Heberprot-P

intralezyonel EGF

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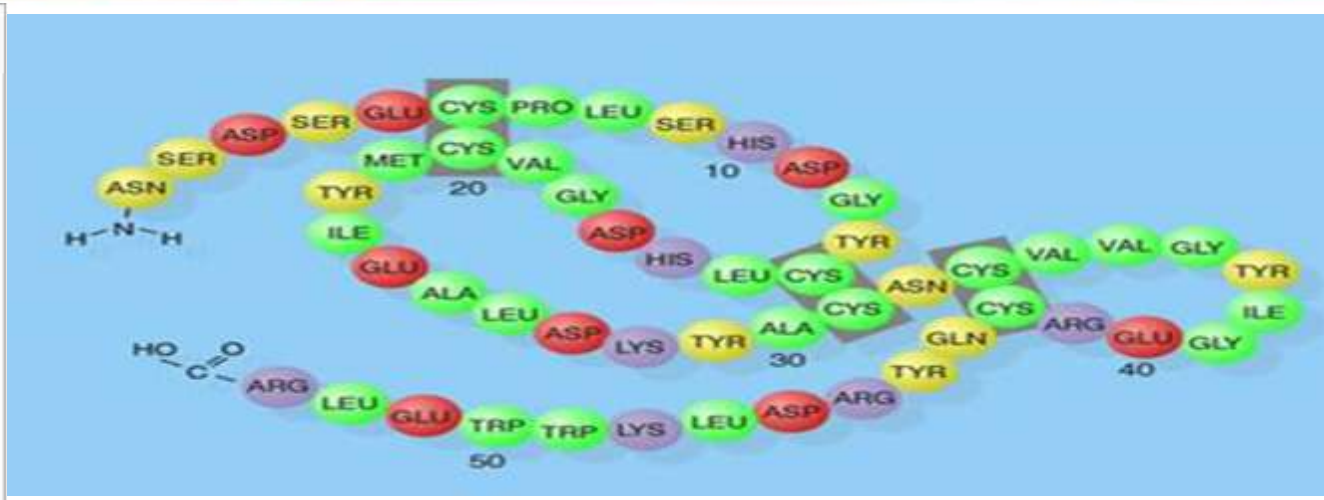
HASBIOTECH İLAÇ SAN VE TİC. A.Ş.

Heberprot-P

Stanley Cohen (biyokimyacı)

Stanley Cohen (biyokimyacı)

Doğum	17 Kasım 1922 (93 yaşında) Brooklyn, New York
Vatandaşlığı	Amerika Birleşik Devletleri
Dalı	Biyokimya
Çalıştığı yerler	Washington University in St. Louis
Öğrenim	University of Michigan
Önemli başarıları	Sinir Büyüme Faktörleri
Aldığı ödüller	Nobel Fizyoloji veya Tıp Ödülü (1986) Franklin Madalyası (1987)



THE STIMULATION OF EPIDERMAL KERATINIZATION BY A PROTEIN ISOLATED FROM THE SUBMAXILLARY GLAND OF THE MOUSE*

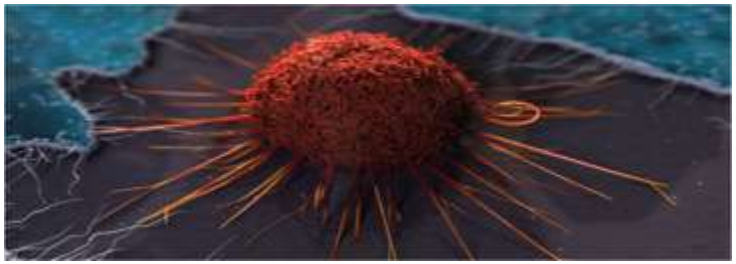
STANLEY COHEN, PH.D.** AND GEORGE A. ELLIOTT, D.V.M.

Heberprot-P


MOLEKÜLÜN KEŞFİ
Klinik Dışı Hayvan Deneyleri
SİTOPROTEKTİF ÇALIŞMALAR
DAÜ ÇALIŞMALARI
GENOTOKSİK VE MALİGNİTE ÇALIŞMALARI

EGF ile çeşitli laboratuar hayvanlarında, uzun süreli bir dizi klinik dışı güvenilirlik çalışması yapılmış, ürünün genotoksik olmadığı gösterilmiştir.

EGF, tekrarlayan ve ekzojen uygulamalar dahil olmak üzere test edilen koşullarda normal hücrelerde malign dönüşümü tetiklememiştir.



Effect of human epidermal growth factor on the tumor cell line A431: in vivo analysis of tumor growth inhibition and gene expression

RESEARCH

Carcinogenesis & Mutagenesis

Epidermal Growth Factor (EGF) and Platelet-Derived Growth Factor (PDGF) as Tissue Healing Agents: Clarifying Concerns about their Possible Role in Malignant Transformation and Tumor Progression

CONSIDERATIONS ON THE TRANSFORMING POTENTIAL OF THE EPIDERMAL GROWTH FACTOR

Jorge Berlanga,[1] Silvia Alvarez,[1] José de la Fuente[2] and Pedro López-Saura[2]

[1]Mammalian Cells Genetics Division, [2]Clinical Trials Division, Center for Genetic Engineering and Biotechnology. PO Box 6162, Havana 10600, Cuba. Telef: (53-7) 21 8164; Fax: (53-7) 21 8070; 33 8008; E-mail: jorge.berlanga@cigb.edu.cu

ABSTRACT

The epidermal growth factor (EGF) is a potent mitogen for a variety of epithelial and mesenchyma derived cells. Cells treated with EGF exhibit transient metabolic changes and a morphologic phenotype which mirror those found in malignant counterparts. EGF binds to a specific membrane receptor with intrinsic tyrosine kinase activity coded by a cellular proto-oncogene, whose mutated form has been largely implicated in malignancy. Experimental evidence indicates that EGF potentiates chemical carcinogenesis in vivo as well as viral transformation in vitro. Thus EGF has been historically considered as a tumor promoter. Nevertheless, recent experimental findings, mostly derived from preclinical models, strongly suggest that EGF treatment is insufficient to initiate benign or malignant transformation. On the contrary, in certain scenarios EGF may act as a potent cytoprotective agent for normal cells, and sensitizes cancer cells to anti-tumor therapy. All these experimental data provide fundamental basis for the clinical use of EGF in terms of safety. The clinical experience accumulated so far suggests that EGF does not seem to initiate carcinogenesis.

