

ORIGINAL ARTICLE

Clinical Allergy

Low incidence of heparin-induced skin lesions in orthopedic surgery patients with low-molecular-weight heparins

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Summary

Background: Heparins are widely prescribed for prevention and therapy of arterial and venous thromboembolic diseases. Heparin-induced skin lesions are the most frequent adverse effect of subcutaneous heparin treatment in non-surgical patients (7.5%–39.8%); no data exist on surgical patients. Commonly, they are due to a delayed-type hypersensitivity reaction (DTH), but may also be a manifestation of life-threatening heparin-induced thrombocytopenia (HIT). Lesions of both entities resemble initially. The risk of HIT is highest among heparin-anticoagulated orthopedic surgery patients.

Objective: To determine incidence and causes of heparin-induced skin lesions in major orthopedic surgery patients.

Methods: In a prospective cohort study, consecutive patients with subcutaneous low-molecular-weight heparin (LMWH) treatment were examined for cutaneous adverse effects. Further diagnostics (skin biopsy, clinical/laboratory assessment for thrombosis, bleeding, HIT, cross-allergies) were performed.

Results: Six of 316 enrolled patients (1.9%; 95% CI: 0.4%–3.4%) developed heparin-induced skin lesions. All were caused by a DTH reaction, and none was due to HIT or other rare heparin-associated skin diseases. Therapeutic use (dosage) of LMWH was identified as only risk factor (odds ratio: 3.1, 95% CI: 1.4–4.9; $P = .00141$). In addition to DTH, 5 thromboembolic, 4 major bleeding complications but no cases of HIT or cross-allergies were observed.

Conclusions and Clinical Relevance: Orthopedic surgery patients have—unlike non-surgical patients—a low risk for heparin-induced skin lesions during LMWH treatment; all lesions were due to a DTH reaction. The risk for DTH differs considerably between individual patient cohorts. No association with HIT was observed. These data help to tailor anticoagulatory treatment individually and to increase patient safety.

KEYWORDS

delayed-type drug hypersensitivity reaction to heparin, DTH, heparin, heparin-induced delayed-type hypersensitivity reaction, heparin-induced thrombocytopenia, HIT, low-molecular-weight heparin, orthopedic surgery, skin

1 | INTRODUCTION

Skin lesions are frequent adverse reactions during subcutaneous heparin treatment. While many causes have been described for heparin-induced skin lesions, they most commonly result from delayed-type hypersensitivity (DHT) reactions.¹⁻³ Prospective epidemiological investigations showed that 7.5% of medical patients treated with low-molecular weight heparins (LMWH) develop a DTH reaction.⁴ In obstetric patients, heparin-induced skin lesions were observed in 29%-40% of the patients. Albeit the cause of these reactions has not been determined, they are most likely caused by a DTH reaction to heparins.^{5,6} Recent findings from our group support these observations of a high incidence of DTH responses to heparins in a prospective cohort of obstetric patients; that is, 19.8% of patients developed a DTH reaction to heparin.⁷ This may point towards a distinct risk to develop DTH responses in different patient populations. On the other hand, the second most frequent reason for skin lesions is life-threatening immune heparin-induced thrombocytopenia (HIT).^{1,8-10} This complication occurs mostly in the subcohort of orthopedic and cardiovascular surgery patients rather than in medical or obstetric patients.¹¹⁻¹⁴ Because currently there are no data available on heparin-induced skin lesions in patient populations other than medical or obstetric cohorts, and skin lesions in surgical patients—due to the higher incidences of HIT in these patients—are more likely to be associated with HIT,¹⁵ we prospectively evaluated the incidence and causes of heparin-induced skin lesions in orthopedic surgery patients treated with LMWH.

Of note, initial HIT-associated skin lesions resemble clinically DTH reactions to heparins; therefore, anticoagulation must be switched immediately to a non-heparin anticoagulant, that is danaparoid, lepirudin, argatroban, fondaparinux.¹⁶ Contrariwise, DTH reactions are not life-threatening conditions but require switch to another heparin or fondaparinux as generalized reactions may occur, although cross-allergies among different heparins are observed in >30%.¹

2 | MATERIALS AND METHODS

2.1 | Study cohort

In-patient orthopedic surgery patients at the Department of Trauma and Orthopedic Surgery at the Goethe University Hospital Frankfurt were screened for study eligibility. Patients aged 18 years or older with a prophylactic or therapeutic indication for subcutaneous LMWH treatment for a minimum of 7 days⁴ following major orthopedic surgery were included. Patients with a history of HIT, allergic reactions to heparin, pre-existing skin disorders involving possible heparin injection sites and patients with immunosuppressive therapies or immunodeficiencies were excluded. Investigation and procedures were approved by the ethics committees of the Goethe University Frankfurt and were registered at ClinicalTrials.gov (NCT00510432). The study was performed in accordance with the Declaration of Helsinki.

