JOURNAL OF
CONTEMPORARY MEDICINE

DOI:10.16899/jcm.1143566
J Contemp Med 2022;12(6):827-831

Original Article / Orijinal Araştırma

Experience in a Epidermal Growth Factor Use in Diabetic Foot Ulcers

Diyabetik Ayak Ülserlerinde Epidermal Büyüme Faktör Kullanımı Deneyimlerimiz

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Abstract

Aim: The global diabetes prevalence in 20-79 year olds in 2021 was estimated to be 536.6 million people. Diabetic foot ulcers are one of the most common complications of diabetes. It negatively influence the patients' quality of life. Multidisciplinary treatment is required in the treatment of diabetic foot ulcers. In our study, we shared our experience of using intralesional epidermal growth factor in foot ulcers with diabetic neuropathy.

Material and Method: The study was conducted retrospectively with 29 patients who applied to our clinic due to diabetic foot wounds between January 2014 and December 2020, who had no wound infection and osteomyelitis, who underwent epidermal growth factor in accordance with the study criteria. In our study, epidermal growth factor of 75µg/day 3 times a week was applied intralesionally to diabetic ulcers for 4-8 weeks.

Results: A total of 29 patients were included in the study. 21 of the patients were male and 8 of them were female. The mean age was 59.82. One patient had signs of osteomyelitis. The mean ulcer width of the patients was found to be 3.44 cm².

Conclusion: Three important results were obtained from the study. First; The efficacy of epidermal growth factor in the treatment of patients with diabetic foot ulcers has been observed. The second important finding was to ensure the safe epithelialization of the standing ulcers without impairing the quality of life of the patients. Thirdly, after debridement, treatment with epidermal growth factor was found to provide a significant improvement in wounds.

Keywords: Diabetes, epidermal growth factor, diabetic foot ulcer

Öz

Amaç: Küresel diyabet prevalansı 2021 yılında 20-79 yaşlarındaki 536,6 milyon kişi olduğu tahmin edilmektedir.

Diyabetik ayak ülserleri diyabetin en yaygın komplikasyonlarından birisidir. Hastaların yaşam kalitesini olumsuz etkilemektedir. Diyabetik ayak ülserlerinin tedavisinde multidisipliner tedavi gerekmektedir. Çalışmamızda diyabetik nöröpatili ayak ülserlerinde intralezyonel epidermal büyüme faktörü kullanım deneyimlerimizi paylaşılmıştır.

Gereç e Yöntem: Çalışma Ocak 2014 - Aralık 2020 tarihleri arasında polikliniğimize diyabetik ayak yarası nedeniyle müracaat eden, yara enfeksiyonu ve osteomyeliti olmayan çalışma kriterlerine uygun epidermal büyüme faktörü uygulanan 29 hasta ile retrospektif olarak yapılmıştır. Çalışmamızda tedavide, haftada 3 kez 75µg/gün epidermal büyüme faktörü 4-8 hafta intralezyonel olarak diyabetik ülserlere uygulandı.

Bulgular: Toplam 29 hasta çalışmaya alındı. Hastalardan 21 tanesi erkek, 8 tanesi kadındı. Yaş ortalaması 59,82 idi. Bir hastada osteomyelit bulgusu vardı. Hastaların ülser genişlikleri ortalama 3,44 cm² olarak bulundu. Epidermal growth faktörün uygulandığı hastaların yara iyileşmesinin hızlandığı 4-8 haftalık sürede iyileştiği görülmüştür.

Sonuç: Çalışmadan üç önemli sonuç çıkarılabilir. Birincisi; epidermal büyüme faktörünün, diyabetik ayak ülserleri olan hastalarda tedavide etkinliği gözlemlenmiştir. İkincisi; hastaların yaşam kalitelerini bozmadan ayakta bulunan ülserlerin güvenli şekilde epitelize olmasını sağlamıştır. Üçüncüsü; debritman sonrası epidermal büyüme faktörü ile tedavisiyle yaralarda gözle görülür bir düzelme sağlanmıştır.

