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Research Article

Clinical Features, Diagnosis, Treatment, and Prognosis of Heparin-Induced Bullous Hemorrhagic Dermatosis

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Background. Heparin-induced bullous hemorrhagic dermatosis (HBHD) is a rare cutaneous adverse effect of heparin and has unclear clinical features. We explored the clinical features of HBHD to provide evidence for the safe use of heparin. *Methods*. We collected HBHD-related case reports for a retrospective analysis by searching the Chinese and English databases from inception to December 31, 2022. *Results*. Seventy-two patients, including 51 males (70.8%), were included, and they had a median age of 71.5 years (range: 21, 94). Low-molecular-weight heparin was used in 62 patients (86.1%), and unfractionated heparin was used in 10 patients (13.9%). The median time for HBHD to appear was 7 days (range: 0.25, 270). Lesions appeared far from the injection site, and the extremities (57 patients, 79.2%) were the most frequently involved site. The blisters were mainly located in the intraepidermal (34 patients, 47.2%), subcorneal (10 patients, 13.9%), and subepidermal (9 patients, 12.5%) regions. Thirty-seven patients (51.4%) had no obvious dermal inflammatory infiltration, and 20 patients (27.8%) had lymphocytic inflammatory infiltration. Sixty-seven patients (93.1%) recovered from their skin lesions after the discontinuation of heparin or despite continuing heparin and at a median treatment time of 14 days (range: 2, 141). *Conclusion*. HBHD is a rare self-limiting disease that occurs far from the injection site. Clinicians should be aware of BHD during the administration of heparin. Heparin can be discontinued or continued depending on the patient's condition.

1. Introduction

Heparin is the most widely used anticoagulant for the treatment and prevention of thromboembolic diseases, including acute coronary syndrome, deep vein thrombosis, pulmonary thromboembolism, and autoimmune diseases, which are associated with an increased risk of thrombosis [1]. The types of heparin are divided into unfractionated heparins (UFHs) and low molecular weight heparin (LMWH), which act as anticoagulants by activating antithrombin III [2]. Bleeding is the most common treatment complication, and other complications include heparin-induced thrombocytopenia, liver injury, osteoporosis, and skin reactions [3]. Adverse skin reactions can include erythema, urticaria, hematoma at the injection site, skin necrosis, contact dermatitis, and intradermal microvascular thrombosis [4]. Bullous hemorrhagic dermatosis (BHD) is a rare and underrecognized cutaneous complication of heparin therapy that occurs in a different area than the injection site. The knowledge regarding heparin-induced bullous hemorrhagic dermatosis (HBHD) is based mainly on case reports. The clinical features, treatment, and prognosis of HBHD patients remain unclear. Here, we discuss the clinical features of HBHD to provide evidence for the rational use of heparin.

2. Methods

2.1. Retrieval Strategy. We collected case reports, case series, and clinical studies of HBHD by searching the PubMed, Embase, Cochrane Library, Wanfang, China National Knowledge Infrastructure, and China Science and Technology Journal Database databases. The retrieval period was from the establishment of the database to December 31, 2022. The search terms included heparin, unfractionated heparins, low molecular weight heparin, enoxaparin, tinzaparin, bemiparin, dalteparin, reviparin, anticoagulants, hemorrhagic bullous dermatosis, hemorrhage, blisters, and bullae.

2.2. Inclusion and Exclusion Criteria. HBHD-associated patients were included. Reviews, mechanistic studies, duplicates, animal studies, systematic reviews, and meta-analyses were excluded.

2.3. Data Collection. We designed tables and extracted patient information, including nationality, sex, age, heparin type, administration regimen, medical history, concurrent medications, clinical manifestations, laboratory tests, histopathology, direct immunofluorescence, treatment, and prognosis.

2.4. Statistical Analysis. Statistical analysis was performed using SPSS 22 software. Count data are represented by *n* (%), and continuous data are represented by median values (minimum and maximum).

