J Surg Med. 2019;3(9):672-675.
DOI: 10.28982/josam.617669

Research article
Araştırma makalesi

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Effect of growth hormone and somatomedin-C axis on fracture healing

Kırık iyileşmesinde büyüme hormonu somatomedin-C aksının etkisi

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Ethics Committee Approval: Ankara Numune Training and Research Hospital Clinical Research Ethics Committee approved the study (Date: 14.04.2014 Decision No: 161/2014).
Etik Kurul Onayı: Ankara Numune Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurul çalışmayı onayladı (Tarih: 14.04.2014 Karar No: 161/2014).

Conflict of Interest: No conflict of interest was declared by the authors.
Çıkar Çatışması: Yazarlar çıkar çatışması bildirmemişlerdir.

Financial Disclosure: The authors declared that this study has received no financial support.
Finansal Destek: Yazarlar bu çalışma için finansal destek almadıklarını beyan etmişlerdir.

Published: 9/20/2019
Yayın Tarihi: 20.09.2019

Abstract

Aim: Many studies have examined the effects of different calciotropic hormones on fracture healing, whereas few studies focus on growth factors. Local detection of somatomedin C (IGF-1) in fracture callus, application of growth hormone (GH) and IGF-1 as non-union treatment, and low GH and IGF-1 levels in osteoporotic fractures indicate that these hormones are effective in fracture healing. However, most of these studies are based on post fracture GH and IGF-1 levels. GH and IGF-1 are also involved in acute phase response and can change due to trauma. The aim of this study is to investigate the change in GH and IGF-1 levels in patients treated with osteotomy, in which an iatrogenic fracture is created, and to evaluate the effect of these hormones on fracture healing by comparing the results before and after the fractures.

Methods: Patients who were diagnosed with developmental dysplasia of the hip and underwent surgery between 2014-2015 were prospectively followed for this cohort study. Forty-one patients were included, and two groups were formed. Patients who underwent open reduction and soft tissue release without osteotomy (n=20) were included in the first group. Patients who underwent pelvic osteotomy (n=21), in which iatrogenic fractures were created, were included in the second group. Blood samples were obtained from all patients pre-operatively and on the 1st and 28th postoperative days. Friedman and Mann-Whitney U tests were used for statistical analysis.

Results: Mean age of the first group, comprising 19 females (95%) and 1 male (5%), was 11.25 months (Range: 6-25 months). Mean age of the second group, including 17 females (85.7%) and 4 males (14.3%), was 74.4 months (Range: 24-120 months). While there was no significant difference between pre- and postoperative GH values in the first group (P=0.05), postoperative GH levels were significantly higher than preoperative GH levels in the second group (P<0.001). Postoperative IGF-1 levels were significantly lower than preoperative IGF-1 levels in both groups (P<0.001). When the difference of preoperative and postoperative 1st day GH and IGF-1 values were compared between two groups, GH changes were found significantly higher in the second group (P<0.001) whereas serum IGF-1 changes were significantly lower in the second group (P=0.043).

Conclusion: IGF-1 is inadequate in the investigation of fracture healing due to its short half-life and local production. On the other hand, GH plays an active role in fracture healing and increases significantly in comparison to pre-fracture values. Considering the GH increase during fracture healing, it may be beneficial to support patients with pathological fracture healing with growth hormone.

Keywords: Fracture healing, Iatrogenic fracture, Growth hormone, Somatomedin C

Öz

Amaç: Birçok çalışma, farklı kalsitropik hormonların kırık iyileşmesi üzerindeki etkilerini incelemiş, az sayıda çalışma ise büyüme faktörlerine odaklanmıştır. Kırık kallusunda lokal somatomedin C (IGF-1) tespiti, büyüme hormonu (GH) ve IGF-1'in kaynamama tedavisi olarak uygulanması ve osteoporotik kırıklarda saptanan düşük GH ve IGF-1 seviyeleri, bu hormonların kırık iyileşmesinde etkili olduğunu göstermektedir. Bununla birlikte, bu çalışmaların tümü kırık sonrası GH ve IGF-1 seviyelerine dayanır, ancak GH ve IGF-1 akut faz yanıtında rol oynar ve travma nedeniyle seviyeleri değişebilir. Bu çalışmanın amacı osteotomi ile tedavi edilen böylece bir iatrojenik kırık oluşturulan hastalarda GH ve IGF-1 seviyelerindeki değişimi araştırmak ve bu hormonların kırık iyileşmesi üzerindeki etkisini kırık öncesi ve sonrası sonuçları karşılaştırarak değerlendirmektir.

