

## Original Article

# Usefulness of Danaparoid sodium in patients with Heparin-induced thrombocytopenia after cardiac surgery

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## ABSTRACT

**Objective:** Thrombocytopenia is a common problem in cardiovascular surgery patients. However, heparin-induced thrombocytopenia (HIT) is a rare but life-threatening complication of prophylaxis or treatment with heparin. Prompt management of HIT with an alternative anticoagulant is necessary due to the extreme risk of thrombotic complications. Therefore, we evaluated the effects of danaparoid in the treatment of HIT in patients with cardiac surgery who are at moderate to high risk of HIT.

**Methods:** A prospective observational study involving 418 postcardiac surgery patients who received unfractionated heparin and low-molecular weight heparin was conducted in an educational tertiary cardiac care hospital in Iran. All patients were assessed for HIT type II based on thrombocytopenia and pretest clinical scoring system, the “4T’s” score. HIT patients were treated with 1500–2500 units intravenous bolus danaparoid sodium followed by 200–400 units/h for a mean of 5 days. Successful response to danaparoid therapy, defined as augmentation in platelet count and improvement of thrombotic events was assessed in all patients treated with danaparoid.

**Findings:** According to pretest clinical score (4T’s), the probability of HIT was high in 14 (3.3%) patients and intermediate in three ones (0.7%). 15 patients with HIT were treated with danaparoid. One death occurred in danaparoid-treated group due to persistent thrombocytopenia. The rest of patients were treated successfully with danaparoid without any major thrombotic complication.

**Conclusion:** According to our data and the previous studies, HIT can be managed prosperously with danaparoid in postcardiac surgery patients. However, with the absence of any increase in platelet count after 3–5 days of danaparoid therapy and/or the occurrence of a new thrombotic event, danaparoid cross-reactivity with heparin should be suspected.

**Keywords:** Cardiac surgery; danaparoid; heparin-induced thrombocytopenia

## INTRODUCTION

Heparin is used frequently for both thrombophylaxis and treatment of thrombotic events in many clinical situations including cardiovascular surgery and invasive procedures, acute coronary syndrome, venous thromboembolism, atrial fibrillation,

peripheral occlusive disease, dialysis and during extracorporeal circulation.<sup>[1]</sup> Heparin-induced thrombocytopenia (HIT) is a serious and potentially life-threatening side effect of heparin which often remains unrecognized in hospitalized patients as a result of common thrombocytopenia in these patients. HIT is an immune response, and it is associated with a risk of thrombosis.<sup>[2]</sup> Up to 8% of patients on heparin will develop heparin-dependent antibodies, but only 1–5% of patients will progress to develop HIT.<sup>[3]</sup> Most often HIT occurs 5–10 days after the administration of heparin; however, the onset of HIT can also be rapid or delayed. In patients received heparin within the past 100 days, HIT may present within the first 3 days or even hours after re-exposure to heparin (rapid-onset HIT).<sup>[4]</sup> Rarely, HIT occurs

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several days to even few weeks after heparin withdrawal (delayed-onset HIT).<sup>[5]</sup>

The recognition of HIT is still a challenging issue. The appropriate management of HIT requires high clinical suspicion, early laboratory assessment, and rapid administration of an alternative anticoagulant.<sup>[6]</sup> When HIT is suspected, the probability of HIT should be estimated using clinical symptoms. Clinical diagnosis is based on pretest clinical score (4T's) which consists of four features: The degree of thrombocytopenia (a drop of platelet count to below  $100 \times 10^9/L$  or a drop of  $>50\%$  from the patient's baseline platelet count), the timing of the onset, the presence of new or progressive thrombosis, and whether an alternative cause of thrombocytopenia is likely.<sup>[7]</sup> This scoring system assesses the probability of HIT as high, intermediate and low.<sup>[8]</sup>

Heparin-induced thrombocytopenia is strongly associated with thrombosis as approximately 40–75% of patients develop thrombosis. Venous thrombosis occurs more often than arterial thrombosis.<sup>[9]</sup> Several studies have shown that HIT is more frequent in postcardiac surgery patients than other settings. Heparin given during cardiac surgery is highly immunogenic as 25–50% of postcardiac surgery patients develop heparin-dependent antibodies during the next 5–10 days. Therefore, this population is at relatively high risk for developing HIT complications.<sup>[10]</sup> Thrombocytopenia may occur secondary to hemodilution and platelet consumption in postcardiac surgery patients. It is usually seen on postoperative days 2–3 and followed by the thrombocytosis (peaking at day 14) and then subsequent return to preoperative baseline by 1 month after surgery. Therefore, thrombocytopenia during the first four postoperative days is rarely attributable to HIT and mostly related to postsurgery thrombocytopenia.<sup>[11]</sup>

