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INVESTIGATIVE REPORT

Hydroxyethyl Starch-induced Pruritus: Clinical Characteristics and Influence of Dose, Molecular Weight and Substitution

Sonja STÄNDER[1], Laura RICHTER[1], Nani OSADA[2] and Dieter METZE[1]
[1]*Competence Center for Chronic Pruritus, Department of Dermatology, and* [2]*Institute of Informatics, University Hospital Münster, Münster, Germany*

Severe persistent pruritus is a common, but incompletely characterized, complication of hydroxyethyl starch (HES) infusion. This retrospective study aimed to assess HES-induced pruritus by electron microscopic findings, pruritus characteristics, and response to stimuli, and to determine the impact of HES dosage, molecular weight and substitution. Seventy patients with electron microscopy-proven HES-induced pruritus were included. HES-laden vacuoles were observed in skin macrophages of all patients. The median latency between HES exposure and pruritus onset was 3 weeks, and the median duration of pruritus was 6 months. Pruritus was severe, or very severe, in 80% of patients. Mechanical stimuli triggered pruritus in 74% of patients. Although the median cumulative dose of HES was 300 g, 15% of patients developed pruritus after only 30 g. There were no significant differences between HES 130/0.4 and HES 200/0.5 in pruritus latency, duration or severity. HES-induced pruritus thus may occur at any dose, molecular weight or substitution. ***Key words: hydroxyethyl starch; tissue storage; pruritus; dose; molecular weight; molar substitution.***

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Sonja Ständer, Professor for Dermatology and Clinical Neurodermatology, Competence Center Chronic Pruritus, Department of Dermatology, University Hospital Münster, Von-Esmarch-Straße 58, DE-48149 Münster, Germany. E-mail: sonja.staender@uni-muenster.de

Hydroxyethyl starch (HES) is currently the most frequently infused colloid in intensive care units worldwide (1). This artificial colloid is synthesized by hydroxyethylation of partially hydrolysed corn or potato starch. HES solutions contain a polydisperse mixture of molecules differing in molecular weight and molar substitution of hydroxyethyl moieties at the C2, C3 and C6 positions of the constituent glucose units. HES contained in typical solutions available for clinical use averages 70, 130 or 200 kDa in molecular weight and 0.4 or 0.5 in substitution, and these solutions are designated accordingly; for example, HES 130/0.4 or HES 200/0.5. In humans, the metabolic fate of infused HES consists of plasma persistence, urinary excretion and tissue uptake (2).

A major site of HES uptake and storage is the skin, where its presence can be demonstrated by tissue staining and immunoelectron-microscopy in diverse cell types (3, 4). HES can appear in skin cell vacuoles as soon as 90 min after a single dose of 30 g, and persist there in some cases for 4 years or longer (5, 6).

A frequent consequence of HES storage in skin is severe prolonged refractory pruritus (7). In randomized trials, this complication was found to be dose-dependent (8, 9). At higher doses, the incidence of HES-induced pruritus has typically ranged from approximately 30% to over 60% of patients (3, 4, 8–12).

The clinical characteristics of HES-induced pruritus have not yet been fully delineated. For instance, while symptoms have commonly been classified as severe, quantification of symptom severity on a validated scale has not thus far been reported. It also remains unclear whether pruritus can be avoided by limiting the dose of HES. Two studies have provided evidence that pruritus develops only above a threshold cumulative HES dose of approximately 150 g (3, 4, 10). Other observations have indicated that pruritus can be provoked by much lower doses (7).

Another open question is whether lower molecular weight and substitution can mitigate the risk of pruritus. A meta-analysis has indicated that this is not the case (13). Nevertheless, it continues to be argued that HES 130/0.4 poses minimal risk of pruritus (14). This particular HES solution has achieved widespread clinical acceptance, and in some countries has become the predominant colloid used by intensive-care physicians (15). Until recently, the safety of HES 130/0.4 has not been adequately assessed (16).

One objective of the present study was to characterize HES-induced pruritus with respect to electron microscopic findings, anatomical pattern of itching, pruritus characteristics, and response to stimuli. A further aim was to determine the impact of HES dose, molecular weight and substitution.