Key words: EGF, carcinogenesis, malignancy, toxicity

Biotecnología Aplicada 1998;15:65-68

Heberprot-P

ENZİMATİK YIKIMIN ARTMASI

YÜKSEK KAN ŞEKERI

EGF VE RESEPTÖRLERİN FİZYOLOJİSİNDE BOZULMA

DOKU ONARIMINDA YAVAŞLAMA VE KRONİKLEŞME

İLERİ EVRE DİYABETİK AYAKTA GENEL TEDAVİ

ENFEKSİYON KONTROLÜ

DEBRİDMAN

İSKEMİ DEĞERLENDİRİLMESİ

PANSUMAN

KAN ŞEKERİ REGÜLASYONU

YÜKTEN KURTARMA

REVASKÜLARİZASYON

YARDIMCI TEDAVİLER

EN ÖNEMLİ AMPUTASYON NEDENİ: DİYABETİK AYAK ÜLSERİ

ENZİMATİK

YÜKSE

EGF REPLASMAN TEDAVİSİ

KRONİKLEŞME

EGF: A replacement therapy

Diabetes & Metabolism

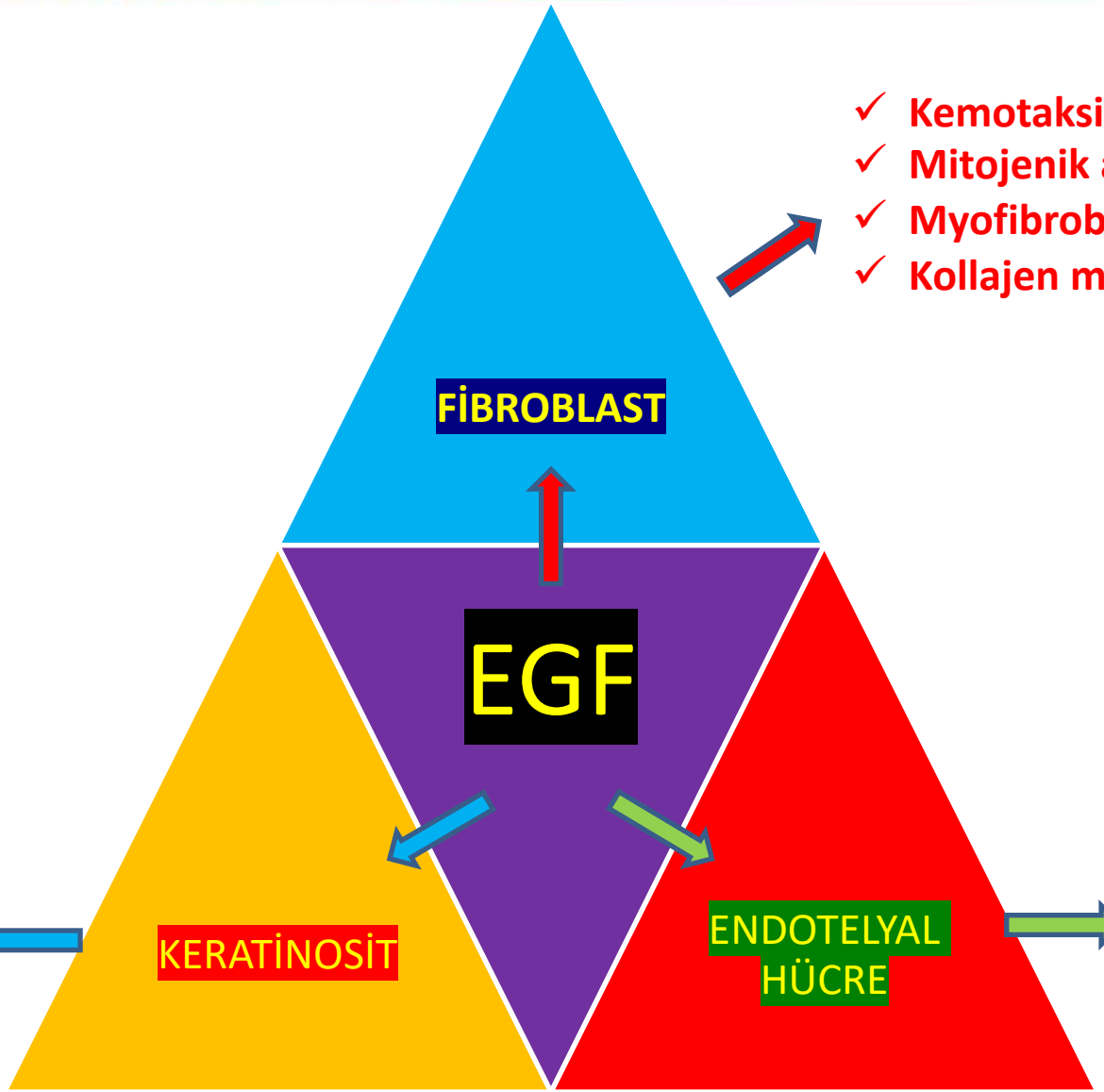
Berlanga-Acosta et al., J Diabetes Metab 2013, 4:7
http://dx.doi.org/10.4172/2155-6156.1000285

Review Article | Open Access

Type 2 Diabetes Mellitus (T2DM): Biological Overview from Pathways to Organelles and its Translation toward a Torpid Wound Healing Process

Jorge Berlanga-Acosta[1*], Pedro López-Saura[2], Isabel Guillen-Pérez[3], Gerardo Guillen-Nieto[1], Boris Acevedo-Castro[4] and Luis Herrera-Martínez[4]

Heberprot-P

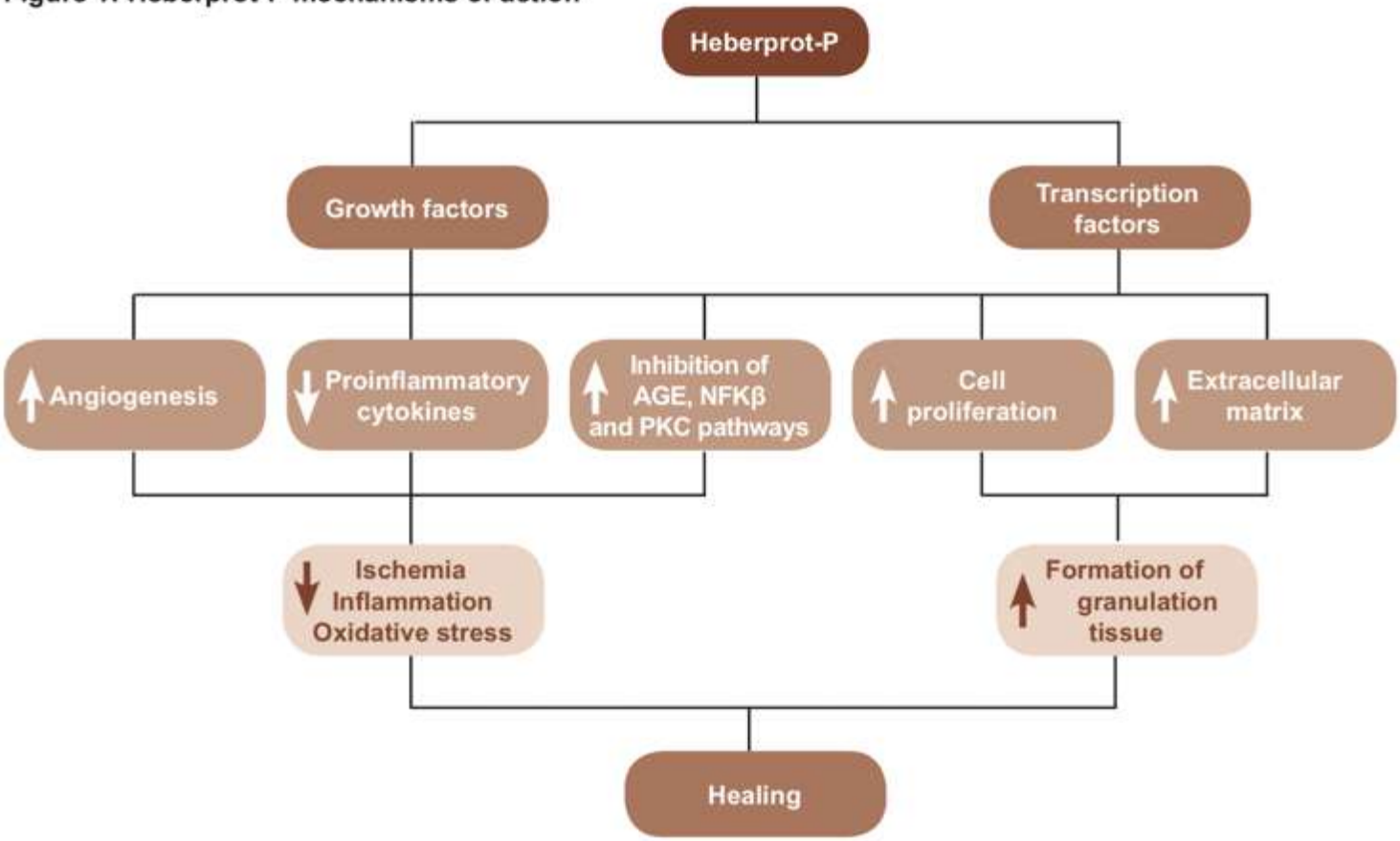


- ✓ Kemotaksi
- ✓ Mitojenik aktivite
- ✓ Myofibroblast dönüşümü
- ✓ Kollajen matris oluşumu