Anahtar Kelimeler: Diyabet, epidermal büyüme faktör, diyabetik ayak ülseri

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Received *(Geliş Tarihi)*: 13.07.2022 **Accepted *(Kabul Tarihi)*:** 01.11.2022

INTRODUCTION

The global diabetes prevalence in 20-79 year olds in 2021 was estimated to be 10.5% (536.6 million people), rising to 12.2% (783.2 million) in 2045.[1] Diabetic foot ulcers (DFU) are one of the most common complications of diabetes. It negatively affects the patients' quality of life.[2] Annual incidence in diabetic patients is over 2%. Foot ulcer is detected with a rate of 5-7.5% in patients with peripheral neuropathy.[3] It is estimated that 15% of diabetic patients develop diabetic ulcers at some point in their lives.[1] 10-30% of patients with DFU are amputated.[3] DFU patients are determined to stay in hospital for more than 50% of their hospital stay compared to non-ulcer diabetic patients.[1]

According to Turkey Diabetes, Hypertension, Obesity and Endocrinology Diseases Prevalence Study, Diabetes prevalence increased from 7.7% to 13.7% (90% increase) and obesity increased by 40%. It was also found that impaired glucose tolerance increased 106% compared to a prevalence study conducted 11 years ago.[4]

The most important issues to be considered in the treatment of patients with diabetic foot ulcers are metabolic control, wound debridement, wound care (dressing), removal of pressure if there is pressure, treatment of infection and revascularization if necessary.[5] In the new treatment method, the first is the wound closure with a graft or flap, while the second is the treatment with intralesional epidermel growth factor (EGF). EGF treatment is mostly preferred in patients with low-grade neuropathic ulcers.[1] Clinical studies have shown the efficacy of EGF in low-grade neuropathic foot ulcers.[6]

In our clinic, we planned to demonstrate the effectiveness of intralesional EGF in foot ulcers with diabetic neuropathy.

MATERIAL AND METHOD

Twenty-nine patients who applied to our outpatient clinic due to diabetic foot wounds between January 2014 and December 2020 and who were treated with EGF without wound infection and osteomyelitis were included in the study. The data of the patients were collected in the forms created. The patient's age, gender, number of years of diabetes, additional disease status, infection status, osteomyelitis status, information about which foot is involved, and which part of the foot is affected are included in the forms. EGF treatment was planned for the patients in terms of infection and osteomyelitis, after consultation with the infectious diseases unit. Patients with infection or osteomyelitis were included in the study after treatment with osteomyelitis, and debridement was performed before treatment in case of it is required. In the treatment, 75µg / day EGF was administered to diabetic ulcer patients intralesionally for 4-8 weeks, 3 times a week. The progress of the wounds was monitored and recorded every week. The EGF was obtained in accordance with the cold chain at +4 degrees. It was diluted with 5 ml of saline and applied intralesionally to the periphery and base of the wound (**Figure 1**).

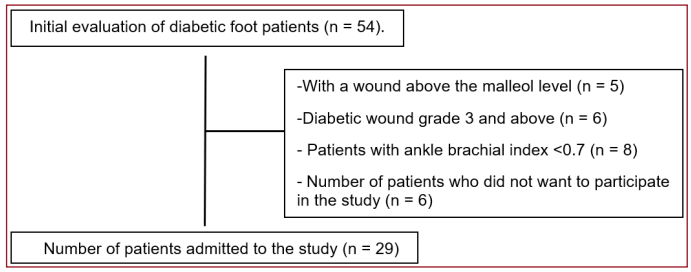

Figure 1: Study work flow chart

The study was carried out with the permission of Kayseri City Training and Research Hospital Ethics Committee (Date: 01.04.2021, Decision No: 353) and made in accordance with the Principles of the Declaration of Helsinki.

RESULTS

In the evaluation of the patient's data, a total of 29 patients were included in the study. Of the patients, 72.4% (n=21) were male and 27.6% (n=8) were female. The mean age was 61.9±11.2 years. Additional disease was detected in almost all (93%) of the patients participating in the study. One patient had signs of osteomyelitis. The patient was included in the study again after treatment for osteomyelitis. The mean ulcer width of the patients was found to be 3.44 cm². Of the ulcers, 62% had a fibrotic appearance, 31% had necrotic material, and 7% had a granular appearance.

