the general medical floor, was $\$3,464,460$. This resulted in an increase of $\$56,578.52$ per HIT panel ordered. The additional cost from the use of argatroban was found to be $\$90,000$, or $\$1,475.41$ per case. The cost of argatroban was a major factor in the cost increase for patients who had a HIT panel ordered. The patients were immediately switched to argatroban and maintained on therapy until the HIT panel was conclusively resulted as negative, or the patient was adequately anticoagulated with another nonheparin agent. Finally, the average amount of pRBC transfusions ordered after a HIT panel was ordered was 0.61 units. This resulted in an increased cost, on average, of $\$138.65$ per HIT panel ordered.

These variables were used to calculate the daily costs for the use of enoxaparin compared with UFH for prophylactic and therapeutic anticoagulation [Formula 1 and Table 3]. While there was a cost-saving associated with the use of SQ UFH for prophylaxis instead of enoxaparin ($\$12.39$ vs. $\$19.64$), it was noted that there was a major cost discrepancy between the use of therapeutic enoxaparin and IV UFH; therapeutic enoxaparin cost $\$30.66$, while IV UFH cost $\$162.30$. IV UFH use was associated with a higher incidence rate of HIT panel orders and subsequently a higher likelihood of increased length of stay, use of alternative anticoagulation, blood transfusion post-HIT panel order, and request for expert consultation. These factors all contributed to the higher daily cost of IV UFH. In addition, 3 cases of HIT were identified, all in patients who were placed on IV UFH.

DISCUSSION

The findings of this study illustrate that the use of IV UFH for therapeutic anticoagulation is significantly more expensive than the use of therapeutic enoxaparin when considering the potential for increased ordering of HIT panels and the downstream effects of this diagnosis. While the "Avoid heparin" protocol made mention of potential

cost-savings associated with the use of enoxaparin, our study is the first study to quantify the magnitude of cost-savings associated with the use of therapeutic enoxaparin compared with IV UFH. Furthermore, our study was able to show that the major cost-savings associated with enoxaparin had to do with therapeutic anticoagulation rather than prophylaxis. There are many hospitals that still prioritize the use of UFH due to the ease of use, especially considering the ability to be turned on and off quickly. However, this study shows the potential expense of that style of practice. Due to the availability of data from the pharmacy and laboratory, this cost analysis could be performed with a robust formulation in order to properly quantify the relevant costs associated with the need for HIT panel testing.

There are some limitations to consider in regard to this study. This study was conducted using data from a single community hospital. The practice of HIT panel ordering was impacted by different providers, with surgeons and medical personnel ordering HIT panels incongruously. HIT panels are typically utilized based on probability of thrombocytopenia being due to use of anticoagulation, by way of the 4T score. The 4T score evaluates the possible other causes of thrombocytopenia, the percentage of reduction of platelets, the timing of the thrombocytopenia, and the presence of thrombosis, with a scoring system that categorizes the probability of HIT.^[8-10] In some cases from our retrospective review, HIT panels were ordered without a proper assessment of the probability of HIT. Furthermore, the presence of HIT was possibly undervalued due to the incomplete imaging in some of these cases for whom HIT was suspected.^[3,4,11,12] In evaluating our cases, however, no further interventions were required beyond the use of alternative anticoagulation, and therefore, these costs were not factored into the daily cost formulation. In addition, variance in the ordering of prothrombin and partial thromboplastin time testing did not allow for uniform factoring of these laboratory tests into the cost formulation. Despite these potential unknowns, it is felt that the significance of these added costs was relatively small and would not substantially alter our conclusions.

There are other cost savings that were not included in the analysis due to variability in ordering and practice. These include the opportunity costs associated with additional nursing time for management of patients with suspected HIT, the additional cost of equipment associated with management of suspected HIT, and the cost of additional laboratory testing for patients with suspected HIT. However, these costs would be expected to further drive up the costs associated with suspected HIT, and therefore, our cost analysis would underestimate the true cost associated with

suspected HIT. As such, the discrepancy in daily costs associated with therapeutic enoxaparin and IV UFH would be even greater, with IV UFH expected to have a higher cost due to the higher association with HIT.

Finally, this study was significantly underpowered, because it was at a single community hospital and evaluated primarily as a case series with subsequent cohort cost analysis. Considering that the hospital started using enoxaparin as the primary alternative anticoagulant in April 2015, there were not enough cases of HIT panel ordering to significantly power the study.

CONCLUSION

This study shows that there is a significant cost reduction available to hospitals that are still primarily using IV UFH as a means of anticoagulation. These findings may prompt physicians to consider the use of enoxaparin for therapy early on during the hospitalization, to avoid the potential complications associated with HIT. These changes in practice may also result in significant downstream cost reductions, contributing to safer, more cost-effective patient care.

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Conflicts of interest

There are no conflicts of interest.

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