Original Article

The Effect of Topical Vitamin K1 on the Treatment of Cetuximab-Induced Skin Rashes in Metastatic Colorectal Cancer Patients

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Abstract

Background: Considering the prevalence of cetuximab-induced rashes in colorectal cancer patients and its impact on patient's quality of life and treatment, this study aimed at investigating the effect of topical vitamin K1 on the treatment of skin rashes in metastatic colorectal cancer patients treated with cetuximab.

Materials and Methods: This randomized, controlled, triple-blind, clinical trial was conducted on 49 metastatic colorectal cancer patients who were candidates for cetuximab treatment and referred to Omid Hospital in Isfahan during 2021–2022. Vitamin K1 cream with a concentration of 0.1% in the intervention group (n = 25) and placebo cream in the control group (n = 24) were prescribed twice a day (in the morning and before bedtime) for eight weeks. The rash grade was recorded based on common terminology criteria for adverse events-4 (CTCAE-4) criteria before the intervention and in the fourth and eighth weeks during the intervention.

Results: During the intervention, skin rash grades in the fourth and eighth weeks with the means of 1.00 ± 0.64 and 0.84 ± 0.55, respectively, were significantly lower in the intervention group, as compared with the control group with the means of 1.42 ± 0.65 and 1.25 ± 0.68, respectively (P value < 0.05). Moreover, the severity of skin rashes decreased significantly in the intervention group over time during eight weeks (P value < 0.05); however, its decrease was not significant in the control group (P value > 0.05).

Conclusion: Topical vitamin K1 cream had a significant effect on reducing the severity of cetuximab-induced skin rashes over eight weeks of treatment.

Keywords: Cetuximab, colorectal cancer, skin rash, vitamin K1

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Introduction

Colorectal cancer is the most common malignancy of the gastrointestinal system and the fourth most common cancer worldwide.[1,2] One of the significant strategies in the treatment of malignancies of epithelial origin, such as colorectal cancer and head and neck squamous cell carcinoma, is the mechanism of blocking the epidermal growth factor receptor (EGFR) pathway. Cetuximab is a monoclonal antibody that binds to EGFR and deactivates it.[3,4] While this treatment method is usually better tolerated than conventional chemotherapy methods, it has a unique complication related to its mechanism of action. EGFR is expressed not only in tumor cells but also in epidermal cells. Therefore, skin disorders including skin rashes, itching, dry skin, hypertrichosis, and nail disorders are observed in approximately 80% of patients treated with cetuximab.[5-7] In case of lack of proper management, skin

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disorders can lead to dose reduction and finally discontinuation of treatment in about 15–25% of patients.[8] Skin problems are rarely life-threatening; however, they disrupt the quality of life and the completion of treatment, so the effective management of skin problems is also essential for obtaining the maximum effect of treatment and maintaining the quality of life.[9] Consequently, according to the clinical guidelines, the use of orally administered tetracyclines, 1% moisturizing hydrocortisone cream, and topical steroids is recommended to solve these problems. However, the mentioned treatments have weak effects or are accompanied by significant complications.[10,11] As a result, recently some studies have introduced the use of vitamin K1 topical cream as an effective prevention method against EGFR-induced skin rashes[12-14] and stated that this cream as a nonsteroidal topical substance is usually free from complications and has acceptable efficacy in preventing or reducing the severity of cetuximab-induced skin rashes.[12-14] In contrast, some other studies have not found topical vitamin K1 to be effective in preventing acneiform rashes during cetuximab treatment or have not reported a significant effect on improving rashes of grade 2 or higher.[9,15-17]

Therefore, it seems that more studies are still required to investigate the required duration of the administration of this cream and its effectiveness on different degrees of cetuximab-induced skin rashes. This study aimed at investigating the effect of topical vitamin K on the skin rashes of metastatic colorectal cancer patients treated with cetuximab.

Materials and Methods

This study was a randomized, controlled, triple-blind, clinical trial. The study population included all metastatic colorectal cancer patients that were candidates for cetuximab treatment and were referred to Omid Hospital in Isfahan from September 2021 to March 2022.

At the confidence level of 95%, the test power of 80%, and taking into account the average effect size of 0.6, the sample size was determined to be 24 cases in each group and was then increased to 27 cases in each group considering the 10% possible dropout.