METHODS

Patients with electron microscopy-proven HES-induced pruritus were included in this retrospective study. Ethics committee approval was secured. Data were collected during the period from June 2010 to August 2011. In the case of patients seen at University Hospital Münster, data were assembled from patient records and telephone inquiries. Biopsies of additional patients were sent for diagnostic evaluation from referring hospitals or clinical practices, and in those instances patient data were obtained by telephone after informed consent was granted. According to a previously described diagnostic algorithm, it is feasible to diagnose HES-

induced pruritus from findings communicated by telephone, with electronic microscopic confirmation reserved only for doubtful cases (17). Nevertheless, HES-induced pruritus was confirmed by electron microscopy for all patients in this study.

Outcome measures

The primary study outcome measures consisted of pruritus latency, duration and severity, cumulative HES dose and HES treatment duration. Secondary outcome measures were the number, size and cell types of HES storage vacuoles and pruritus localization, quality, timing and pattern.

Data collection

Data were collected on patient demographics and diverse pruritus parameters, i.e. latency, duration, severity, anatomical localization, pruritus characteristics, and stimuli influencing pruritus. Pruritus severity was quantified on a 0–10-point visual analogue scale (VAS), which is a validated method of pruritus assessment (18, 19). VAS scores of 0 correspond to the absence of pruritus, >0 but <3 to mild pruritus, ≥ 3 but <7 to moderate, ≥ 7 but <9 to severe, and 9–10 to very severe (19). The impact of pruritus on patient quality of life (QoL) was also evaluated by 4 questions (QoL disturbed, sleep disturbed, private life disturbed and work life disturbed). If the answer was yes, we asked for the severity (weak, severe) of impairment and details. Where available, HES indication, molecular weight, substitution, concentration and infusion regimen were documented.

Electron microscopy

Examination of biopsy specimens by electron microscopy was performed as previously described (6). Specimens were processed with Karnovsky's fixative and then 1% osmium tetroxide, dehydrated, and embedded in Epon resin mixture (Merck, Darmstadt, Germany). Ultra-thin sections were created with diamond knives, and after mounting on copper grids the sections were stained with uranyl acetate and lead citrate. The size, number and cell types of HES storage vacuoles were recorded for one representative specimen. Since the specimens were analysed for routine diagnostic purposes only, no serial sections were created.

Statistical analysis

Summary statistics for continuous variables consisted of the mean, standard deviation (SD), median and interquartile range (IQR). In the computation of percentages the total number patients with available data for a particular parameter was used as the denominator. Progression between localized and generalized pruritus was evaluated by exact McNemar test. Significant differences between patients receiving HES 130/0.4 vs. HES 200/0.5 were determined by exact Mann–Whitney test. The median magnitude of difference and its 95% confidence interval (CI) were quantified by exact Hodges-Lehmann estimation.

RESULTS

Patients

A total of 70 patients were included in the study. Forty-eight patients (69%) presented at University Hospital Münster, while 8 (11%) were referred from other university hospitals, 8 (11%) from regional hospitals, and 6 (9%) from private practices. In the case of referral patients, the provisional diagnosis of HES-induced pruritus was established by the referring hospital or practice.

For 37 patients (53%) all the study data required could be secured from patient records. In the remaining 33 cases (47%), only partial data were available in patient records, and supplementary data, such as HES solution type or dosage or, in the case of some referral patients, pruritus questionnaire responses were obtained by telephone contact. In all patients seen at University Hospital Münster, biopsies and completion of pruritus questionnaires were contemporaneous.

Patients received HES over the period from 1993 to 2008 (Fig. 1). Biopsies were collected from November 1998 to July 2009. The median time elapsed from pruritus onset to biopsy was 3.2 months (IQR 2.2–19.3 months).

Mean $\pm$ SD age of patients was 54.5 ± 15.1 years. Other patient attributes are summarized in Table I. Hearing loss/tinnitus was the most common diagnosis, accounting for 40% of patients, while surgery or trauma totalled 28%.

