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Attributable Healthcare Cost and Length of Hospital Stay Associated with Heparin-Induced Thrombocytopenia

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Abstract

Background: Heparin-induced thrombocytopenia (HIT) is a serious adverse drug reaction associated with an increased length of hospital stay (LOS) and utilization of healthcare services and even more so if heparin-induced thrombotic thrombocytopenia (HITT) occurs.

Objective: To determine the attributable healthcare cost and LOS of patients experiencing HIT compared with control subjects.

Methods: A retrospective case-control study conducted in hospitalized patients with HIT and their control subjects from January 1to December 31, 2013. Of the 462 HIT assay performed, 29 HIT cases and 141 matched control subjects were evaluated. Healthcare costs elements attributed to HIT included laboratory tests, non-heparin anticoagulant, medical imaging, physician visits and LOS. The healthcare costs and LOS of cases, HIT and HITT, and control subjects were determined in US$, year 2013.

Result: Compared to the control subjects, the attributable healthcare cost and LOS were $3159 and 8 days for HIT cases and $18256 and 19 days for HITT cases, respectively. The HITT cases incurred median healthcare costs of $22893 compared with $7799 ($p<0.001$) for HIT cases without complication.

Conclusion: Heparin-induced thrombocytopenia is significantly associated with increased healthcare costs and an increased LOS. These findings suggest that using low-molecular-weight-heparin (LMWH) is one of the strategies aiming to reduce the incidence of HIT.

Keywords: Heparin-induced thrombocytopenia; Healthcare cost; Length of hospital stay

Introduction

Heparin-induced thrombocytopenia (HIT) is a well known life-threatening, immune-mediated reaction to all heparin preparations [1-6]. Of the patients who were exposed to unfractionated heparin (UFH) preparation, 3-5% developed HIT. Up to 2% of those exposed low-molecular-weight-heparin (LMWH) also developed HIT [7-9]. Patients who developed HIT had a high rate of venous thromboembolic complications leading to increased morbidity and mortality [4-6,10]. The healthcare costs are increased when patients develop HIT and even more so if heparin-induced thrombotic thrombocytopenia (HITT) occurs. Patients, at the very least, require longer hospital stay for parenteral administration of nonheparin anticoagulant as well as management of any thrombotic complications [11].

Although it is known that HIT and HITT have been associated with a negative impact on patient outcomes, the attributable healthcare costs associated with this adverse drug reaction have not been extensively studied. The objective of this study was to evaluate the healthcare costs and length of hospital stay (LOS) involved with HIT and identifies the main cost driver elements, based on a patient-oriented approach.

Methods

A retrospective case-control study design was used. All patients were newly diagnosed with a positive HIT using enzyme-linked immunosorbent assay (ELISA), confirmed clinically (using the pretest probability '4Ts'), were identified during the period from 1 January to 31 December 2013. The study was conducted in the King Abdulaziz Medical City (KAMC), teaching tertiary care centre in Riyadh, Saudi Arabia. Control subjects were matched using the following criteria: age (±1 year), sex, admitting services and admission date. From a pool of negative HIT subjects during the study period, 4-5 control subjects were identified for each case patient. Data on demographic characteristics (age, gender, non-heparin interventions, laboratory requests, medical imaging requests, length of hospital stay and admission classifications) were collected electronically from the hospital's Medical Informatics databases. Total healthcare cost of illness analysis, predefined HIT-relevant cost parameters (medication costs, bed costs, diagnostic and therapeutic interventions, laboratory tests, blood transfusions) were based on data from the Business Centre, KAMC.

Healthcare resource utilization variables

The attributable direct Healthcare costs of HIT included (i) investigational laboratory tests for HIT and mentoring laboratory tests for HIT treatment; (ii) Non-heparin anticoagulant use for HIT; (iii) diagnostic medical imaging related to HIT and it's treatment; (iv) physician visits; (v) additional hospital days attributable to HIT illness. The components and unit prices for individual variables are listed in Table 1.

Variables	Cost description	Unit cost
Laboratory test		
HIT investigation		
HIT ELISA	Test kit, reagents and lab technician time	96
Platelet count	Machine, reagents and lab technician time	25
Monitoring tests		
aPTT	Tests performed during non-heparin anticoagulant administration including reagents and lab technician time	21
INR/PT		21
Pharmacy		
Non-heparin anticoagulant		
Argatroban (250 mg vial)	Drug acquisition, pharmacist and technician time for preparation and consumable material (piggyback, needles, syringes, alcohol swaps, etc.)	692
Fondaparinux (5 and 7.5 mg)	Cost/syringe unit dose	48
Warfarin (1,2,2.5 and 5 mg)	Cost/tablet unit dose	1
Medical imaging related to HIT		
Spiral CT	Machine, contrast and imaging technician time	479
MRI	Machine, contrast and imaging technician time	638
Ultrasound	Machine and imaging technician time	240
Chest X-ray	Machine and imaging technician time	53
Echocardiography	Machine and imaging technician time	199
Physician visit	Consultant visits and consultations	75
Bleeding management		
Platelet	Blood product transfusion/2units	825
Blood	Blood transfusion/2units	638
Hospitalization/day by bed type		
ICU	Cost/day	399
Surgical/ medical ward	Cost/day	173

