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Original article

Investıgatıon into the Effect of Epıdermal Growth Factor and Hyaluronıc Acıd on Fracture Healıng in a Rat Femoral Fracture Model

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Abstract

This study aimed to investigate the role of an exogenous Epidermal growth factor and a hyaluronic acid-based scaffold on fracture healing in a rat femoral fracture model
Forty-eight male Wistar-Albino rats, each weighing a mean 392 grams (range= 350-450 grams) and aged 8.2 months (6-9 months), were used for this experimental study. All surgical procedures were performed on the left femur by a single surgeon. An open femoral fracture was created in all rats. The animals were randomly divided into one of the four groups: control (12), Epidermal growth factor (12), hyaluronic acid-based (12) and combined (12). In the fourth and sixth weeks, samples were processed and analyzed using biomechanical and histological methods. Fracture healing was significantly improved in the combined group compared to the control one, Epidermal growth factor and hyaluronic acid-based groups in all parameters at both experimental time points. At the fourth and sixth weeks after surgery, fracture healing in the Epidermal growth factor and hyaluronic acid-based groups was significantly increased at histological evaluation compared to controls. In addition, compared with Epidermal growth factor, hyaluronic acid-based and control groups, a significant difference in callus tissue was detected in the combined group at fourth and sixth weeks time points in biomechanical features.This study has shown that combining local Epidermal growth factor and hyaluronic acid-based scaffold accelerates bone healing and strengthens the bony callus histologically and biomechanically. Using Epidermal growth factor/hyaluronic acid-based combined scaffolds may represent a possible future strategy in trauma surgery.

Keywords: epidermal growth factor, hyaluronic acid, fracture, healing, bone callus.

1. Introduction

Fracture healing is a complex and tightly coordinated process that aims to restore bone to its original preinjury state [1]. It involves various anatomical, biomechanical, and biochemical factors and processes [2]. With the technological advancements in medicine, the mechanism of fracture healing has been enlightened in detail especially in the last 2 decades [3]. Through these investigations, some molecules and factors have also been identified which stimulate callus formation and accelerate fracture healing.

Hyaluronic acid (HA) is a linear polysaccharide with a high molecular weight. It is an unimmunized glycosaminoglycan that is synthesized in the cell membrane [4]. HA is found in the extracellular gap of all tissues [5]. However, in some tissues, especially in early callus tissue, it is found in greater concentrations [6].

In recent literature, it is shown that HA stimulates the migration, proliferation, and differentiation of progenitor cells and increases the osteoblastic activity, and is effective in angiogenesis [5-7]. HA also increases the effects of some cytokines and growth factors in early osteogenic events. According to Bhakta et al, HA increases the effect of BMP-2 and increases osteogenesis in a rat in vivo ectopic bone model [8].

Epidermal growth factor (EGF) is a single polypeptide chain growth factor which is formed by a 53-amino acid sequence. There are 3 intramolecular bisulfides bonds that determine EGF activity [9]. Upon activation of EGF-receptors via EGF-ligands, PI3 kinase and MAP kinase pathways are activated intracellularly, thus resulting in cell proliferation and a decrease in apoptosis is observed [10]. There are many current experimental studies in the literature for the analysis of the effect of human EGF on rats, and its cytoprotective, mitotic, and cell-differentiation effects have been shown [11,12]. *In vitro* effects of EGF on bone metabolism have also been reported in the current literature. According to Yarram et al, with the activation of the MAP kinase pathway, osteoblast metabolism is also activated [13].

In the current literature, there are very few new studies on in vivo data for the effect of EGF on long bone healing with callus tissue formation. Therefore, it is hypothesized that, with the application of EGF during a trauma surgery, a durable callus can be achieved and duration of bone healing can also be shortened. Furthermore, when EGF is combined with HA on an acellular mesh, the effect of EGF can be further increased. In light of this information, this in vivo experimental model was built up to enlighten the possible effects of exogenous EGF by comparing it with HA and the effect of the combination on fracture healing.

2. Materials and methods

Animals. Forty-eight male Wistar Allbino rats, each weighing a mean 392 g (350-450 g) and aged 8.2 months (6-9 months) were selected for this experiment, which were kept under standard laboratory conditions (temperature 21-24°C, with relative humidity, 12-hour light and 12-hour darkness) in special cages under specified pathogen-free conditions with free access to water and food (ad libitum) at the laboratory animal unit. Young adult male rats were chosen to obtain optimal metabolic activity for fracture healing.

Rats were divided randomly into 4 equal groups of 12 rats; the first group received intralesionary EGF, the second group received intralesionary HA scaffold, the third received Combined group, in which EGF is impregnated on HA scaffold, and forth was the control group. It is planned at the fourth and sixth weeks to select 6 rats from each group randomly for biomechanical and histological analysis. For the mechanical analysis, 4 contralateral (nonfractured) femurs were also harvested.

