The Facts about Heparin Induced Thrombocytopenia (HIT)

Abstract
This whitepaper addresses the frequently asked questions regarding the occurrence of heparin induced thrombocytopenia (HIT). HIT is an adverse drug reaction caused by a patient's immune response to the presence of heparin. Heparin is frequently used in the care of critically ill patient population as an antithrombotic agent and is often integrated in catheter coatings, including catheters used during intravascular temperature management (IVTM). The incidence of HIT in patients receiving heparin therapy ranges from 0.2 to 3.0%. In addition, IVTM product surveillance data from the manufacturer show a HIT occurrence of 0.0007%. Thus, the benefits of IVTM as a therapy for critically ill patients outweigh the rare risk of HIT, and covalently bonded heparin catheters are likely innocent bystanders in patients who do develop HIT.

Key Takeaways

1) HIT is rare and is generally associated with higher doses of heparin.
2) Heparin is frequently used in the hospital setting, especially in the critical care and resuscitation patient populations, which are prone to thrombus formation.
3) In heparinized catheter coatings, heparin is covalently bound to the coating and acts as an antithrombotic and antimicrobial agent without the release of free heparin.
4) Based on the IVTM catheter manufacturer's product surveillance data, the reported rate of HIT in IVTM patients is 0.0007%, and in IVTM patients without systemic heparinization, no cases of HIT have been reported.

What is HIT?

HIT, or heparin induced thrombocytopenia, is an adverse drug reaction caused by the emergence of antibodies that activate platelets in the presence of heparin[1]. There are two types of HIT which can occur: nonimmune and immune-mediated[2]. Nonimmune HIT, which occurs more frequently, is associated with mild decreases in platelet counts (100,000–150,000/µL) and not considered to be harmful[1-3]. In contrast, immune-mediated HIT occurs less frequently but is associated with very low platelet counts (< 100,000/µL or < 50% of baseline), and patients with immune-mediated HIT are at much higher risk of developing thrombosis[1-3].

How does HIT occur?

The pathophysiology of HIT is likely explained by the formation of an immune complex between free heparin and platelet factor 4 (PF4). Upon the formation of this complex, the body releases antibodies to bind to the complex, first to activate platelets and then subsequently

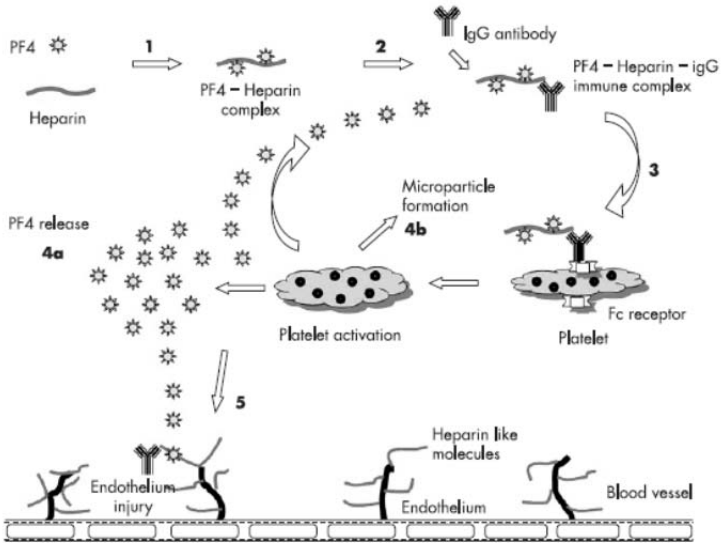

Figure 1. Pathophysiology of HIT. (1) Heparin binds with PF4 and act as immunogens. (2) IgG antibody thus produced forms PF4–heparin–IgG multimolecular complex. (3) The complex then binds via Fc receptor to platelets and activates them (4a) activated platelet releases additional PF4 and (4b) prothrombotic microparticles. (5) Immune complex interacts with endothelial cells and promotes immune mediated endothelial damage.[1]

destroying endothelial cells (see Figure 1). It is also likely that other antigens contribute to this process; however, they have not yet been identified[2]. In immune-mediated HIT, this disruption of platelets can lead to clot formation, potentially evolving to a deep vein thrombosis (DVT) or pulmonary embolism (PE). From a timeline standpoint, HIT usually occurs about 6-12 days after the initiation of heparin therapy[4].

