# BULLOUS HEMORRHAGIC DERMATOSIS INDUCED BY HEPARIN

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# BULLOUS HEMORRHAGIC DERMATOSIS INDUCED BY HEPARIN: A CASE REPORT

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**Abstract**

**Introduction**: Bullous haemorrhagic dermatosis is a rare clinical disorder which is usually related to a treatment with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), characterized by multiple intra-epidermal haemorrhages distant from the site of injection.

**Case report**: A 62-year-old male patient with coronary heart disease who received heparin treatment experienced several tense, haemorrhagic bullae located on the right arm area, close to the injection site, and followed by the formation of several hematomas on his back trunk 2 days after received UFH. The lesions were regressed after the discontinuation of heparin and supportive topical treatments.

**Discussion**: The lesions in this patient have similar characteristic with heparin-induced skin necrosis and demonstrate thrombocytopenia probably related to heparin. There are some proposed hypotheses of pathophysiology which have included hypersensitivity reaction and idiosyncratic reaction with dose-related reaction. Given the clinically course, the discontinuation of heparin treatment was essential for lesions regression, despite other supportive cares.

**Conclusion**: Heparin-induced skin lesions may indicate the presence of life-threatening heparin-induced thrombocytopenia. An early diagnosis is crucial to enable discontinuation of heparin if required.

*Keyword: low molecular weight heparin, UFH, bullous haemorrhagic dermatosis, hypersensitivity, idiosyncracy, dose-related reaction*

## Introduction

Heparin is potential anticoagulants used in the prophylaxis and management of thromboembolic disorders, including patients with Acute Coronary Syndrome (ACS). On the market today, there are two dosage forms available: the unfractionated heparins (UFHs) and the other named the low-molecular-weight heparins (LMWHs).[1] Previously, several adverse effects of heparin already reported such as heparin related clooting derangement that can caused bleeding issue, heparin related thrombocytopenia (HIT), and several type of cutaneous reactions. These cutaneous side effects may be localized or generalized, vary in form, from allergic reactions (*e.g.,* erythema, urticaria, dermatitis) to a more severe condition named intradermal micro vascular thrombosis associated with heparin-induced thrombocytopenia (HIT).[2] Rarely, there is a type of cutaneous complication, named bullous haemorrhagic dermatosis. Perrinaud *et al*., reported a condition of bullous haemorrhagic dermatosis developed right after heparin injection and manifested clinically in the form of multiple haemorrhagic intraepidermal bullae that developed in the patient's body location that actually far from the heparin injection sites.[2] Mechanism underlying pathogenesis of these lesions is still not completely clear, however some mechanisms are considered as follows, including delayed type (type IV) hypersensitivity response, type II Immune mediated thrombocytopenia, type I allergic reaction, skin necrosis and pustulosis.[3] Epidemiologically, this side effect of heparin is quite rare and not often reported.

Here we reported a case of bullous haemorrhagic dermatosis induced by heparin, and to our knowledge this is the first time reported in Indonesia. Furthermore, we also want to review the current literature regarding this condition and its underlying mechanism.

## Case Illustration

A 62-year-old man with an acute inferior STEMI was admitted to the emergency department due to primary Percutaneous Coronary Intervention (PCI). After undergone the intervention, due to his renal insufficiency condition, he was administered continuous infusion of UFH. Two days after the heparin administration, the patient underwent numerous haemorrhagic bullae that felt painful and tense right on his lower right arm, near the site of heparin injection. He also suffers from several hematomas on his back trunk.

Results of laboratory studies showed a low haemoglobin concentration of 12, 2 g/dl. A decreased platelet count was noticed in 4 days hospitalization, from 478.000/uL in the first day of hospitalization to 196.000/uL. A biopsy specimen of the bullae revealed intra-epidermal bullae with red blood cells, without thrombotic or vascular lytic changes. Depending on the clinical and histopathology findings, heparin-induced bullous haemorrhagic dermatosis was suspected.

Heparin was discontinued and the patient was given normal saline wound dressing twice a day, mupirocin 2% ointment, emollient soothing lotion, and bullae aspirations. Within one week, the bullous haemorrhagic lesions were dried out and improved. The patient was discharged without any recurrence of haemorrhagic bullous lesions.