- ✓ Kemotaksi
- ✓ Epitelizasyon

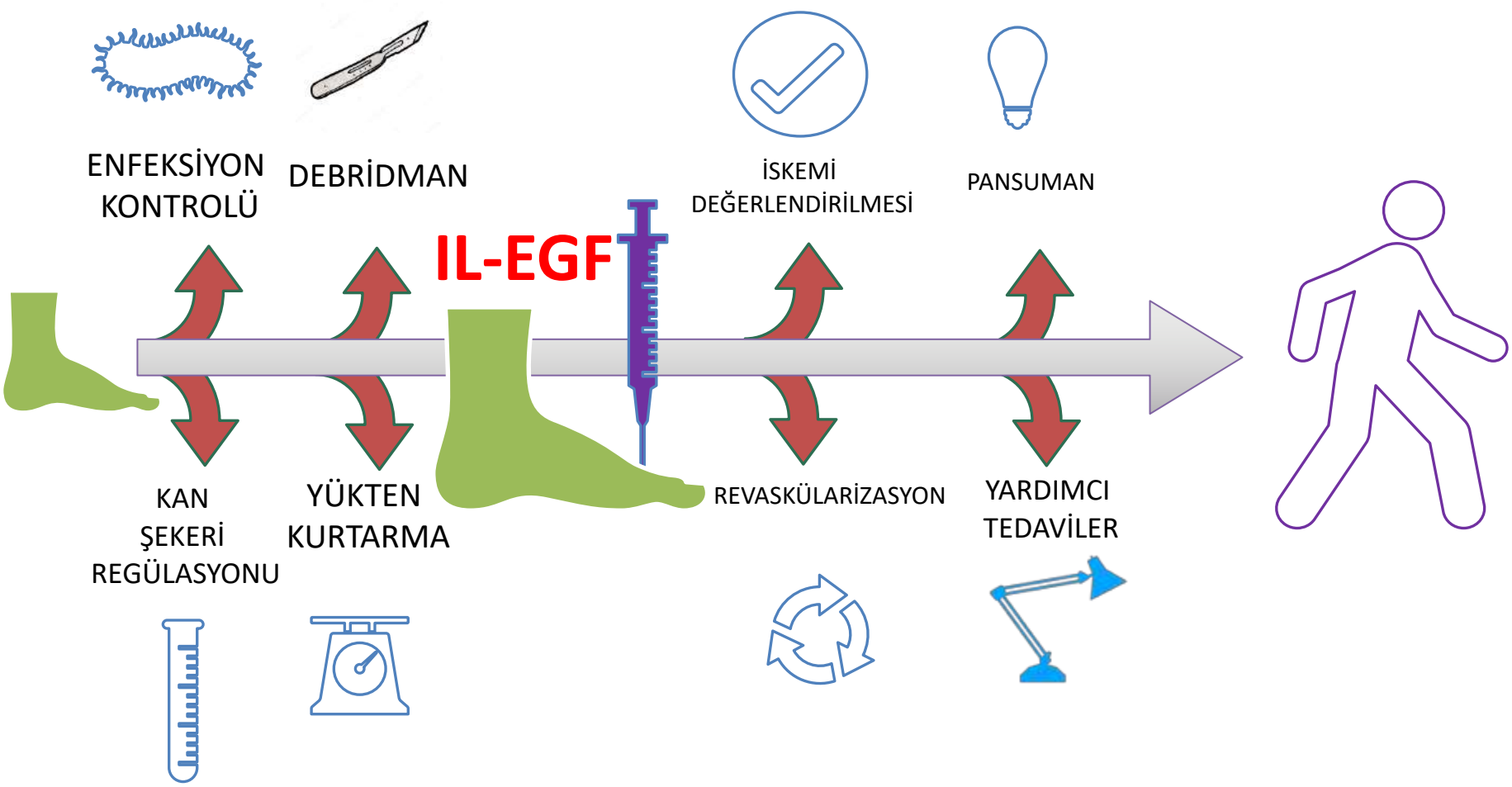
- ✓ Kemotaksi
- ✓ Anjiogenez

Figure 1: Heberprot-P mechanisms of action



İLERİ EVRE DİYABETİK AYAKTA GENEL TEDAVİ

HAS BIOTECH



GROWTH FACTORS
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informa healthcare

Efficacy of intralesional recombinant human epidermal growth factor in chronic diabetic foot ulcers

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Advances in Pharmacoepidemiology & Drug Safety
López-Saura et al., Adv Pharmacoepidem Drug Safety 2013, 2:2
http://dx.doi.org/10.4172/2167-1052.1000128
Research Article Open Access

Medical Practice Confirms Clinical Trial Results of the Use of Intralesional Human Recombinant Epidermal Growth Factor in Advanced Diabetic Foot Ulcers

Pedro A López-Saura*, Isis B Yera-Alos[2], Carmen Valenzuela-Silva[1], Odalys González-Diaz[2], Amaurys del Rio-Martin[2], Jorge Berlanga-Acosta[2], José I Fernández-Montequin[2], Boris Acevedo-Castro[2], Ernesto López-Mola[2] and Luis Herrera-Martinez[2]

[1]Clinical Research Direction, Center for Genetic Engineering and Biotechnology, Havana (CIGB), Cuba
[2]Clinical Research Direction, CIGB, Cuba

Fernández-Montequin JI, Infante-Cristiá E, Valenzuela-Silva C, Franco-Pérez N, Savigne-Gutiérrez W, Arzaza-Sanz H, Morejón-Vega L, González-Benavides C, Elsiwo-Musenden O, García-Iglesias E, Berlanga-Acosta J, Silva-Rodríguez R, Betancourt BY, López-Saura PA, for the Cuban Citoprot-P Study Group. Intralesional injections of Citoprot-P® (recombinant human epidermal growth factor) in advanced diabetic foot ulcers with risk of amputation. Int Wound J 2007;4:333–343.

Acosta JB, Savigne W, Valdez C, Franco N, Alba JS, del Rio A, López-Saura P, Guillén G, Lopez E, Herrera L, Fernandez-Montequin J. Epidermal growth factor intralesional infiltrations can prevent amputation in patients with advanced diabetic foot wounds. Int Wound J 2006;3:232–239.

ORIGINAL ARTICLE
Acta Orthop Traumatol Turc 2016;50(3):277–283
doi: 10.3944/AOTT.2015.14.0434

Intralesional application of epidermal growth factor in limb-threatening ischemic diabetic foot ulcers

Şamil AKTAŞ[1], Selçuk BAKTIROĞLU[2], Levent DEMİR[1], Önder KILIÇOĞLU[2], Murat TOPALAN[2], Erdem GÜVEN[2], Bengüsu MİRASOĞLU[1], Fatih YANAR[2]

[1]İstanbul University İstanbul Faculty of Medicine, Department of Underwater and Hyperbaric Medicine, Istanbul, Turkey
[2]İstanbul University İstanbul Faculty of Medicine, Department of General Surgery, Istanbul, Turkey

ORIGINAL ARTICLES

An Assessment of Intralesional Epidermal Growth Factor for Treating Diabetic Foot Wounds

The First Experiences in Turkey

Bulent M. Ertugrul, MD*
Benjamin A. Lipsky, MD†
Ulas Guvenc, MD‡
and the Turkish Intralesional Epidermal Growth Factor Study Group for Diabetic Foot Wounds
§

Berlanga-Acosta J, Gavilondo-Cowley J, López-Saura P, González-López T, Castro-Santana Guillén-Nieto G, Herrera-Martinez L. Epidermal growth factor in clinical practice–a review of clinical indications and safety implications. Int Wound J 2009; 6:331–346

Review Article

Diabetic Foot Ulcers and Epidermal Growth Factor: Revisiting the Local Delivery Route for a Successful Outcome

Jorge Berlanga-Acosta,[1] José Fernández-Montequín,[1] Calixto Valdés-Pérez,[1] William Savigne-Gutiérrez,[1] Yosel Mendoza-Mari,[1] Ariana García-Ojalvo,[1] Viviana Falcón-Cama,[1] Diana García-del Barco-Herrera,[1] Maday Fernández-Mayola,[1] Héctor Pérez-Saad,[1] Eulogio Pimentel-Vázquez,[1] Alexis Urquiza-Rodríguez,[1] Moshe Kaliberdy,[2] and Gerardo Guillén-Nieto[1]

Clinical Research on Foot & Ankle
Herrera et al., Clin Res Foot Ankle 2017, 5:
DOI: 10.4172/2329-9509.1000248
Review Article OMICS International

The Effectiveness of Achilles Lengthening Plus Intralesional Human Recombinant Epidermal Growth Factor to Prevent Recidivism of Neuropathic Diabetic Forefoot Ulceration

Aristides I García Herrera*, Ridel de Jesus Febles Sanabria and Miriam Molmer Cartaya

Department of Vascular Surgery, Matanzas Medical Science University, Cuba
Matanzas Medical Science Information Center, Matanzas Medical Science University, Cuba

Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: A randomized double-blinded controlled trial

Ramiro Gomez-Villa, MD[1]; Francisco Aguilar-Rebolledo, MD, PhD[2]; Juan Miguel Teran-Soto, MD[2]; Maria Rosy Fabian-Victoriano, ETN[1]; Ximena Garrido-Espindola, ETN[1]; Adriana Garcia-Solis, MD[2]; Augus... Sneider, MD[2]; José Contreras-Ruiz, MD[2]