How often is heparin used in the critical care setting?

Heparin use is common in the hospital especially for critical care and resuscitation population, mainly due to the widespread use of endovascular and interventional procedures as well as anticoagulation therapy. For example, patients undergoing diagnostic angiography and aneurysm repair receive thromboprophylaxis with either heparin (5000 IU every 12 hours intramuscularly) or enoxaparin (40 mg daily intramuscularly) after aneurysm repair. During cerebral angiography, the sheath and catheter are constantly flushed with a heparinized saline solution (3000 IU of heparin in 1000 ml of normal saline). Patients who undergo endovascular coil embolization procedures receive a 4000–5000 IU heparin bolus at the beginning of the procedure, followed by a heparin infusion during and for 24 hours after the procedure[5].

What are the risk factors for HIT?

Up to 8% of patients receiving heparin are at risk to develop the HIT antibodies[1]. However, only about 0.2-3.0% on heparin therapy will develop immune-mediated HIT and subsequently 23-52% of these patients may suffer from more serious events such as thrombosis[3,6]. HIT appears to be more common with higher doses of heparin[4]. It is unclear whether previous exposure to heparin increases the likelihood of developing HIT, although multiple exposures to heparin could potentially contribute to a cumulative effect[6]. Moreover, previous studies have shown a greater incidence of HIT with the use of bovine-derived heparin compared to porcine-derived heparin[1,4]. In general, HIT also appears to occur more often with unfractionated heparin (UFH) vs. low-molecular weight heparin (LMWH) as well as in post-surgery patients[1,6-7]. Further study of the UFH and LMWH and the binding properties of heparin with the PF4 complex may lead to the development of better heparin drugs in the future[7].

A meta-analysis by Warkentin et al. also suggests that gender is a risk factor, as the data showed female patients are more likely to develop HIT than male patients[8]. It is possible for individual batches of heparin to have higher incidence of HIT, even when derived from the same source[4]. Another risk factor is the number of interventional procedures such as aneurysm clipping and angioplasty that are performed per patient, as a higher number of these procedures could result in an increase in HIT occurence[6].

How is HIT diagnosed?

The diagnosis of HIT is clinical and is confirmed by laboratory testing. The criteria of HIT can vary, but frequently a diagnosis of HIT includes the following[1]:

- Normal platelet count before the commencement of heparin
- Thrombocytopenia defined as a drop in platelet count by 30% to $<100 \times 10^9$/L or a drop of >50% from the patient's baseline platelet count
- Onset of thrombocytopenia typically 5–10 days after initiation of heparin treatment, which can occur earlier with previous heparin exposure (within 100 days)

- Acute thrombotic event
- The exclusion of other causes of thrombocytopenia
- The resolution of thrombocytopenia after cessation of heparin
- HIT antibody seroconversion

What is the purpose of including heparin in a catheter coating?

Many critically ill patients require a central venous catheter (CVC) for hemodynamic monitoring, pharmacotherapy, and blood sampling. The same patient population is also prone to thrombosis, and thus one could conclude that an antithrombotic agent such as heparin could be bonded directly to a coating applied to a catheter to make it less thrombogenic. A meta-analysis on heparin bonded pulmonary artery catheters showed that clot formation was reduced within 24 hours of catheter insertion[9]. In addition, fibrin formation is considered to be a contributing factor in catheter-related bloodstream infections (CRBI), and thus the use of heparin in catheters has the potential to reduce the rate of CRBI[10].

How is heparin integrated into a catheter coating?