The experimental protocol was approved by the Gulhane University Animal Experimentation Ethics Committee on February 26, 2019 (Etik -2019 /02-2 019/0 2), and the study was conducted according to ARRIVE guidelines. Throughout the experiments, 2 independent veterinarians were involved in monitoring the rats.

Surgery. Anesthesia was induced through an intraperitoneal injection of a combination of Ketamin (Ketalar®, Pfizer, Istanbul, Turkey) 90 mg/kg and Xylazin (Rompun®, Bayer, Turkey) 10 mg/kg. No preoperative or postoperative systemic antibiotic prophylaxis was administered. All surgical procedures were performed on left femurs under aseptic conditions (limb shave + povidone iodine surgical scrub) by a single surgeon. Under general anesthesia, an open femoral fracture was created in all rats as described by Neagu et al and Claes et al. [14,15]. After preoperative preparation, a 2 cm standard lateral incision was made parallel to the axis of femoral shaft. The interval between the inferior of the "Tensor Fascia Lata" and the superior of the "Biceps Femoris" was dissected bluntly the access to femoral shaft. To create a simple transverse fracture, both cortices were weakened via a 0.75 mm Kirschner wire and a bicortical fracture was created with a 1 mm osteotome without causing any defect (Figure 1a and b).

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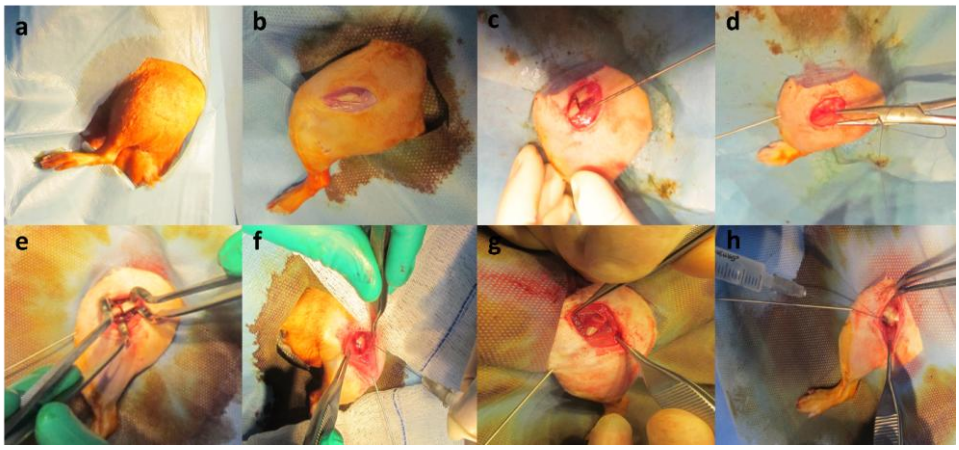

Figure 1 – a) Surgical field preparation; b) Lateral incision and surgical dissection of left femur; c) Open shaft fracture; d) Surgical closure of fascia; e) Reduction with K-wire; f) Intralesional injection of EGF (EGF group); g) HA scaffold implantation (HA group); h) Implantation of HA scaffold combined with EGF (Combined group); EGF, Epidermal Growth Factor; HA, Hyaluronic Acid; K-wire, Kirschner wire

Fracture fixation was achieved via a 1.5 mm Kirschner wire, which was applied antegrade from the fracture area through "Trochanter Major". After the adequate reduction was achieved, the Kirschner wire was applied retrogradely. Then, fascia was sutured with a 3-0 Vicryl suture (Ethicon®, Johnson&Johnson, New Brunswick, New Jersey, USA). Skin was sutured with 2-0 Prolene suture (Doğsan®, İstanbul, Turkey) and Neo-Caf Sprey (Intervet®, Milano, Italy) was applied as dressing (Figure 1c, d, and e).

For the EGF group, 75 μg lyophilized Heberprot-P® (Center for Genetic Engineering and Biotechnology, Cuba/Has Biotech, Turkey) was diluted with 10 cm3 saline and applied 7.5 μg/cm3 per rat to the fracture line intraoperatively prior to wound closure (Figure 1f). Dosage selection was determined blindly since there is no current literature on fracture healing with EGF. For the HA group, after the fracture was reduced, a 2×0.5 cm Hyalofast® (Anika Therapeutics, Padova, Italy/Soylu Medical, Istanbul, Turkey) was enlaced to the fracture line via a Right-Angled Clamp (Figure 1G). For the Combined group, 7.5 μg/cm3 Heberprot-P® impregnated 2×0.5 cm Hyalofast® was applied to the fracture line (Figure 1h).