Clinical Care/Education/Nutrition/Psychosocial Research

Granulation Response and Partial Wound Closure Predict Healing in Clinical Trials on Advanced Diabetes Foot Ulcers Treated With Recombinant Human Epidermal Growth Factor

Current Therapeutic Research

Curative Metatarsal Bone Surgery Combined with Intralesional Administration of Recombinant Human Epidermal Growth Factor in Diabetic Neuropathic Ulceration of the Forefoot: A Prospective, Open, Uncontrolled, Nonrandomized, Observational Study

Aristides I. García Herrera, MD, PhD*, Ridel de Jesús Febles Sanabria, MD, MS, Liliana de los Angeles Acosta Caballita, MD, Miriam Molmer Cartaya, for the Matanzas Group of Diabetic Foot Ulceration

BMC Pharmacology & Toxicology

Review Article

Glucose Toxic Effects on Granulation Tissue Productive Cells: The Diabetics' Impaired Healing

Jorge Berlanga-Acosta,[1] Gregory S. Schultz,[2] Ernesto López-Mola,[1] Gerardo Guillen-Nieto,[1] Marianela García-Siveira,[1] and Luis Herrera-Martinez[1]

International Wound Journal
International Wound Journal ISSN 1742-4801

ORIGINAL ARTICLE

Healing enhancement of diabetic wounds by locally infiltrated epidermal growth factor is associated with systemic oxidative stress reduction

Ariana García Ojalvo[1], Jorge Berlanga Acosta[1], Yosel Mendoza Mari[1], Maday Fernández Mayola[1], Calixto Valdés Pérez[2], William Savigne Gutiérrez[2], Ileydis Iglesias Marichal[2], Eduardo Álvarez Seijas[2], Alicia Molina Kausteman[1], Angélica Estrada Pacheco[1] & David G. Armstrong[3]

BMC Pharmacology and Toxicology 2013, 14:44
http://www.biomedcentral.com/2050-6511/14/44
RESEARCH ARTICLE Open Access

Active post-marketing surveillance of the intralesional administration of human recombinant epidermal growth factor in diabetic foot ulcers

Isis B Yera Alos[1*], Lidia Alonso-Carbonell[1], Carmen M Valenzuela Silva[1], Angela D Tuero-Iglesias[1], Martha Moreira-Martínez[2], Ivonne Marrero-Rodríguez[2], Ernesto López-Mola[1] and Pedro A López-Saura[1]

HEBERPROT-P

EGF (HEBERPROT – P®) ve Diyabetik Ayak Tedavisi

Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study

José I Fernández-Montequín, Carmen M Valenzuela-Silva, Odalys Gonzalez Díaz, William Savigne, Natasha Sancho-Soutelo, Fidel Rivero-Fernández, Pablo Sánchez-Penton, Lourdes Morejón-Vega, Heriberto Artaza-Sanz, Aristides García-Herrera, Cecilio González-Benavides, Carlos M Hernández-Cañete, Alberto Vázquez-Proenza, Jorge Berlanga-Acosta, Pedro A López-Saura, for the Cuban Diabetic Foot Study Group*

Faz III Çalışma

Çift Kör, Randomize, Çok Merkezli, Plasebo Kontrollü n=149

Grup I : **75 µg** Heberprot-P ile tedavi (n=53)
Grup II : **25 µg** Heberprot-P ile tedavi (n=48)
Grup III : **Plasebo** (n=48)

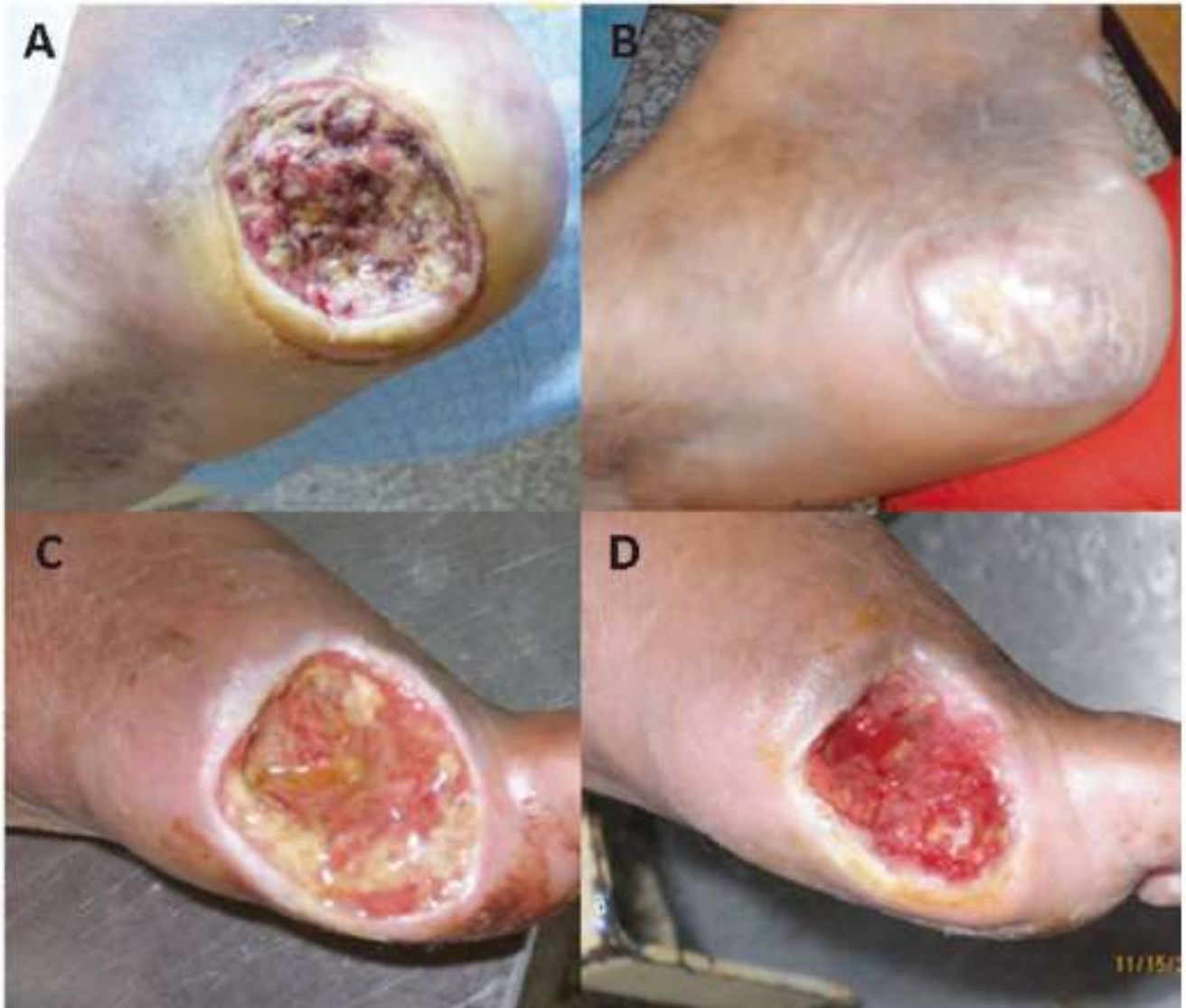
- Wagner Sınıflandırması Grade 3/4
- Yanıt değerlendirmesi-
  - 2 hafta sonunda tam ya da kısmi yanıt oranı
    - Yetersiz yanıt < %25
    - Minimal yanıt % 25-50
    - Kısmi yanıt % 50-75
    - Tam yanıt % 75-100
- fazladır ve yarısından fazlası **iskemik**
- Haftada 3 kez, 25µg veya 75µg Heberprot-P veya plasebo, intralezyonal uygulandı.