The integration of heparin into the catheter coating requires a manufacturing process which chemically bonds the heparin to the catheter coating. SurModics heparin or hydrophilic coatings utilize a photo activation technology to create an intra-matrix crosslink among the coating components and covalently attaches the coating to the surface of the catheter. The components in the SurModics coating include PVP (polyvinylpyrrolidone) as the main bulk of the coating with photo-linking capability. Added to the PVP are modified heparin derivatives with attached photo-linkable groups as well, achieving the covalent bonds between the heparin components and the coating matrix. The covalent bonds formed between the heparin and the catheter coating are such that the heparin does not dissolve in blood. Subsequently, there is no measureable systemic heparin that detaches from the catheter coating. It is important to note that in catheters used for intravascular temperature management, the heparin used is porcine-derived, which as mentioned earlier, has a lower incidence of HIT[1,4].

What is the incidence of HIT in patients receiving a heparin-coated CVC?

Abdelkafi, et al. conducted a randomized controlled trial of 246 hemato-oncologic patients receiving a CVC to determine if heparin-coated catheters were safe and effective in reducing infection in patients at high risk of developing CRBI[10]. Patients were randomized to receiving either a heparin-coated catheter with 50mL/day of normal saline in a continuous infusion (the heparin-coated group) or a non-coated catheter with a continuous infusion of low-dose unfractionated heparin (the control group). All CVCs were placed in the subclavian vein, and there was no difference in the mean catheter duration between the heparin-coated and control groups (23 vs. 22 days, P=0.8). The results showed a statistically significant reduction in the incidence of CRBI in the heparin-coated group compared with the control group (0.9 events per 1000 catheter-days vs. 3.5 events per 1000-catheter days, P=0.027). There was no incidence of HIT in the trial as measured by the demonstration of heparin-dependent immunoglobulin antibodies, and no difference in the rate of bleeding was observed between the heparin-coated and control groups (6 vs. 7 patients, P=1.00).

What is the incidence of HIT with IVTM catheters?
Post-market surveillance of IVTM catheters based on the manufacturer's internal complaint database shows a HIT rate of 1 out of 140,000 heparin-bonded catheters sold between May 2009 and September 2015 (0.0007%)[11]. In this single report of HIT, the patient was anticoagulated because he had a valvular implant and heparin was delivered. The patient developed HIT and heparin was stopped. Based on the information provided by the site, the HIT event was probably related to the heparin that was administered to the patient and unrelated to ZOLL device. Although underreporting of complaints from hospitals is possible, even with an underreporting rate of less than 1 out of 250 occurrences, the HIT rate would be less than the lowest reported immune-mediated HIT rate of 0.2%.

Does the use of heparin-coated catheters cause HIT?
The use of heparin-coated catheters is unlikely to cause HIT, and two plausible explanations are detailed here. First, the available research conducted on the pathophysiology of HIT was done using free heparin, suggesting that heparin must be free in order to bind to the PF4 complex. When heparin is included in a catheter coating, it is covalently bound to the coating, and thus there is no active free heparin released from the catheter into the bloodstream. Secondly, the amount of heparin bound to a catheter coating is negligible compared to the dose a patient receives from infusions of free heparin; thus it is unlikely that the HIT would be caused by the heparin-coated catheter.

There are few reports in the literature that implicate heparin-coated devices and HIT. Laster et al. reported 12 cases of presumed HIT associated with heparin-coated pulmonary artery catheters[12]. It is important to note that ionically bonded heparin coated catheters, which have a relatively rapid timeframe for heparin leaching due to a weaker bond strength compared to covalently bonded heparin catheters, were used in this study. Furthermore, all of the patients received heparin at the time of insertion of the pulmonary artery catheters. They estimated that approximately 0.4% of their patients with ionically bonded heparin coated pulmonary artery catheters were susceptible to HIT.