2.2 | Study procedures

Prior to study enrolment, written informed consent for study participation was obtained from each patient. After inclusion, each patient's data regarding age, sex, indication for admission, type of surgical procedure and previous exposure to subcutaneous anticoagulants were recorded. Female patients were asked whether they were pregnant, were taking hormonal contraceptives or hormonal replacement therapy. From each patient's clinical records information about the patient's current anticoagulation therapy (preparation, duration, dosage, change or switch of heparin therapy), height and weight (to calculate body mass index) were obtained. A clinical examination of the heparin injection sites as well as a full-body examination of the skin was performed 2-3 times before discharge. If a heparin-induced skin lesion was identified (based on changes of any aspects of subjectively stated symptoms by the patient, eg itching, or of skin colour or texture when compared to the condition before heparin exposure), a second investigator examined the patient. Next, further diagnostic workup was performed including skin biopsy for hematoxylin/eosin staining, platelet count monitoring, clinical pre-test probability assessment for underlying HIT (4Ts score),¹⁷ heparin-induced platelet activation test (HIPA) and enzyme-linked immunosorbent assay (ELISA) to detect antiplatelet factor 4 (PF4)/heparin antibodies as described elsewhere.⁴ We refrained from allergologic testing due to a relatively low sensitivity and specificity we found in a previous study.¹⁸ Any investigations that needed to be repeated to confirm the diagnosis were performed 1-3 weeks later. Biopsy samples were obtained from suspected skin lesions under local anesthesia with Scandicain 1%. The samples were stained with hematoxylin/eosin. A DTH reaction to heparin was diagnosed based on history, clinical presentation and histology, characterized by perivascular infiltrates of lymphocytes and eosinophils.¹⁸ HIT was diagnosed based on clinical presentation (4Ts score ≥ 4 points) and positive laboratory HIT diagnostics.¹⁹ The diagnosis would be corroborated further, if the skin lesions presented as necrosis or progressed towards necrosis, and/or histology showed thrombotic occlusions of dermal vessels,^{3,19,20} because there are hardly any non-HIT explanations for the presence of necrotizing skin lesions at heparin injection sites.³ However, necrosis was not considered an absolute prerequisite for diagnosis of HIT, because early cutaneous erythematous reactions due to HIT and DHT may look similar.¹ Histologic characteristics indicating other differential diagnoses were documented as well.¹ Because all patients with heparin-induced skin lesions underwent clinical pre-test probability assessment for underlying HIT using the 4T's score,¹⁷ platelet count levels and diagnostic procedures to detect thromboembolic complications, for example vascular ultrasound, phlebography, CT scans, were analysed as well. To rule out any HIT-associated thromboembolic complications, patients with heparin-induced skin lesions were clinically screened according to the Wells score²¹ for DVT with subsequent ultrasound assessment if indicated.

Indication for and selection of heparin therapy, and decision to switch anticoagulant therapy were made by the treating physicians.

Results of this subcutaneous provocation in case of continued treatment and switch of therapy were recorded. The following heparins were used by the treating physicians: certoparin sodium (Novartis, Nuernberg, Germany), enoxaparin sodium (Sanofi-Aventis, Frankfurt, Germany) and nadroparin calcium (GlaxoSmithKline, Munich, Germany).

Furthermore, secondary safety outcome parameters of all patients—with or without skin lesions—(thromboembolic complications, bleedings, HIT, blood transfusions, hemoglobin levels) were documented at inclusion and before discharge of the patient. Major bleeding episodes were defined according to the criteria of the International Society on Thrombosis and Haemostasis (ISTH) for surgical patients.²²

In case of bleeding complications, serum creatinine levels, age, body weight were used to determine glomerular filtration rates (GFR) by Cockcroft Gault in order to associate bleeding complications with possible bioaccumulation during heparin use, if heparin levels were not measured by chromogenic anti-factor Xa assays.

2.3 | Statistics

Sample size was calculated using Bias 8.4.6 software (Epsilon, Hochheim Darmstadt, Germany). A sample size of at least 312 patients was calculated to determine the incidence of heparin-induced skin lesions with a precision of at least $\pm 1.5\%$ and a confidence of 0.95. Age, BMI, duration of exposure and time of onset of skin lesions during heparin therapy were calculated and expressed as the mean $\pm$ SD or median and range. The open-source software R (www.r-project.org) was used for further statistical analyses. Unadjusted odds ratios including 95% confidence intervals were calculated by logistic regression analysis on single covariates. To determine covariates that are important to predict the development of DTH, unbiased random forest importance analysis using R package cforest (a) was used. A logistic regression model combining the covariates determined by random forest importance was further optimized in a step-wise manner to minimize Akaike's information criterion (AIC). The influence of covariates was assessed with a likelihood-ratio test each.

3 | RESULTS

We screened a total of 336 patients. Of those, 316 patients (94.0%) could be included into the study. Reasons for the non-inclusion of 20 patients were no or minor surgery ($n = 9$), missing informed consent due to dementia ($n = 5$) or insufficient language proficiency ($n = 2$), heparin therapy < 7 days ($n = 2$), and refusal to study participation ($n = 2$). In most patients, heparins were administered as post-operative thrombosis prophylaxis (295/316; 93.4%). Fourteen of 316 patients (4.4%) had a therapeutic indication for heparin therapy, and in the remaining 7 patients (2.2%), there was a switch from a prophylactic and therapeutic dose of heparin due to suspected or confirmed VTE. In the majority of patients (168/316; 53.2%), nadroparin

was used as initial anticoagulant, in 119 of 316 patients (37.7%) enoxaparin. In 28 of 316 patients (8.9%) and in 1 of 316 patients (0.3%), a combination of nadroparin and enoxaparin, and nadroparin and certoparin, respectively, was used as an anticoagulant. Further data on basic patient characteristics and heparin treatment are shown in Tables 1 and 2.

3.1 | Patients with skin reactions

We observed heparin-induced skin lesions in 6 of the 316 patients (Table 2), amounting to an incidence of 1.9% (95% CI: 0.4%-3.4%). Five patients with cutaneous reactions to heparins showed erythematous lesions that were limited to the injection sites, and 4 of these patients also reported itching (Figure 1). One patient reported only strong itching in the areas of injection 5 days after start of therapy without erythematous changes. Secondary generalization of skin lesions was not observed in any of the patients. In none of the cases, skin lesions progressed towards necrosis, and in all 6 skin biopsies, a lymphocyte dermal infiltration with a varying degree of additional eosinophil infiltration with the absence of microthromboses in dermal vessels, which would be suggestive of underlying HIT, was observed (Figures 1 and 2, Table 3). Therefore, a DTH response as cause of the heparin-induced skin lesions based on clinical and histologic features was diagnosed in all 6 patients.

