ORIGINAL RESEARCH PAPER
VOLUME-6 | ISSUE-6 | JUNE-2017 | ISSN No 2277 - 8179 | IF : 4.176 | IC Value : 78.46
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

# THE EFFECT OF REGEN-D 60 GEL ON THE RATE OF HEALING OF GINGIVAL EPITHELIUM: A RANDOMIZED CLINICAL TRIAL

Dental Science

**Dr. Shivaprasad Bilichodmath** — Reader, Department of Periodontology, Rajarajeswari Dental College and Hospital, Rajiv Gandhi University of Health Sciences, Bangalore-560074, India

**Dr.Vinaya Kumar R** — Reader department of periodontology, Rajarajeswari dental college and hospital Rajiv gandhi university of health sciences, Bangalore-560074, India

**Dr. Sruthi. K.Nair** — Post graduate student, Rajarajeswari Dental College and Hospital, Rajiv Gandhi University of Health Sciences, Bangalore-560074, India.

**Dr.Nayan Jyoti Deka** — Post graduate student, Rajarajeswari Dental College and Hospital, Rajiv Gandhi University of Health Sciences, Bangalore-560074, India.

**Dr. Rekha B M** — Post graduate student, Rajarajeswari Dental College and Hospital, Rajiv Gandhi University of Health Sciences, Bangalore-560074, India.

## ABSTRACT

**Aim:** To assess the effect of Regen-D 60 Gel on the rate of healing of gingival epithelium.

**Materials and methods:** A total of 40 sites in 10 patients (6 males and 4 females, 18 to 32 years old) with uniformly dense bands of pronounced bilateral melanin pigmentation on the facial aspect of the maxilla and mandible were selected. Sites extending from distal of the right canine to the midline and distal of the left canine to the midline underwent depigmentation. In each patient 4 quadrants were randomly allocated to one of the four treatment groups. Group I with patients who underwent depigmentation with diode laser along with application of REGEN-D 60 gel, group II with patients who underwent depigmentation with diode laser alone, group III with patients who underwent depigmentation with tetrafluoroethane along with REGEN-D 60 gel and group IV with patients who underwent depigmentation with tetrafluoroethane alone. REGEN-D 60 gel was applied randomly to treated sites following depigmentation to assess the healing. Gingival index (GI) (Silness and Loe, 1964) was recorded at baseline and 1 month after the procedure. Healing Index (Landrey, Turnbull and Howley, 1988) was assessed at day 1, day 7, day 14 and at 1month respectively.

**Results:** Inter group comparison of healing index scores at various time intervals showed a statistically significant difference ($p<0.0001$). The change in the healing index scores between various groups from day 1 to day 14 was statistically significant ($p<0.05$)

**Conclusion:** REGEN-D 60 gel may have a beneficial effect on the rate of healing of gingival epithelium.

## KEYWORDS:

Epidermal growth factor, Gingival epithelium, Gingival index, Healing index.

## INTRODUCTION

Esthetics has become an important aspect of dentistry and clinicians have to face the challenge of achieving acceptable gingival contour, along with addressing the biological and functional challenges. Pigmentation is a discolouration of the oral mucosa due to a wide variety of lesions and conditions. Oral pigmentation has been associated with a variety of exogenous and endogenous etiologic factors.[1] Gingival depigmentation is an aesthetic procedure, which helps to improve the smile and the overall appearance of an individual. The colour of the pigmented gingiva varies from light to dark brown or black.[2-5]

Wound healing within the oral cavity is an extremely complex mechanism where numerous characters may intervene, such as cell and/or tissue interrelations, growth factors and salivary components. The periodontium represents an inimitable histological system, because of the individual connection between the epithelium and connective tissue forming the dento-gingival junction. At the level of the superficial periodontium, the free gingival mucosa repairs through regeneration based on epithelial restoration, while the dento-gingival junction supports only the development of granulation tissue with subsequent cicatrisation.[6,7]