3. Results

3.1. Basic Characteristics. Seventy-two patients from 49 studies were included, with a median age of 71.5 years (range: 21, 94) (Table 1). These patients included 51 men (70.8%), mainly from Spain (23 patients, 31.9%) and America (20 patients, 27.8%). Thirty-seven patients (51.4%) received other drugs at the same time, and 28 patients (38.9%) received anticoagulants or antiplatelets simultaneously. Forty-eight patients (66.7%) received heparin to treat thrombotic disease, and 24 patients (24.3%) received heparin to prevent thrombotic disease.

3.2. Heparin Management. Enoxaparin (53 patients, 73.6%) was the most commonly used drug for HBHD, and the other commonly used drugs included UFH (10 patients, 13.9%) and tinzaparin (in 4 patients, 5.6%) (Table 2). Sixty-three patients (87.5%) received subcutaneous injections of the drugs, and 9 patients (12.5%) received intravenous injections of the drugs. The median time to lesion onset was 7 days (range 0.25, 270) after exposure to heparin. Nine patients (12.5%) were previously given heparin.

3.3. Clinical Characteristics. The clinical characteristics of the 72 patients are summarized in Table 3. The main regions that the lesions were located were the extremities (57 patients, 79.2%), hands (19 patients, 26.4%), abdomen (12 patients, 16.7%), trunk (10 patients, 13.9%), ankles (9 patients, 12.5%), and feet (9 patients, 12.5%). The back (3 patients, 2.8%), face (3 patients, 2.8%), groin (2 patients, 2.8%), and chest (2 patients, 2.8%) regions were also frequently involved. The rare lesion sites were the neck (1 patient, 1.4%), scalp (1 patient, 1.4%), and oral mucosa (1 patient, 1.4%). Some patients experienced cutaneous pruritus (3 patients, 4.2%) and pain (2 patients, 2.8%).

3.4. Laboratory Tests. Of 56 patients, 50 (69.4%) had normal platelet counts. Among 53 patients, 39 (54.2%) had normal coagulation parameters and 8 (11.1%) had a prolonged activated partial thromboplastin time. Twenty-two patients (30.6%) had a normal international normalized ratio. The test results for antiheparin platelet factor 4 antibodies were negative in six patients (8.3%).

3.5. Histopathology. Histopathological analysis of 57 patients revealed the presence of erythrocytes and fibrin in the intraepidermal (34 patients, 47.2%), subcorneal (10 patients, 13.9%), subepidermal (9 patients, 12.5%), intracorneal (1 patient, 1.4%), intradermal (1 patient, 1.4%), and intraepidermal/subepidermal (1 patient, 1.4%) bullae. No obvious inflammatory infiltration was observed in the dermis of 37 patients (51.4%). Lymphocytic inflammatory infiltrates were present in 11 patients (15.3%). Eosinophils were found within the dermal inflammatory infiltrate in 2 patients (2.8%), neutrophils were found within the dermal inflammatory infiltrate in 2 patients (2.8%), monocytes were found within the dermal inflammatory infiltrate in one patient (1.4%), a mixture of eosinophils and neutrophils were found within the dermal inflammatory infiltrate in 3 patients (4.2%), and lymphocytes and eosinophils were found within the dermal inflammatory infiltrate in one patient (1.4%). Direct immunofluorescence (DIF) did not detect immunoreactants in 18 out of 19 patients.

3.6. Treatment and Prognosis. The treatment and prognosis of the 72 HBHD patients are summarized in Table 4. Forty-four patients (61.1%) stopped using heparin, 20 patients (27.8%) continued to use heparin, the dose of heparin was reduced in 1 patient (1.4%), and the treatment details were not described in 7 patients (9.7%). Twenty-one patients (29.2%) switched to other anticoagulants, including oral anticoagulants (15 patients, 20.8%), fondaparinux (2 patients, 2.8%), and another LMWH (4 patients, 5.6%). Sixty-seven patients (93.1%) recovered completely, and the outcomes of 5 patients (6.9%) were not reported. The causes of the deaths of four patients were not related to BHD. In 46 patients, the median recovery time of the skin lesions was 14 days (range: 2, 141). One patient experienced BHD again after reusing enoxaparin following improvement in the patient's BHD.