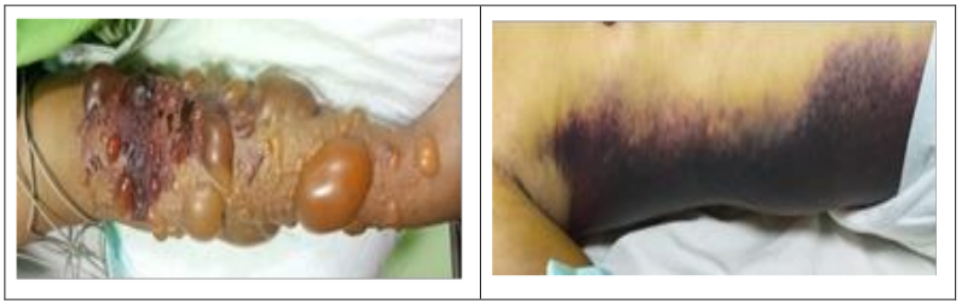

**Figure 1: Clinical presentation of a patient with definite bullous hemorrhagic dermatosis due to heparin administration. (A) On the area of lower right arm, there are multiple bullae and vesicles, some filled with blood (hemorrhagic) and in its perimeter developed clear indurated erythema, (B) Hematomas developed on the back trunk**

**Discussion**

Bullous haemorrhagic dermatosis (BHD) is a blistering eruption typically associated with either unfractionated or low-molecular weight heparins.[4] In 2006, Perrinaud *et al.,* reported the incidence of the first 3 cases of BHD subsequently right after heparin injection given subcutaneously.[2] Since then, along with the more widespread use of heparin injection among thromboembolic patients, the more cases have heparin related side effect been published from all over the world; and until to date, only limited number of cases has been made available on the internet.

Our case related to patient with acute coronary syndrome who were admitted to hospital to receive primary percutaneous coronary intervention (PCI) and given heparin during hospitalization. It is already known from previous reports that there was consistently an immediate chronological relationship between the initiation of heparin products to susceptible individual until the onset of definite bullae formation; the duration is between 5 to 21 days though there were cases with very rapid onset, occured in 2-3 days.[5] In our case, the patient developed painful, nunmerous tense haemorrhagic bullae that vary in size, at his right arm 2 days after heparin adminstration. The most severe lesions were on the cubital fossa, near the injection site of the heparin. The severity of the lesions is inconsistent with other haemorrhagic bullae which have been previously reported, because it was only begin as a clinically benign course with no involvement of pain or even pruritus.[6] Therefore, we also suspect other heparin-induced cutaneous reaction including Heparin-induced skin necrosis (HISN). HISN typically develops with painful erythematous lesion on the injection site within days to weeks of heparin treatment.[7]

Heparin rarely causes diffuse necrosis, and it may signify the life-threatening cutaneous manifestation of heparin-induced thrombocytopenia (HIT), a serious paradoxical hypercoagulable state, as it may cause arterial and venous thromboembolic complications.[8] The incidence of thrombocytopenia was reported ten times higher with UFH than with LMWH.[7] The pathogenesis of this condition is not clear.[9] Since our patient was received weight-based protocol continuous intravenous UFH, we hypothesize, it related to dose-related reaction. In some studies, the underlying mechanism may be due to a condition of idiosyncratic reaction that triggered by heparin or its metabolite[2], in this patient, heparin was the only new drug temporarily associated with the skin eruption. Furthermore, the laboratory test results in our patient showed a 59% decreased platelet count from baseline followed by spontaneous

platelet convalescence occurred in the next 2 days after discontinuation of UFH. The condition of thrombocytopenia occurs in at least 85–90% of patients with HIT and marked by a decrease in platelet count of that can be found in 50% patients and skin lesions occured in 10-20% of patients with HIT.[7] In our patient, HIT occurred within 3 days after start of heparin treatment and it is intriguing that this finding is inconsistent with the characteristic of HIT that occurs between 5-14 days after start of heparin.[7] In our case, we did not include further assessment, such as platelet count monitoring.[10] Repetitive platelet monitoring between days 4 and 14 is highly encouraged, as a pre-emptive option, in all patients who have a risk for heparin-induced thrombocytopenia.[7,11] Specific underlying condition of the patients must also be considered as a potential risk.[12,13]

Even though management of BHD remains unclear, discontinuation of heparin or other possible causes is mandatory and supportive care of the lesions are important in the treatment of this disease.[5,14,15] Although in some severe cases, high dose steroid should be considered.[5] Some clinicians reported similar cases, but even when heparin was kept administered for some time and fortunately, the lesions improved. This improvement maybe due to the natural origin of this disease that it is typically self-limiting.[3]

The weakness of this report lies on not performed direct immunofluorescence, therefore the involvement of complement and immunoglobulin in this haemorrhagic blister formation could not be determined.[16-18]

**Conclusion**

Bullous haemorrhagic dermatosis secondary to heparin treatment has been reported in the literature but is under-recognized in clinical practice. Hence, knowledge of the characteristic clinical features of heparin-induced BHD are important for clinicians, especially if HIT is suspected, as it may lead to serious morbidity and mortality.

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