Yöntemler: Bu prospektif kohort çalışma için, 2014-2015 yılları arasında gelişimsel kalça çıkığı nedeniyle cerrahi olarak tedavi edilen hastalar tarandı. 41 hasta çalışmaya dahil edildi ve iki grup oluşturuldu. Sadece açık redüksiyon ve yumuşak doku gevşetmesi yapılan hastalar ilk grup olarak belirlendi. Pelvik osteotomi yapılan ve böylece bir iatrojenik kırık oluşturulan hastalar ikinci grup olarak belirlendi. Birinci gruba 20 hasta, ikinci gruba 21 hasta dahil edildi. Operasyon öncesi, postoperatif 1. gün ve 28. günde tüm hastalardan kan örneği alındı. İstatistiksel analizler için Friedman ve Mann-Whitney U testleri kullanıldı.

Bulgular: İlk grupta ortalama yaş 11,25 aydı (6-25 ay). Hastaların 19'u (95%) kadın, biri (5%) erkekti. İkinci grupta ortalama yaş 74,4 aydı (24-120 ay) ve 17 (85,7%) hasta kadın, dört (14,3%) hasta erkekti. İlk grupta pre-operatif ve postoperatif GH değerleri arasında anlamlı fark bulunmazken (P=0,05); ikinci grupta postoperatif GH değerleri daha yüksekti (P<0,001). Postoperatif IGF-1 düzeyleri her iki grupta anlamlı düşüş göstermekteydi (P<0,001). Pre-operatif ve postoperatif GH ve IGF-1 değerleri iki grup arasında karşılaştırıldığında, ikinci grupta postoperatif 1. günde GH değerleri anlamlı olarak daha yüksek seyrederken (P<0,001) aynı ölçümlerde serum IGF-1 düzeylerinde anlamlı düşüş saptandı (P=0,043).

Sonuç: IGF-1, kısa yarı ömrü ve yerel üretimi nedeniyle kırık iyileşmesinin araştırılmasında yetersizdir. Öte yandan, GH kırık iyileşmesinde aktif bir rol oynar ve kırık öncesi değerlere kıyasla önemli ölçüde artar. GH seviyesinin kırık iyileşmesi sırasında vücutta arttığı göz önüne alındığında, kırık iyileşmesinin patolojik olduğu düşünülen hastalarda GH desteği verilmesi yararlı olabilir.

Anahtar kelimeler: Kırık iyileşmesi, İatrojenik kırık, Büyüme hormonu, Somatomedin C

How to cite / Atıf için: Kaya Ö, Doğan Ö, Çalışkan E, Gencer B, Kocaoğlu H, Biçimoğlu A. Effect of growth hormone and somatomedin-C axis on fracture healing. J Surg Med. 2019;3(9):672-675.

Introduction

Many systemic and local factors are effective in fracture healing. In the literature, there are many studies examining the effects of different calciotropic hormones on fracture healing, whereas few studies focus on growth factors [1-5]. The secretion of growth hormone (GH) begins in fetal life and continues to be secreted during the whole life in decreasing amounts [6]. It regulates various metabolic processes throughout the body, effects protein, lipid and carbohydrate metabolism and has a major effect on longitudinal growth [6,7]. Somatomedin C (IGF-1), which is a small peptide bound to serum proteins, is responsible for the peripheral effects of GH [1]. It is secreted as a result of the autocrine and paracrine effects of cells in peripheral tissues such as bone [1-3]. Studies have demonstrated that the GH and IGF-1 axes affect the skeleton both directly and indirectly through steroids, parathyroid hormone, and vitamin d metabolites [8-10]. Local detection of IGF-1 in fracture callus, application of GH and IGF-1 as non-union treatment in different studies and low GH and IGF-1 levels in osteoporotic fractures indicate that these hormones are effective in fracture healing [8-13]. However, most of these studies are based on post fracture GH and IGF-1 levels, whereas GH and IGF-1 are also involved in acute phase response and their levels in serum change due to trauma [14].