In addition, there is a paucity of cases of HIT in the setting of covalent bonded heparin coated intravascular devices. Kasirajan et al. reported an analysis of 27 cases of suspected HIT following covalently bonded heparin-coated vascular grafts[13]. The authors conclude that the HIT observed appeared to be related the systemic administration of heparin, and among the cases in which platelet count recovery was reported after heparin was discontinued, the majority were cases in which the grafts were left in the circulation. The relative paucity of HIT in the setting of heparin-coated devices suggests that these cases may represent delayed-onset HIT, with the presence of the heparin-coated device being merely coincidental[14].

Can heparin-coated catheters continue to be used in patients who develop HIT?
The continued use of a heparin-coated catheter in a HIT patient may depend on the position of the patient on the spectrum of HIT severity. Depending on the severity of the HIT, a clinician may determine that the risk of catheter removal is greater than the risk of HIT symptoms present. Again, the pathophysiology of HIT may be a factor, given that heparin must be free in

order to bind to the PF4 complex, which makes it unlikely that the heparin coated catheter would cause further detriment to the patient.

In addition, the timing of the HIT diagnosis could be a factor for post-cardiac arrest patients. As described earlier, the sequence of events is such that HIT develops 5-10 days after the initiation of heparin therapy[1]. In contrast, the therapeutic hypothermia protocol for post-cardiac arrest typically takes 3-4 days, with the most critical step of cooling taking place within the first 24 hours. In a clinical setting, the diagnosis of HIT usually takes about 24 hours to complete, based on the required laboratory confirmation described earlier. Thus, in most post-cardiac arrest cases, the therapeutic hypothermia protocol would be near completion by the time that HIT would be diagnosed and confirmed.

How should patients who develop HIT be managed?

Treatment recommendations are provided for patients with acute HIT occurring one to two weeks after implantation of a heparin-coated device (Table 1). As previously suggested, these recommendations are based on the rationale that the HIT is related to delayed-onset HIT mechanisms and that the heparin-coated device is likely an "innocent bystander"[14].

Table 1: Suggested Management for a Patient with Acute HIT Occurring One to Two Weeks After Implantation of a Heparin-Coated Device[14]

Anticoagulation

1. Therapeutic-dose anticoagulation with an alternative, nonheparin anticoagulant, aiming for high-therapeutic levels, either:
   a. Indirect factor Xa inhibitor (e.g., danaparoid[a], fondaparinux) with antifactor Xa monitoring (if available); or
   b. DTI (e.g., bivalirudin, argatroban, hirudin)—caution: beware "PTT confounding" due to HIT-associated consumptive coagulopathy or recent use of warfarin; ideally, patients should be monitored by direct DTI levels, if available.
2. Use ancillary coagulation parameters to assess response to therapy (e.g., measure daily D-dimer and fibrinogen levels).[b]
3. Avoid warfarin until thrombocytopenia has resolved (give vitamin K by iv route if HIT is diagnosed only after a vitamin K antagonist has already been given).[c]

Antiplatelet therapy

1. Adjunctive therapy with aspirin and/or clopidogrel.
2. High-dose iv IgG (1 g/kg given twice [one or two days apart]) to interrupt HIT antibody- induced platelet activation.
3. Avoid platelet transfusions.

Surgical considerations

1. Recommend "watchful waiting" *without* device removal.
2. Thromboembolectomy in case of partial or complete obstruction of a heparin-coated vascular graft.

Laboratory investigations for HIT antibodies

1. Refer blood to laboratory that can assess heparin-independent platelet activation by functional (platelet activation) assay (e.g., McMaster Platelet Immunology, Hamilton, Canada; or Ernst-Moritz-Arndt University, Greifswald, Germany).
2. Repeat testing every 5–10 days to document waning of anti-PF4/H immune response (including decrease in heparin-independent platelet-activating properties).

[a]Danaparoid has theoretical advantages in this clinical situation: (a) rapid anticoagulation can be achieved with iv bolus administration; (b) antifactor Xa levels can be measured; (c) high-therapeutic concentrations of danaparoid inhibit HIT antibody-induced platelet activation.
[b]D-dimer levels should decrease, and fibrinogen levels should increase, if satisfactory anticoagulation is being achieved.
[c]Vitamin K antagonists (e.g., warfarin) are contraindicated during the acute phase of HIT treatment because of the risk of precipitating microthrombosis (e.g., venous limb gangrene).
Abbreviations: DTI, direct thrombin inhibitor; HIT, heparin-induced thrombocytopenia; iv IgG, intravenous (high-dose) gammaglobulin; PF4/H, platelet factor 4/heparin; PTT, partial thromboplastin time.