HES was infused for haemodilution in 60% of patients and volume expansion in 40% (Table I). The concentration of the HES solution was predominantly 6%.

Electron microscopic findings

In 83% of patients multiple HES storage vacuoles were observed per cell (Table SI[1]). In the majority (59%), the vacuole sizes varied. HES-laden vacuoles were present in macrophages of all patients. In addition, HES storage in endothelial and/or nerve cells was demonstrated in 41% of patients. HES storage was observed in many, but not all, cutaneous nerves; however,

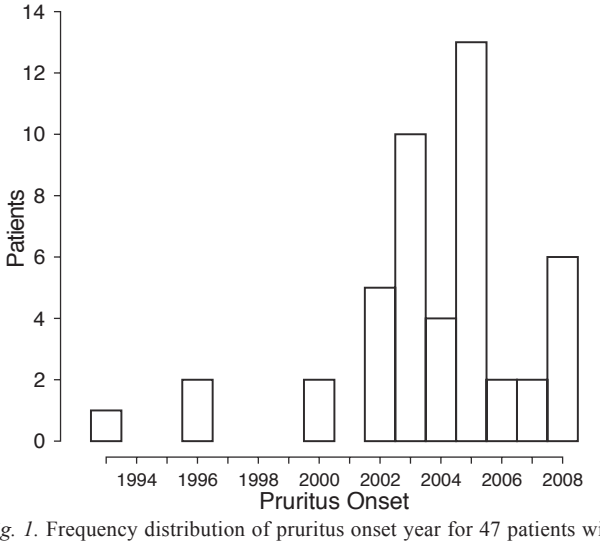

Fig. 1. Frequency distribution of pruritus onset year for 47 patients with available data for pruritus onset year.

[1]http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1639

Table I. *Patients (*n = *70) and hydroxyethyl starch (HES) solutions*

Parameter	*n* (%)
Age	
<40 years	12 (17.4)
40–70 years	46 (66.7)
>70 years	11 (15.9)
Gender	
Male	37 (52.9)
Female	33 (47.1)
Diagnosis/intervention	
Hearing loss/tinnitus	20 (40.0)
Surgery	8 (16.0)
Trauma	6 (12.0)
Subarachnoid haemorrhage	4 (8.0)
Vestibular syndrome	4 (8.0)
Hypovolaemia	2 (4.0)
Ocular infarction	2 (4.0)
Other[a]	4 (8.0)
Indication for HES infusion	
Haemodilution	30 (60.0)
Volume expansion	20 (40.0)
Type of HES solution	
HES 200/0.5	36 (78.3)
HES 130/0.4	8 (17.4)
HES 70/0.5	2 (4.3)
HES concentration	
6%	38 (82.6)
10%	5 (10.9)
6 and 10%	3 (6.5)

[a]One each of vascular stenosis, transient ischaemic attack, facial paresis, and dizziness. In some patients, the information on indication, concentration and solution was not available.

more extensive neuronal storage could not be ruled out, since serial sections were not examined.

Pruritus parameters

Pruritus developed a median of 3 weeks (IQR 1–3.5 weeks) after HES infusion (Fig. 2a). Pruritus development was not delayed in 7 patients (18%). The longest latency between HES infusion and pruritus onset in any individual patient was 78 weeks. The median duration of pruritus was 6 months (IQR 2–17.5 months). In one-third of patients, pruritus persisted for at least 12 months and in 4 patients (10%) for at least 36 months (Fig. 2b).

The median VAS pruritus severity score was 9 (IQR 8–9.9). As judged by VAS score (Fig. 2c), pruritus was very severe in 17 patients (57%) and severe in 7 (23%).

At the time of pruritus onset, pruritus was generalized in 31% of patients (Table II). However, over time the majority of patients (56%) ultimately experienced generalized pruritus. When localized, pruritus most often affected the trunk, legs and arms. Patients were significantly more likely to progress from localized to generalized pruritus than vice versa (odds ratio (OR) 5.0; 95% CI 1.07–46.9; $p = 0.039$).