At fourth and sixth weeks, rats were sacrificed via cervical dislocation under general anesthesia. All left femurs were disarticulated and exited en bloc and detached from muscle tissues surrounding the femur without manipulating the fracture line.

Biomechanical investigations. Biomechanical healing was assessed via Instron 5565-A (Instron Company®, Mass, Norwood, USA) by "three-point bending test". In this test, the maximum load that callus tissue can absorb is defined as "maximum force" which represents callus tissue strength, and elastic deformation ability of callus is defined as "stiffness" which represents the resistance offered by the whole bone to the applied displacement during the elastic region and is analogous to a simple spring constant (K) [16,17]. To be able to obtain accurate and standardized data, all femurs were placed anteroposteriorly on a 3.2 mm support which was 2 cm from the center at which load was applied. A load was applied 1 mm/min on femurs and "maximum force" and "stiffness" values were recorded.

Histological Investigations. All femurs were dissected 1 cm distal and proximal to the fracture line and immersed in a 10% formaldehyde solution for 2 weeks. Fixation was applied with Bouin's solution for 2 days. After the fixation, decalcification was carried out using a solution of 10% acetic acid, 0.85% NaCl, and 10% formalin.

Paraffin-embedded specimens were cut longitudinally in 3-4 μm slides. Hemat oxylin-eosin-stained specimens were examined under a light microscope and scored with the Huo Scoring System in a blinded manner by a pathologist [18].

All femurs were also evaluated under scanning electron microscope (SEM). For evaluation, all femurs were fixated with 2.5% glutaraldehyde solution and cleaned with Sorenson phosphate buffer (pH 7.4) and further fixated with osmium tetroxide.

All specimenswere dehydrated with acetone and 100 Angstrom Gold Palladium was pulverized and observed under Zeiss Evo LS 15 (Jena®, Oberkochen,

Germany) electron microscope at an accelerating voltage of 5-30 kV.

Statistical analysis. Prior to the study, a power analysis was conducted to ensure an accurate sample size. Since a one-way mixed analysis of variance (ANOVA) method was planned to be used in further evaluations [n = 20/kr + 1] formula was used as stated by Arifin et al. [19]. Therefore, a minimum of 32 rats were required for 4 groups and 2 repeated measure times. To account for possible losses during the experiment, a corrected sample size of 48 rats was determined by predicting 1 loss per 3 rats.

All experiments in this study were independently repeated at least 3 times with consistent results. The data are presented as mean and standard deviation (SD) of the mean. Statistical analysis was carried out using the Statistical Package for the Social Sciences Statistics software, version 11.5 for Windows (SPSS Inc., Chicago, IL, USA). Kruskal–Wallis and one-way ANOVA tests were used for statistical comparisons. Mann–Whitney U-test was used to compare 2 different groups if statistically significant, p-values of less than 0.05 were considered statistically significant.

3. Results

During the experiment and follow-up period, 10 of 48 rats were lost in the first 24 hours without any specific cause (4 in control group, 2 in HA group, 2 in EGF group, and 2 in combined group) and excluded from the study. No sign of infection was observed. Overall, 38 rats were included in study: 8 in control group, 10 in EGF group, 10 in HA group, and 10 in Combined group. During the Daily follow-ups, no signs of weight-loss, behavioral changes, wound complications, etc. were observed. At fourth week and sixth week, 4 rats in control group, 5 rats in EGF group, 5 rats in HA group, and 5 rats in combined group were randomly selected and analyzed.

All results including biomechanical and histological assessments are listed in Table 1 and statistical analyses in Tables 2 and 3 and statistical graphs in Figure 2.

Table 1 – Overall mean or median results on biomechanical and histological assessments

	Maximum Force (N) Mean (SD)	**Stiffness (N/mm) Mean (SD)**	**Histological assessment Median (Min- Max)**
CL	145.9 (± 2.73)	331.74 (± 110.78)	N/A
Control	0	0	1.0 (1.0 – 1.0)
EGF	0	0	4.0 (3.0 – 4.0)
HA	0	0	3.0 (3.0 – 3.0)
Combined	18.81 (± 3.69)	56.11 (± 2.93)	5.0 (5.0 – 6.0)
Control	10.92 (± 1.21)	36.37 (± 20.69)	2.0 (2.0 – 2.0)
EGF	17.70 (± 2.60)	36.13 (± 15.38)	4.0 (3.0 – 4.0)
HA	16.20 (± 2.80)	36.28 (± 10.11)	3.0 (3.0 – 4.0)
Combined	58.18 (± 7.08)	94.11 (± 32.66)	7.0 (6.0 – 7.0)