Montequin JI et al ,Intralesional injections of recombinant human epidermal growth factor promote granulationand healing in advanced diabetic foot ulcer: multicenter, randomised, placebo-controlled, double-blind study. Int Wound J **2009;6:432-443**

EGF (HEBERPROT – P®) ve Diyabetik Ayak Tedavisi

Table 2 Granulation response to treatment with intra-lesional rhEGF

	Group I ($N = 53$)	Group II ($N = 48$)	Group III ($N = 48$)	P (χ^2 test)
After 2 weeks of treatment				
Complete + partial response (≥50% granulation)	44 (83·1%)	34 (70·8%)	19 (39·6%)	0·000015
Difference versus control group (95% CI)	43·8 (24·3; 62·6)	31·2 (10·3; 52·2)		
Odds ratio (95% CI)	7·5 (2·9; 18·9)	3·7 (1·6; 8·7)		
After the end of treatment				
Complete response (>75% granulation)	46 (86·8%)	34 (70·8%)	28 (58·3%)	0·005
Difference versus control group (95% CI)	28·5 (9·8; 47·1)	12·5 (−8·6; 33·6)		
Odds ratio (95% CI)	4·7 (1·8; 12·5)	1·7 (0·7; 4·0)		
Weeks to complete response (median; 95% CI) P versus group III (log rank test)	3 (2·6–3·4) P = 0·006	3 (2·3–3·7) P = 0·031	5 (3·2–6·8)	


A
B
C
D

Heberprot-P

Yera-Alos *et al. BMC Pharmacology and Toxicology* 2013, **14**:44
http://www.biomedcentral.com/2050-6511/14/44

BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

Active post-marketing surveillance of the intralesional administration of human recombinant epidermal growth factor in diabetic foot ulcers

Isis B Yera-Alos[1*], Liuba Alonso-Carbonell[1], Carmen M Valenzuela-Silva[2], Angela D Tuero-Iglesias[2], Martha Moreira-Martínez[3], Ivonne Marrero-Rodríguez[4], Ernesto López-Mola[2] and Pedro A López-Saura[2]

Heberprot-P

Yera-Alos et al. BMC Pharmacology and Toxicology 2013, 14:44
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BMC Pharmacology & Toxicology

RESEARCH ARTICLE Open Access

Active post-marketing surveillance of the intralesional administration of human recombinant epidermal growth factor in diabetic foot ulcers

Isis B Yera-Alos[1*], Liuba Alonso-Carbonell[1], Carmen M Valenzuela-Silva[2], Angela D Tuero-Iglesias[2], Martha Moreira-Martínez[3], Ivonne Marrero-Rodríguez[4], Ernesto López-Mola[2] and Pedro A López-Saura[2]

	Ischemic	Non-ischemic	Total
Complete granulation	486/790	905/1044	1392/1835
%	61.5	86.7	75.9
(95% CI)	(58.1; 64.9)	(84.6; 88.7)	(73.9; 77.8)
Weeks to complete granulation median (95% CI)	6 (5.6; 6.3)	4 (3.8; 4.2)	5 (4.8; 5.2)
Healing	371/742	641/916	1012/1659
			.0
			62.9)
			.1
			57.4)
Relapses: (yea			(1488)
			9; 6.2)
Amputations			1835
			.0
(95% CI)	(19.9; 25.7)	(2.7; 5.0)	(10.5; 13.5)

IL-EGF İLE TEDAVİ SÜRESİ:
İSKEMİK ÜLSERLERDE **6** HAFTA
NON-İSKEMİK ÜLSERLERDE **4** HAFTA

Heberprot-P

İLK BİR YILDA REKÜRRENS %40
ÜÇ YILDA %60
BEŞ YILDA %65

The NEW ENGLAND JOURNAL of MEDICINE

N Engl J Med 2017;376:2367-75.
DOI: 10.1056/NEJMra1615439

Diabetic Fo
David G. Armstro

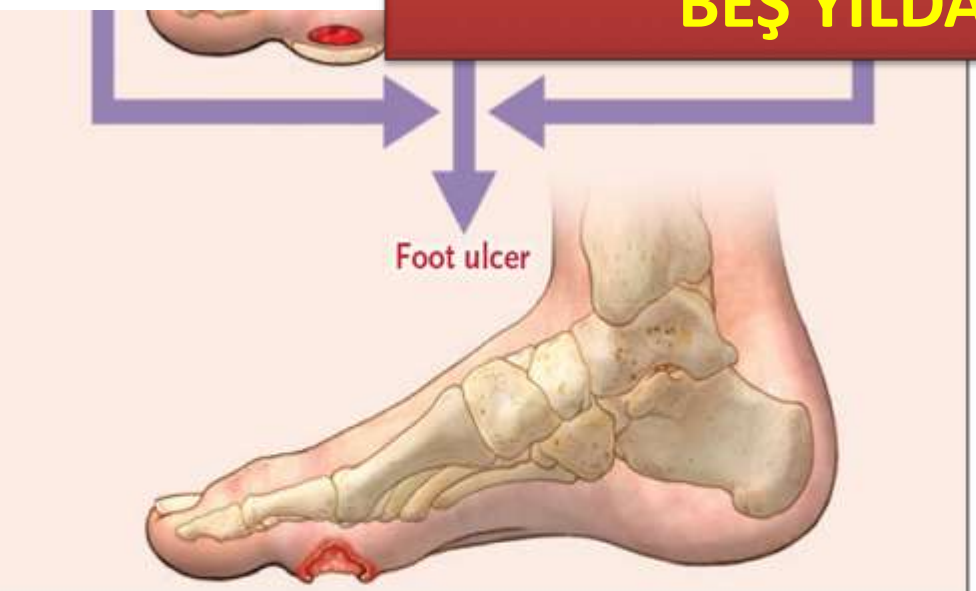

Figure 1. Common Pathway of Diabetic Foot Ulcer Occurrence and Recurrence.
Diabetic foot ulcers and their recurrences are caused by a number of factors that ultimately lead to skin breakdown. These factors include sequelae related to sensory, autonomic, and motor neuropathies.

tly.[27]

ULCER RECURRENCE AND REMISSION

Unfortunately, even after the resolution of a foot ulcer, recurrence is common. By reviewing 19 compatible studies on incidence rates for ulcer recurrence,[28-46] we estimate that roughly 40% of patients have a recurrence within 1 year after ulcer healing, almost 60% within 3 years, and 65% within 5 years (Fig. 2). Thus, it may be more useful to think of patients who have achieved wound closure as being in remission rather than being healed. The concept of remission may also provide a better framework for allocating resources, organizing care, and communicating

Heberprot-P

Yera-Alos et al. BMC Pharmacology and Toxicology 2013, 14:44
http://www.biomedcentral.com/2050-6511/14/44

Heberprot-P rekürrens oranı

1.YIL: %5

2.YIL: %6

3.YIL: %7

included (intention-to-treat) %	47.0	61.4	55.1
(95% CI)	(43.4; 50.4)	(58.4; 64.4)	(52.9; 57.4)
Relapses: (years-person of follow- up)	26/333 (561)	49/584 (927)	75/917 (1488)
Rate per year (95% CI)	4.6 (2.9; 6.4)	5.3 (3.8; 6.7)	5.0 (3.9; 6.2)
Amputations during treatment	180/790	40/1044	220/1835
%	22.8	3.8	12.0
(95% CI)	(19.9; 25.7)	(2.7; 5.0)	(10.5; 13.5)

The Journal of Foot & Ankle Surgery 000 (2018) 1–6

Contents lists available at ScienceDirect

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journal homepage: www.jfas.org

Original Research

The Long-Term Outcomes Following the Application of Intralesional Epidermal Growth Factor in Patients With Diabetic Foot Ulcers

Murat Kahraman, MD[1], Abdulhamit Misir, MD[2], Turan Bilge Kizkapan, MD[3], Mustafa Ozcamdalli, MD[4], Erdal Uzun, MD[5], Mahmut Mutlu, MD[6]

https://doi.org/10.1053/j.jfas.2018.08.041

- Haziran 2012 ve Şubat 2013 arasında 34 hastadaki (28 erkek ve 6 kadın) 36 lezyon standart tedaviye ek olarak intralezyonel EGF ile tedavi edilmiştir.
- 3 hastada yara infeksiyonu yinelemiştir ve bu hastalarda EGF tedavisi sonlandırılmıştır.
- 33/36 lezyonda (%91.7) yara kapanması gerçekleşmiştir.
- Advers etkiler 11 hastada üşüme-titreme, 5 hastada esneme, 21 hastada yanma ve 17 hastada bulantı şeklinde ortaya çıkmıştır.
- Bu advers etkiler nedeniyle tedavinin kesilmesi gerekmemiştir. Tedavi ilerledikçe advers etkilerin ortaya çıkışı artmıştır.
- 29 (%87.9) lezyonda tam yanıt (>%75 granülasyon dokusu veya yara kapanması) gözlenmiştir.
- 5 yıllık takipte, 4 hasta (%11.8) diyabetik, kardiyak ve serebrovasküler komplikasyonlar nedeniyle gerçekleşen ölüme bağlı olarak takipte kaybedilmiştir.
- Geriye kalan 27 (%79.4) hastada (27 lezyon, %93.1) ülserler ortadan kalkmıştır 2 (%6.7) hastada (2 lezyon, %6.9) ayak parmaklarında ülser yinelenmiş ve ayak parmakları ampüte edilmiştir.