4. Discussion

BHD is a nonpruritic, tensive, hemorrhagic bullosa that can develop on normal skin. HBHD occurs at a distant location from the heparin injection site and usually appears 7 days

Table 1: Basic characteristics of 72 patients with HBHD.

Parameters		Result
Age	Years	71.5 (21.94)[b]
Sex	Female	21 (29.2%)
	Male	51 (70.8%)
Country	Spain	23 (31.9%)
	USA	20 (27.8%)
	France	8 (11.1%)
	Turkey	5 (6.9%)
	Austria	4 (5.6%)
	India	4 (5.6%)
	Indonesia, Korea, Portugal, Brazil, Qatar, Tunisia, Canada, China	1 (1.4%)
Medical history	Ischemic heart disease	23 (31.9%)
	Atrial fibrillation	15 (20.8%)
	Cancer	15 (20.8%)
	Pulmonary thromboembolism	13 (18.1%)
	Hypertension	11 (15.3%)
	Deep vein thrombosis	10 (13.9%)
	CHF, DM, COPD	6 (8.3%)
	Hypercholesterolemia, craniocerebral tumor	4 (5.6%)
	Aortic valve replacement	3 (4.2%)
	Hypothyroidism, obesity, ESRD, amyloidosis, HIV, cardiomyopathy, ischemic stroke, SVCS hepatitis B/C, chylothorax, lepromatous leprosy, UC, BPH, GCA, KT, SHPT, PH, PAH, bullous pemphigoid, pericarditis, atrial thrombus, occlusion of retinal arteries	2 (2.8%) / 1 (1.4%)
Concurrent medications (37)[a]	Antiplatelet drugs/anticoagulant drug	28 (38.9%)
	Statins	7 (9.7%)
	Steroids, nitrate esters, ACEI	5 (6.9%)
	Diuretic, amiodarone, hypoglycemic drugs	4 (5.6%)
	PPI, beta receptor blocker	3 (4.2%)
	Diltiazem, paracetamol, codeine	2 (2.8%)
	Levetiracetam, eplerenone, mexiletine, metolazone, daratumumab, trimetazidine, escitalopram, ceftazidime, etizolam, levocarnitine, emtricitabine, tenofovir, efavirenz, buflomedil, tamsolusin, voriconazole, calcitonin, hydralazine, levothyroxine, venlafaxine, escitalopram, thyroxin, amoxycillin-clavulanic acid	1 (1.4%)
Indication	Treatment	48 (66.7%)
	Prevention	24 (24.3%)

ACEI, angiotensin-converting enzyme inhibitor; AT, atrial thrombus; BPH, benign prostatic hyperplasia; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ESRD, end-stage renal disease; GCA, giant cell arteritis; HIV, human immunodeficiency virus; KT, kidney transplantation; SHPT, secondary hyperparathyroidism; PH, portal hypertension; PAH, pulmonary artery hypertension; SVCS, superior vena cava syndrome; UC, ulcerative colitis. [a]Represents the number of patients out of the 72 who had information available for this particular parameter. [b]Median (minimum-maximum).

Table 2: Heparin administration regimen in 72 patients with HBHD.

Parameters		Result
Heparin type	Enoxaparin	53 (73.6%)
	Tinzaparin	4 (5.6%)
	Bemiparin	1 (1.4%)
	Dalteparin	1 (1.4%)
	Reviparin	1 (1.4%)
	UFH	10 (13.9%)
	LMWH	2 (2.8%)
Drug delivery route	Intravenously	9 (12.5%)
	Subcutaneously	63 (87.5%)
Time to lesions (70)[a]	Days	7 (0.25, 270)[b]
Daily dose		41 (56.9%)
Previous heparin treatment		9 (12.5%)

UFH, unfractionated heparin; LMWH, low molecular weight heparin. [a]Represents the number of patients out of 72 for whom information regarding this particular parameter was provided. [b]Median (minimum-maximum).

Table 3: Clinical features of 72 patients with HBHD.