Most patients (71%) experienced both itching and other forms of discomfort, such as stinging, burning and tingling (Table SII[1]). In 60% of cases, pruritus occurred throughout the day. In 84% of patients, pruritus occurred as periodic attacks. The median frequency of the attacks was 3.5 (IQR 1–10) per day. Attacks lasted for a median of 10 min (IQR 1.5–41.5 min).

Pruritus was triggered by mechanical stimuli in 74% of patients. The most frequent specific stimuli provoking pruritus were: pressure, rubbing, heat, scratching, sweating and clothing (Table SIII[1]).

Among patients seen at University Hospital Münster, in all of whom pruritus parameters were assessed with no delay after biopsy, the median VAS score (8.5; IQR 8–10) coincided closely with that of the referral patients (9; IQR 9–9.4). Pruritus quality, timing and pattern were generally similar between the University Hospital Münster and referral patients (Table SII[1]).

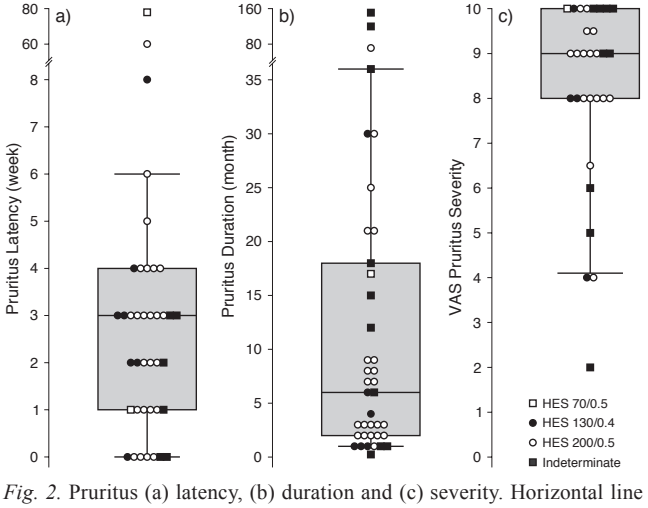

Fig. 2. Pruritus (a) latency, (b) duration and (c) severity. Horizontal line inside each box shows median value. Lower and upper error bars indicate respectively the 10th and 90th percentiles and the box bottoms and tops the 25th and 75th percentiles. HES, hydroxyethyl starch; VAS, visual analogue scale.

Quality of life

Pruritus impaired QoL for 89% of patients. Sleep disturbances were experienced by 88%. Pruritus imposed limitations on private life for 89% of patients and work life for 68%. Specific adverse outcomes were noted for 6 patients: job loss for 2 and, in one each, separation from partner, reduced capacity at work, inability to participate in sport, and depression with neglect of household duties.

Table II. Pruritus localization after hydroxyethyl starch exposure

Localization	Initial *n* (%)	Subsequent *n* (%)
Generalized	13 (31.0)	27 (56.2)
Trunk	16 (38.1)	13 (27.1)
Legs	11 (26.2)	9 (18.8)
Arms	6 (14.3)	11 (22.9)
Head	3 (7.3)	4 (8.3)
Neck	1 (2.4)	2 (4.2)
Genitoanal area	0 (0.0)	3 (6.2)
Hands	0 (0.0)	2 (4.2)

HES dose and duration of exposure

The median cumulative dose of HES was 300 g (IQR 150–575 g). The corresponding median cumulative HES volume was 3,500 ml (IQR 1,750–6,750 ml). Less than 150 g of HES was infused cumulatively in 24% of patients. Seven patients (15%) developed pruritus after receiving only 30 g of HES (Fig. 3a).

The median duration of the HES regimen was 10 days (IQR 6–12). Six patients (13%) developed pruritus after exposure to HES on a single day and a total of 11 patients (24%) on just 1–2 days (Fig. 3b).

HES molecular weight and substitution.

For 46 patients the type of HES solution infused could be established (Table I). Of those, 38 (78%) received HES 200/0.5 and 8 (17%) HES 130/0.4. HES 70/0.5 was infused in the remaining 2 patients. Among patients receiving HES for haemodilution, HES 200/0.5 was used in 88%. Only in one patient was HES 130/0.4 administered for haemodilution. The indication for fluid infusion was also haemodilution for both HES 70/0.5 recipients.