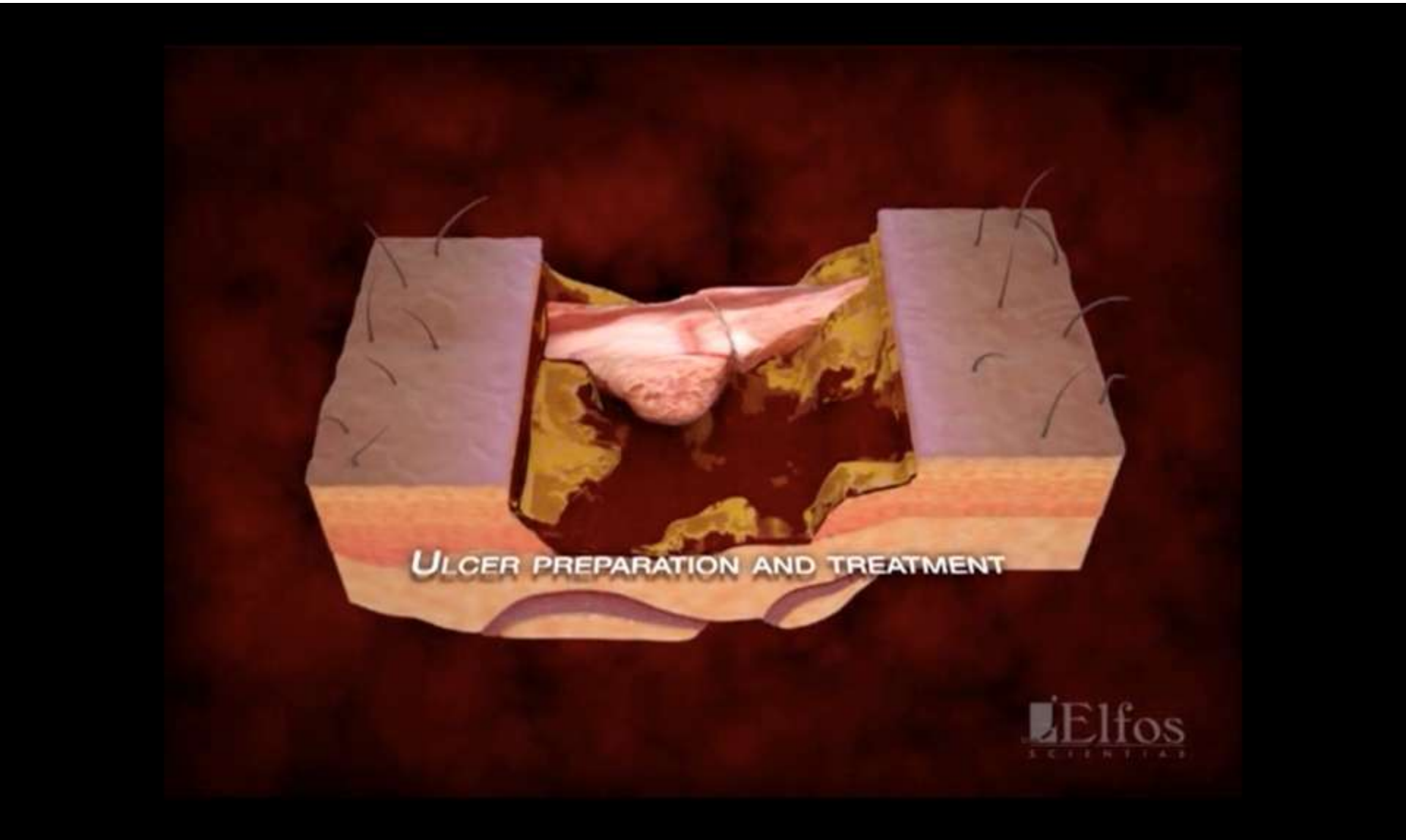
HEBERPROT-P-FAZ IV

- KISA SÜREDE TEDAVİ
- RELAPS SAYISINDA AZALMA

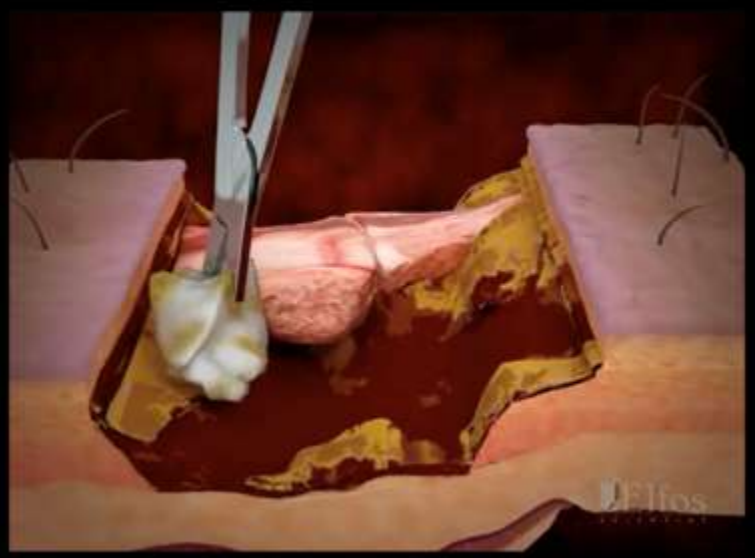
Heberprot-P

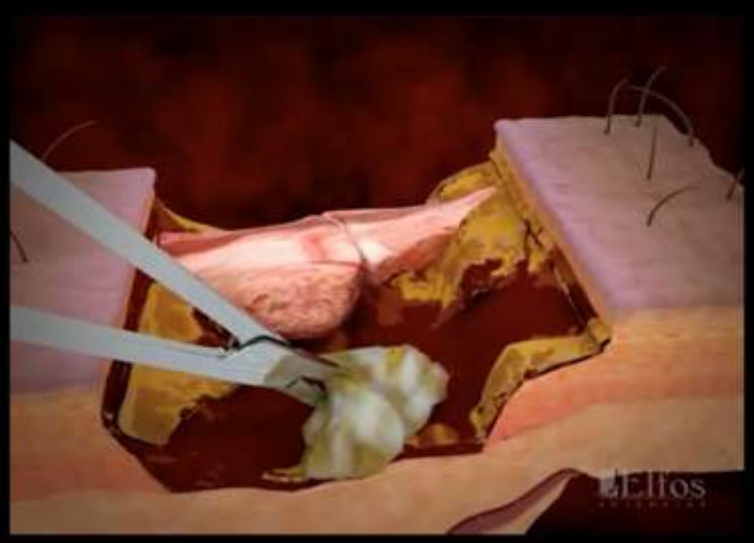
Advers Etki	Hasta (No. (%))
Soğuma ve Titreme	66 (37.9)
Bulantı	40 (22.9)
Uygulama bölgesinde ağrı	37 (21.3)
Kusma	12 (6.9)
Hipotansiyon	8 (4.6)
Tedavi bölgesindeki enfeksiyon	8 (4.6)
Yanma hissi	6 (3.4)
Ateş	4 (2.3)
Hipertansiyon	4 (2.3)
Eritema	4 (2.3)
Göğüs ağrısı	3 (1.7)
Çarpıntı	3 (1.7)
Bayılma	3 (1.7)
Respiratuvar distres	1 (0.6)
Baş dönmesi	1 (0.6)
Kangren	1 (0.6)