In detail, patient #1 received VTE prophylaxis with nadroparin initially for spondylodesis that was switched to enoxaparin postoperatively. Due to pulmonary embolism, anticoagulation was switched to a therapeutic dose of enoxaparin. Skin lesions developed 70 days after start of anticoagulation, treatment was alternated to certoparin 6 days later. Skin lesions were regressive thereafter. In patient #2, the DTH response was elicited by prophylactic nadroparin, which was switched to a therapeutic dose of nadroparin due to suspected DVT. Erythematous skin lesions developed on day 8 after the initiation of anticoagulation. Heparin was switched to a prophylactic dose of fondaparinux 4 days later (on day 12) after DVT had been ruled out. Fondaparinux was then maintained for 9 days, and it was well tolerated while skin lesions were completely regressive. In patient #3, skin lesions developed during VTE prophylaxis with nadroparin on day 10. Treatment was discontinued on day 13 because it was not indicated anymore and skin lesions were fully regressive thereafter. In patient #4, the causative LMWH nadroparin was switched

TABLE 1 Basic patient characteristics

Total number of patients, n (%)	316 (100.0)
Female gender, n (%)	169 (53.5)
Age, years ($\pm$ SD)	62.7 $\pm$ 16.6
Major orthopedic surgery, n (%)	
Spine/vertebrae	119 (37.7)
Upper extremity	8 (2.5)
Lower extremity	189 (59.8)

SD, standard deviation.

TABLE 2 Patient characteristics stratified according to patients with or without delayed-type hypersensitivity to heparins

Characteristics	All	Without DTH	With DTH
n (%)	316 (100.0)	310 (98.1)	6 (1.9)
Female gender, n (%)	169 (53.5)	165 (53.2)	4 (66.7)
Age, years ($\pm$ SD)	62.7 $\pm$ 16.6	62.7 $\pm$ 16.7	63.2 $\pm$ 12.5
BMI ($\pm$ SD)	27.3 $\pm$ 5.9	27.2 $\pm$ 0.3	33.4 $\pm$ 6.0
Pregnant, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Hormone substitution, n (%)	13 (4.1)	6 (1.9)	0 (0.0)
Previous heparin therapy, n (%)	248 (78.5)	242 (78.1)	6 (100.0)
Indication for LMWH, n (%)			
Prophylaxis	295 (93.4)	292 (94.2)	3 (50.0)
Therapy	14 (4.4)	13 (4.1)	1 (16.7)
Atrial fibrillation	9 (2.8)	8 (2.5)	1 (0.3)
VTE	5 (1.6)	5 (1.6)	0 (0.0)
Prophylaxis and therapy	7 (2.2)	5 (1.6)	2 (33.3)
New VTE	5 (1.6)	4 (1.3)	1 (0.3)
Suspected VTE ruled out	2 (0.6)	1 (0.3)	1 (0.3)
LMWH preparation, n (%)			
Nadroparin only	168 (53.2)	165 (53.2)	3 (50.0)
Enoxaparin only	119 (37.7)	118 (38.1)	2 (33.3)
Nadroparin/enoxaparin	28 (8.9)	26 (8.4)	1 (16.7)
Nadroparin/certoparin	1 (0.3)	1 (0.3)	0 (0.0)
Contains nadroparin	197 (62.3)	196 (63.2)	4 (66.7)
Duration of heparin treatment, days (range)	10 (7-332)	10 (7-332)	15.5 (12-86)
Duration to onset of skin lesions, days (range)	-	-	11 (12-70)
Initial skin reaction to, n (%)			
Nadroparin	-	-	3 (50.0)
Enoxaparin	-	-	3 (50.0)
Characteristics of skin lesions, n (%)			
Local erythema	-	-	5 (83.3)
Local pruritus	-	-	5 (83.3)
Generalized reaction	-	-	0 (0.0)
Skin necrosis	-	-	0 (0.0)
Histology, n (%)			
Lymphohistiocytic infiltrate	-	-	6 (100.0)
Dermal microthromboses	-	-	0 (0.0)
Wells score, points ($\pm$ SD)		-2.1 $\pm$ 0.1	-1.6 $\pm$ 0.2
Revised Lo Score, points ($\pm$ SD)		N/A	3.0 $\pm$ 0.4

BMI, body mass index; DTH, delayed-type hypersensitivity; LMWH, low-molecular-weight heparin; N/A, not applicable; SD, standard deviation; VTE, venous thromboembolism.

to prophylactic enoxaparin on day 18 after onset of skin reactions on day 12 after start of anticoagulation. Patient #5 was treated with enoxaparin for VTE prophylaxis in association with total hip replacement. Erythematous skin lesions developed on day 15 after the start of treatment. Anticoagulation was then switched to nadroparin on day 19, and skin lesions were regressive. In patient #6, DTH was caused by therapeutic enoxaparin during bridging anticoagulation from phenprocoumon which was administered for atrial fibrillation. Skin lesions developed on day 9. LMWH was maintained until day

12 and switched back to anticoagulation with oral vitamin K antagonist. Erythemas slowly disappeared after the discontinuation of enoxaparin. Based on switching to another anticoagulant, which is a sensitive, specific and practical approach of finding an alternative heparin-based anticoagulant,^{1,18} cross-allergies were not detected in any of the patients (Table 3).