Table 2 – Statistical comparison of all parameters between each other at 4th weeks

Groups	**Maximum Force**	**Stiffness**	**Histological Assessment**
CL – Control	p = 0.014	p = 0.014	N/A
CL - EGF	p = 0.007	p = 0.007	N/A
CL - HA	p = 0.007	p = 0.007	N/A
CL - Combined	p = 0.014	p = 0.014	N/A
EGF - Control	p = 1.000	p = 1.000	p = 0.009
HA - Control	p = 1.000	p = 1.000	p = 0.005
EGF - HA	p = 1.000	p = 1.000	p = 0.050
Combined - Control	p = 0.011	p = 0.011	p = 0.007
Combined - EGF	p = 0.005	p = 0.005	p = 0.006
Combined - HA	p = 0.005	p = 0.005	p = 0.004

Note: CL: Contralateral, N/A: Not Available. Statistically significant values (p<0.05) are represented in bold

Table 3 – Statistical comparison of all parameters between each other at sixth weeks

Groups	Maximum Force	Stiffness	Histological Assessment
CL – Control	p = 0.021	p = 0.021	N/A
CL - EGF	p = 0.014	p = 0.014	N/A
CL - HA	p = 0.014	p = 0.014	N/A
CL - Combined	p = 0.014	p = 0.014	N/A
EGF - Control	p = 0.014	p = 1.000	p = 0.007
HA - Control	p = 0.014	p = 0.806	p = 0.009
EGF - HA	p = 0.465	p = 0.917	p = 0.221
Combined - Control	p = 0.014	p = 0.027	p = 0.009
Combined - EGF	p = 0.009	p = 0.016	p = 0.006
Combined - HA	p = 0.009	p = 0.009	p = 0.007

Note: CL: Contralateral, N/A: Not Available. Statistically significant values (p<0,05) are represented in bold

Biomechanical healing was assessed with "maximum force" and "stiffness" values. At fourth week, the mean "maximum force" and "stiffness" values of the control, EGF, and HA groups were 0 since not a durable callus was formed. However, a remarkable callus tissue was formed in the combined group. At six weeks, the mean "maximum force" values of all groups were statistically significant when compared with the control group ($p < 0.05$). In terms of "stiffness," callus structure of the HA, EGF, and control groups were similar ($p = 1.00$). However, the structure of the callus tissue was "stiffer" compared with the other groups ($p < 0.05$). At fourth and sixth week, the contralateral group was significant with all other groups biomechanically.