The aim of this study is to investigate the change in GH and IGF-1 levels in patients treated with osteotomy, in which iatrogenic fractures are created, and to evaluate the effect of these hormones on fracture healing by comparing the pre-fracture and post fracture results.

Materials and methods

Following the approval of the ethics committee (Decision Date and Number: 14.04.2014; 161/2014), patients who were diagnosed with developmental dysplasia of the hip (DDH) and underwent surgery between 2014 and 2015 were prospectively followed. This study included 41 patients between the ages of six months and ten years, those within 25-97% percentile in terms of weight and height development and without additional systemic disease. Patients with syndromes, endocrine or metabolic diseases and growth and developmental delays were excluded from the study.

Evaluation

Blood samples from peripheral venous veins were obtained from all patients pre-operatively and on the 1st and 28th postoperative days. All blood samples were obtained in the morning, between 08:00-10:00, following a fasting of eight hours. IGF-1 and GH levels were measured with Radio Immune Assay and Electrochemiluminescence Immunoassay methods, respectively [15]. All results are presented as nanograms/ml.

GH and IGF-1 hormones are involved in both bone metabolism and acute phase response. Therefore, in order to distinguish whether the changes in the levels of these hormones were due to the response to surgical stress or fracture healing, two patient groups were formed [14]. Patients who underwent open reduction and soft tissue release without any osteotomy (n=20) constituted the first group. Patients who underwent pelvic osteotomy (n=21), in which iatrogenic fractures were created, were part of the second group.

Surgical technique

Open reduction and soft tissue loosening was performed via limited posteromedial approach to the patients in the first group, as this technique is our routine approach to DDH, and commonly used in our clinic. The limited posteromedial approach technique was previously discussed in our studies [16,17]. The posterior margin of tendineum adductor longus was incised 5 cm and layers were cut until tendon was reached. Following tenotomy of adductor longus tendon, the lesser trochanter was used as a guide to reach the iliopsoas tendon and incise it. 1 ml of contrast material was injected into the joint capsule and hip radiographs were filmed in human position. If the patient had grade one reduction based on Tönnis intraoperative grading system and/or an appropriate safe zone, surgery was concluded. On the other hand, if the patient had a grade two or three reduction and/or a narrow safe zone, arthrotomy was performed. The inferomedial capsule was opened and *ligamentum teres* and transverse acetabular ligament were incised. Reduction was confirmed with x-ray radiographies obtained in the human position, hip spica cast was applied and surgery was concluded. The patients in the second group received pelvic osteotomy through a bikini incision. The iliac wing apophysis was dissected and tilted medially and laterally. A tricortical graft was obtained from the iliac wing. Periacetabular osteotomy was performed through the sciatic notch with the help of gigli wire. Then, the tricortical graft was placed on the osteotomy line by tilting the acetabulum. After confirming the reduction by obtaining x-rays on human position and checking movements of the hip, long leg cast was applied, and surgery was concluded. All surgeries were performed by the same surgical team.

No additional treatment was administered to any of the patients during the postoperative period. The cast was removed at the postoperative third month and hip abduction orthosis was performed to patients of the first group. The cast was removed at one and a half-month follow-up in the second group. Nonunion or union delay was not observed in any patient.

Statistical analysis

Data were evaluated for normal distribution, and Friedman test was used to evaluate the difference in both groups separately. Mann-Whitney U test was used to evaluate the significance of difference between the two groups. The post-hoc power was calculated as 0.95, considering the correlation between two groups. $P<0.05$ was deemed statistically significant, and SPSS 11.5 package program was used for analysis.