Comparison of patients with and without DTH to heparin showed no difference regarding age, gender distribution, previous heparin therapy, LMWH preparation used, duration of heparin

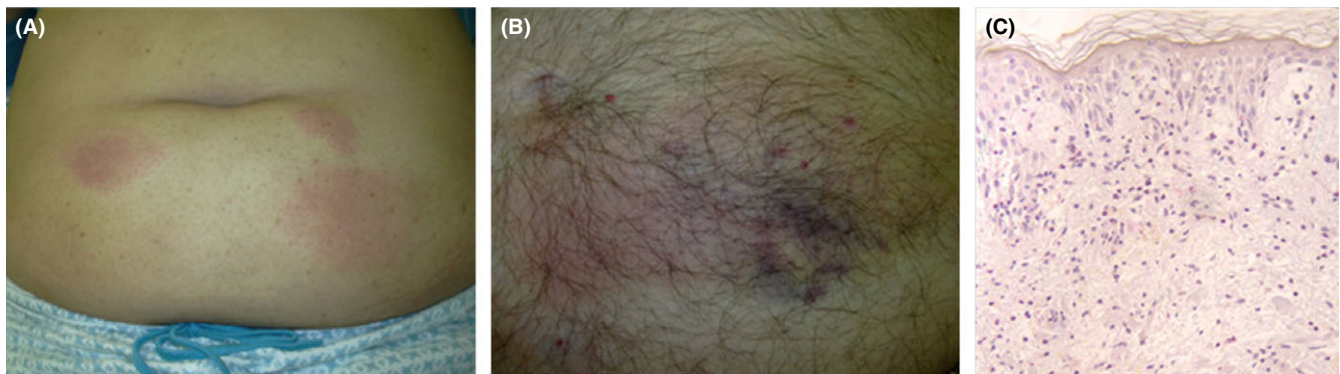


FIGURE 1 A, B, Clinical presentation of heparin-induced delayed-type hypersensitivity reactions (DTH). Mostly, skin reactions are restricted to the area of heparin injections. They present as localized, infiltrated, erythematous, itching maculae and/or plaques. Sometimes surrounding papules are observed. Generalized reactions occur in 3%-10% of patients. C, Histology of a skin biopsy of a patient with DTH reaction to heparin shows a characteristic dermal infiltration with lymphocytes and few eosinophils

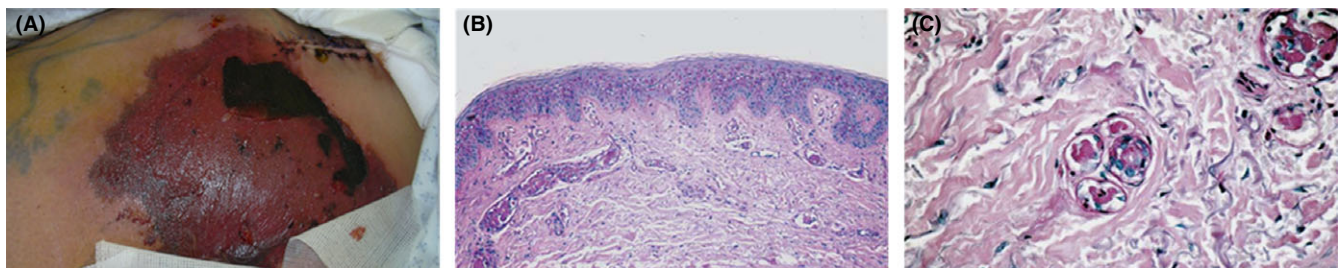


FIGURE 2 A, Clinical presentation of a cutaneous necrosis in a patient with underlying heparin-induced thrombocytopenia (HIT). B, C, Microthromboses in dermal vessels in a patient with HIT-associated skin necrosis (reproduced from Peitsch et al²⁰ by permission of Springer)

TABLE 3 Characteristics of patients with skin reactions to heparins

#	Gender	Age	BMI	Hormones	Previous heparin therapy	Indication	Initial reaction to	Skin necrosis	Onset of skin lesions (days)	Switch of heparin after (days)	Switch to	Skin reaction regressive after switch /stop
1	Female	63	61.0	No	Yes	Prophylaxis Therapy (PE)	ENO	No	70	76	CER	Yes
2	Male	44	24.7	No	Yes	Prophylaxis Therapy (suspected DVT)	NAD	No	8	12	FON	Yes
3	Female	74	37.9	No	Yes	Prophylaxis	NAD	No	10	13	Stop of anticoagulation	Yes
4	Female	53	24.2	No	Yes	Prophylaxis	NAD	No	12	18	ENO	Yes
5	Female	69	31.6	No	Yes	Prophylaxis	ENO	No	15	19	NAD	Yes
6	Male	76	21.2	No	Yes	Therapy (Afib)	ENO	No	9	12	Switch to phenprocoumon	Yes

Afib, atrial fibrillation; BMI, body mass index; CER, certoparin; DVT, deep vein thrombosis; ENO, enoxaparin; FON, fondaparinux; NAD, nadropanin; PE, pulmonary embolism.

treatment and hormone intake. In a multivariate logistic regression after determining relevant covariates in a random forest analysis and further optimization of the AIC, only therapeutic dosage of heparin emerged as independent and significant risk factor on the onset of DTH (odds ratio [OR]: 3.1, 95% CI: 1.4-4.9; $P = .00141$). Nadropanin use, however, was not a significant risk factor in this model (OR: 1.7, 95% CI: 1.4-4.9; $P = .00141$; Table 4).