Epidermal growth factor (EGF) is a low molecular weight polypeptide which was first purified from the mice submandibular gland, but since then has been found in many human tissues including submandibular gland, parotid gland.8 EGF belongs to a family of growth factors that regulate cell proliferation, migration and differentiation through binding to receptor kinases on target cells. EGF is proved to act as a mitogen and also as a differentiation factor for many cell types. It can also be found in urine, saliva, milk, and plasma.[9]

EGF plays a role in a variety of biological actions, including promotion of epidermal development, wound healing, eruption of the incisors, activation of various transport systems and changes in cellular metabolism, in addition to mitogenesis, stimulation of pituitary secretion of adrenocorticotropic hormone (ACTH), growth hormone (GH), inhibition of gastric and thyroid hormone secretion. Moreover, most evidence indicates that it is an important hormone in the male reproductive system.[10]

Literature has shown an enhanced wound healing after application of epidermal growth factor. Recombinant human epidermal growth factor (REGEN-D 60) is supplied as a topical gel which is thought to have an important function in epidermal growth, differentiation and in reducing healing time drastically over the natural course leaving minimal scars with quality healing. Recently, a study showed enhanced healing of chronic diabetic foot ulcers (DFU) following application of REGEN-D TM 150 by significantly reducing the duration of healing in addition to providing excellent quality of wound healing and reepithelization.[11]

Till date, to the best of our knowledge, there are no available data showing the effect of REGEN-D 60 gel on the rate of healing of gingival epithelium. Therefore, the present study was undertaken to analyse the effect of REGEN-D 60 gel on the healing of epithelium following gingival depigmentation.

## MATERIALS AND METHODS

The triple blind randomized controlled trial was carried out between February 2015 to August 2015 in accordance with the Helsinki declaration of 1975, as revised in 2000. The patients were selected from the outpatient section of the Department of Periodontology, Rajarajeswari Dental College and Hospital, Bangalore, India. Each patient signed a written informed consent prior to his/her participation in the study after obtaining approval from the Institutional Ethical Committee. The trial was registered at Clinical Trial Registration of India (CTRI) bearing number REF/2016/03/011026. A total of 40 sites in 10 patients (6 males and 4 females, 18 to 32 years old) with uniformly dense bands of pronounced bilateral melanin pigmentation

on the facial aspect of the maxilla and mandible were selected. Sites extending from distal of the right canine to the midline and distal of the left canine to the midline underwent depigmentation. Study groups were divided into four which included group I with patients who underwent depigmentation with diode laser along with application of REGEN-D 60 gel, group II with patients who underwent depigmentation with diode laser alone, group III with patients who underwent depigmentation with tetrafluoroethane along with REGEN-D gel and group IV with patients who underwent depigmentation with tetrafluoroethane alone.

Only motivated patients who were conscious about their esthetics were enrolled for the study. Smokers, patients with diabetes and other debilitating systemic diseases or conditions, pregnant or lactating females, patients with clinically diagnosed periodontitis, pathologic factors causing gingival pigmentation were excluded from the study. In each patient 4 quadrants were randomly allocated to one of the four treatment groups as depicted in consort flowchart (Fig-1). REGEN-D 60 gel was applied randomly to treated sites following depigmentation to assess the healing. Gingival index (GI) (Silness and Loe, 1964) was recorded at baseline and 1month after the procedure. Healing Index (Landrey, Turnbull and Howley, 1988)21 was assessed at day 1, day 7, day 14 and at 1 month respectively.

## CLINICAL PROCEDURES

### Laser technique

The diode laser (SIRO Laser Xtend, Sirona Dental Systems, Germany, 970 nm) was set at 3 W and ablation was performed in a contact, continuous wave mode following infiltration anesthesia, The laser beam was guided in a 'brushstroke' pattern from the mucogingival junction towards the free gingival margin including the interdental papilla until the entire area was free of pigmentation.

### Cryosurgery by tetrafluoroethane

Tetrafluoroethane (TFE) (DUPONT Fluorochemicals, USA) was applied after the pigmented area was isolated, air dried and anaesthetised. TFE was sprayed on a cotton swab and immediately rolled gently over the pigmented area maintaining a freezing zone for about 30-40 seconds.