Table 1: Cost description and associated unit cost (US$). aPTT= activated partial thromboplastin; CT= computed tomography; HIT=heparin-induced thrombocytopenia; ELISA=enzyme-linked immunosorbent assay; ICU=intensive care unit; MRI= magnetic resonance imaging; INR=international normalization ratio.

Statistical Analysis

Data were summarized using median and interquartile ranges due to the skewed (Shapiro-Wilks test $p<0.05$) cost distribution. We used Chi-square tests to compare categorical variables, Student's t-tests to compare differences in means, and Mann Whitney U tests to compare differences in medians. All p-values were two-tailed and statistically significant at an alpha of <0.05.

Result

From January 1 through December 31, 2013, there were 9,989 adult hospital admissions who received low-molecular-weight heparin (LMWH) and 6,890 who received unfractionated heparin (UFH) for venous thromboembolism prophylaxis or therapeutic purposes. The incidence of HIT in patients receiving LMWH (enoxaparin) and those receiving UFH was 0.05% and 0.35%, respectively ($p<0.0001$), with an overall incidence of 0.17%. During the study period there were 462 suspected HIT cases, based on the HIT assays performed in the serology lab. Of those 462 suspected HIT cases, 29 patients were HIT positive (using ELISA assay and confirmed clinically using pre-test probability '4Ts') and 141 matched control subjects were identified and evaluated. The demographic characteristics and healthcare cost data for all case patients (HIT+HITT) and their matched control subjects without HIT are provided in Table 2. With respect to age, sex and admitting services the two groups were statistically similar. Cardiac science and surgery departments admitted the most patients. Significantly, case patients had longer LOS ($P<0.001$). The healthcare costs for each case patient and control subjects were determined. The median (IQR) healthcare cost per case patient was $9469 (6308-17246) compared to $4640 (3985-5791) for the matched control subjects ($P<0.001$).

Characteristics	Case patients (HIT +HITT; n=29)	Control subjects (n=141)	P Value
Age			
Median years, (IQR)	67 (55-73)	66 (52-75)	0.911
Sex, no. (%)			0.382
Male	11 (37.9)	58(41.1)	
Female	18 (62.1)	83(58.9)	
Admitting departments, no. (%)			0.842

Cardiac Science	9 (31.0)	43 (30.5)	
Surgery	8 (27.6)	39 (27.7)	
Intensive care	4 (13.8)	20(14.2)	
Internal Medicine	4 (13.8)	19 (13.5)	
Oncology/Hematology	3 (10.3)	15 (10.6)	
Hepatobiliary Science	1 (3.5)	5 (3.5)	
Length of hospital stay			
Mean (±SD)	26.2 (±11.9)	15.1(±8.4)	<0.001
Median (IQR)	25 (16-33.5)	13 (9-18)	<0.001
Cost, median (IQR)			
Length of hospital stay	4417(2681-7730)	2249(1557-3114)	<0.001
Laboratory test	1137(906-1319)	549(465-645)	<0.001
Medical imaging	479(159-1177)	130(0.0-185)	<0.001
Non-heparin anticoagulant	896(528-6242)	41(0.0-210)	<0.001
Physician visit	1920(1400-2240)	1760(1440-2080)	0.595
Total	9469(6308-17246)	4640(3985-5791)	<0.001

Table 2: Demographic characteristics of heparin-induced thrombocytopenia case patients and control subjects. HIT=heparin-induced thrombocytopenia; HITT=heparin-induced thrombocytopenia with thrombosis; IQR=interquartile range; SD=standard deviation.

Table 3 summarizes the demographics of the subgroups of case patients. Of the 29 case patients with HIT, eight case patients with HIT were complicated with thrombosis (HITT). Among the eight cases with HITT, three patients developed deep vein thrombosis (DVT), one patient with pulmonary embolism (PE), three patients developed lower limb ischemia and one patient was diagnosed with a stroke. There were no statistical differences between the two subgroups in terms of age and sex. The median LOS of HITT cases was higher than HIT cases but not statistically significant (P=0.079), while the median healthcare cost of HITT was statistical significant compared to HIT cases without thrombosis (P<0.001).