3.2 | Skin lesions and heparin-induced thrombocytopenia

Two of 6 patients with heparin-induced skin reactions had a 4Ts pre-test probability score of 5 points (according to Lo et al¹⁷) and 4 points (according to Warkentin et al³), respectively, indicating an intermediate risk (4-5 points) of underlying HIT. DVT was suspected

TABLE 4 Risk factors for delayed-type hypersensitivity reactions (DTH) to heparin in orthopedic patients

Risk factor	a) Unadjusted			b) Adjusted			c) Adjusted		
	OR	95% CI	P-value	OR	95% CI	P-value	OR	95% CI	P-value
Male sex	−0.56	(−2.3 to 1.1)	.508	−0.52	(−2.4 to 1.4)	.587	ND	ND	ND
Age	0.0017	(−0.048 to 0.051)	.945	ND	ND	ND	ND	ND	ND
BMI	0.11	(0.019 to 0.2)	.033	0.041	(−0.068 to 0.15)	.455	ND	ND	ND
Prior heparin exposure	17	(−4200 to 4200)	.0864	16	(−4000 to 4000)	.17	ND	ND	ND
Nadroparin	1.1	(−1.0 to 3.3)	.255	1.6	(−0.77 to 4)	.134	1.7	(−0.59 to 4.0)	.09682
Enoxaparin	0.14	(−1.5 to 1.8)	.863	ND	ND	ND	ND	ND	ND
Certoparin	13	(−4700 to 4700)	.845	ND	ND	ND	ND	ND	ND
Max. heparin exposure duration (days)	0.0065	(−0.0087 to 0.022)	.49	0.011	(−0.012 to 0.034)	.483	ND	ND	ND
Therapy	2.8	(1.1 to 4.5)	.00313	2.7	(0.7 to 4.6)	.0134	3.1	(1.4 to 4.9)	.00141
Prophylaxis	−1.5	(−3.7 to 0.7)	.25	ND	ND	ND	ND	ND	ND
Hormone intake	−15	(−3600 to 3500)	.476	ND	ND	ND	ND	ND	ND

BMI, body mass index; CI, confidence interval; ND, not determined; OR, odds ratio.

As identification of risk factors was initially not considered as a study endpoint, the data have to be interpreted with care, owing to a possible selection bias.

(a) OR including 95% CI and likelihood-ratio test *P*-value (unadjusted for multiple testing); logistic regression on single covariates. (b) Adjusted OR including 95% CI and likelihood-ratio test *P*-value; to determine covariates that are important to predict the development of DTH, unbiased random forest importance analysis using R package cforest (a) was used. (c) Adjusted OR including 95% CI and likelihood-ratio test *P*-value; a logistic regression model combining the covariates determined by random forest importance was further optimized in a step-wise manner to minimize Akaike's information criterion.

in 1 patient with a 4Ts score of 5 points, but this could be ruled out sonographically. Pulmonary embolism occurred in the other patient. This was not associated with the onset of skin lesions in the context of HIT because skin lesions only occurred on day 70 after start of anticoagulation. Nevertheless, laboratory testing was performed with an antiplatelet factor 4/heparin enzyme immunoassay and a functional heparin-induced platelet activation assay. Results were negative in both patients. Further therapy with LMWH was not complicated by new or progressive VTE. The remaining 4 patients had 4Ts scores of 2 and 3 points, respectively. Due to the associated low risk of HIT, further laboratory testing was not initiated. Clinically neither thromboembolic HIT-sequelae nor necrotic skin lesions occurred in the further course.

3.3 | Further safety outcomes

Regarding venous thromboembolic complications, Wells score assessment was performed in 311 of 316 patients (98.4%) with a mean of -1.1 ± 0.8 points. Reasons for not assessing the Wells score were leg amputation in 4 and cast of both legs in 1 of 5 patients (1.6%). None of the patients had a Wells score of ≥ 3 points which would be suggestive of underlying thrombosis. However, 5 venous thromboembolic complications occurred in 316 patients (1.6%) despite prophylactic anticoagulation with LMWH, with DVT in 2 patients, PE in another 2 patients and DVT with PE in 1 patient. In 2 more patients with suspected DVT, the diagnosis was ruled out by venous sonography. Because platelet monitoring showed a drop in platelet counts $>30\%$ in 2 of these 5 VTE patients, laboratory HIT

diagnostics was performed, but did not confirm underlying HIT as cause of VTE.

Regarding bleeding complications, a decrease in hemoglobin levels by ≥ 2 g/dL postoperatively compared with preoperative hemoglobin levels was documented in 245 of 316 (77.5%). A decrease in hemoglobin levels by <2 g/dL postoperatively was found 58 of 316 patients (18.4%). In 13 of 316 patients (4.1%), pre- or postoperative hemoglobin levels were not documented. In 128 of 316 patients (40.5%), 2 or more units of packed red blood cells (RBC) were necessary intra- or postoperatively. However, in the majority of patients the extent of intra- and postoperative blood loss was expected. Only 4 of 316 patients (1.3%) fulfilled ISTH major bleeding criteria.²² These were surgical site bleedings with need for reoperation in 1 patient and prolonged surgical site bleedings with need for transfusion of RBCs in 3 patients.

4 | DISCUSSION

The study was designed to determine for the, so far unknown, incidence and causes of heparin-induced skin lesions in orthopedic surgery patients during treatment with low-molecular-weight heparins. While recent studies in non-surgical patients have shown that heparin-induced skin lesions are due to a DTH response to heparins in the vast majority of patients,^{1,4,7,23} orthopedic patients offer another intriguing clinical aspect: these patients have the highest risk to sustain HIT which is >50 - to 100-fold higher compared to medical or obstetric patients, and HIT-associated skin lesions show in up to

20% of patients.^{15,24} Conversely, in 29%-50% of patients with heparin-induced skin lesions, underlying HIT was demonstrated.^{8,10} Thus, we further investigated whether heparin-induced skin lesions in orthopedic surgery patients during LMWH treatment might rather be due to HIT-induced skin lesions instead of a DHT reaction.