The study inclusion criteria consisted of patients over 18 years of age with metastatic colorectal cancer who were candidates for treatment with cetuximab (rat sarcoma gene (RAS) non-mutant (WILD type)) and had grade 1–4 skin complications (according to CTCAE criteria) after receiving cetuximab. Moreover, not having radiotherapy history, not having previous skin lesions (including rash, acne, pustule, and inflammatory erythema), not being pregnant and breastfeeding, not having a previous history of allergy to compounds containing vitamin K, not suffering from psychiatric disorders, and not taking drugs that interfere with the use of topical vitamin K were regarded as the other inclusion criteria. If cetuximab treatment was discontinued for any reason by the attending physician or if the patient did not wish to continue cooperating in the study, the patient was excluded from the study.

After obtaining the code of ethics from the ethics committee of Isfahan University of Medical Sciences (approval code: IR.MUI.MED.REC.1400.326), the clinical trial code (approval code: IRCT20150304021338N3), and written consent from eligible patients to enter the study, 54 patients were randomly selected. Then, random numbers were generated by random allocation software and divided into two parts. Each number was written on a piece of paper and placed in an envelope. Then, each patient was asked to choose one envelope from among the envelopes. According to the selected envelope, the patient was assigned to one of two groups.

As mentioned, the studied patients had metastatic colorectal cancer, were found to have rat sarcoma gene (RAS) wild type specified by the performed genetic tests and, as a result, were candidates for treatment with cetuximab (Erbitux Brand, Merck Pharmaceutical Company) considering the standard protocol as follows: 400 mg/m2 intravenous injection as a loading dose and then 250 mg/m2 weekly or 500 mg/m2 every two weeks without a loading dose. Both of the mentioned methods are identical.

At the beginning of the study, the patients' demographic information including their age and gender was recorded. During the examination, the extent and degree of the spread and incidence of cetuximab-induced skin rashes were evaluated and recorded. Before starting the study, the degree and grade of skin rashes were determined and recorded based on CTCAE4 criteria in terms of scores ranging from 0 to 4. It should be noted that grade 5 lesions (fatal lesions) were not taken into consideration in this study [Table 1].

The patients' performance status (PS) was recorded according to the PS criteria of the World Health Organization (Eastern Cooperative Oncology Group (ECOG)/WHO score system) as a score between 0 and 4 [Table 2].[18] According to this criterion, a score of 5 means a nonliving person, which had no relevance in this study. The sites of metastatic lesions were also recorded.

To comply with ethical principles, topical hydrocortisone cream was prescribed by the attending physician for all patients during the process of receiving cetuximab. In addition, the patients in the intervention group were treated with 0.1% topical vitamin K cream twice a day (one knuckle at a time) in the morning and before bedtime for eight weeks from the onset of skin rashes. Patients in the control group were also treated with a placebo topical cream following a similar instruction to that of the intervention group.

It should be noted that at the time of prescribing cetuximab, these items were recommended by the attending physician: Avoid prolonged sun exposure, tanning booths, and sun lamps during treatment with cetuximab and use sunscreen and wear protective clothing when outdoors.

Table 1: Rash grade based on common terminology criteria for adverse events version 4 (CTCAE4)

Skin and subcutaneous tissue disorders					
Adverse event	**1**	**2**	**3**	**4**	**5**
Rash acneiform	Papules and/or pustules covering <10% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10–30% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental Activities of daily living (ADL)	Papules and/or pustules covering >30% body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care Activities of daily living (ADL); associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % body surface area (BSA), which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death

Table 2: Patients' performance status according to the performance status criteria of the World Health Organization (ECOG/WHO score system)

ECOG/WHO score system (0–5)	Definition	Karnofsky score
0	Fully active, able to carry on all pre-disease activities without restriction	90–100
1	Restricted physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature	70–80
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hour	50–60
3	Capable of only limited self-care, confined to bed or chair for 50% or more of waking hours	30–40
4	Completely disabled; cannot carry on any self-care; confined to bed or chair	10–20

ECOG=Eastern Cooperative Oncology Group, WHO=World Health Organization, PS=performance score

The manner of using the drug combination for the first time was taught to the patients in both groups under the supervision of the researcher, and the necessary recommendations including limiting the use of hot water, using vitamin cream on the face and body after washing, bathing, and shaving, and avoiding simultaneous use of alcoholic creams or other medicated creams (except sunscreen creams and creams with no therapeutic effect) were given to the patients. It was requested from the patients of both groups to refer in case of new rashes or an increase in the intensity of previous rashes.