Characteristics	**HIT case patients (n=21)**	**HITT case patients (n=8)**	**P Value**
Age			
Median years, (IQR)	64(57-75)	58(27-68)	0.45
Sex, no. (%)			0.976
Male	8(38.1)	3(37.5)	
Female	13(61.9)	5(62.5)	
Length of hospital stay			
Mean (±SD)	24.3(±13)	31(±9)	0.182
Median (IQR)	21(15-30)	32(21-37)	0.079
Cost, median (IQR)			
Length of hospital stay	3633(2595-5190)	7909(4919-8817)	<0.001
Laboratory test	1276(944-1378)	1062(752-1238)	0.143
Medical imaging	293(0.0-592)	1197(1184-1446)	<0.001
Non-heparin anticoagulant	672(490-970)	9504(7268-11880)	<0.001
Physician visit	1760(1240-2080)	2120(1620-2800)	0.142
Total	7799(5815-10386)	22893(16647-25432)	<0.001

Table 3: Demographic characteristics of cases (n=29). HIT=heparin-induced thrombocytopenia; HITT=heparin-induced thrombocytopenia with thrombosis; IQR=interquartile range. SD=standard deviation.

The total attributable healthcare costs and LOS of HIT patients are summarized in Table 4. All patients, both controls and cases, had an ELISA assay done. All HITT patients were treated with intravenous argartroban as nonheparin anticoagulant, while the majority HIT patients without thrombosis were treated with subcutaneous fondaparinux.

Outcomes	**HIT case patients (n=21)**	**HITT case patients (n=8)**	**All (HIT+HITT) (n=29)**
Total LOS, days			
Median (IQR)	21(15-30)	32(21-37)	25(16-33)
Attributable LOS	8	19	12
Total healthcare cost			
Median (IQR)	7799(5815-10389)	22893(16647-25432)	9469(6308-17246)
Attributable	3159	18256	4829

Table 4: Total attributable length of hospital stay and healthcare cost (US$) associated with heparin-induced thrombocytopenia. HIT: Heparin-induced thrombocytopenia; HITT: Heparin-induced thrombocytopenia with thrombosis; IQR: Interquartile range.

The potential annual healthcare cost savings attributable to LMWH prescribing over UH is illustrated in Table 5. If the total of 16879 patients during the study period who are entitle to received heparin (LMWH or UFH) in KAMC prescribed LMWH instead of UFH a total

healthcare cost saving of $44065would be attributed to lower cases of HIT associated with LMWH.

Variable	Using LMWH	Using UFH
Potential annual patients on heparin	16879	16879
Median length of hospital stay (day)	13	13
Daily cost of heparin (US$)	$10(40mg daily)	$8(5000IU twice daily)
Total annual healthcare cost of heparin	$2,194,270	$1,755,416
Annual no. of HIT patients based on HIT incidence	8	59
Median healthcare cost of HIT	$9469	$9469
Total healthcare cost of HIT/year	$75,752	$558,671
Total annual healthcare cost of heparin plus healthcare cost of HIT	$2270022	$2314087
Potential annual healthcare cost saving attributable to		
prescribing LMWH=$2314087-$2270022=$44065		

Table 5: Potential annual healthcare savings using LMWH. HIT: Heparin-Induced Thrombocytopenia; LMWH: Low-Molecular-Weight-Heparin; UFH: Unfractionated Heparin.

Discussion

A total of 29 newly diagnosed HIT IHhcases during the period of January 1 to December 31, 2013 from our previous study [12] were included along with a total of 141 matched control subjects. The incidence of HIT in this study was 0.05% in patients receiving LMWH (enoxaparin) and 0.35% in those receiving UFH, with an overall incidence of 0.17%. The incidence rate reported in this study is lower than previously published Figures 1-5,7 This study provides the direct medical healthcare costs associated with positive HIT cases and negative HIT subjects at a tertiary healthcare centre in Riyadh, Saudi Arabia. The result showed that the median healthcare cost incurred in the management of positive HIT was significantly more than the healthcare cost incurred in the management of control matched subjects. The increased healthcare cost is primarily due to increased LOS and HIT management. Data on the economic impact of HIT are still limited and focus on the direct healthcare costs. American authors who conducted a retrospective nested case-control study found that admissions that included development of HIT incurred an average healthcare cost of $56,364 compared with $15,231 for admissions without HIT [13]. Another small retrospective case-control analysis found that HIT patients had a 14.5 days increase in LOS, incurring an average loss of $14,387-$20,170 per patient [14]. Similarly, two European studies found a mean incremental healthcare cost of €3500-€9000 with higher costs in surgical patients than in medical patients, and the increased cost was driven by extended LOS and nonheparin anticoagulant [15-16].

The main costs of healthcare elements in this study for the control subjects were the laboratory testing in order to rule out HIT, monitoring platelet count levels and the use of nonheparin anticoagulant. The vast majority of the control subjects received fondaparinux. Only one patient received argatroban for two days, and was then switched to LMWH.

