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Original Article

The Effect of Topical Heparin Gel on Reducing Hand–Foot Syndrome Symptoms in Cancer Patients Treated with Capecitabine

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Abstract

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Background and Aims Hand–foot syndrome (HFS) is a distinct and relatively frequent toxic skin reaction associated with certain chemotherapy agents, particularly capecitabine. Given the complications of this syndrome and the critical importance of timely and accurate treatment, the present study aims to investigate the efficacy of topical heparin gel in alleviating HFS in cancer patients undergoing treatment with capecitabine.

Methods A total of 40 patients with grade $\leqslant 1$ HFS associated with capecitabine were randomly assigned to intervention and control groups. The intervention group received heparin sulfate gel four times a day (21 days) along with capecitabine treatment, while the control group received only capecitabine and placebo gel. The changes in the severity of HFS and clinical manifestations, including erythema, swelling, blisters, hyperkeratosis, and bleeding, at baseline and 3 weeks posttreatment were evaluated. The data were subsequently validated by Fisher's or Chi-square tests.

Results At the beginning of the study, there were no significant differences between the two groups regarding disease manifestations. However, after the intervention, a significant difference was observed between the groups in terms of erythema and swelling ($p = 0.001$). There were no significant differences between the groups in other manifestations, such as blisters, bleeding, and scaling ($p = 0.99$). Comparison of the degree of HFS in the intervention group showed that 11 patients experienced improvement after the intervention, while all patients in the control group remained at the same degree of syndrome as before the intervention.

Conclusion The management of HFS in cancer treatment includes a combination of prevention, patient education, symptom improvement, and dose-intensity management. According to the results, it can be said that due to the positive effect of topical heparin gel in improving HFS caused by capecitabine and due to the absence of side effects, the use of topical heparin gel is recommended.

Keywords

- topical
- heparin sulfate gel
- hand–foot syndrome
- capecitabine
- chemotherapy
- cancer

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Key Points

- Hand–foot syndrome (HFS) is a distinct and relatively frequent toxic skin reaction associated with capecitabine.
- The efficacy of topical heparin gel in alleviating HFS in cancer patients was investigated.
- Topical heparin gel is recommended due to its positive effect in improving HFS caused by capecitabine.

Introduction

The epidermis of the hands and feet is a specialized area of the skin subjected to high levels of biochemical stress and homeostatic mechanical. Hand–foot syndrome (HFS) or palmar-plantar erythrodysesthesia is an adverse side effect associated with many chemotherapeutic agents, including high-dose methotrexate, cytarabine, and especially oral fluoropyrimidines such as capecitabine (Xeloda).[1] HFS causes redness, swelling, and pain on the palms and soles of the feet. Thick calluses, blisters, or ulcers may also appear, making it difficult to walk or use hands. Furthermore, infectious complications can enhance severity.[2] However, not all patients develop HFS, and the severity of symptoms may differ. Usually, this condition is not life-threatening and rarely requires hospitalization, but it may cause significant discomfort and may affect the daily activities and quality of life of patients.[3] The occurrence of HFS in patients treated with capecitabine is estimated to be between 36 and 70%.[4] The primary approach to managing this toxicity is to either discontinue chemotherapy or adjust the dosage until symptoms improve.[1] Supportive measures, such as analgesics, pyridoxine, oral or topical corticosteroids, and moisturizing creams, are being explored to alleviate pain and discomfort or even to prevent the onset of HFS.[5–7] However, these treatments may be inadequate in severe cases, which could lead to temporary or permanent discontinuation of chemotherapy.

Several topical therapies have been evaluated to prevent HFS. The most well-studied remedy is applying a urea-based cream to the palms of the hands. Using these creams for the soles of the feet is a safe and effective technique for preventing further levels of HFS.[8] Other interventions that have been tested are neurotropin,[9] hydrocolloid dressings with ceramide,[10,11] heparin,[2,12] bis-glyceryl ascorbate,[13] 1% topical pyridoxine (vitamin B6),[14] lanolin, hyaluronic acid,[15] hydrocolloid dressing,[16] topical dimethyl sulfoxide,[15,17,18] and vaseline.[19]

Heparan sulfate (HS) is a highly anionic linear polysaccharide with a strong ability to bind a wide range of proteins under physiological conditions. HS binds to cell surface and matrix proteins, as well as cytokines and chemokines.[20] These interactions influence the maturation and activation of inflammatory cells, the diffusion and adhesion of leukocytes at the endothelium, and their extravasation and chemotaxis.[21] Heparin with anticoagulant activity can inhibit the proliferation of various cell types.[22] In vivo treatment impedes the proliferation of fibroblasts, vascular smooth muscle cells, keratinocytes, and melanocytes, while simultaneously promoting collagen synthesis. Heparin emulates the physiological effects of HS; however, its efficacy is dose-dependent, influencing the plasma membranes of cells in both the dermis and epidermis.[23]

Furthermore, heparin has been demonstrated to modify the binding of keratinocytes, which regulates their proliferation by different mechanisms. Growth factor (KGF) binds to its receptor, influencing cellular proliferation through the mitogenic signal.[24,25] Heparin may be a targeted treatment for inhibiting hyperkeratosis, according to recent research. This study aimed to assess the safety and efficacy of a 3-week topical heparin therapy for capecitabine-induced HFS symptoms.