There were no significant differences between HES 130/0.4 and HES 200/0.5 in either cumulative HES dose ($p = 0.41$) or duration of HES exposure ($p = 0.37$). Two of the 8 HES 130/0.4 recipients (25%) developed pruritus after a cumulative dose of only 30 g, compared with 5 of 36 patients receiving HES 200/0.5 (14%).

The median latency between HES exposure and pruritus onset was the same for HES 130/0.4 (3 weeks; IQR 2–3.5 weeks) and HES 200/0.5 (3 weeks; IQR 1–4 weeks). Although pruritus persisted for a median of 2 months (95% CI –3 to 8 months) longer in patients receiving HES 200/0.5 than HES 130/0.4, this difference was not statistically significant ($p = 0.23$). Median VAS pruritus severity score also did not differ significantly ($p = 0.56$) between recipients of HES 130/0.4 (8; IQR 7–8.5) and HES 200/0.5 (9; IQR 8–9.1).

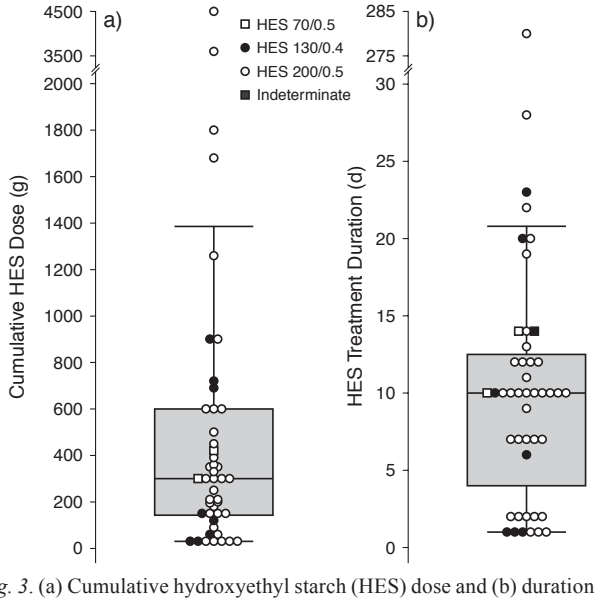

Fig. 3. (a) Cumulative hydroxyethyl starch (HES) dose and (b) duration of treatment with HES. Graphic conventions as in Fig. 1.

DISCUSSION

The first reports of pruritus after HES exposure began to appear as early as 1981 in granulocyte donors (20–22). In the first reported case, pruritus developed after 2 exposures to HES 450/0.7 totalling 66 g (20). A 1982 report described 4 cases of pruritus (21). In one case, pruritus ensued after administration of HES 450/0.7 totalling 60 g over 2 days, and in the other 3 cases after 120 g over 7 days. Subsequent clinical studies have demonstrated severe chronic pruritus after administration of HES (10, 23).

The present study confirms that pruritus can be precipitated by very low HES doses. In 15% of patients a dose of just 30 g, equivalent to a single 500 ml infusion of 6% HES, resulted in pruritus. In previous studies suggesting a 150 g threshold dose, patients receiving low doses may have been under-represented (3, 4, 10). In one of those studies, for example, the reported standard deviation for dose indicated that nearly all patients had received at least 150 g HES, and so few if any recipients of low doses were at risk for pruritus (10).

No clinically relevant differences could be detected between HES 130/0.4 and HES 200/0.5 in pruritus latency, duration or severity. This observation is consistent with a recent meta-analysis of clinical studies in which whole-body tissue uptake of HES 130/0.4 and HES 200/0.5 were closely similar (2). The present study is the first to provide quantitative data for severity of HES-induced pruritus on a validated VAS scale. These data, indicating severe or very severe symptoms in 80% of cases, highlight the extreme discomfort experienced by affected patients. Unsurprisingly, therefore, 89% of the patients suffered impairment in their QoL, including sleep disturbances in 88%. Such adverse effects have been previously described (24–26).