4.1 | Incidence of skin lesions and risk factors

Interestingly, we found that the incidence of heparin-induced skin lesions during LMWH treatment was considerably lower in orthopedic surgery patients compared with different previously assessed patient cohorts. More specifically, the incidence we registered was 1.9% (95% CI: 0.4%-3.4%) in orthopedic patients compared to 7.5% in medical patients⁴ and 19.8% in obstetric patients.⁷ All lesions were diagnosed clinically and histologically—by the detection of a lymphohistiocitary infiltrate and the absence of microthromboses in dermal vessels—as a DHT reaction. All skin lesions were fully regressive and none progressed to skin necrosis. Negative laboratory HIT assessment ruled out any association of the observed skin lesions with HIT. However, contrary to the mentioned previous findings, our results on surgical patients are in line with recently published data that underline the importance of the type of heparin preparation as well as the type of skin lesion in the clinical allocation of heparin-associated skin reactions: non-necrotizing heparin-induced skin lesions are almost invariably a manifestation of DTH, and not of HIT, at least when they are caused by LMWH treatment.^{3,23}

Regarding DTH risk factors, we found that a therapeutic as opposed to a prophylactic LMWH dose has a higher risk to elicit skin lesions. It seems plausible that prolonged exposure to heparin—as previously identified⁴—and therapeutic LMWH dose are 2 risk factors that interact; that is, a therapeutic dose is often the reason for a prolonged duration of treatment. However, the risk factor *prolonged heparin exposure* only showed in non-surgical patients who had more often a therapeutic indication for anticoagulation than surgical patients.⁴

However, these data have to be interpreted with caution, as the study was not powered to detect risk factors for the development of DTH reactions in orthopedic surgery patients. The low number of patients with DTH in this study may explain in part, why the determined (or excluded) risk factors vary from a recent meta-analysis.²⁵

The reason for the observed low incidence of DTH reactions in orthopedic surgery patients remains unclear. A recent meta-analysis has clearly identified younger age (<55 years), female sex, obesity (BMI > 25), prior heparin exposure and a long duration of heparin therapy (>11 days) as patient-related risk factors and nadroparin treatment as strong drug-related risk factor for DTH²⁵ from 3 large prospective investigations on the incidence of DTH.^{4,7,26} Compared to the cohort of medical patients that was previously assessed for heparin-induced skin lesions,⁴ the patients from this surgical cohort showed higher rates of female patients and of previous heparin exposures, a higher BMI and a longer duration of heparin therapy, and were exposed more frequently to high allergenic nadroparin.

Although it is speculative, there are robust data that suggest that peri- and postoperative conditions might have an influence on the actually expected higher sensitization rate in orthopedic surgery patients. It is well known that major surgery triggers stress reactions that go along with various metabolic changes and can lead to a profound, prolonged increase in cortisol levels after stimulation of the hypothalamic-pituitary-adrenocortical axis (HPA). Pro-inflammatory cytokines from the surgical wound (eg interleukin [IL]-1 and interleukin-6 and tumour necrosis factor α [TNF- α]) can further stimulate HPA axis-mediated cortisol release but have also a direct extrapituitary effect on adrenal cortisol production.^{27,28} Cortisol levels may stay increased for more than 7 days after surgery proportionally to the level of operative stress.²⁹⁻³¹ Glucocorticoids (GCs) are potent anti-inflammatory and immunosuppressant agents, and it is known that already small changes in glucocorticoid levels are already immunomodulatory and may influence leucocyte trafficking.³²⁻³⁵ GCs may influence the onset of a drug-specific, T cell-mediated DHT reaction^{36,37} in multiple ways. Among others, GCs may inhibit antigen uptake and processing by dendritic and Langerhans cells, generation of pro-inflammatory eicosanoids and cytokines,^{32,35,38} CD4⁺ T cell activation and signalling, dendritic cell activity and differentiation,^{32,39} and leucocyte trafficking.^{32,35} However, a conceivable stress hormone, that is corticosteroid, level-modulated allergic susceptibility to develop DTH reactions at the observed low incidence in orthopedic surgery patients, requires further investigations.

4.2 | Safety outcomes

The safety outcomes of the present study showed an overall safe application of LMWH in orthopedic surgery patients with no cases of HIT (0.0%), a total of 5 venous thromboembolic events (1.6%) and 4 major surgical site bleeding complications in 316 patients (1.3%).²² Because in 2 of these patients, kidney function was moderately (GFR 59 mL/min/1.73 m²) and severely (GFR 23 mL/min/1.73 m²) decreased and neither LMWH doses were adjusted to impaired kidney function nor anti-Xa level monitoring was performed, it is conceivable that bioaccumulation may have triggered the bleeding complications in these 2 patients.

4.3 | Therapeutic implications

Regarding the therapeutic implications of our findings, we suggest an individual approach for heparin use in major surgery patients that takes into account drug-related factors (eg renal clearance, HIT risk, antagonizability, osteoporosis, anti-inflammatory and anti-metastatic effects). Furthermore, patient-related risk factors that contribute to sensitization to heparins (eg younger age, female gender, obesity (BMI > 25), prior heparin exposure, extended anticoagulation required) must be considered. However, these patient-related risk factors seem to play a lesser role in orthopedic surgery patients than in medical or obstetric patients. Regarding heparin preparation-related risk factors, nadroparin showed no significantly increased risk for sensitization in surgical patients, while previous studies found a