### Application of REGEN-D 60 gel

REGEN-D 60 gel (Bharath Biotech International Limited, India) was applied over the treated depigmentation sites using a cotton swab in a swiping motion.

## STATISTICALANALYSIS

Data analysis was performed using the patient as the experimental unit. The statistical analysis was done using SPSS version 15.0 statistical analysis software. The gingival index scores and healing index scores were statistically analysed by Kruskal Wallis ANOVA. The intragroup comparison was done using Wilcoxon's signed rank test to evaluate the difference between gingival index scores at baseline and one month and healing index scores at various time intervals. The intergroup comparison was done using the Mann-Whitney U-test to determine if a difference exists between the 4 groups.

## RESULTS

Forty sites were evaluated in the study of which 20 sites underwent depigmentation followed by application of REGEN-D 60 gel. Throughout the study no local allergic reaction, pain, swelling, or any side effects were observed.

The difference in the mean gingival index in between the groups at baseline and 1 month was statistically significant ($p<0.0001$) (Table 1). Pair wise comparison of gingival index at baseline and at 1 month revealed statistically significant difference in the mean gingival index ($p<0.05$) as shown in Table1. Reduction in the mean gingival index scores from baseline to 1 month in group III and group IV was statistically significant ($p<0.05$) (Table 2).

Inter group comparison of healing index scores at various time intervals showed a statistically significant difference ($p<0.0001$) (Table 3). Pairwise comparison in between the groups also revealed a statistically significant result as shown in Table 3. The change in the healing index scores between various groups from day 1 to day 14 was statistically significant ($p<0.05$) (Table 4).

Group III showed the greatest reduction in gingival index scores when compared to all the groups (Fig 2) while Group I showed the best improvement in healing when compared to other groups (Fig 3).

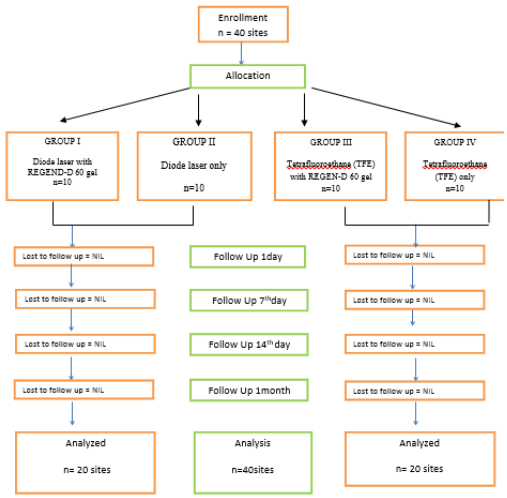


**Figure 1:- Consort flow chart**

| Groups | Baseline | | | | 1 month | | | | Changes from baseline to 1 month | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Sum of ranks | Mean | SD | Median | Sum of ranks | Mean | SD | Median | Sum of ranks |
| Group I | 0.77 | 0.25 | 0.63 | 27.75 | 0.59 | 0.18 | 0.48 | 30.85 | 0.18 | 0.29 | 0.18 | 24.00 |
| Group II | 0.39 | 0.22 | 0.30 | 11.75 | 0.31 | 0.10 | 0.33 | 10.15 | 0.08 | 0.18 | 0.08 | 15.55 |
| Group III | 0.69 | 0.21 | 0.60 | 24.90 | 0.49 | 0.12 | 0.45 | 25.20 | 0.21 | 0.14 | 0.14 | 23.00 |
| Group IV | 0.57 | 0.18 | 0.53 | 17.60 | 0.42 | 0.08 | 0.40 | 15.80 | 0.14 | 0.15 | 0.13 | 19.45 |
| H-value | 11.5390 | | | | 19.5170 | | | | 3.2560 | | | |
| P-value | 0.0090** | | | | 0.0001** | | | | 0.3570 | | | |
| Pair wise comparisons by Mann-Whitney U test | | | | | | | | | | | | |
| Group I vs Group II | p=0.0156 | | | | p=0.0004** | | | | p=0.3258 | | | |
| Group I vs Group III | p=0.4497 | | | | p=0.1988 | | | | p=0.7055 | | | |
| Group I vs Group IV | p=0.0211* | | | | p=0.0025** | | | | p=0.1988 | | | |
| Group II vs Group III | p=0.0284* | | | | p=0.0025** | | | | p=0.0757 | | | |
| Group II vs Group IV | p=0.0452* | | | | p=0.1988 | | | | p=0.3258 | | | |
| Group III vs Group IV | p=0.0588 | | | | p=0.0697 | | | | p=0.6232 | | | |