The 3 weeks median latency in this study is comparable to the 4 weeks median reported in a study of 85 cardiac surgery patients receiving HES 200/0.62 (26). The delayed onset of symptoms is probably a major factor in under-recognition of HES-induced pruritus. Typical indications of HES infusion are haemodilution for acute hearing and volume replacement in the settings of surgery and intensive care. Such patients are often discharged within 1–3 weeks, i.e. frequently before the likely onset of pruritus. Accordingly, in many patients no clear relationship between infusion therapy and induction of pruritus is established.

The clinical course of HES-induced pruritus is protracted, as indicated by the median 6 months duration of symptoms in this study. Remarkably, pruritus persisted at least one year in one-third of patients. Turnover of HES-

laden skin cells may help explains the slow abatement of symptoms. In longer-lived cells types of other organs, stored HES may remain indefinitely, since no specific intracellular enzymes capable of catabolizing HES are known to exist. Persistent HES has been observed in renal tubular cells as long as 10 years (27).

As has been previously reported (24, 28, 29), pruritus was found to be generalized in the majority of cases and, when localized, frequently affected the trunk and extremities. Also consistent with previous studies was the occurrence of pruritus in periodic attacks, which have been termed "pruritic crises" (10, 12). While these crises may abate over time, initially they can occur up to approximately 25 times per day, sometimes lasting up to approximately 90 min, and their detrimental impact on patient QoL may be extreme.

The mechanisms of HES-induced pruritus are not fully understood, although HES storage in small cutaneous nerves may play a central role (30). HES storage is proportional to HES dose, and more extensive storage is associated with the development of pruritus (5). Conversely, gradual disappearance of stored cutaneous HES over a period of months to years coincides temporally with the extinction of pruritus symptoms (6). Mechanical and electrical stimulation of affected skin in a patient with HES-induced pruritus elicited itching, stinging and burning (31), which were the most common sensations experienced by the patients in the present study. These observations may point to the involvement of mechanosensitive C- and Aδ-fibres, which have recently been shown to mediate pruritus (32). HES-induced pruritus is generally refractory to antihistamines, and it is tempting to speculate that this type of pruritus may be mediated at least in part by a separate class of histamine-independent C-fibres responsive to the protease mucunain found in the tropical plant *Mucuna pruriens* (33, 34).

Limitations of the present study included retrospective design and lack of a control group. With no control group it was not possible to determine the incidence rate of HES-induced pruritus or the influence of dose, molecular weight and substitution on that rate. In the newly reported randomized Crystalloid vs. Hydroxyethyl Starch Trial (CHEST) of 7,000 patients in intensive care units, the incidence of pruritus after infusion of HES 130/0.4 at the relatively low mean daily dose of 31.6 g was 4.0%, compared with 2.2% of patients receiving 0.9% sodium chloride (35). In the CRYSTMAS study comparing HES 130/0.4 and 0.9% sodium chloride among 196 patients with severe sepsis, no difference in pruritus was observed (36). According to a meta-analysis that included both CHEST and the CRYSTMAS study (37), pruritus was significantly increased by HES 130/0.4 with a pooled relative risk of 1.81 (95% CI 1.37–2.38).

In addition, in the present study the inclusion of only 8 HES 130/0.4 recipients limited statistical power to demonstrate differences vs. HES 200/0.5. In an unpublished randomized trial of 187 patients with sudden hearing loss, as summarized elsewhere (38), the incidence of pruritus was significantly higher, by over 2-fold among patients receiving 10% HES 130/0.4 (19%) than 6% HES 200/0.5 (8%).

The kidney is a major site of HES storage (39), and such storage has been associated with renal failure (40). In 4 recent meta-analyses of randomized trials, HES significantly increased the usage of renal replacement therapy (37, 41–43). Newly issued Surviving Sepsis Guidelines recommend against the administration of HES (44).

The results of the present study do not support the theory that either dose limitation or choice of HES solution can reliably avert HES-induced pruritus. For that purpose alternative fluids should be considered. Effective treatments are much needed to help patients who develop pruritus after HES exposure. Further research into the mechanisms involved may enable the identification of such treatments.

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