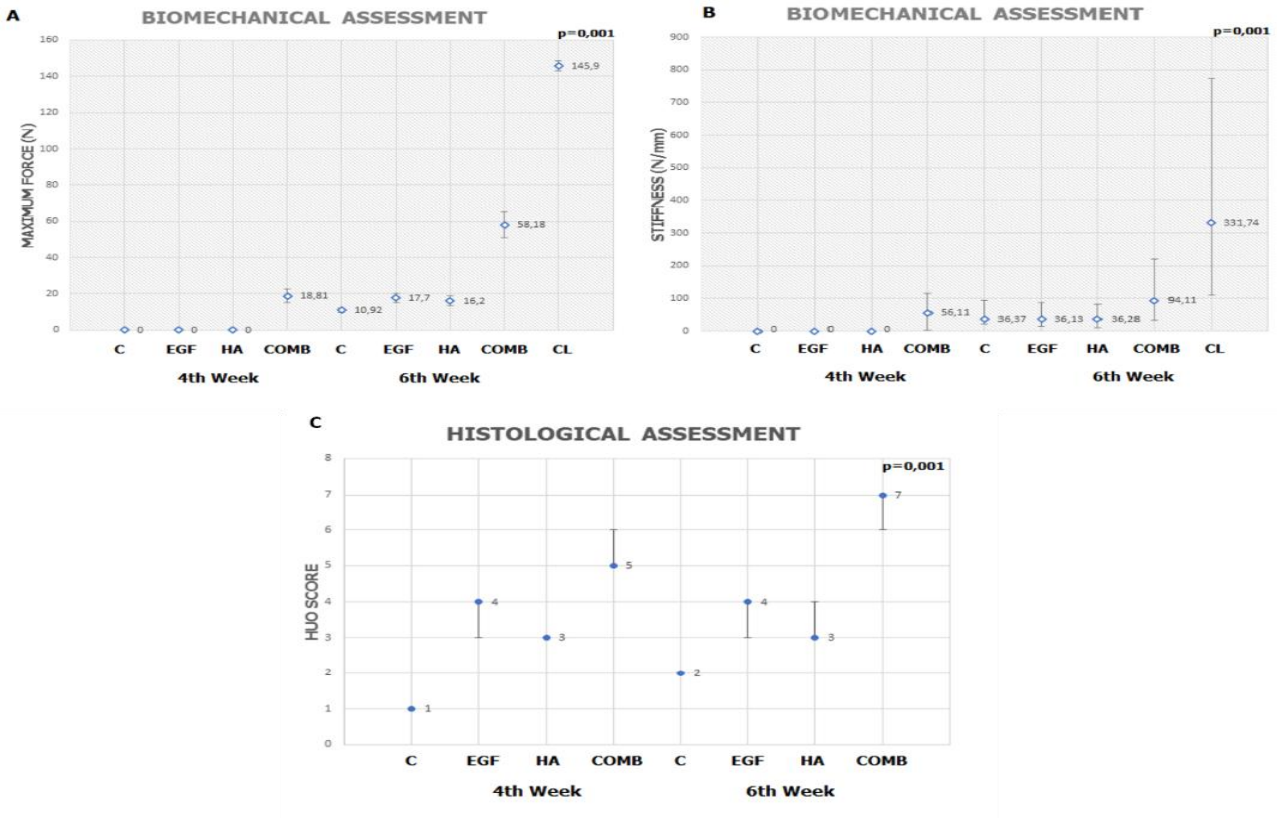

Figure 2 – Statistical graphs of biomechanical and histological assessments; a) Maximum force assessment; b) Stiffness assessment; c) Histological assessment (C: control group, EGF: EGF group, HA: HA group, COMB: combined group, CL: contralateral group); Dots indicate mean values and error bars represent minimum–maximum values. EGF, epidermal growth factor; HA, hyaluronic acid

Despite the fact that the most durable callus tissue was formed at combined group, the durability of the callus tissue is not as the strong as original bone tissue ($P < 0.05$) (Figure 2a and b).

Light microscope samples of all groups are listed in Figure 3. All samples were scored with Huo classification system to be able to obtain quantitative data for histologic changes (Table 1). At fourth week, in fracture area, fibrous tissue was seen in control group (Figure 3a).

SEM results of all groups are shown in Figure 4. Results of SEM investigation were assessed qualitatively. Even though SEM results could not be assessed quantitatively, significant changes were also remarkable. At the fourth week, in the control group, fracture lines were purely visible (Figure 4a). The main difference between the EGF and HA groups was the trabecular bone formation in the EGF group (Figure 4a) and the fibrous tissue majority in the HA group (Figure 4e). In the combined group, newly formed regenerative bone tissue was observed (Figure 4g).