*p<0.05*<0.0001

**Table 1:** Comparison of four groups (I, II, III, IV) with respect to gingival index scores at baseline and 1 month by Kruskal Wallis ANOVA

| Groups | 0 | Mean | S D | Mean Diff. | SD Diff | % of change | Z-value | p-value |
|---|---|---|---|---|---|---|---|---|
| Group I | Baseline | 0.77 | 0.25 | 0.18 | 0.29 | 23.18 | 1.2741 | 0.2026 |
| | 1 month | 0.59 | 0.18 | | | | | |
| Group II | Baseline | 0.39 | 0.22 | 0.08 | 0.18 | 19.90 | 1.3624 | 0.1731 |
| | 1 month | 0.31 | 0.10 | | | | | |
| Group III | Baseline | 0.69 | 0.21 | 0.21 | 0.14 | 29.68 | 2.8031 | 0.0051** |
| | 1 month | 0.49 | 0.12 | | | | | |
| Group IV | Baseline | 0.57 | 0.18 | 0.14 | 0.15 | 25.44 | 2.4973 | 0.0125* |
| | 1 month | 0.42 | 0.08 | | | | | |

*p<0.05, **p<0.01

**Table 2:** Comparison of baseline and 1 month with respect to gingival index scores in four groups (I, II, III, IV) by Wilcoxon matched pairs

| Groups | Day 1 | | | | Day 7 | | | | Day 14 | | | | 1 month | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Sum of ranks | Mean | SD | Median | Sum of ranks | Mean | SD | Median | Sum of ranks | Mean | SD | Median | Sum of ranks |
| Group I | 1.90 | 0.32 | 2.00 | 32.00 | 2.50 | 0.53 | 2.50 | 27.75 | 3.00 | 0.00 | 3.00 | 28.50 | 3.90 | 0.32 | 4.00 | 53.70 |
| Group II | 1.30 | 0.48 | 1.00 | 20.00 | 2.00 | 0.00 | 2.00 | 18.00 | 2.80 | 0.42 | 3.00 | 24.50 | 3.00 | 0.00 | 3.00 | 17.50 |
| Group III | 1.10 | 0.32 | 1.00 | 16.00 | 2.10 | 0.32 | 2.00 | 19.95 | 2.60 | 0.52 | 3.00 | 20.50 | 3.00 | 0.47 | 3.00 | 17.80 |
| Group IV | 1.00 | 0.00 | 1.00 | 14.00 | 1.90 | 0.32 | 2.00 | 16.50 | 2.00 | 0.00 | 2.00 | 8.50 | 2.70 | 0.48 | 3.00 | 13.00 |
| H-value | 21.6670 | | | | 12.9000 | | | | 22.7500 | | | | 25.4610 | | | |
| P-value | 0.0001** | | | | 0.0050** | | | | 0.0001** | | | | 0.0001** | | | |
| Pair wise comparisons by Mann-Whitney U test | | | | | | | | | | | | | | | | |
| Group I vs Group II | p=0.0235* | | | | p=0.0588 | | | | p=0.4497 | | | | p=0.0007** | | | |
| Group I vs Group III | p=0.0025** | | | | p=0.1306 | | | | p=0.1306 | | | | p=0.0022** | | | |
| Group I vs Group IV | p=0.0007** | | | | p=0.0376* | | | | p=0.0002** | | | | p=0.0004** | | | |
| Group II vs Group III | p=0.4497 | | | | p=0.7055 | | | | p=0.4497 | | | | P=0.9999 | | | |
| Group II vs Group IV | p=0.2568 | | | | p=0.7055 | | | | p=0.0025** | | | | p=0.2568 | | | |
| Group III vs Group IV | p=0.7055 | | | | p=0.4727 | | | | p=0.0233* | | | | p=0.3075 | | | |