The mean ulcer formation time was determined as 16.2 days. Of the ulcers, 44.8% were localized in *the right foot and 55.2% were localized in the left foot. The mean duration of diabetes was found to be 20.9±7.4 years. All of the patients were receiving insulin. Before the patients were enrolled in the study, debridement was performed. The wound was cleaned and then treatment was started. Amputation was required in 17.2% of patients. Of the patients, 96.5% had a single ulcer, and 3,4% had more than one ulcer. EGF was applied to the patients 3 times a week at 75µg / day. The application was performed for 4 weeks in 65.5%, 6 weeks in 24.2%, and 8 weeks in 10.3% of the patients. In the follow-up of the patients, the ulcers of 19 patients healed after 4 weeks of treatment. The ulcers of seven patients healed after 6 weeks of treatment. The ulcers of three patients responded to the treatment in 8 weeks (**Table 1**) (**Figure 2, 3, 4**).

No local infection was observed in the follow-up of EGF in terms of its side effects. Sensitivity was observed in 58.6%, burning in 44.8%, chills in 96.5%, fever in 17.2%, and vomiting in 24.1% of the patients and hypotension in 58.6% of the patients. Headache symptoms were observed after administration in 62% of the patients (**Table 2**).

Figure 2: Diabetic foot ulcer on the sole of the foot that has been cleaned and EGF treatment has been initiated

Figure 3: Grafting treatment of granulated diabetic foot ulcer

Figure 4: Diabetic foot ulcer in the heel area that began to epithelize after EGF treatment.

Table 1. Clinical data of the patients

Patient characteristics	Mean	Number of patients, Percent (n,%)
Gender		
Female		8 (27.6)
Male		21 (72.4)
Age Range (33-84 years)	59.82	
Osteomyelitis		
No		28 (96.6)
Yes		1 (3.4)
Additional disease		
Yes		27 (93.1)
No		2 (6.9)
Ulcer width (1-15 cm^2)	3.44	
Wound condition		
Fibrotik		18 (62.1)
Necrotic		9 (31.0)
Granüle		2 (6.9)
Ulcer duration (7-30 days)	16.2	
Localization		
Right foot		13 (44.8)
Left foot		16 (55.2)
Diabetes mellitus duration (8-35 years)	20.2	
Insulin use		
Yes		29 (100)
No		0 (0)
Debridement		
Yes		29 (100)
No		0 (0)
Amputation		
Yes		5 (17.2)
No		24 (82.8)
Multiple ulcer conditions		
No		28 (96.6)
Yes		1 (3.4)
EGF duration (weeks)		
4 Week		19 (65.5)
6 Week		7 (24.2)
8 Week		3 (10.3)
Number of applications per week with EGF		
3 times a week		29 (100)
Others		0 (0)

Table 2. Side effects due to EGF

Side effects in patients	Number of patients / Percentage (n /%)
Local infection	
Yes	0 (0)
No	29 (100)
Sensitivity	
Yes	17 (58.6)
No	12 (41.7)
Burn	
Yes	13 (44.8)
No	16 (55.2)
Shake	
Yes	28 (96.6)
No	1 (3.4)
Fever	
Yes	5 (17.2)
No	24 (82,.8)
Vomiting	
Yes	7 (24.1)
No	22 (79.3)
Hypotension	
Yes	17 (58.6)
No	12 (41.4)
Headache	
Yes	18 (62.1)
No	11 (37.9)

DISCUSSION

Diabetic foot ulcers are an important cause of morbidity, and impaired quality of life results in high treatment costs and it is the most important risk factor for lower extremity amputation. Five years mortality in diabetes and extremity ischemia is 30%. Mortality rate in individuals who have undergone amputation due to DFU is approximately 50%.[7] It is well known that hyperglycemia is the primary trigger of vascular functional disorders, microvascular decline, angiogenesis disorder, vascular endothelial cell toxicity that causes medial and intima thickening in the vessels. Accordingly, prolongation and delay in wound healing and recurrence of wounds in DFU's cause an increase in amputation risk and mortality.[8]

Main predisposing factors in the formation of DFU are peripheral neuropathy and ischemic hypoxia due to macrovascular or microvascular damage.[8] Neuropathy is usually present in patients with diabetic foot ulcer and foot ulcers are characterized by loss of sensation, and patients generally have few specific complaints.[9] Biomechanics and the use of low-quality shoes are among the important factors contributing to these conditions.[10]