Parameters		Result
Symptoms (5)[a]	Pruritus	3 (4.2%)
	Pain	2 (2.8%)
Size (24)[a]	Mm	1–70
Location of lesions (71)[a]	Extremities	57 (79.2%)
	Hands	19 (26.4%)
	Abdomen	12 (16.7%)
	Trunk	10 (13.9%)
	Ankles	9 (12.5%)
	Feet	9 (12.5%)
	Back	3 (4.2%)
	Face	2 (2.8%)
	Groin	2 (2.8%)
	Chest	2 (2.8%)
	Neck	1 (1.4%)
	Scalp	1 (1.4%)
	Oral mucosa	1 (1.4%)
Laboratory test		
Platelet count (56)[a]	Normal	50 (69.4%)
	Slight thrombocytopenia	6 (8.3%)
Coagulation parameters (53)[a]	Normal	39 (54.2%)
	Prolonged APTT	8 (11.1%)
	Elevated prothrombin time	4 (5.6%)
	Decreased prothrombin time	3 (4.2%)
	Elevated fibrinogen level	2 (2.8%)
INR (24)[a]	Normal	22 (30.6%)
	Elevated	2 (2.8%)
H-PF4 (7)[a]	Negative	6 (8.3%)
	Positive	1 (1.4%)
Anti-Xa (4)[a]	Normal	2 (2.8%)
	Slightly elevated	2 (2.8%)
Histopathology (57) [a]		
Level of split	Intraepidermal	34 (47.2%)
	Subcorneal	10 (13.9%)
	Subepidermal	9 (12.5%)
	Intraepidermal/subepidermal	1 (1.4%)
	Intracorneal	1 (1.4%)
	Intradermal	1 (1.4%)
	Fibrinoid necrosis	1 (1.4%)
Inflammatory infiltrate (20)[a]	Lymphocytic	11 (15.3%)
	Neutrophil and eosinophils	3 (4.2%)
	Eosinophils	2 (2.8%)
	Neutrophils	2 (2.8%)
	Lymphocytic and eosinophilic	1 (1.4%)
	Monocyte	1 (1.4%)
DIF (19)[a]	Negative	18 (25.0%)
	C3 deposition of dermoepidermal junction	1 (1.4%)

APPT, activated partial thromboplastin time; DIF: direct immunofluorescence; H-PF4, heparin-platelet factor 4; INR, international normalized ratio.
[a]Represents the number of patients out of 72 for whom information regarding this particular parameter was provided.

after heparin administration. HBHD is found mainly in the extremities, hands, and abdomen and is rarely accompanied by itching and pain. It should be noted that the oral mucosa may also be involved [5]. HBHD lesions can vary in size from 1 mm to 70 mm and appear as black hemorrhagic blisters. HBHD is age independent and can occur at any age. Nearly all heparins can cause HBD, and enoxaparin is the most common cause of HBHD, which may be related to the fact that enoxaparin is the most commonly used low molecular weight heparin [6].

Male sex can be a risk factor for HBHD, and 70% of the people with HBHD are male. A higher heparin dose may not be a risk factor for HBHD. BHD occurred in patients receiving both therapeutic and prophylactic doses of heparin, with one patient receiving only one dose of enoxaparin [7]. In this study, we found that 39% of the patients were also

Table 4: Treatment and prognosis of 72 patients with HBHD.

Parameters		Result
Treatment	Discontinued	44 (61.1%)
	Continued	20 (27.8%)
	Unspecified	7 (9.7%)
	Dose reduction	1 (1.4%)
	Switch to other anticoagulants	21 (29.2%)
	Oral anticoagulant	15 (20.8%)
	Fondaparinux	2 (2.8%)
	Other low molecular weight heparin	4 (5.6%)
	Rechallenge	1 (1.4%)
Outcome	Recovery	67 (93.1%)
	Unspecified	5 (6.9%)
	Death	4 (5.6%)
Time to resolution (46)[a]	Days	14 (2, 141)[b]

[a]Represents the number of patients out of 72 for whom information regarding this particular parameter was provided. [b]Median (minimum-maximum).

taking other anticoagulants or antiplatelet drugs. The combination of these drugs increases the tendency to bleed [8]. Other drugs given concomitantly may also cause bullae, e.g., warfarin, paracetamol, and furosemide [9–11].