Although it is obvious that the healthcare cost impact of HIT and HITT is large and utilized many healthcare resources, the actual direct healthcare costs attributable to this adverse drug event remain largely unclear. The median healthcare costs incurred in the management of HITT cases were three times greater than the healthcare costs of managing HIT cases. Increased LOS related to the complications of HIT and their management using argatroban as non-heparin anticoagulant were the main elements that led to greater overall healthcare costs in the HITT cases. The median LOS of HITT cases was 11 days more and utilized ICU facilities more than HIT cases. Similarly, a small Canadian study found that healthcare costs incurred in the management of HITT cases were more than seven times greater than the healthcare costs of HIT cases [17].

The use of LMWH instead of UFH in hospitalized patients in KAMC and other healthcare centres in Saudi Arabia could save a lot of resource utilization services. This translates into a healthcare cost saving of $44065/year. Likewise, a retrospective study analyzing the cost of LMWH versus UFH showed that $32,981/year could be saved [13]. In another prospective clinical study, authors analyzed data from patients' registry. They found no difference in LOS, however, overall healthcare costs using UFH were much higher than the healthcare costs using LMWH [18].

One of the limitations of the costing analysis presented in this study was the use of Business Centre data for drug and other resources services pricing. Since our study data was derived in 2013 from a single-centre, the result may not apply to other healthcare centres due to variation in drug and resource utilization services charges.

Conclusion

In this single-centre, retrospective case-control study, the attributable healthcare costs of a case of heparin-induced thrombocytopenia (HIT+HITT) at KAMC was $4829 and was

associated with a significantly longer LOS. The use of LMWH can reduce, but not eliminate, the incidence of HIT.

References

1. Warkentin TE, Chong BH, Greinacher A (1998) Heparin-induced thrombocytopenia: towards consensus. Thromb Haemost 79: 1-7.
2. Warkentin TE (2003) Heparin-induced thrombocytopenia: pathogenesis and management. Br J Haematol 121: 535-555.
3. Jappe U (2006) Allergy to heparins and anticoagulants with a similar pharmacological profile: an update. Blood Coagul Fibrinolysis 17: 605-613.
4. Kelton JG, Warkentin TE (2008) Heparin-induced thrombocytopenia: a historical perspective. Blood 112: 2607-2616.
5. Arepally GM, Ortel TL (2006) Clinical practice. Heparin-induced thrombocytopenia. N Engl J Med 355: 809-817.
6. Warkentin TE (2012) HITlights: a career perspective on heparin-induced thrombocytopenia. Am J Hematol 87 Suppl 1: S92-99.
7. Kelton JG, Arnold DM, Bates SM (2013) Nonheparin anticoagulants for heparin-induced thrombocytopenia. N Engl J Med 368: 737-744.
8. Linkins LA, Dans AL, Moores LK, et al. (2012) Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141: e495S-e530S.
9. Al-Eidan FA (2015) Pharmacotherapy of heparin-induced thrombocytopenia: therapeutic options and challenges in the clinical practices. J Vasc Nurs 33: 10-20.
10. Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, et al. (2012) Clinical features of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thromb Haemost 94: 132-135.
11. Udeh CI, Douglas A, Udeh BL, Hata JS (2013) Heparin induced thrombocytopenia: a clinical and economic review. OA Anaesthetics 1: 3.
12. Al-Eidan FA (2015) Is the Incidence Trend of Heparin-Induced Thrombocytopenia Decreased by the Increased Use of Low-Molecular-Weight-Heparin? Mediterr J Hematol Infect Dis 7: e2015029.
13. Creekmore FM, Oderda GM, Pendleton RC, Brixner DI (2006) Incidence and economic implications of heparin-induced thrombocytopenia in medical patients receiving prophylaxis for venous thromboembolism. Pharmacotherapy 26: 1438-1445.
14. Smythe MA, Koerber JM, Fitzgerald M, Mattson JC (2008) The financial impact of heparin-induced thrombocytopenia. Chest 134: 568-573.
15. Wilke T, Tesch S, Scholz A, Kohlmann T, Greinacher A (2009) The costs of heparin-induced thrombocytopenia: a patient-based cost of illness analysis. J Thromb Haemost 7: 766-773.
16. Elalamy I, Le Gal G, Nachit-Ouinekh F, Lafuma A, Emery C, et al. (2009) Heparin-induced thrombocytopenia: an estimate of the average cost in the hospital setting in France. Clin Appl Thromb Hemost 15: 428-434.
17. Nanwa N, Mittmann N, Knowles S, Bucci C, Selby R, et al. (2011) The direct medical costs associated with suspected heparin-induced thrombocytopenia. Pharmacoeconomics 29: 511-520.
18. Baroletti S, Piovella C, Fanikos J, Labreche M, Lin J, et al. (2008) Heparin-induced thrombocytopenia (HIT): clinical and economic outcomes. Thromb Haemost 100: 1130-1135.