It is worth mentioning that the cream prepared for the intervention group was composed of injectable vitamin K1 (phytonadione) (VIKDIC Brand, Caspian Pharmaceutical Company) with a concentration of 0.1% and was dissolved and diluted in the cream base. The mentioned combination was prepared by a clinical pharmacist. Placebo cream was also prepared with a cream base and without any other additives by the same clinical pharmacist and in a sterile environment so that it was completely similar to vitamin K cream in terms of color, shape, smell, and consistency.

Then, to maintain blinding requirements, two creams were placed in completely similar containers with the same volume, marked with A and B labels, and provided to the researcher. In this way, the researcher, the patient, the person evaluating the patients' clinical information, and the statistical analysis specialist were not aware of the type of intervention in each of the two groups.

Finally, the skin rash grade (based on CTCAE4 criteria) was recorded in the fourth and eighth weeks after the intervention.

Data analysis

The collected data were entered into Statistical Package for the Social Sciences (SPSS) software (Ver. 26). Qualitative and quantitative data were presented as means ± standard deviation (SD) or n (%), respectively. According to the results of the Kolmogorov–Smirnov test indicating the normal data distribution, univariate analysis of variance was used to compare the means of quantitative variables between the two groups by adjusting the patients' age, gender, PS, and site of metastasis. Furthermore, the repeated-measures analysis of variance was used to compare the changes in quantitative variables before and after the intervention by adjusting the patients' age, gender, PS, and site of metastasis. The Chi-squared test was also used to compare the frequency distribution of qualitative data. In all analyses, a significance level of less than 0.05 was considered.

Results

Two of the 27 patients in the intervention group (one due to discontinuation of treatment with cetuximab and one due to non-referral in subsequent follow-ups) and three of the 27 patients in the control group (two due to discontinuation of treatment with cetuximab and one due to non-referral in subsequent follow-ups) were excluded from the study [Figure 1].

Of the 25 patients in the intervention group with a mean age of 57.28 ± 8.91 years, 80% and 20% were male and female, respectively, while of the 24 patients in the control group with a mean age of 57.67 ± 8.30 years, 79.2% and 20.8% were male and female, respectively (P value > 0.05). Also, the percentage types of chemotherapy regimen with cetuximab including 5 Fluorouracil, Oxaliplatin, Leucovorin (FOLFOX)/

Capecitabine, Oxaliplatin (CAPEOX), 5 Fluorouracil, Leucovorin, Irinotecan (FOLFIRI), and Irinotecan in the intervention group were 44%, 44%, and 12%, respectively, and in the control group, it was 54.2%, 37.5%, and 8.3%, respectively. In addition, there was no significant difference between the two groups in terms of types of chemotherapy, PS, and site of metastasis (P value > 0.05) [Table 3].

Furthermore, there was no significant difference between the two groups in terms of the skin rash grade before the intervention (1.56 ± 0.58 vs. 1.46 ± 0.66; P value = 0.407), but the skin rash grade in the intervention group in the fourth and eighth weeks with the means of 1.00 ± 0.64 and 0.84 ± 0.55 during the intervention was significantly lower than the skin rash grade in the control group in the fourth and eighth weeks with the means of 1.42 ± 0.65 and 1.25 ± 0.68, respectively (P value < 0.05). Moreover, with the passage of time during 8 weeks, the severity of skin rash decreased significantly in the intervention group over 8 weeks of treatment (P value < 0.05), while a slight and insignificant decrease was observed in the intensity of these rashes in the control group (P value > 0.05) [Table 4, Figure 2].

In addition, it was also found that in the group receiving vitamin K, before and during the eighth week of the intervention, the skin rash grades did not differ significantly between different types of chemotherapy (P value > 0.05), but in the fourth week during the intervention, the skin rash grades in patients under FOLFOX/CAPEOX plus cetuximab with a mean of 1.36 ± 0.51 were significantly higher than the