Results

Mean age of the first group, comprising 19 females (95%) and 1 male (5%), was 11.25 months (Range: 6-25 months). Mean age of the second group, including 17 females (8.57%) and 4 males (14.3%), was 74.4 months (Range: 24-120 months). While there was no significant difference between pre- and postoperative GH values in the first group ($P=0.05$), postoperative GH levels were significantly higher than preoperative GH levels in the second group ($P<0.001$). GH

values of both groups are presented in Table 1. Postoperative IGF-1 levels were significantly lower than preoperative IGF-1 levels in both groups (P<0.001) (Table 2). When the difference of preoperative and postoperative 1st day GH and IGF-1 values were compared between two groups, GH changes were found significantly higher in the second group (P<0.001) whereas serum IGF-1 changes were significantly lower in the second group (P=0.043). Also, GH levels were significantly higher in the second group (P=0.027) and IGF-1 levels lower (P=0.01) on the 28th postoperative day compared to preoperative values. There was no significant difference between GH and IGF-1 values on the postoperative 1st and 28th days (P=0.419; P=0.285, respectively). The comparison of preoperative and postoperative GH and IGF-1 values between two groups is presented in Table 3.

Table 1: Comparison of preoperative and postoperative growth hormone values in both groups

	Group 1 (n=20)		Group 2 (n=21)	
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)
Preoperative	2.62 (2.21)	1.79 (0.49-8.80)	0.88 (1.95)	0.34 (0.07-8.80)
Postoperative 1st day	5.30 (4.35)	3.31 (0.41-14.30)	4.27 (5.96)	2.47 (0.46-26.13)
Postoperative 28th day	2.69 (2.15)	2.58 (0.40-10.50)	2.02 (2.58)	0.72 (0.15-9.40)
P-value	0.05		<0.001	

n: patient population, SD: standard deviation, min: minimum, max: maximum

Table 2: Comparison of preoperative and postoperative somatomedin C values in both groups

	Group 1 (n=20)		Group 2 (n=21)	
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)
Preoperative	34.39 (24.72)	25 (8.20-120)	160.63 (98.82)	136 (56.6-497)
Postoperative 1st day	30.80 (29.6)	25 (10.72-152)	124 (77.02)	110 (35-273)
Postoperative 28th day	43.55 (24.01)	31.34 (19.30-106.5)	156.01 (109.16)	122 (55.4-549)
P-value	<0.001		<0.001	

n: patient population, SD: standard deviation, min: minimum, max: maximum

Table 3: Comparison of preoperative and postoperative growth hormone and somatomedin C values in two groups

	Group 1 (n=20)		Group 2 (n=21)		
	Mean (SD)	Median (min-max)	Mean (SD)	Median (min-max)	*P*-value
GH change on preop. and postop. 1st day	124.09 (147.48)	114.7 (-57.3-535.04)	1817.1 (2922.6)	429.4 (-83-10878.9)	<0.001
IGF-1 change on preop. and postop. 1st day	-7.99 (28.59)	0 (-61.2-47.3)	-23.05 (26.26)	-18.82 (-58.1-25.27)	0.043
GH change on preop. and postop. 28th day	68.58 (253.8)	-2.79 (-83.7-1106.9)	528.01 (812.53)	102.35 (-93-2628.6)	0.027
IGF-1 change on preop. and postop. 28th day	45.57 (64.77)	16.9 (-32.8-176.8)	-2.69 (20.98)	-4.2 (-37.4-46.3)	0.010
GH change on postop. 1st and 28th day	-2.21 (114.34)	-43.9 (-94.0-348.7)	20.72 (154.03)	-61.49 (-99.2-368.9)	0.419
IGF-1 change on postop. 1st and 28th day	68.43 (80.82)	49.19 (-29.9-264.3)	46.09 (73.0)	17.95 (-34.1-226.45)	0.285

n: patient population, SD: standard deviation, min: minimum, max: maximum, preop: preoperative, postop: postoperative

Discussion

Understanding the physiological and biochemical interactions between cells in fracture healing enables the investigation of the factors that may affect this process [18]. Many studies, which were all performed by examining posttraumatic GH and IGF-1 levels only, confirm the systemic effect of GH-IGF axis on fracture healing [4,5,8-12]. However, it must not be forgotten that these hormones are also involved in acute phase response and their levels change due to traumas not involving fractures, as well [14]. Also, there are many metabolic factors that may affect GH and IGF-1 values. By using iatrogenic fractures instead of traumatic fractures in our study, we determined patients' pre-fracture GH and IGF-1 levels, which was necessary for comparison with post-fracture values and not reference ranges indicated in the literature. To exclude surgical stress, two groups were formed. We believe this prospective study is important because it includes the comparison of pre-fracture and post-fracture GH and IGF-1 values among two separate groups.