It is not clear whether there is a cross-reaction between UFHs and LMWH. One patient developed BHD after enoxaparin administration, but UFHs could be used safely [12]. While there may be cross-reaction between low molecular weight heparin, one patient developed BHD after using enoxaparin and one patient also developed hemorrhagic blistered skin disease after continuing to use tinzaparin [13]. LMWH may also cross-react with fondaparinux. One patient developed BHD after using tinzaparin, but the patient was switched to fondaparinux after the patient developed another outbreak of BHD [14]. The cross-reaction between fondaparinux and LMWH may be a result of their identical five-sugar sequence structures. Heparin induces the production of platelet-aggregating immunoglobulins that can lead to thrombocytopenia, skin necrosis, and thrombotic events. Obesity, diabetes, and broad-spectrum antibiotic therapy are risk factors for these complications [15].

Skin biopsies and DIFs have played an important role in distinguishing BHD from other skin lesions, such as bullous pemphigoid, bullous pemphigoid drug eruption, bullous erysipelas, and necrotizing fasciitis. Biopsy of BHD lesions reveal congested vesicles and blisters within the epidermis or intraepidermally but no vasculitis or capillary thrombosis. Approximately, 51% of the patients had no inflammatory infiltration in their tissue biopsies, and infiltration of inflammatory cells, such as lymphocytes, eosinophils, and neutrophils, were only visible in a few patients.

The pathogenesis of HBHD has not been elucidated. The skin lesions in this condition are far from the injection area, which suggests that the drug reaction may be a systemic rather than a local response. Heparin-induced skin injury is currently believed to involve five major mechanisms, including delayed hypersensitivity, immune-mediated thrombocytopenia, type I anaphylaxis, skin necrosis, and impetigo [16, 17]. Heparin-induced bleeding tendencies can be ruled out as a cause of the BHD in these HBHD patients based on their normal coagulation function and platelet counts. Immune-mediated heparin-associated thrombocytopenia (HIT) and delayed hypersensitivity can be further ruled out by the absence of HPF4 antibodies and intraepidermal/subepidermal bulla-negative DIF test results. The DIF in one patient showed that C3 was strongly positive at the dermoepidermal junction, possibly due to underlying bullous pemphigoid [18]. Perrinaud et al. suggested that this mechanism may be due to a particular reaction, but the real cause remains unclear [19].

An optimal treatment for BHD is not available. Most patients with BHD fully recovered after heparin discontinuation. Some patients have gradually recovered from BHD despite the continuation of heparin. The median time to resolution of bullous lesions was 2 weeks. One HBHD patient with severe hemorrhagic rupture experienced BHD recurrence after a reintroduction of enoxaparin [18]. The continued use of heparin may be a risk factor for the severity of BHD [20–22]. Nevertheless, further research is needed to determine which conditions can still be treated with heparin and which ones that heparin needs to be discontinued. Steroids may be an option in patients with severe hemorrhagic bullous lesions [19].

5. Limitations

This study has several limitations. First, the data are based on case reports and series that contain more unknown factors than those of controlled studies. Second, not all the literature provided complete clinical data; for example, only 57 patients underwent skin biopsies. Third, the number of included patients was small, and more studies are needed to clarify the risk factors and optimal treatment for HBHD. Finally, whether different types of BHD are induced by different heparins is important for protocol replacement.

6. Conclusions

In summary, HBD is a rare adverse event of heparin that is curable with either continuation or suspension of heparin therapy. Clinicians and pharmacists should inform patients

of the possible occurrence of HBHD and monitor patients carefully during heparin therapy. The clinician should decide whether to continue with heparin or switch to oral anticoagulants based on the patient's situation.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Chunjiang Wang, Jian Zhang, and Liping Peng conceptualized and designed the study, performed analysis and interpretation, and reviewed the manuscript. Ronghui Li, Hanqing Zeng, Zuojun Li, Chunjiang Wang, Jian Zhang, and Liping Peng wrote, revised, and retrieved the data. All the authors have read and approved the final manuscript.

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