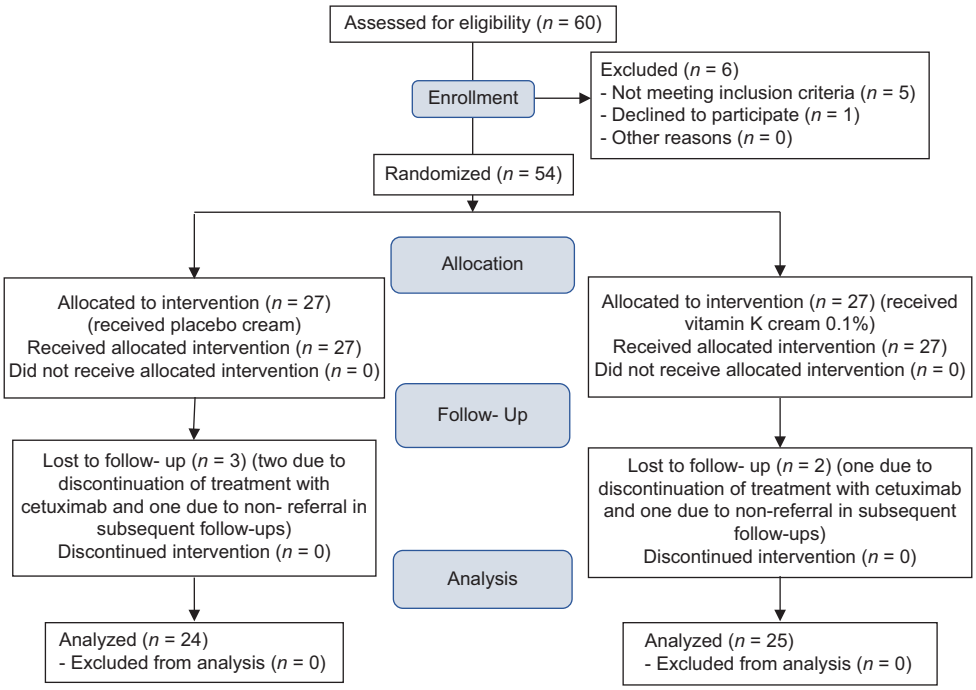


Figure 1: Consort flow chart of patients

Table 3: Patients' basic and clinical characteristics in the two study groups

Variables		Intervention group (n=25)	Control group (n=24)	P
Sex	Male	20 (80.0%)	19 (79.2%)	0.942
	Female	5 (20.0%)	5 (20.8%)	
Age; year		57.28±8.91	57.67±8.30	0.876
Type of chemotherapy	FOLFOX/CAPEOX	11 (44%)	13 (54.2%)	0.733
	FOLFIRI	11 (44%)	9 (37.5%)	
	IRINOTECAN	3 (12%)	2 (8.3%)	
PS score*	1	13 (52.0%)	13 (54.2%)	0.483
	2	11 (44.0%)	8 (33.3%)	
	3	1 (4.0%)	3 (12.5%)	
Metastasis location	Liver	13 (52.0%)	8 (33.3%)	0.510
	Lung	5 (20.0%)	5 (20.8%)	
	Liver and lung	5 (20.0%)	9 (37.5%)	
	Other	2 (8.0%)	2 (8.3%)	

FOLFOX: 5Fluorouracil, Oxaliplatin, Leucovorin; FOLFIRI : 5Fluorouracil, Leucovorin, Irinotecan; CAPEOX: Capecitabine, Oxaliplatin

two types of chemotherapy FOLFIRI and IRINOTECAN plus cetuximab with an average of 0.82 ± 0.60 and 0.33 ± 0.27, respectively (P value < 0.05). However, in the control group, there was no significant difference in the skin rash grades among the three types of chemotherapy in any of the three follow-up times (P value > 0.05) [Figure 3].

Discussion

The results of the present study revealed that topical vitamin K1 cream had a significant effect on the improvement of cetuximab-induced skin rashes in such a way that the skin rash grade was significantly lower in the intervention group, as compared with the control group, in the fourth and eighth weeks during the administration of this cream. During eight weeks, the intensity of these skin rashes decreased significantly in the intervention group over time, while this decrease was insignificant and minor in the control group.

In line with the findings of this study, Hofheinz *et al*. evaluated the effect of topical vitamin K1 in addition to the administration of doxycycline on the treatment of cetuximab-induced skin