strong correlation (OR 30).^{4,7,25} One suitable alternative may be the pentasaccharide fondaparinux. Due to molecular properties, the latter seems to have a low allergenic potential and significantly reduces the total number of VTE compared to LMWH after major orthopedic surgery.⁴⁰ This might be also a reasonable choice in case allergic skin lesions have already developed²⁶ because cross-allergies occur in >30% of patients.¹ It is also possible to use non-heparin anticoagulants, that is apixaban, dabigatran, rivaroxaban, which are all approved for thrombosis prophylaxis in orthopedic surgery.⁴¹ This must be considered especially in case therapeutic anticoagulation is required because this showed in our model to be an independent significant risk factor for eliciting DTH reactions. As typical complication in major surgery patients postoperative bleedings may occur. In patients with postsurgical high bleeding risk and a DTH reaction to heparins but the indication for extended anticoagulation, intravenously administered unfractionated heparin which can be titrated and which is readily antagonizable can be applied due to its known compartment tolerance.¹ In case skin lesions develop during LMWH treatment, clinical pre-test probability risk assessment is warranted due to the higher risk of HIT-associated skin lesions and a higher risk of HIT in orthopedic surgery patients.^{3,9,24}

5 | LIMITATIONS

The incidence of heparin-induced skin lesions in our study cohort during LMWH treatment was compared with non-surgical patients from a previous study.⁴ Although we were not aware of any changes in heparin preparations by the manufacturers, it cannot be excluded that other unknown drug-related factors might have contributed to the observed lower frequency of skin reactions compared to non-surgical patients.

Furthermore, because our study was not designed to detect differences between risk factors or between different heparin preparations, and heparin selection and patient allocation to a specific heparin preparation were due to the treating physicians, data on risk factors and on drug-specific differences in sensitization potentials and cross-allergies must be interpreted carefully. We cannot comment on UFH effects because this preparation was not applied in our study population. Because the incidence of HIT in orthopedic surgery patients was not a primary end-point of our study, was underpowered to answer this question and would require a different screening strategy, conclusions regarding this aspect are limited.

However, for several reasons we think that our results are generalizable. (i) This was an all-comer study with only few exclusion criteria. (ii) Previously identified risk factors for sensitization, that is previous heparin therapy, longer duration of heparin treatment, female gender, nadroparin use, were more frequent in the orthopedic surgery patient cohort compared to the medical patient cohort. This should rather lead to an overestimation of the incidence of DTH reactions in the surgical patient cohort. (iii) To minimize potential sources of biases, clinical examinations and

diagnostic tests were performed in duplicate by 2 investigators or methods, that is clinical assessment of skin lesions, histologic analysis of skin biopsies, conduct of laboratory HIT diagnostics with different assays, that is platelet factor 4/heparin-enzyme-linked immunosorbent assay, heparin-induced activation assay, interpretation of laboratory data, that is monitoring of platelet counts and hemoglobin levels. Thus, we think that it is safe to conclude that the presence of a heparin-induced DTH response to LMWH is associated with a lower risk of heparin-associated skin reactions compared to medical patients.⁴

In conclusion, we report an incidence of 1.9% (95% CI: 0.4%-3.4%) of heparin-induced skin lesions in a cohort of major orthopedic surgery patients during anticoagulation with LMWH. All cutaneous reactions were due to a DHT reaction. Compared to the high (20%-40%) and intermediate (7.5%) risk in obstetric or medical patients to develop a DTH response to subcutaneously administered heparin, the risk is considerably lower in orthopedic surgery patients. Unlike previous data, none of the skin lesions was associated with life-threatening HIT although orthopedic surgery patients are among the group with the highest risk to sustain HIT. Within the limitations of this study, we identified therapeutic LMWH dosage as a significant risk factor for DTH reactions as opposed to prophylactic treatment. Previously identified risk factors seem to play a lesser role in surgical patients.

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CONFLICT OF INTEREST

Marc Schindewolf: speaker's fees from Aspen, Bristol-Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Sanofi-Aventis; travel grants from Bristol-Myers Squibb, Bard, Cook, Bayer Healthcare; advisory board member of Bayer Healthcare, Bristol-Myers Squibb, Daiichi Sankyo, Sanofi-Aventis. Edelgard Lindhoff-Last: speaker's fees from Bayer Healthcare, Boehringer Ingelheim, GlaxoSmithKline, Sanofi-Aventis; advisory board member of Bayer Healthcare, Boehringer Ingelheim, GlaxoSmithKline. The other authors have no conflict of interests to declare.

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REFERENCES

1. Schindewolf M, Lindhoff-Last E, Ludwig RJ, Boehncke WH. Heparin-induced skin lesions. *Lancet*. 2012;380:1867-1879.
2. Scherer K, Tsakiris DA, Bircher AJ. Hypersensitivity reactions to anticoagulant drugs. *Curr Pharm Des*. 2008;14:2863-2873.
3. Warkentin TE, Linkins LA. Non-necrotizing heparin-induced skin lesions and the 4T's score. *J Thromb Haemost*. 2010;8:1483-1485.