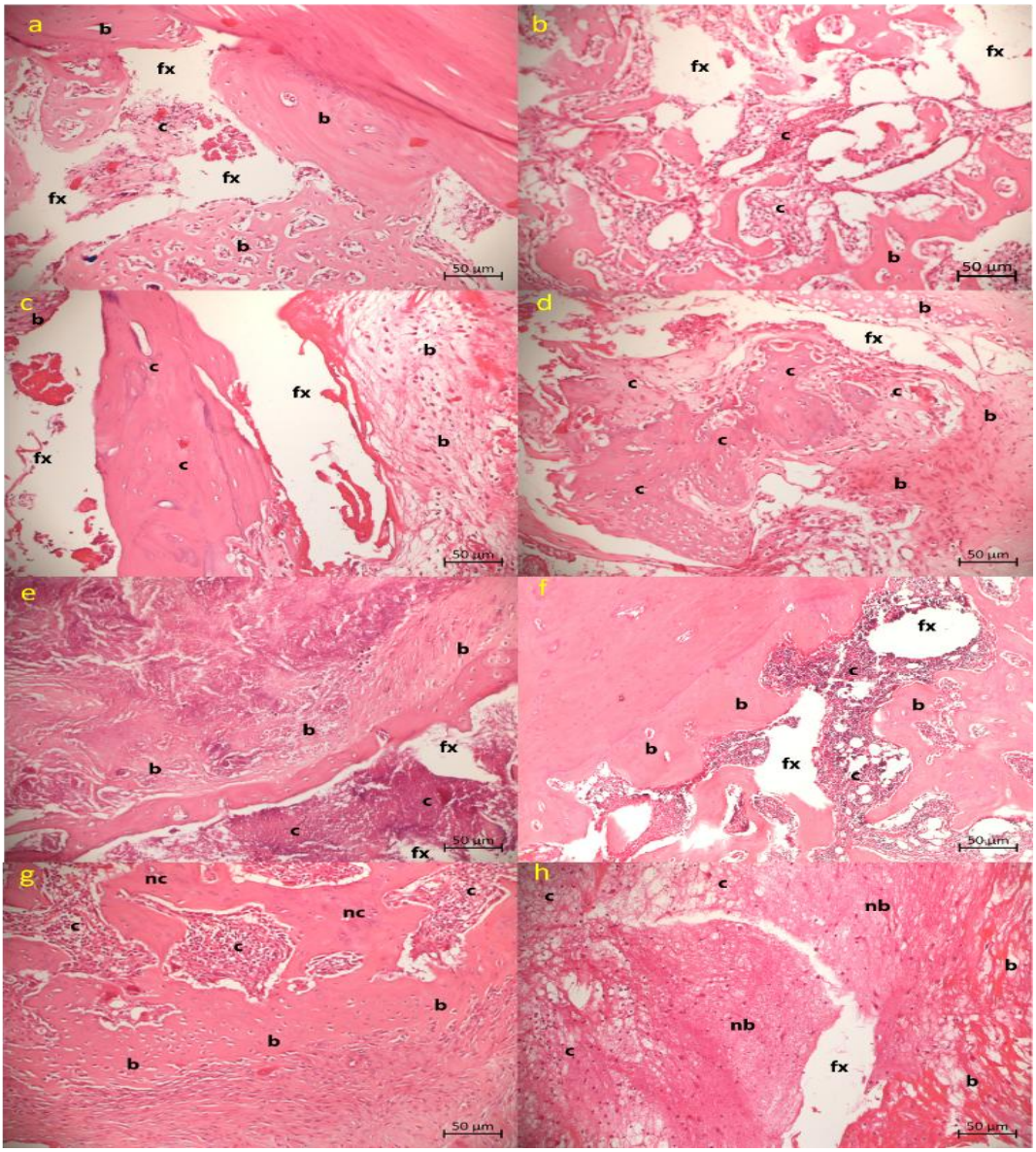

Figure 3 – Light microscopic samples of a) control group at fourth week; b) control group at sixth week; c) EGF group at fourth week; d) EGF group at sixth week; e) HA group at fourth week; f) HA group at sixth week; g) combined group at fourth week; h) combined group at sixth week; b, bone; c: callus tissue; fx, fracture line; nb, newly formed bone tissue; nc, newly formed cartilage tissue

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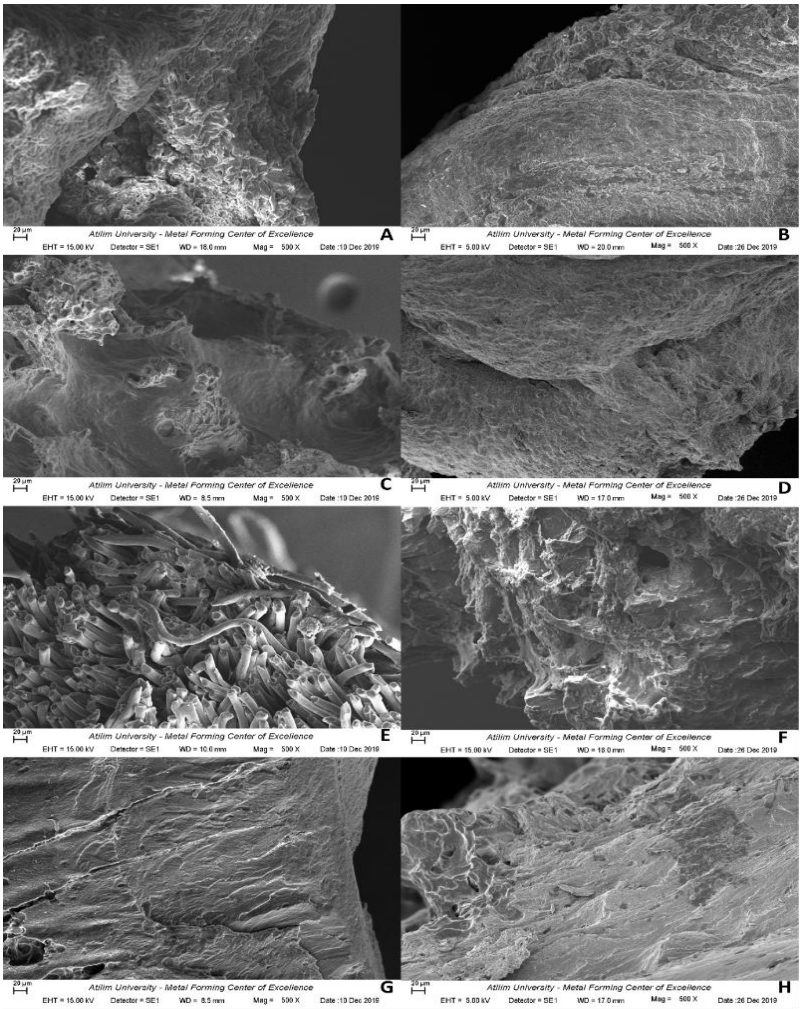