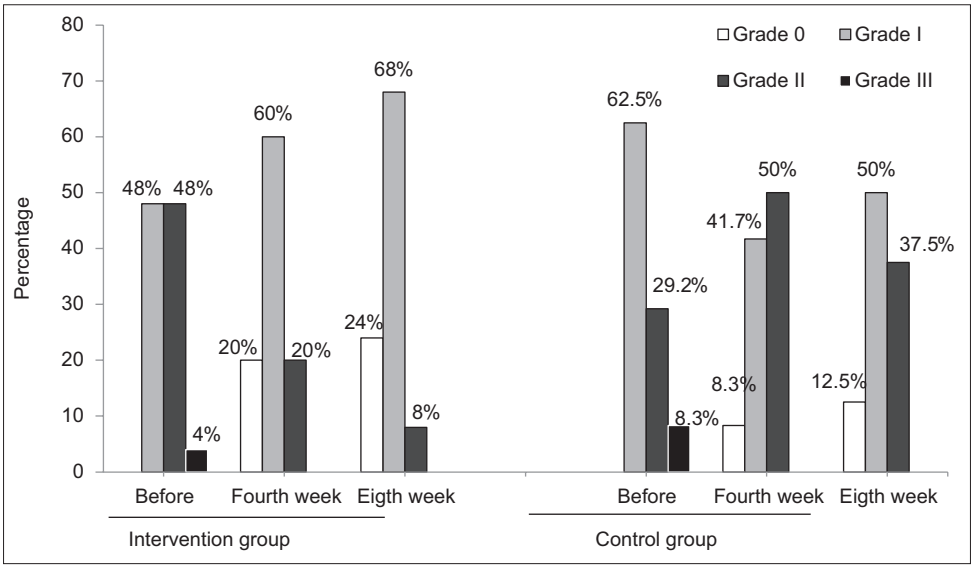
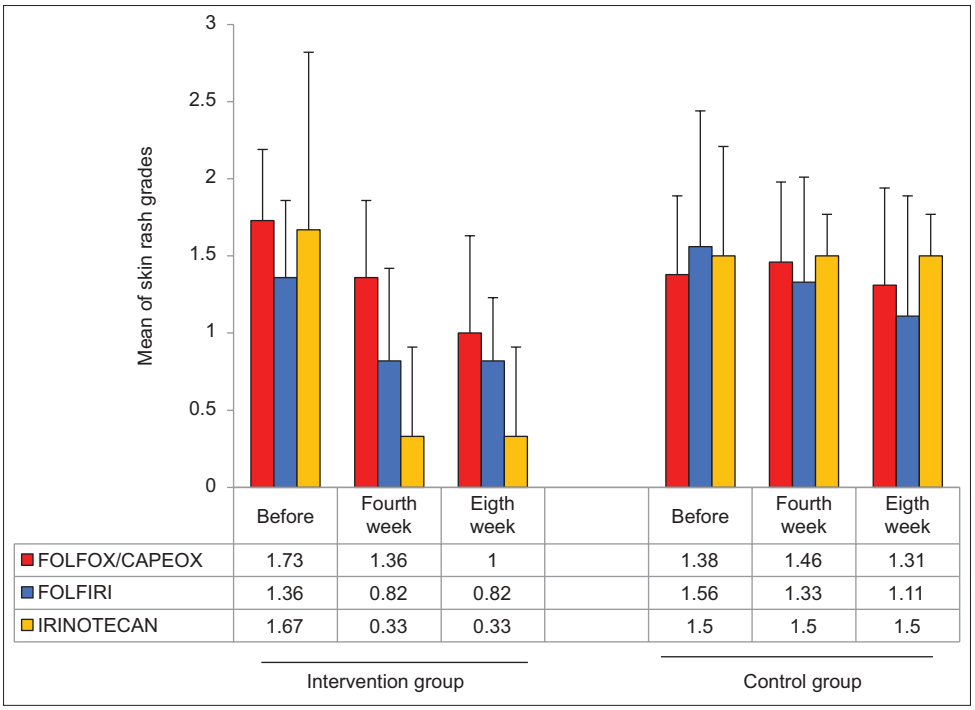


Figure 2: Frequency of skin rash grades during the follow-up periods in the two study groups



	Before	Fourth week	Eigth week		Before	Fourth week	Eigth week
FOLFOX/CAPEOX	1.73	1.36	1		1.38	1.46	1.31
FOLFIRI	1.36	0.82	0.82		1.56	1.33	1.11
IRINOTECAN	1.67	0.33	0.33		1.5	1.5	1.5

Figure 3: Mean of skin rash grades based on type of chemotherapy in the two study groups. FOLFOX: 5Fluorouracil, Oxaliplatin, Leucovorin; FOLFIRI: 5Fluorouracil, Leucovorin, Irinotecan; CAPEOX: Capecitabine, Oxaliplatin

Table 4: Mean skin rash grade in the follow-up period in the two study groups

Skin lesion grade	Intervention group ($n=25$)	Control group ($n=24$)	P*
Before intervention	1.56±0.58	1.46±0.66	0.417
Fourth week	1.00±0.64	1.42±0.65	0.022
Eighth week	0.84±0.55	1.25±0.68	0.035
P**	0.002	0.078	