Patients and Methods

We conducted a clinical trial study on newly diagnosed gastrointestinal and head and neck cancer patients treated with capecitabine. This research was conducted on patients referred to Hajar and Kashani Shahrekord Hospitals in Iran with the mentioned characteristics in 2022. Before starting the study, each participant carefully read the informed consent form and signed the consent form.

Study Design and Participants

Inclusion criteria include newly diagnosed cancer patients for gastrointestinal tract and head and neck cancer treated with capecitabine, age 18 years or older, adequate bone marrow, liver, pancreas, and kidney function, and evidence of early onset of HFS (with a degree of at least one from the beginning of the appearance). Also, the exclusion criteria were if the patient already had a skin or inflammatory disease, the patient's unwillingness to continue cooperation, and in case of allergy to the gel. A total of 40 cancer patients treated with capecitabine were randomly selected and included in the study. The sample size was determined based on the information of previous studies[2] and considering the average pain reduction equal to 2 and the standard deviation of 1.6, as well as the first type error of 0.01 and the second type error of 0.10 equal to 20 people in each group. Patients were divided into two groups of 20 via a simple randomization method; envelopes containing cards A and B were randomly distributed among the patients. In addition to the conventional chemotherapy treatment, group A received heparin sulfate gel (Felbra) 40 mg (Daro Teb pharmaceutical firm) four times a day for 21 days, while group B received only the standard treatment. They received the gel in the form of a placebo (manufactured by the same pharmaceutical manufacturer, Daro Teb, and resembling heparin gel). The study began concurrently with the start of cancer treatment and the emergence of HFS (at least first degree). The chemotherapeutic medication utilized on the patients was capecitabine.

Randomization and Blinding

This study was conducted in a double-blind manner; in this way, neither the patient nor the researcher was aware of the type of intervention. It should be noted that both groups of patients were not deprived of the main and standard treatment. Also, before starting the intervention, the patient was fully assured that he would not be deprived of the main treatment.

Assessment of the Treatment Response

The effectiveness of heparin sulfate gel treatment as a clinical improvement in 3 weeks was recorded by the researcher in the relevant checklist including erythema, swelling syndrome, hyperkeratosis, and blisters. Changes in the degree of HFS were evaluated by a research group team using photographs taken at baseline and at 3 weeks of treatment. The team consisted of two oncologists unaware of the identification, chemotherapy treatment, and administration of the heparin sulfate gel combination received by the patients. To maintain objectivity, the photos were encrypted.[2] It should be noted that in phase III clinical studies, heparin gel with doses of up to 160 mg per day for 4 months, except for the case of mild sensitivity, does not lead to detectable toxicity.[2] Our intervention did not have any side effects for the patients.

Statistical Analyses

After collecting the data, they were entered into SPSS software version 24, to describe the data, frequency and percentage indices were used for qualitative variables, and standard deviation ± mean indices were used for quantitative variables. Checking the normal distribution for the variables was done using the Kolmogorov test. Fisher's or Chi-square test was used for qualitative variables to check the difference between groups, and the independent *t*-test was used for normal quantitative variables. In all the tests, the level of significance was $p \leq 0.05$.

Results

Patient Characteristics

A total of 40 cancer patients in the age range of 20 to 70 years, 20 in the intervention group and 20 in the control group, participated in this study. In total, 23 patients were female and 17 were male ($p = 0.75$). The average age of the participants was 63.25 ± 12.50 in the intervention group and 62.95 ± 13.57 in the control group ($p = 0.94$). In terms of the level of education of the participants, 50% of the intervention group and 50% of the control group were under diploma ($p = 0.54$), and in terms of the type of cancer, 40% of the intervention group and 55% of the control group had colon cancer ($p = 0.25$; ►Tables 1 and 2). According to the significant levels in ►Tables 1 and 2, the two intervention and control groups had no significant differences between each other in terms of qualitative (gender, level of education, type of cancer) and quantitative (age) demographic characteristics.

Clinical Outcomes of Topical Heparin Treatment

The results of this study indicated that prior to the intervention, there were no significant differences between the intervention and control groups regarding disease manifestations, including erythema, swelling, blisters, bleeding, and flaking (►Table 3). Postintervention analysis revealed a significant difference in erythema between the two groups; specifically, 100% of patients in the intervention group exhibited no erythema compared with only 20% of patients in the control group ($p < 0.001$). Similarly, a significant difference was observed in swelling; 100% of patients in the intervention group had no swelling postintervention, whereas 50% of patients in the control group continued to experience swelling ($p < 0.001$).