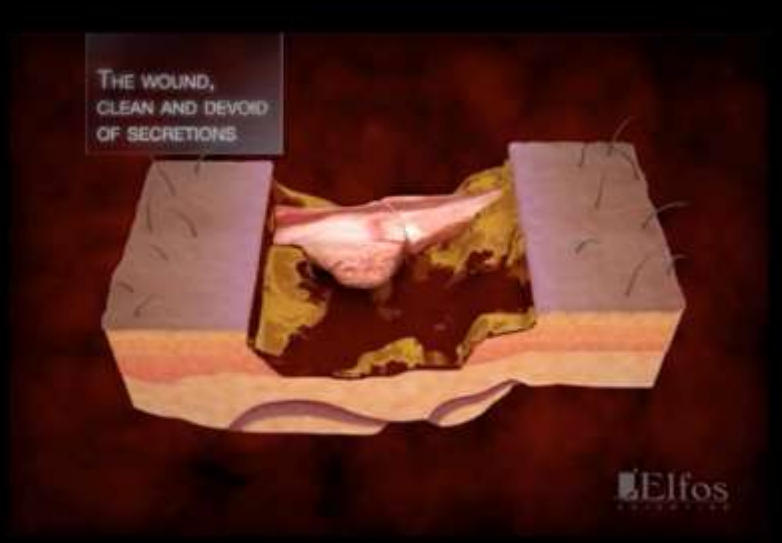
Uygulama Yöntemi



Uygulama Yöntemi







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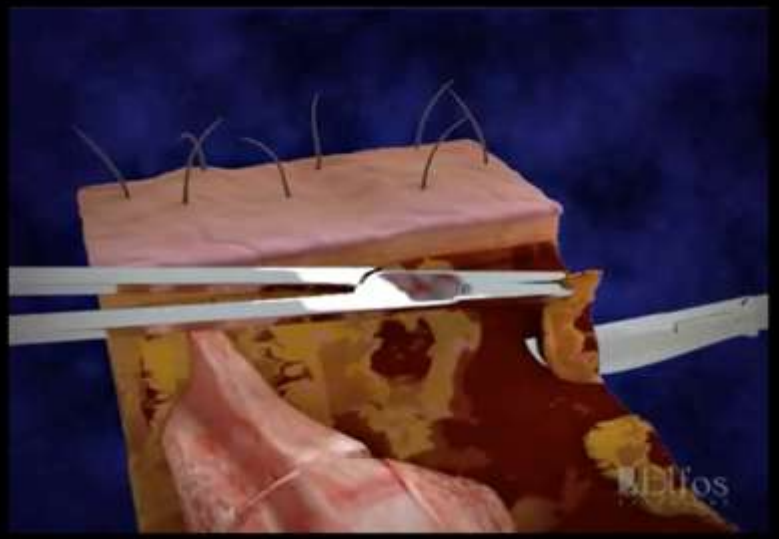

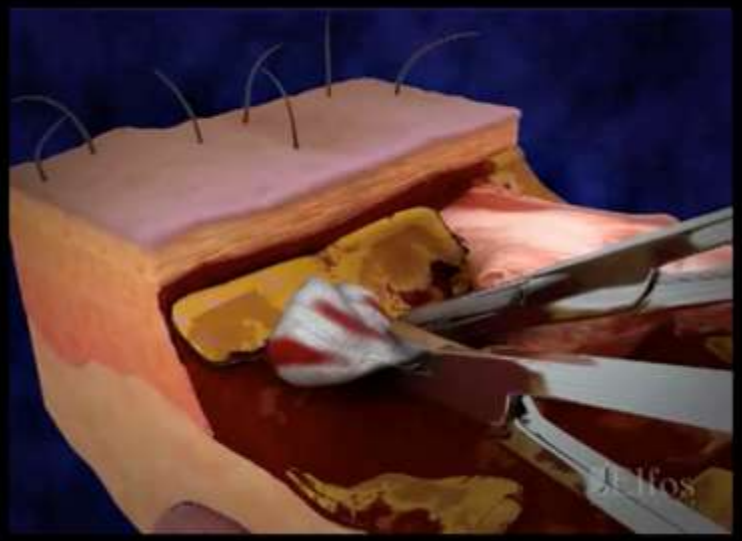

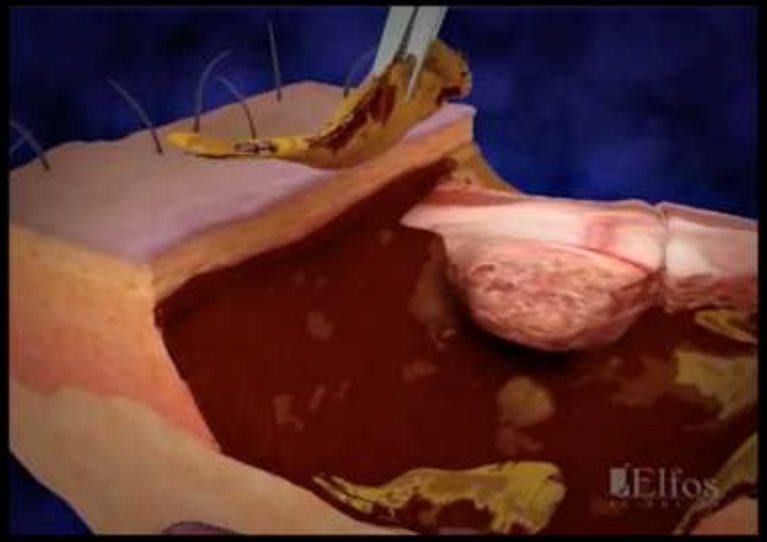

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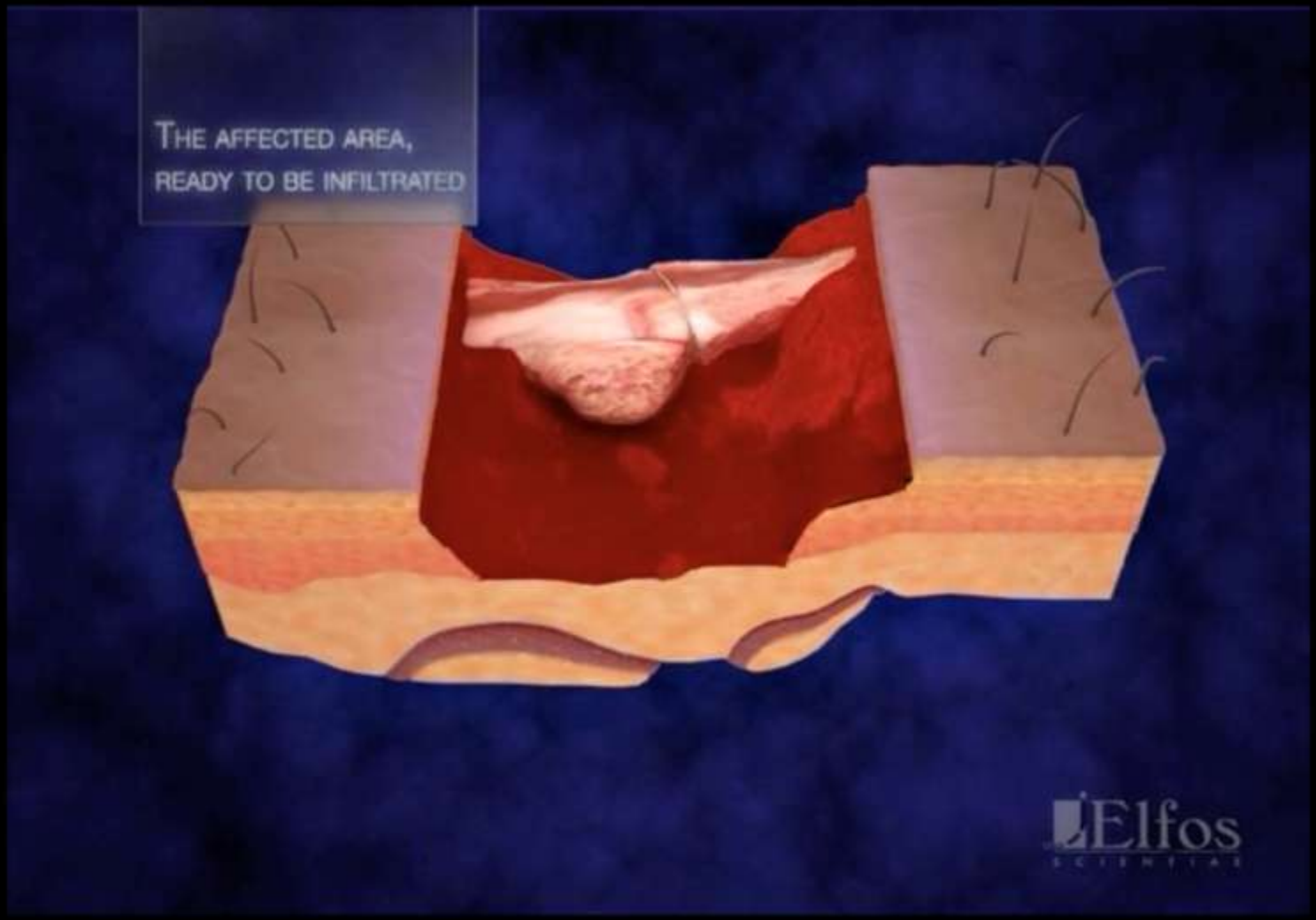