Most often, the thrombocytopenia in HIT is of moderate severity (most patients have platelet count between 20 and  $150 \times 10^9/L$ ). Only 10% of patients have reported to present with platelet count  $<20 \times 10^9/L$ . About 10% of patients have platelet count  $>150 \times 10^9/L$  that are recognized either by significant platelet count fall ( $>50\%$ ) or clinical events such as thrombosis or skin lesions.<sup>[9]</sup>

As with other patients, HIT is highly thrombogenic in postcardiac surgery patients. It was revealed that 38–81% of these patients with HIT will develop thrombosis. Although postcardiac surgery patients have a relatively similar frequency of thrombosis to nonsurgical patients, conversely, arterial thrombosis predominates over venous thrombosis in these patients.<sup>[12]</sup> Arterial thrombosis most often affects

large lower-limb arteries and less often cause thrombotic strokes and myocardial infarction.<sup>[13]</sup> HIT is also associated with saphenous graft occlusion after coronary bypass grafting. Venous thromboembolism such as deep vein thrombosis and pulmonary embolism is also common.<sup>[14]</sup>

Treatment of HIT in postcardiac surgery patients is similar to other cases of HIT; discontinuation of heparin or low-molecular weight heparin (LMWH) and initiation of a rapidly acting, nonheparin anticoagulant. For patients with suspected (nonlow pretest probability) or confirmed HIT, heparin should be stopped, and full dose anticoagulation with an alternative anticoagulant commenced. Currently, alternative nonheparin anticoagulants for the treatment of HIT include: Danaparoid (grade 1B), argatroban (grade 1C), lepirudin (grade 1C), fondaparinux (grade 2C), and bivalirudin (grade 2C).<sup>[15]</sup>

Investigations on the use of danaparoid in cardiac surgery show varying results from clots in the bypass circuit or major postoperative bleeding to no complication. Since we have little and temporary access to Food and Drug Administration-approved drugs in our country (argatroban and lepirudin), in this study we evaluated the efficacy of danaparoid in the treatment of HIT in patients with cardiac surgery who are at moderate to high risk of HIT.

## METHODS

A prospective observational study involving 418 postsurgery (coronary artery bypass graft, mitral valve replacement and aortic valve replacement) patients who received unfractionated heparin (UFH) and LMWH for thrombophylaxis was conducted in an educational tertiary cardiac care center of Iran University of Medical Sciences, Tehran, Iran. This study was done from July 2011 to July 2012. The study was approved by the Research Center Committee of Iran University of Medical Sciences.

A thorough history was taken from each patient. Routine platelet count monitoring was done daily during hospitalization. All patients were assessed for HIT based on thrombocytopenia and clinical symptoms.

Two methods were used for the diagnosis of HIT; the pretest clinical score (4T's) [Table 1] and the Naranjo scale.<sup>[8,16]</sup> Further evaluation was performed for the investigation of lower limb arterial and venous thrombosis and pulmonary embolism in patients with suspected (nonlow pretest probability) HIT. All patients were evaluated for gastrointestinal (GI) bleeding.

In patients with moderate to high pretest probability, heparin or LMWH was discontinued, and danaparoid was used as an alternative. Patients were treated with 1500–2500 units intravenous (IV) bolus danaparoid sodium followed by 200–400 units/h for a mean of 5 days.

Response to danaparoid therapy was defined as augmentation in platelet count, improvement of thrombotic events and prevention of the new ones. Anti-Xa monitoring was not done due to unavailability of the test.

All data analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA). A  $P = 0.05$  was used as a cut-off for statistical significance for the test. Comparisons between the percentages of two outcomes (death or improvement) in danaparoid-treated group were done using  $\chi^2$  or Fisher's exact tests.

## RESULTS

According to pretest clinical score (4T's), the probability of HIT was high in 14 (3.3%) patients and intermediate in three ones (0.7%). Using the Naranjo scale, HIT was considered very likely for twelve (2.9%) patients and possible for five patients (1.1%). In 14 patients, HIT occurred within 5–10 days postsurgery. One patient presented with

delayed-onset HIT while the other two experienced rapid-onset HIT. Besides to thrombocytopenia, 14 patients out of 17<sup>th</sup> also developed one of these complications: Lower extremity arterial thrombosis, deep venous thrombosis, pulmonary emboli and GI bleeding. Among these patients presented with HIT, eleven patients received heparin and the other six ones reconceived LMWH in thromboprophylaxis doses. Patient characteristic is summarized in Table 2.