*p<0.05, **p<0.0001

**Table 3:** Comparison of four groups (I, II, III, IV) with respect to healing index scores at day1, 7, 14 and month by Kruskal Wallis ANOVA test

| Groups | Changes from Day 1 to Day 7 | | | | Changes from Day 1 to Day 14 | | | | Changes from Day 1 to 1 month | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Median | Sum of ranks | Mean | SD | Median | Sum of ranks | Mean | SD | Median | Sum of ranks |
| Group I | 0.60 | 0.52 | 1.00 | 16.50 | 1.10 | 0.32 | 1.00 | 17.00 | 2.00 | 0.47 | 2.00 | 23.65 |
| Group II | 0.70 | 0.48 | 1.00 | 18.50 | 1.50 | 0.53 | 1.50 | 25.00 | 1.70 | 0.48 | 2.00 | 18.15 |
| Group III | 1.00 | 0.00 | 1.00 | 24.50 | 1.50 | 0.53 | 1.50 | 25.00 | 1.90 | 0.32 | 2.00 | 22.05 |
| Group IV | 0.90 | 0.32 | 1.00 | 22.50 | 1.00 | 0.00 | 1.00 | 15.00 | 1.70 | 0.48 | 2.00 | 18.15 |
| H-value | 6.0940 | | | | 10.1470 | | | | 3.2460 | | | |
| P-value | 0.1070 | | | | 0.0170* | | | | 0.3550 | | | |
| Pair wise comparisons by Mann-Whitney U test | | | | | | | | | | | | |
| Group I vs Group II | p=0.7055 | | | | p=0.1306 | | | | p=0.3075 | | | |
| Group I vs Group III | p=0.1306 | | | | p=0.1306 | | | | p=0.7337 | | | |
| Group I vs Group IV | p=0.2568 | | | | p=0.7055 | | | | p=0.3075 | | | |
| Group II vs Group III | p=0.2568 | | | | P=0.9999 | | | | p=0.4497 | | | |
| Group II vs Group IV | p=0.4497 | | | | p=0.0500* | | | | P=0.9999 | | | |
| Group III vs Group IV | p=0.7055 | | | | p=0.0500* | | | | p=0.4497 | | | |

*p<0.05

**Table 4:** Comparison of four groups (I, II, III, IV) with respect to healing index scores at changes from day1 to 7, 14 and month by Kruskal Wallis ANOVA

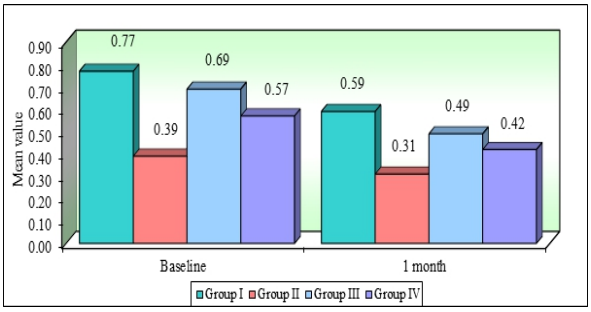


**Fig 2:** Comparison of four groups (I, II, III, IV) with respect to gingival index scores at baseline and 1 month

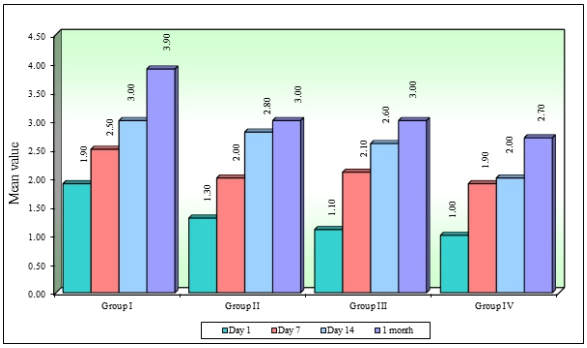


**Fig 3**: Comparison of four groups (I, II, III, IV) with respect to healing index scores at day 1, 7, 14 and month

## DISCUSSION

To the best of our knowledge, this is the first trial to demonstrate a significant and positive effect of hEGF on the rate of healing of gingival epithelium.