Figure 4 – Scanning electron microscopic samples of a) Control group at fourth week; b) Control group at sixth week; c) EGF group at fourth week; d) EGF group at sixth week; e; HA group at fourth week; f; HA group at sixth week; g) Combined group at fourth week; h) Combined group at sixth week. EGF, epidermal growth factor; HA, hyaluronic acid

At sixth week, rarely new formed bone tissue was observed in the Control group (Figure 4b). Mostly regenerative bone formation was visible in the EGF group (Figure 4d) in contrast with the HA group at which fibrous tissue and minor newly formed bone tissue were together observed (Figure 4f). However, new bone formation was almost completed in the Combined group (Figure 4h).

4. Discussion

Fracture healing is a complex and dynamic process which is still being investigated with the help of technological and medical developments. In recent years, researchers have focused on cytokines and growth factors that could accelerate fracture healing, promote early mobilization, and prevent complications, particularly nonunion.

In this experimental study, the effect of HA scaffold and EGF alone and in combination of them on fracture healing were compared. It is observed that, the combination of HA scaffold and EGF increases callus strength and durability, thus decreasing fracture healing time. Furthermore, one dose of intralesional EGF application also stimulates fracture healing as much as HA scaffold. Thus, the combination of EGF and HA scaffold provides a synergistic effect on fracture healing.

To create a uniform fracture line and reduction, we preferred the open femoral shaft fracture model in our study. Even though the first experimental animal model was introduced by Jackson et al in 1970, it was a closed femoral fracture model and severe complications like unstandardized callus formation, deep tissue infections, and death were observed [20]. Despite the

technical difficulties, the open femoral fracture model was preferred in our study, which was introduced by Neagu et al. and Claes et al. [14,15].

Hyaluronic acid is a major component of extracellular matrix. With the technological developments, to create a scaffold in various orthopedic operations, HA alone or containing acellular matrix products are widely used [21]. In the current literature, scaffolds containing HA are used as periosteal grafts and accelerates fracture healing [22]. Histological evaluations show that scaffold grafts fill the defective area and protect the tissue from fibrous tissue penetration. Furthermore, several studies show that HA-containing scaffolds induce extracellular matrix formation, angiogenesis, and osteogenesis [23]. In our study, HA scaffolds increase fracture healing similarly to current literature.

In the current literature, there is no available literature that provides evidence of the correlation between EGF and callus formable fracture healing. However, according to Marquez et al, EGF improves primary bone healing especially when combined with liposomal scaffolds [24]. According to Hernandez-Flores et al, combination of EGF and ascorbic acid improves unicortical tibial bone defect biomechanically [25].

Furthermore, a new study by Dominguez-Hernandez shows an increase in bone healing with EGF and ascorbic acid application [26]. However, these studies are unicortical fractures and do not involve callus formation. According to Bilal et al, it is shown that EGF increases fracture healing and vascularization in rat tibial defect healing with antibiotic embedded polymethyl methacrylate scaffold [27].

In our study, EGF alone and in combination of EGF and HA improve bicortical and callus-formed femoral shaft fracture healing both histologically and biomechanically. With our literature review, one of our aims was to compare the effect of HA, which is a widely used molecule, and EGF on fracture healing, and it is observed that fracture healing is induced by EGF as well as HA. Furthermore, EGF can be applied injectably whereas HA must be applied intraoperatively.

Currently, there are also no data available on the effect of HA and EGF combination on fracture healing. However, Kondo et al reported that combination of EGF and HA on diabetic wound healing improves re-epithelization but no significant difference is found when compared with HA alone [28]. Su et al. also showed that EGF and HA scaffold combination improves wound healing in rabbits.

4. Conclusions

In our study, we observed that the effect of EGF could be increased with the application on a scaffold, which ensured the sustained release of EGF on the fracture line [29].

Our study had limitations, including a relatively short follow-up period and an inability to investigate radiologically. Longer follow-ups and the use of micro-CT could provide more detailed measurements of callus tissue and enable more detailed inferences.

The use of a single dose of 7.5µg/cm^3 of intralesional EGF in the treatment of long bone shaft fractures results in similar biomechanical and histological fracture healing outcomes as those achieved with HA scaffold treatment. Furthermore, the combination of EGF and HA scaffold leads to even greater improvements in fracture healing compared to the use of either treatment alone.

Conflicts of Interest. The authors declare no conflicts of interest.

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Author Contributions: Authors equally contributed to this work. All authors have read and agreed to the published version of the manuscript.