Fifteen patients out of 17 patients were treated with danaparoid. 14 (93%) patients were treated successfully with danaparoid as their platelet count increased to the baseline value, and the thrombosis complications were resolved. One patient in danaparoid-treated group died due to persistent thrombocytopenia. Platelet count not only improved in this patient but also worsened to  $15 \times 10^9/L$  during therapy. Eventually, the patient died due to severe GI bleeding. Two patients did not receive danaparoid as a result of danaparoid shortage, both of which were died. In order to prevent bleeding, platelet transfusion was performed for one patient. Unfortunately, DVT was progressed, and platelet was decreased substantially. Finally, the patient was died as a result of persistent thrombocytopenia. According to the results, about 93% of patients were completely improved in danaparoid-treated group whereas 7% of patients were died. However, the statistical deference

**Table 1: Pretest clinical scoring system (the “4T’s” score) for the diagnosis of HIT**

4T's category	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall 50% from baseline and platelet nadir $\geq 20 \times 10^9/L$	Platelet count fall 30-50% from baseline or platelet nadir $10-19 \times 10^9/L$	Platelet count fall 30% from baseline or platelet nadir $10 \times 10^9/L$
Timing of platelet count fall	Clear onset between days 5 and 10 or platelet fall $\leq 1$ -day, with heparin exposure within 30 prior days	Fall in platelet counts consistent with onset between days 5 and 10 but timing is not clear due to missing platelet counts or onset after day 10 of heparin exposure or fall in platelet counts $\leq 1$ -day with prior heparin exposure (between 30 and 100 days ago)	Platelet count fall within 4 days, without recent heparin exposure
Thrombosis or other squeal	New thrombosis, skin necrosis, or acute systemic reaction after unfractionated heparin exposure	Progressive/recurrent thrombosis or unconfirmed but clinically suspected thrombosis	No thrombosis or thrombosis preceding heparin exposure
Other causes of thrombocytopenia	None apparent	Possible other causes present	Probable other causes present

The 4T's score is assigned by summing the values for each of the four categories. A score of 1, 2, or 3 is considered low; 4 or 5 is considered intermediate; and 6, 7, or 8 is considered high. HIT=Heparin-induced thrombocytopenia

**Table 2: Patient's characteristics, 4T's score, timing of platelet nadir, thrombosis complications, and type of the anticoagulant drug in patients suspected to HIT (n=17)**

Parameters	4T's score		Timing of platelet nadir (post-surgery)			Thrombosis complications	Type of anticoagulant	
	High	Intermediate	<5 days	Within 5-10 days	>10 days		Heparin	Enoxaparin
Number (%) of patients	14 (82)	3 (18)	2 (12)	14 (82)	1 (6)	14 (82)	11 (65)	6 (35)

HIT=Heparin-induced thrombocytopenia

was not significant ( $P = 0.067$ ). Clinical data of patients treated with/without danaparoid are summarized in Table 3.

## DISCUSSION

Heparin-induced thrombocytopenia is a serious and potentially life-threatening side effect of heparin which often remains unrecognized in hospitalized patients.<sup>[2]</sup> Postcardiac surgery patients are at relatively high risk for developing HIT and its serious complications like thromboembolic ones. Furthermore, it was revealed that HIT antibodies and HIT-associated thrombotic events are more frequent in patients receiving UFH than in those treated with LMWH.<sup>[3]</sup> Our data was similar to previous studies in this regard as 65% of patients who developed HIT were treated with UFH versus 35% with LMWH.

Previously, it was thought that stopping heparin is enough for avoiding subsequent thrombosis in isolated HIT (HIT without thrombosis). However, several investigations revealed that 25–50% of patients managed with the heparin cessation alone, developed thrombosis.<sup>[9]</sup> This percent may be higher in postcardiac surgery patients with arterial thrombosis predominance. Thus, in patients strongly suspected to have HIT, heparin and LMWH should be stopped, and an alternative nonheparin anticoagulant should be substituted. Danaparoid, lepirudin, argatroban, bivalirudin, and fondaparinux are reasonable alternative anticoagulants for treating HIT.<sup>[10]</sup>