Undoubtedly, one of the worst complications of diabetes is DFU.[2] There are many factors that affect its treatment. Each of these factors should be considered separately. The ultimate goal of the treatment of diabetic foot ulcers is to close the wound completely as soon as possible.[2] Basic treatment approaches can be listed as strict metabolic control, good wound care, debridement, and appropriate antimicrobial therapy.[11] However, intralesional EGF treatment stands out as one of the complementary treatment options that benefit selected patients.[2]

The optimal management of diabetic foot ulcers is possible with a combination of various treatment methods. Generally, the healing of the ulcers occurs slowly in 2 to 5 months. This causes great costs and difficulties in health care.[9]

Epidermal Growth Factor plays a mitogenic role in wound healing in the area of ulceration and increases the migration of cells responsible for wound closure, granulation formation, angiogenesis, wound contraction by myofibroblasts, proliferation of epithelial cells and migration in the ulcer area.[12] Growth factors are reduced in scar tissue in chronic wounds.[2]

According to Acosta et al, 29 diabetic patients with ischemic and neuropathic components were treated for 8 weeks, who received 25µg / day EGF 3 times a week. It was observed that after 8 injections, 86% of the patients had increased granulation tissue in the wounds, and re-epithelization developed in an mean of 66 days in 77% of the patients. It was found that in patients with potential amputation risk, amputation was prevented by the application of EGF at a rate of 58%.[13] Similar to this study, amputation was prevented at a rate of 82.7% in our study.

In a comparative study conducted by Fernandez-Montequin et al, it was found that intralesional EGF 75µg / day / week (23 patients) and 25µg / day / week (18 patients) granulation formation was ranked as 83% and 61%, respectively.[14] We applied EGF three times a week at 75µg / day in our patients. We found that the wounds were re-epithelialized or granulated in 19 (65.5%) patients with 4 weeks of application, 7 (24.2%) patients with 6 weeks of application, and 3 (10.3%) patients with 8 weeks of application. Eight weeks of application was usually required in large ulcers. Ulcer diameter affects the healing time of the wound. The mean ulcer width in our study was calculated as 3.44 cm^2.

The importance of surgical intervention is now recognized in the treatment and prevention of chronic ulcers. Prophylactic surgical intervention is applied to prevent the ulcer from causing more serious conditions. The aim is to eliminate deformity and reduce the risk of ulceration and amputation.[10] In our study, the wounds were debrided before starting treatment in all cases with DFU. In the study, finger amputations were performed in 5 patients (17.2%) due to necrotic areas on the fingers before starting treatment. Other ulcerated areas were treated with EGF and resulted in epithelization. Patients were consulted with infectious diseases. Patients with suspected osteomyelitis were excluded from the study and their treatments were given. After the treatment, EGF treatment was started.

Side effects of epidermal growth factor are often pain and burning at the application site, chills, local infection, and fever. Of the side effects, 90% are mild or moderate.[10] In our study, tremors were the most common (96.5%) side effect which were followed by sensitivity (58.6%) and burning (44.8%). Fever (17.2%), vomiting (24.1%), headache (62%), and hypotension (58.6%) were observed more commonly. All of these side effects improved with the follow-up of the patients during the application.

CONCLUSION

Diabetic foot ulcers are one of the most common complications of diabetes. Annual incidence in diabetic patients is over 2%. Foot ulcer is seen in 5-7.5% of patients with peripheral neuropathy. 10-30% of patients with diabetic foot ulcers go to amputation. Mortality rate in patients with lower extremity amputation is 50-60%. Epidermal Growth Factor plays a mitogenic role in wound healing in the area of ulceration and increases the migration of cells responsible for wound closure, granulation formation, angiogenesis, wound contraction created by myofibroblasts, proliferation of epithelial cells and migration in the ulcer area. The side effect of EGF is 90% mild or moderate. The most common side effect is pain and burning in the application area.

The efficacy of EGF has been determined by our clinical experience in the treatment of patients with DFU. EGF

ensured the safe epithelialization of ulcers on the feet without impairing the quality of life of patients. Treatment of wounds with EGF after debridement provides a very significant improvement.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Training and Research Hospital Ethics Committee (Date: 01.04.2021, Decision No: 353).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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