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Егеуқұйрықтардың сан сүйегі сынуы моделіндегі эпидермальді өсу факторы мен гиалурон қышқылының сүйек жазылуына әсерін зерттеу

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Түйіндеме

Осы зерттеудің мақсаты – экзогенді эпидермальды өсу факторы мен гиалурон қышқылы негізіндегі каркастың егеуқұйрықтардың сан сүйегі сыну моделінде сүйек жазылуына әсерін зерттеу болды. Бұл эксперименттік зерттеуге орташа салмағы 392 г (диапазон = 350-450 г) және жасы 8,2 ай (6-9 ай) болатын 48 еркек Wistar-Albino тұқымды егеуқұйрықтар қатыстырылды. Барлық хирургиялық араласуларды бір хирург сол жақ сан сүйегінде орындады. Барлық жануарларда ашық сан сүйегі сынуы модельденді. Егеуқұйрықтар кездейсоқ түрде 4 топқа бөлінді: бақылау тобы (12); эпидермальді өсу факторы тобы (12); гиалурон қышқылы тобы (12); аралас тобы (12). 4-ші және 6-шы апталарда алынған үлгілер биомеханикалық және гистологиялық әдістермен зерттелді. Аралас тобында сүйек сынуының жазылуы бақылау, эпидермальды өсу факторы және гиалурон қышқылы топтарымен салыстырғанда барлық көрсеткіштер бойынша екі мерзімде де айтарлықтай жақсарғаны анықталды. Операциядан кейінгі 4 және 6 апталарда эпидермальді өсу факторы және гиалурон қышқылы топтарында гистологиялық бағалау кезінде сүйек жазылуы бақылау тобына қарағанда едәуір тезірек жүрді. Сонымен қатар, эпидермальды өсу факторы, гиалурон қышқылы және бақылау топтарымен салыстырғанда аралас тобында 4 және 6 апталарда сүйек мүйізгегінің биомеханикалық қасиеттерінде айқын айырмашылық байқалды. Бұл зерттеу нәтижелері эпидермальды өсу факторы пен гиалурон қышқылы негізіндегі каркасты жергілікті біріктіріп қолдану сүйектің жазылуын жеделдетіп, сүйек мүйізгегінің гистологиялық және биомеханикалық беріктігін арттыратынын көрсетті. Эпидермальды өсу факторы/гиалурон қышқылы біріктірілген каркастарын қолдану травматологиялық хирургияда болашақта перспективті стратегия болуы мүмкін.

Түйін сөздер: эпидермальді өсу факторы, гиалурон қышқылы, сүйек сынуының жазылуы, сүйек мүйізгегі.

Исследование влияния эпидермального фактора роста и гиалуроновой кислоты на заживление переломов в модели перелома бедренной кости у крыс

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Резюме

Целью данного исследования было изучить роль экзогенного эпидермального фактора роста и гиалуроновой кислоты, использованной в качестве матриксного каркаса, в процессе заживления переломов в экспериментальной модели перелома бедренной кости у крыс. В эксперименте использовали 48 самцов крыс линии Wistar-Albino со средней массой тела 392 г (диапазон 350–450 г) и средним возрастом 8,2 месяца (6–9 месяцев). Все хирургические вмешательства выполнялись одним хирургом на левой бедренной кости. Всем животным был создан открытый перелом бедренной костqи. Крысы были случайным образом разделены на четыре группы по 12 особей: контрольная группа, группа экзогенного эпидермального фактора, группа гиалуроновой кислоты и комбинированная группа (EGF+HA). На четвертой и шестой неделях образцы подвергались биомеханическому и гистологическому анализу. Заживление перелома было значительно улучшено в комбинированной группе по сравнению с контрольной, группой экзогенного эпидермального фактора и группой гиалуроновой кислоты по всем параметрам на обоих временных этапах. На четвертой и шестой неделях после операции гистологическая оценка показала достоверное усиление процессов заживления в группах эпидермального фактора роста и гиалуроновой кислоты по сравнению с контролем. Кроме того, в комбинированной группе наблюдались значительно более выраженные изменения в костной мозоли по сравнению с группами эпидермального фактора роста, гиалуроновая кислота и контрольной по биомеханическим характеристикам. Проведенное исследование показало, что сочетанное местное применение эпидермального фактора роста и матрикса на основе гиалуроновой кислоты ускоряет заживление костей и укрепляет костную мозоль как с гистологической, так и с биомеханической точек зрения. Применение комбинированных каркасов эпидермального фактора роста/гиалуроновой кислоты может представлять собой перспективную стратегию в травматологической хирургии.

Ключевые слова: эпидермальный фактор роста, гиалуроновая кислота, заживление переломов, костная мозоль.

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