4. Schindewolf M, Schwaner S, Wolter M, et al. Incidence and causes of heparin-induced skin lesions. *CMAJ*. 2009;181:477-481.
5. Bank I, Libourel EJ, Middeldorp S, Van Der Meer J, Buller HR. High rate of skin complications due to low-molecular-weight heparins in pregnant women. *J Thromb Haemost*. 2003;1:859-861.
6. Kaandorp SP, Goddijn M, van der Post JA, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med*. 2010;362:1586-1596.
7. Schindewolf M, Gobst C, Kroll H, et al. High incidence of heparin-induced allergic delayed-type hypersensitivity reactions in pregnancy. *J Allergy Clin Immunol*. 2013;132:131-139.
8. Warkentin TE. Heparin-induced skin lesions. *Br J Haematol*. 1996;92:494-497.
9. Warkentin TE, Roberts RS, Hirsh J, Kelton JG. Heparin-induced skin lesions and other unusual sequelae of the heparin-induced thrombocytopenia syndrome: a nested cohort study. *Chest*. 2005;127:1857-1861.
10. Harenberg J, Huhle G, Wang L, Hoffmann U, Bayerl C, Kerowgan M. Association of heparin-induced skin lesions, intracutaneous tests, and heparin-induced IgG. *Allergy*. 1999;54:473-477.
11. Warkentin TE, Sheppard JA, Horsewood P, Simpson PJ, Moore JC, Kelton JG. Impact of the patient population on the risk for heparin-induced thrombocytopenia. *Blood*. 2000;96:1703-1708.
12. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am J Med*. 1996;101:502-507.
13. Warkentin TE, Cook RJ, Marder VJ, et al. Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. *Blood*. 2005;106:3791-3796.
14. Greinacher A, Alban S, Omer-Adam MA, Weitschies W, Warkentin TE. Heparin-induced thrombocytopenia: a stoichiometry-based model to explain the differing immunogenicities of unfractionated heparin, low-molecular-weight heparin, and fondaparinux in different clinical settings. *Thromb Res*. 2008;122:211-220.
15. Warkentin TE. Clinical picture of heparin-induced thrombocytopenia. In: Warkentin TE, Greinacher A, eds. *Heparin-induced Thrombocytopenia*, 3rd edn. New York, NY: Marcel Dekker; 2004:53-106.
16. Kelton JG, Arnold DM, Bates SM. Nonheparin anticoagulants for heparin-induced thrombocytopenia. *N Engl J Med*. 2013;368:737-744.
17. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. 2006;4:759-765.
18. Schindewolf M, Ludwig RJ, Wolter M, et al. Diagnosis of heparin-induced delayed-type hypersensitivity. *Phlebologie*. 2010;39:226-231.
19. Linkins LA, Dans AL, Moores LK, et al. 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*. 2012;141:e495S-e530S.
20. Peitsch WK, Glorer E, Dempfle CE, Back W, Bayerl C, Goerdt S. Cutaneous necroses mainly on the extremities. *Hautarzt*. 2004;55:410-413.
21. Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet*. 1995;345:1326-1330.
22. Schulman S, Angeras U, Bergqvist D, Eriksson B, Lassen MR, Fisher W. Definition of major bleeding in clinical investigations of antihe-mostatic medicinal products in surgical patients. *J Thromb Haemost*. 2010;8:202-204.
23. Schindewolf M, Kroll H, Ackermann H, et al. Heparin-induced non-necrotizing skin lesions: rarely associated with heparin-induced thrombocytopenia. *J Thromb Haemost*. 2010;8:1486-1491.
24. Warkentin TE. New approaches to the diagnosis of heparin-induced thrombocytopenia. *Chest*. 2005;127:35S-45S.
25. Schindewolf M, Recke A, Zillikens D, Lindhoff-Last E, Ludwig RJ. Nadroparin carries a potentially high risk of inducing cutaneous delayed-type hypersensitivity responses. *Contact Dermatitis*. 2017;77:35-41.
26. Schindewolf M, Scheuermann J, Kroll H, et al. Low allergenic potential with fondaparinux: results of a prospective investigation. *Mayo Clin Proc*. 2010;85:913-919.
27. Gibbison B, Angelini GD, Lightman SL. Dynamic output and control of the hypothalamic-pituitary-adrenal axis in critical illness and major surgery. *Br J Anaesth*. 2013;111:347-360.
28. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med*. 1995;332:1351-1362.
29. Juma AH, Ardawi MS, Baksh TM, Serafi AA. Alterations in thyroid hormones, cortisol, and catecholamine concentration in patients after orthopedic surgery. *J Surg Res*. 1991;50:129-134.
30. Di Padova F, Pozzi C, Tondre MJ, Tritapepe R. Selective and early increase of IL-1 inhibitors, IL-6 and cortisol after elective surgery. *Clin Exp Immunol*. 1991;85:137-142.
31. Chernow B, Alexander HR, Smallridge RC, et al. Hormonal responses to graded surgical stress. *Arch Intern Med*. 1987;147:1273-1278.
32. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids. *Nat Rev Immunol*. 2017;17:233-247.
33. Scheiermann C, Kunisaki Y, Frenette PS. Circadian control of the immune system. *Nat Rev Immunol*. 2013;13:190-198.
34. Dimitrov S, Benedict C, Heutling D, Westermann J, Born J, Lange T. Cortisol and epinephrine control opposing circadian rhythms in T cell subsets. *Blood*. 2009;113:5134-5143.
35. Hackstein H, Thomson AW. Dendritic cells: emerging pharmacological targets of immunosuppressive drugs. *Nat Rev Immunol*. 2004;4:24-34.
36. Coombs PR, Gell PG. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell RR, ed. *Clinical Aspects of Immunology*. Oxford: Oxford University Press; 1968:575-596.
37. Pichler WJ. Delayed drug hypersensitivity reactions. *Ann Intern Med*. 2003;139:683-693.
38. Szatmari I, Nagy L. Nuclear receptor signalling in dendritic cells connects lipids, the genome and immune function. *EMBO J*. 2008;27:2353-2362.
39. Löwenberg M, Verhaar AP, van den Brink GR, Hommes DW. Glucocorticoid signaling: a nongenomic mechanism for T-cell immunosuppression. *Trends Mol Med*. 2007;13:158-163.
40. Dong K, Song Y, Li X, et al. Pentasaccharides for the prevention of venous thromboembolism. *Cochrane Database Syst Rev* 2016;10: Cd005134.
41. Prandoni P, Temraz S, Taher A. Direct oral anticoagulants in the prevention of venous thromboembolism: evidence from major clinical trials. *Semin Hematol*. 2014;51:121-130.

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