*: The significance level obtained from the univariate analysis of variance test by adjusting the patients' age, gender, type of chemotherapy, performance status, and the site of metastasis to compare the mean rash grade between the two groups in each of the follow-up periods. **: The significance level obtained from the repeated-measures analysis of variance test by adjusting the patients' age, gender, performance status, and the site of the metastasis to compare the mean rash grade over time during eight weeks in each of the groups

complications and indicated that according to the WoMo criteria, the severity of skin rashes decreased from the fifth week after the use of vitamin K1 cream, while no effect was observed on reducing the percentage of the affected skin surface, and only 20% of grade 2 skin rash was reduced. In addition, less cracking was reported during the skin treatment period, indicating the potential effect of vitamin K1 cream. They claimed that vitamin K1 cream cannot be considered a standard of care for preventing acne-like skin rashes; however, it seems that skin moisturizers containing vitamin K should be further investigated due to the less severity of rashes observed following the use of vitamin K.[17] It must be stated that the mentioned study, like our study, had adjusted other confounding factors such as patients' PS, disease severity, age, and gender in the two studied groups.

Pinto *et al*.'s study on 33 patients with metastatic cancer indicated that vitamin K cream had a favorable effect in managing skin rashes so that the decrease in skin rash to grade 1–0 was observed in 36.4% of patients, and 39.4% of patients showed unchanged grade 2. The increase to grade 3 in skin rash was observed in 24.2% of patients. Good skin rash symptom control was obtained in 69.2% of patients.[19]

Another study suggested that topical vitamin K1 may be useful for cetuximab-induced rashes in patients with metastatic colorectal cancer. In this study, there was no report of any grade 4 rash, and the ratio of grade 3 and 2 skin rashes in the first eight weeks of treatment was reported to be 15% and 22.5%, respectively.[13]

The results of Ocvirk *et al*.'s study addressing the preventive use of vitamin K1 cream to reduce skin problems during treatment with cetuximab in patients with metastatic colorectal cancer indicated that 17.8% of patients had grade 2 skin rash, while 0.7% of them had grade 3 skin rashes during the 8-week treatment period. They stated that the administration of this topical cream can significantly reduce the severity of cetuximab-induced skin rashes.[14] In the eighth week of treatment in our study, grade 2 and 3 skin rashes were reported to be 68% and 8%, respectively, while the control group had a significant percentage of patients with grade 3 skin rashes (37.5%).

With regard to the effectiveness of this cream, it can be stated that phytonadione (vitamin K1) is the main form of vitamin K in the diet and is metabolized into menaquinones (vitamin K2), the active forms, especially menaquinone 4 through an intermediary of menadione (vitamin K3).[20] Vitamin K3 is a strong phosphatase inhibitor and is found to be a strong activator of EGFR. Moreover, as compared to vitamins K1 and K2, vitamin K3 has a protective effect against erlotinib and cetuximab in malignant and normal keratinocytes *in vitro*.[21]

However, a few studies have also reported results contrary to the significant effects of this cream. For example, Jo *et al*. reported that the preventive use of topical vitamin K1 cream was ineffective in reducing acneiform rashes in patients with metastatic colorectal cancer treated with cetuximab.[15]

Furthermore, the effects of vitamin K1 cream on the skin rashes of men and women have been reported differently in another study.[16] According to this study, hormonal modulation or gender-specific expression patterns of EGFR may have a role in yielding more positive effects on female patients' skin rashes. The higher density of sebaceous glands and the terminal character of the facial hair may result in higher EGFR expression in the facial skin in men.[22] Therefore, the ineffectiveness of vitamin K1 in men can be attributed to the frequency of cream administration and the dose of vitamin K1 (0.1%).[22]

Considering the size of the reported effect and the value of vitamin K1 cream (Reconval K1) for women, it can be suggested as a prophylactic treatment besides doxycycline in women who have started anti-EGFR treatments.

Considering the potential role of gender in this respect, the effect of gender as a confounding variable was also adjusted in our study. It should be taken into account that the CTCAE4 criterion was used in the present study to grade skin rashes, which can be considered a limitation of our study, while the WoMo criterion as a more accurate grading system for describing skin reactions related to anti-EGFR drugs was used in some other studies. Hence, it is recommended to carry out more studies evaluating the effect of vitamin K1 in addition to other moisturizers, based on different skin rash grading criteria.

Conclusion

The findings of the present study revealed that topical vitamin K1 cream had a significant effect on reducing the severity of cetuximab-induced skin rashes over eight weeks of treatment.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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