Regarding other manifestations of the disease (blisters, bleeding, and peeling), there were no significant differences between the two groups after the intervention ($p = 0.99$; ►Table 4).

The comparison of HFS severity between patients in the intervention and control groups demonstrates that 55% (11 patients) in the intervention group were classified as first degree after the recovery intervention, 30% (6 patients) as second degree after the first intervention, and 3 patients initially classified as grade 3 were reassigned to grades 1 and 2, respectively. In contrast, all patients in the control group remained at the same severity level of the syndrome before and after the intervention (►Tables 5 and 6, ►Fig. 1).

Table 1 Frequency distribution of demographic information of the intervention and control groups

Variable		Number (%)	Groups		*p*-Value
			Intervention, number (%)	Control, number (%)	
Gender	Male	17 (42.5)	8 (40)	9 (45)	0.75
	Female	23 (57.5)	12 (60)	11 (55)	
Education level	High school	20 (50)	10 (50)	10 (50)	0.54
	Diploma	18 (45)	8 (40)	10 (50)	
	University	2 (5)	2 (10)	0	
Cancer type	Head and neck	1 (2.5)	1 (5)	0	0.25
	Intestine	19 (47.5)	8 (40)	11 (55)	
	Stomach	17 (42.5)	8 (40)	9 (45)	
	Breast	3 (7.5)	3 (15)	0	

Table 2 Average age of participants in two intervention and control groups

Groups	Standard deviation	Average	*p*-Value
Intervention (20 people)	12.50	63.25	0.94
Control (20 people)	12.57	62.95	

Table 3 The frequency of disease manifestations before the study in two intervention and control groups

Variable		Groups		*p*-Value
		Intervention	Control	
Erythema	Yes	19 (95%)	18 (90%)	0.99
	No	1 (5%)	2 (10%)	
Swelling	Yes	14 (70%)	9 (45%)	0.11
	No	6 (30%)	11 (55%)	
Blister	Yes	8 (40%)	3 (15%)	0.08
	No	12 (60%)	17 (85%)	
Bleeding	Yes	0	1 (5%)	0.5
	No	20 (100%)	19 (95%)	
Flaking	Yes	15 (75%)	9 (45%)	0.05
	No	5 (25%)	11 (55%)	

Table 4 The frequency of disease manifestations after the study in two intervention and control groups

Variable		Groups		*p*-Value
		Intervention	Control	
Erythema	Yes	0	16 (80%)	>0.001
	No	20 (100%)	4 (20%)	
Swelling	Yes	0	10 (50%)	>0.001
	No	20 (100%)	10 (50%)	
Blister	Yes	0	1 (5%)	0.99
	No	20 (100%)	19 95%)	
Bleeding	Yes	0	1 (5%)	0.99
	No	20 (100%)	19 (95%)	
Flaking	Yes	8 (40%)	9 (45%)	0.99
	No	10 (60%)	11 (55%)	

Table 5 The syndrome degree status of patients before the study in two intervention and control groups

Groups	Hand and foot syndrome condition			*p*-Value
	Grade 1	Grade 2	Grade 3	0.99
Intervention	11 (55%)	6 (30%)	3 (15%)	
Control	11 (55%)	6 (30%)	3 (15%)	

Discussion

HFS is a prevalent skin reaction linked to various chemotherapeutic drugs, characterized by symptoms on the hands and feet that lead to patient discomfort and a decline in quality of life. Despite numerous studies conducted, there are currently no effective therapies available for preventing or treating HFS.[26–29] Regrettably, the primary approach to managing

Table 6 The status of syndrome degree of patients after the study in two intervention and control groups

Groups	Hand and foot syndrome condition				*p*-Value
	Grade 1	Grade 2	Grade 3	Recovery	>0.001
Intervention	8 (40%)	1 (5%)	0	11 (55%)	
Control	11 (55%)	6 (30%)	3 (15%)	0	

HFS involves reducing the dosage, extending the time between drug administrations, or potentially stopping treatment, which can have negative consequences for patients.[1] In this randomized, placebo-controlled clinical trial, we investigated the effectiveness of applying heparin topically as a convenient and readily available treatment to help alleviate the symptoms of HFS without disrupting chemotherapy.

Our results indicated that many patients responded favorably to treatment with obvious improvements as early as 3 weeks. A significant difference in erythema was observed between the two groups; specifically, 100% of patients in the intervention group had no erythema, compared with just 20% in the control group. Similarly, a significant difference in swelling was observed; 100% of patients in the intervention group experienced no swelling postintervention, whereas 50% of patients in the control group continued to exhibit swelling.