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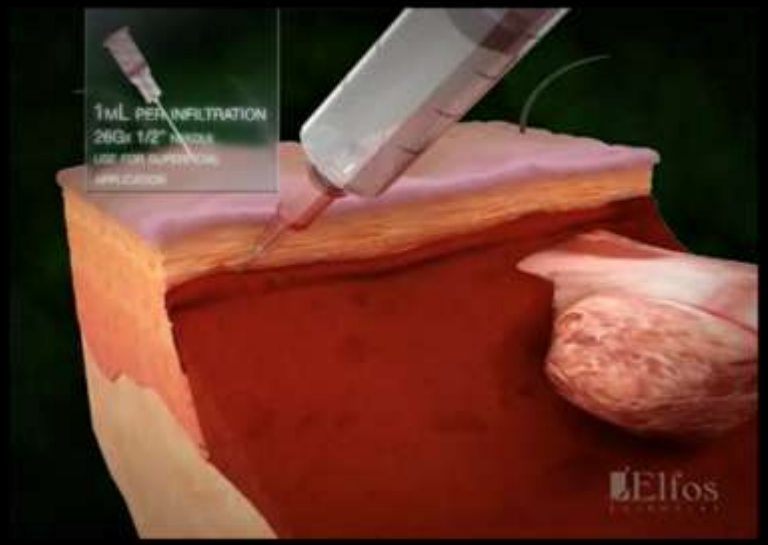

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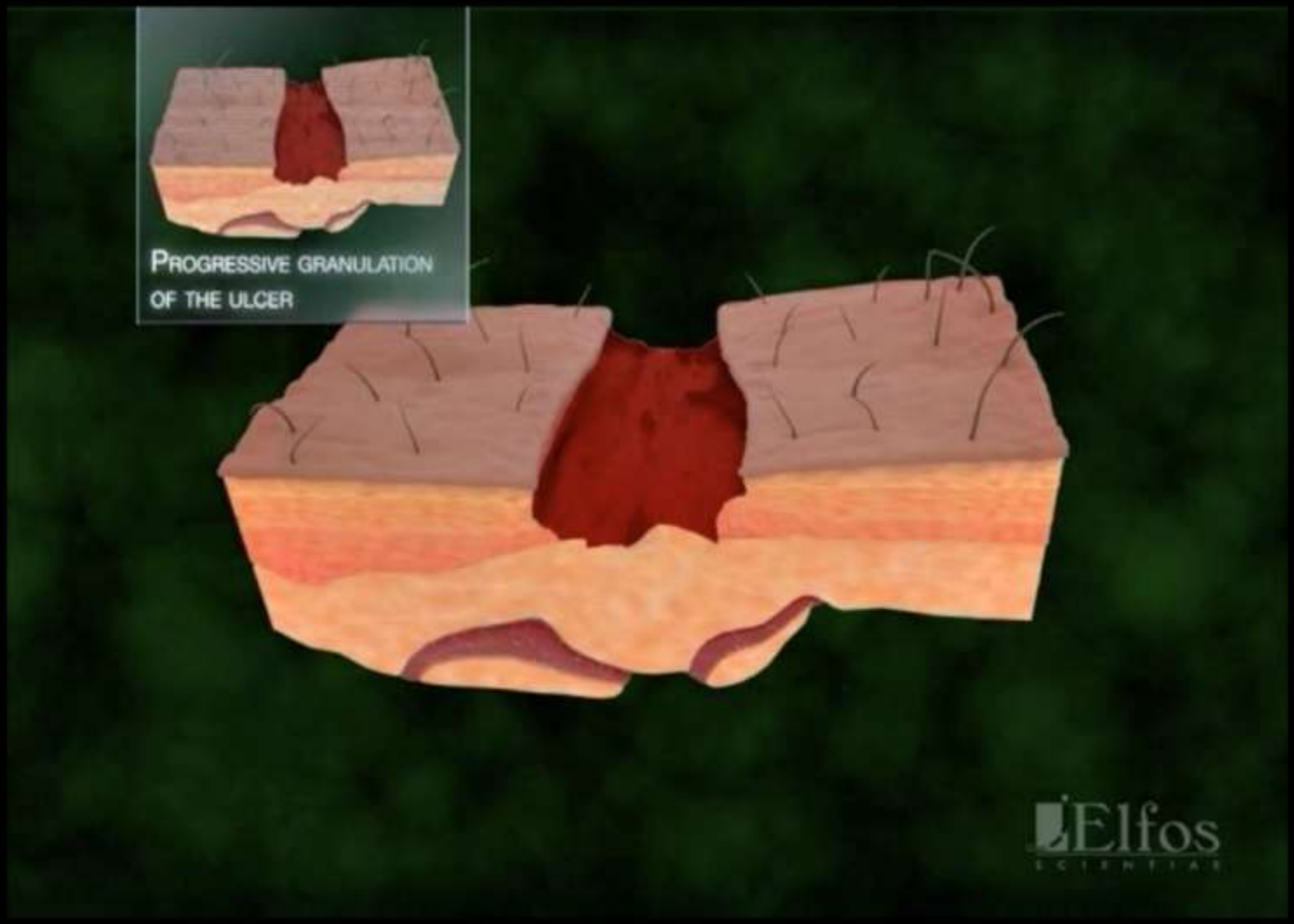

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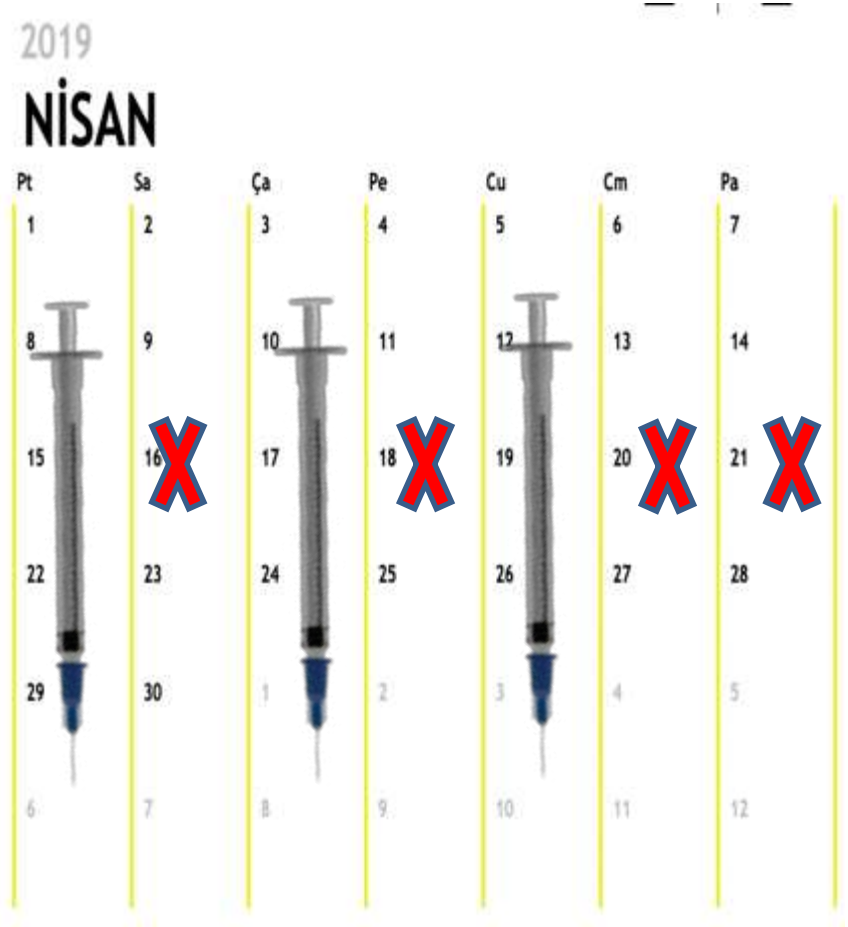

- Her flakon 5cc SF ile sulandırılarak yara içerisine intralezyonel olarak gün aşırı uygulanmalıdır.
- Her uygulamada 1 flakonun tamamı kullanılmalıdır
- Soğuk zincir kurallarına uyulmalıdır.

KONTRENDİKASYONLAR

Heberprot-P

- İleri derecede kalp yetmezliği olanlarda ve kontrol altına alınamayan aritmilerde
- Bilinen kanser hastalığı olanlarda
- Son 2 ayda tromboembolik hadise geçirenlerde
  - MI
  - SVH
  - PE
- Transplantasyon hastalarında
- Gebelerde
- İmmünsüpresan tedavi alanlarda

Kontrendikedir.

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