The gingival tissue is continuously subjected to mechanical and bacterial aggressions. The saliva, epithelial surface and the initial stages of the inflammatory response provide resistance to these actions.12 The degree of keratinisation and cell turnover rate are key considerations for the protective function of the epithelium.12 The oral epithelium undergoes continuous renewal and its thickness is maintained by a balance between new cell formation in the basal and spinous layers and the shedding of old cells at the surface.[12]

In our study we have performed gingival depigmentation with diode laser and followed by application of REGEN-D 60 gel at randomly selected sites. No adverse effects were experienced by the patient throughout the study. The drug administered was in a gel base and was supplied as a 7.5g tube consisting of 60µg of recombinant human epidermal growth factor allowing for even application on the treated sites using a sterile cotton swab.

REGEN-D 60 epidermal growth factor is a new generation therapy with a novel factor used for first and second degree burns, skin grafts and bed sores. It was reported that the application of various epidermal growth factor (EGF) formulations onto experimentally induced wounds enhances epithelialization with the concurrent accumulation of granulation tissue. In particular, the topical application of EGF has been shown to accelerate the healing rate of open wounds.[13-15]

A double-blind randomized pilot study was previously conducted by Falanga et.al with use of human recombinant epidermal growth factor (h-EGF) to treat 44 patients with venous ulceration of the lower extremities. There were no untoward side effects related to the application of h-EGF. However, the authors concluded that it was safe but failed to significantly enhance reepithelialization of venous ulcers.[16]

A previous animal study revealed that topical application of epidermal growth factor accelerates wound healing by myofibroblast proliferation and collagen synthesis in rats.[17] A randomized, double-blind human clinical trial was conducted using skin-graft-donor sites to determine whether epidermal growth factor would accelerate the rate of epidermal regeneration. The authors concluded that epidermal growth factor accelerates the rate of healing of partial-thickness skin wounds.[18]

Complete healing was observed in all the groups with the highest healing index score being observed in group I. This could be attributed to the healing properties of the REGEN-D 60 gel coupled with the biostiumulatory properties of diode laser.

It has been reported that repeated treatment with EGF increases the epithelial cell proliferation in a dose dependent manner and accelerates the wound healing process, whereas a single EGF treatment has not demonstrated a noticeable effect on the wound-healing rate.[19,20] However in contrast to the previous study, present study demonstrated single application of REGEN-D 60 gel which showed a significant gain in the healing index scores in various groups at 14th day. Significant results were not achieved at one month postoperatively. Repeat application of EGF during study period might have improved

the gain in healing index at 1 month. As previously mentioned, this being the first study to assess the healing capacity of REGEN-D 60 gel on oral wounds; the authors decided to perform only a single application of the gel to evaluate its response on the oral mucosa.

Greater reduction in gingival index scores was noted in group 1 and 3 where the REGEN-D 60 gel was used. This further reinforces the evidence available in literature regarding its potential in accelerating wound healing. In the present study we did not encounter any dropout as only patients who were esthetically conscious were recruited.

In conclusion, the topical application of rhEGF gel can induce rapid wound healing in gingival epithelium by accelerating epithelial cell proliferation. Our study demonstrated that topical application of REGEN-D 60 gel provided faster and predictable healing following gingival depigmentation either with laser or tetrefluoroethane. However more scientific research needs to be carried out for better understanding of its exact role in wound healing.

**Conflict of interest**

Authors Dr. Shivaprasad BM, Dr.Vinaya Kumar R, Dr. Sruthi K Nair, Dr Nayan Jyoti Deka, Dr. Rekha BM states that there are no conflicts of interest.