Various studies have investigated the treatment of HSF caused by capecitabine using local treatments, including heparin, retinoids, and celecoxib. In a survey conducted by Rodríguez et al aimed at assessing the safety and effectiveness of topical heparin on the clinical manifestations and anatomopathological changes of capecitabine-induced HSF, it was demonstrated that topical heparin is an effective and safe treatment for the syndrome's clinical manifestations. However, the study emphasizes the need for further research involving more patients to confirm the potential value and clinical utility of topical heparin.[2]

Another study conducted by Inokuchi et al investigated the effect of treating HFS caused by capecitabine using a topical retinoid, showing that the use of a topical retinoid can be effective.[30] Additionally, Roayaei et al found that administering captopril in patients undergoing chemotherapy with a regimen containing capecitabine reduced the symptoms of HFS 4 weeks after the completion of three chemotherapy cycles. These findings are consistent with those of the present study, further supporting the effectiveness of these treatments in managing HFS.[31]

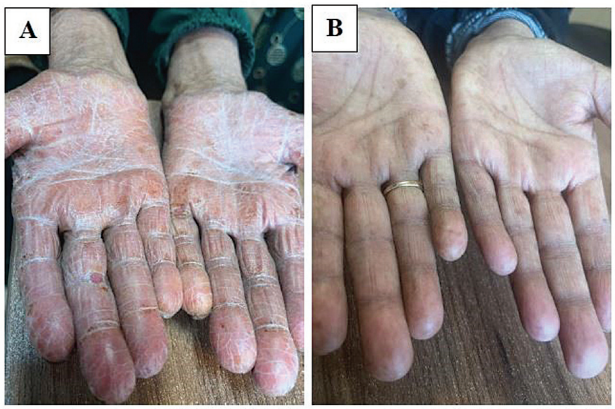

Fig. 1 Improvement of HSF symptoms following treatment with topical heparin gel (**A**) before treatment and (**B**) after treatment. HSF, hand–foot syndrome.

One study that focused on the effect of local interventions on improving the clinical manifestations of HFS was conducted by Shayeganmehr et al. This study investigated the medicinal and clinical effect of celecoxib topical hydrogel for managing HFS caused by chemotherapy. HFS scores were determined at the beginning and end of the trial. Analysis of the differences in HFS grades revealed statistically significant differences between the two groups. Overall, this study demonstrated that celecoxib hydrogel could be a promising intervention for managing the side effects of HFS.[32]

A study conducted by Li et al aimed to evaluate the effectiveness of topical heparin ointment for HFS during multikinase treatment. The results of this study demonstrated that 66.7% of grade 1 patients, 83.3% of grade 2 patients, and 100% of grade 3 patients showed improvement in disease symptoms. Additionally, 15.4% of patients required a dose reduction of multikinase; however, there were no interruptions or discontinuations of the treatment.[33]

Based on our findings, there were no significant differences between the two groups in other manifestations of HFS, including blisters, bleeding, and peeling, after the intervention. The comparison of HFS severity between patients in the intervention and control groups demonstrates that 55% (11 patients) in the intervention group were classified as first degree after the recovery intervention, 30% (6 patients) as second degree after the initial intervention, and 3 patients initially classified as grade 3 were reassigned to grades 1 and 2, respectively. In contrast, all patients in the control group remained at the same severity level of the syndrome before and after the intervention. Therefore, the present study was largely in line with the above studies.

Despite the variations and similarities between the current study and previous studies, it can be concluded that most of the existing research is consistent with the current study. This alignment emphasizes the critical importance of establishing interventions to manage the clinical manifestations of HFS. Treatment for HFS is mostly determined by the severity of the symptoms and their influence on quality of life. HFS is effectively managed during cancer therapy by a combination of prevention, treatments, patient education, and supportive measures.

The current study's findings suggest that the intervention factor, heparin sulfate, is responsible for these changes. It also demonstrates that heparin sulfate has improved the clinical manifestations and, in the end, reduced the severity of HFS. Heparin sulfate not only has been able to improve the inflammatory process of capecitabine-induced HFS, but also prevented these patients from discontinuing treatment, which has significant and valuable clinical significance.

Conclusion

In this study, the effect of topical heparin gel in improving HFS caused by capecitabine was shown. Considering that the management of HFS in cancer treatment includes a combination of prevention, patient education, symptom improvement, and dose intensity management, in most cases, the most effective way to manage HFS after its appearance is dose modification in the form of dose delay or dose reduction or even treatment discontinuation. According to the results, it can be stated that due to the positive effect of topical heparin gel in improving HFS caused by capecitabine and due to the absence of side effects, the use of topical heparin gel is recommended.

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Conflict of Interest

None declared.

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