Danaparoid has been successfully used for the treatment of HIT.<sup>[17]</sup> It is the only drug that its efficacy was established in a prospective randomized trial. Chong *et al.* have shown that danaparoid is more effective than dextran 70 in the treatment of HIT-associated venous and arterial thrombosis.<sup>[18]</sup> In another study, >460 patients with HIT-associated thrombosis were treated with danaparoid with a success rate of over 90%.<sup>[17]</sup> Our study revealed the same success rate as this study (93%). A case report study reported two pregnant women with prosthetic valve who were treated successfully with danaparoid for HIT. Both patients delivered healthy babies.<sup>[19]</sup> A comparison study of danaparoid and lepirudin in heparin-induced thrombocytopenia indicated that the efficacy of therapeutic doses of danaparoid or

lepirudin in preventing death, amputation or new thromboembolic complications do not differ largely, but the risk of bleeding seems to be higher in lepirudin treated patients.<sup>[20]</sup> In this study, we investigated the usefulness of danaparoid in the treatment of HIT after cardiac surgery. According to our results, danaparoid is an appropriate anticoagulant for successful treatment of HIT in postcardiac surgery patients (with a success rate of 93%).

Despite its considerable clinical experience, danaparoid has several disadvantages including a long half-life (25 h), accumulation in renal failure, having no direct antidote and not easily monitored. Kodityal *et al.* reported five HIT patients who developed new thromboembolic complications while receiving danaparoid. Thrombocytopenia not only improved during therapy with danaparoid but also worsened in four patients. Platelet count improved only partially in the other patient. These patients responded relatively dramatical to direct thrombin inhibitors. Possible reasons for danaparoid failure in these patients were assumed to be antithrombin III consumption, insufficiency of low or intermediate doses of danaparoid, and clinically significant cross-reactivity with HIT antibodies.<sup>[21]</sup> High rate of danaparoid failure was reported with doses below 2250 units daily.<sup>[20]</sup> Therefore, for the treatment of strongly suspected HIT patients, therapeutic doses of danaparoid should be administered by the IV route (at least initially).<sup>[10]</sup> Although, a great majority of *in vitro* cross-reactivity of danaparoid with HIT antibodies is clinically irrelevant,<sup>[22]</sup> a number of studies report cases in which clinically relevant cross-reactivity led to unsatisfactory outcomes with danaparoid.<sup>[23]</sup> As a result, with the absence of any increase in platelet count after 3–5 days of danaparoid therapy and/or the occurrence of a new thrombotic event, danaparoid cross-reactivity should be suspected. We assumed that persistent thrombocytopenia was seen in one of our patients may result from danaparoid cross-reactivity with HIT antibodies, a rare complication with danaparoid.

An important issue in the treatment of HIT is that prophylactic platelet transfusion should be avoided in HIT patients without bleeding. The rationale behind this recommendation is that despite low platelet counts in HIT patients, bleeding complications are uncommon.

**Table 3: Clinical data of HIT patients treated with/without danaparoid**

Parameters	Platelet response		New complication	Outcome		P*
	Increase	New fall		Improvement	Death	
Danaparoid treated (n=15)	14 (93)	1 (7)	1 (7)	14 (93)	1 (7)	0.067
Danaparoid not-treated (n=2)	-	2 (100)	2 (100)	-	2 (100)	

Data presented as Number (%) of patients.\*Chi-square or Fisher's exact test. New complication: Progression of thrombosis and/or persistent thrombocytopenia. HIT=Heparin-induced thrombocytopenia

In contrast, the correlation between platelet transfusion and thrombotic events has been reported most of which come from case reports.<sup>[24]</sup> Similar result was seen in our study. While platelet transfusion was administered prophylactically to prevent bleeding in one patient, inadequate posttransfusion platelet increment achieved. The patient experienced no new thrombotic complication, but his previous deep vein thrombosis progressed after platelet transfusion and subsequently led to his death.

Our study serves several limitations such as: Inability to monitor Anti-Xa and unavailability of test for measuring platelet factor 4–reactive HIT antibodies in suspected patients.

Danaparoid may be a less desirable agent in sick ICU patients who may need invasive procedures and may experience bleeding due to co-morbidities and in whom precise monitoring is needed. On the other hand, danaparoid may offer some advantages over direct thrombin inhibitors for less sick HIT patients. HIT can be managed prosperously with danaparoid in postcardiac surgery patients who are at increased risk of HIT-associated thrombotic complications. In order to achieve the best result, adequate doses of danaparoid should be used, and the possibility of clinically relevant antibody cross activity with heparin should be noticed.

## AUTHORS' CONTRIBUTION

All authors contributed in the idea of research, design of study, data analysis and manuscript preparation.

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