## REFERENCES


1. Meyerson MA, Cohen PR, Hymes SR. Lingual hyperpigmentation associated with minocycline therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1995;79:180-184.
2. Chin J, Yeh. Cryosurgical treatment of melanin-pigmented gingiva. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998; 86(6): 660-663.
3. Fatih A, Ali G. Cryosurgical treatment of gingival melanin pigmentation using Tetrafluoroethane. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2007 ; 103(4): 452-457.
4. Hirschfeld I, Hirschfeld L. Oral pigmentation and method of removing it. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1951; 4:1012.
5. Tal H, Landsberg J, Kozlovsky A. Cryosurgical depigmentation of the gingiva : A case report. J Clin Periodontol 1987; 14:614-617.
6. Pollanen MT, Salonen JI, Uitto VJ. Structure and function of tooth-epithelial interface in health and disease. Periodontol 20002003;31(1):12-31.
7. Vitkov L, Krautgartner WD, Hannig M, Surface morphology of pocket epithelium. Ultrastruct Pathol2005;29(2):121-127.
8. Venturi S, Venturi M. Iodine in evolution of salivary glands and in oral health. Nutrition and Health2009; 20 (2): 119-134.
9. Bonassar L.J, Trippel SB, Interaction of epidermalgrowth factor and insulin-like growth factor-I in the regulation of growth plate chondrocytes. Exp. Cell Res.1997; 234:1-6.
10. Liu NA, Flores C, Kinkead T, Carboni A, Menon M, Seethalakshmi L. Effects of sialoadenectomy and epidermal growth factor on testicular function of sexuality mature male mice. J Urol 1994:152, 554-561.
11. Mohan V K. Recombinant human epidermal growth factor (REGEN- DTM 150): effect on healing of diabetic foot ulcers. Diabetes Research and Clinical Practice 2007;78:405-441.
12. Ketany M, Dao A, Ýhsan Z, Bukbayram H, Davut O. The effects of epidermal growth factor deficiency on rat gingival epithelia. Vet. arhiv 2001; 71(2): 85-96.
13. Buckley A, Davidson JM, Kamerath CD, Woodward SC. Epidermal growth factor increases granulation tissue formation dose dependently. J Surg Res 1987;43:322-328.
14. Laato M. Effect of epidermal growth factor (EGF) on blood flow and albumin extravasation in experimental granulation tissue. Acta Chir Scand. 1986;152:401405.
15. Okumura K, Kiyohara Y, Komada F, Iwakawa S, Hirai M, Fuwa T. Improvement in wound healing by epidermal growth factor (EGF) ointment. I. Effect of nafamostat, gabexate, or gelatin on stabilization and efficacy of EGF. Pharm Res. 1990;7:1289-1293.
16. Falanga V, William H. Bucalo , Matthew H. Harris B, Carson P Topical Use of Human Recombinant Epidermal Growth Factor (h-EGF) in Venous Ulcers. The Journal of Dermatologic Surgery and Oncology 1992;18(7) 604-606.
17. Brown GL. Enhancement of wound healing by topical treatment with epidermal growth factor. N Engl J Med. 1989 Jul 13;321(2):76-79.
18. KwonY, Kim HW,Roh DH. Topical application of epidermal growth factor accelerates wound healing by myofibroblast proliferation and collagen synthesis in rat. J Vet Sci. 2006; 7(2): 105-109.
19. Brown GL, Curtsinger L, Brightwell JR, Ackerman DM, Tobin GR, Polk HC etal. Enhancement of epidermal regeneration by biosynthetic epidermal growth factor.J Exp Med 1986;163:1319-1324.
20. Kim JS, McKinnis VS, Adams K, White SR. Proliferation and repair of guinea pig tracheal epithelium after neuropeptide depletion and injury in vivo. Am J Physiol 1997;273:1235-1241.
21. Landry RG, Turnbull RS, Howley T. Effectiveness of benzydamyne HCL in the treatment of periodontal post-surgical patients. Research in clinical forums 1988;10:105-118.