Conclusion

The critically ill patient population is prone to thrombus formation and infection. Heparin is commonly used in this patient population as an antithrombotic and antimicrobial agent, and it

is often integrated into coatings for CVCs and IVTM catheters. The occurrence of HIT is rare in the critical care population, and this is further supported by published literature as well as IVTM product surveillance data. In addition, it is unlikely that the use of covalently bonded heparin catheters causes HIT. Thus, the use of IVTM in the critical care population should be continued as the benefits of providing IVTM therapy greatly outweighs the risk of HIT.

References

1. Ahmed I, Majeed A, Powell R. Heparin induced thrombocytopenia: diagnosis and management update. Postgrad Med J. 2007 Sep; 83(983): 575–582. doi: 10.1136/pgmj.2007.059188.
2. Baroletti SA and Goldhaber SZ. Heparin-induced thrombocytopenia. Circulation. 2006;114:e355-e356. doi: 10.1161/CIRCULATIONAHA.106.632653.
3. Kim GH, Hahn DK, Kellner CP, et al. The incidence of heparin-induced thrombocytopenia Type II in patients with subarachnoid hemorrhage treated with heparin versus enoxaparin. J Neurosurg 110:50–57, 2009.
4. Brieger DB, Mak KH, Kottke-Marchant K, et al. Heparin-induced thrombocytopenia. J Am Coll Cardiol. 1998;31(7):1449-1459. doi:10.1016/S0735-1097(98)00134-X.
5. Kim GH, Hahn DK, Kellner CP, et al. The incidence of heparin-induced thrombocytopenia Type II in patients with subarachnoid hemorrhage treated with heparin versus enoxaparin. J Neurosurg 110:50-57, 2009.
6. Alaraj A, Wallace A, Mander N, et al. Risk Factors for Heparin-Induced Thrombocytopenia Type II in Aneurysmal Subarachnoid Hemorrhage. Neurosurgery 69:1030–1036, 2011. DOI: 10.1227/NEU.0b013e3182284a81.
7. Nguyen T, Greinacher A, Delcea M. Quantitative description of thermodynamic and kinetic properties of the platelet factor 4/heparin bonds. Nanoscale, 2015, 7, 10130.
8. Warkentin TE, Sheppard JI, Sigouin CS, et al. Gender imbalance and risk factor interpretations in heparin-induced thrombocytopenia. Blood Nov 2006; 108:2937-2941. doi:10.1182/blood-2005-11-012450
9. Randolph AG, Cook DJ, Gonzales CA, et al. Benefit of Heparin in Central Venous and Pulmonary Artery Catheters: A Meta-analysis of Randomized Controlled Trials. Chest 1998. 113:1, 165-171.
10. Abdelkafi A, Achour W, Othman TB, et al. Use of Heparin-Coated Central Venous Lines to Prevent Catheter-Related Bloodstream Infection. Journal of Supportive Oncology 2007. 5:6, 273-278.
11. ZOLL internal complaints database.
12. Laster J, Nichols WK, Silver K. Thrombocytopenia associated with heparin-coated catheters in patients with heparin-associated antiplatelet antibodies. Arch Intern Med. 1989. 149:2285-2287.
13. Kasirajan K. Outcomes after heparin-induced thrombocytopenia in Patients with Propaten vascular grafts. Ann Vasc Surg. 2012. 26:802-808.
14. Warkentin T. Heparin-coated intravascular devices and heparin-induced thrombocytopenia. In Heparin-Induced Thrombocytopenia, 5th edition, Warkentin T and Greinacher A, eds. CRC Press, Chapter 20, 2013.