GH levels fluctuate during the day in normal individuals [19,20]. In our study, blood sampling was performed between 08.00-10.00 in the morning, following a fasting of eight hours, which minimized the factors affecting the release of GH and IGF-1.

We found that the difference in pre- and postoperative GH values were significant in patients with iatrogenic fractures. Similarly, when two groups were compared, GH levels were observed significantly higher in the osteotomy group. These results are consistent with the literature [8-12]. Weiss et al. [21], in their prospective study involving 186 patients, examined GH dependent acid labile subunit (ALS), IGF-1 and IGF binding protein (IGFBP-3). They found that GH-dependent ALS and IGFBP-3 levels were significantly lower in patients with nonunion. In their randomized, double blind, placebo-controlled clinical trial of 406 tibial fractures, Rarschke et al. [22] found that GH accelerated healing process significantly in closed tibial fractures. Tran et al. [23] stated that GH clearly demonstrates a positive effect on fracture healing.

Although IGF-1 is locally secreted and affects fracture callus, its systemic effects on fracture healing is controversial. Weiss et al. have examined the blood values of the two groups at the 1st and 8th posttraumatic weeks and found a significant difference between IGFBP-3 and GH-dependent ALS values. IGF-1 serum concentrations, however, were not significantly different. Similarly, Jeevenandam et al. [24] showed that IGFBP-3 and IGF-1 ratios did not change significantly in trauma patients. Weiss et al., based on both these results, reported that serum free IGF-1 level was not associated with fracture healing quality. On the other hand, Di Monaco et al. [25], in their study of 188 hip fractures, found that serum IGF-1 levels are significantly associated with ability to function after hip fracture. In our study, a significant difference was found between preoperative and postoperative IGF-1 values between the two groups. The significant difference in IGF-1 levels between preoperative and postoperative periods and the lower postoperative IGF-1 levels in the osteotomy group suggest that systemic IGF-1 levels may play a role in fracture healing. Various explanations exist for this result. First, unlike the studies in the literature, fractures in patients were iatrogenically formed in our study. There is no trauma other than surgical stress, which may affect serum IGF-1 levels. Secondly, IGF-1 has a noticeably short half-life, is secreted from numerous peripheral tissues [1], and its serum concentration may vary with factors such as hunger [26]. Its local release and effects may have affected the outcome of our study.

Limitations

There are some limitations in our study. First of all, the groups are not homogeneous in age. We tried to overcome this problem by comparing the patients' postoperative GH and IGF-1 levels with that of the preoperative period, and not the reference values; however, we could not control different factors affecting

GH and IGF-1 in children of different age groups. Also, we only evaluated the patients' blood test results and did not incorporate functional or radiological criteria into this study, which could have revealed the relationship between fracture healing and hormone values more clearly. Finally, the hormone levels were measured preoperatively, on the 1st and 28th postoperative days, and not later. Although repeating measurements after completion of fracture healing radiologically and clinically may be useful in examining the effects of GH-IGF-1 axis on fracture healing, we didn't measure the levels in late period because we observed fracture callus radiologically in nearly all of our patients in 28 days, and non-union is not typically a problem in children.

Conclusion

IGF-1 is inadequate in the investigation of fracture healing due to its short half-life and local production. On the other hand, GH plays an active role in fracture healing and increases significantly in comparison to pre-fracture values. Considering that the GH level increases in the body during fracture healing, it may be beneficial to give GH support to patients who exhibit pathological fracture healing.

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The National Library of Medicine (NLM) citation style guide has been used in this paper.

Suggested citation: Patrias K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007-[updated 2015 Oct 2; cited Year Month Day]. Available from: http://www.nlm.nih.gov/citingmedicine