Effect of Parathyroid Hormone on Delayed Union and Non-union Tibia/Fibula Diaphyseal Fractures

Abstract

Introduction: The use of parathyroid hormone (PTH) in the management of fracture disorders is poorly documented. The present study aimed to evaluate the PTH effect on the union of the tibia/fibula diaphyseal fractures.

Methods: This hospital-based study was conducted at Shahid Kamyab Hospital, Mashhad, Iran on patients with non-union or delayed-union fractures of the tibia/fibula. Patients who met the inclusion criteria were enrolled in the study after signing the informed consent. Complete blood count, erythrocyte sedimentation rate, calcium (Ca), phosphorus, magnesium, alkaline phosphatase, creatinine, and blood urea nitrogen were evaluated. Afterwards, in the test group, oral vitamin D (Vit D)-Ca was prescribed in combination with PTH injection at the dose of 8 IU/day for 3 months. The participants in the control group only received oral Vit D-Ca. Patients with specific risk factors, such as digoxin usage or kidney failure were excluded from the study. The individuals were evaluated monthly by clinical and radiographic examinations.

Results: The mean and standard deviation of age in the case and control groups were 16.9±37.7 and 13.8±39.1 years, respectively. The two groups did not have a significant difference in this regard (P=0.73). Overall, 24 cases were male and six were female without a significant difference between the two groups (P=1). Moreover, the two groups were not significantly different in terms of fracture type, fracture shape, fixation method, and final radiographic healing.

Conclusion: We did not find any positive effect for PTH on fracture healing neither clinically nor radiographically during 3 months of prescription.

Keywords: Parathyroid Hormone, Fracture healing , Ununited fractures, Tibial fractures, Diaphyses

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Introduction

The healing process of fractures begins with hematoma formation followed by inflammatory and proliferative phases which result in soft callus formation, ossification, and final remodeling phase [(1).] The endosteal and periosteal osteoprogenitors with neovascularization play an important role in the early phase of repair. Therefore, pathological conditions with a negative effect on progenitor cells, extracellular matrix formation, or angiogenesis can induce non-union [(2, 3).] Some of these influential conditions are osteoporosis, radiation therapy, diabetes mellitus, older age, antiangiogenic therapy, infection, and steroid therapy. Fractures in long bones, such as the tibia and fibula, have slow union [(4).] Local application of osteoinductive cytokines, namely bone morphogenetic protein-2 and -7, and bone grafting are among the methods for inducing union [(5).] However, these approaches generally need surgery and are accompanied by the risk of mortality. Based on these reasons, the establishment of noninvasive methods in non-union treatment is of great importance [(6, 7).]

Non-union is observed in approximately 5% bone fractures, and these conditions require additive treatments. Although advanced therapies are increasingly being evolved for the healing of non-union fractures, it is important to assess the clinical effects of these new methods [(8, 9).]

Intermittent administration of parathyroid hormone (PTH) induces callus formation by reducing apoptosis and stimulating osteoblasts [10], which results in an elevated life span of osteoblasts. Moreover, PTH may lead to cancellous bone formation by stimulating the osteoblasts and diminishes the risk of nonvertebral and vertebral fractures after a mean treatment period of 19 months [11]. In addition, PTH is known to play a crucial role in the homeostasis of phosphorus (P) and calcium (Ca) with anabolic effects in bone. Daily low-dose injections induce osteoblastic bone formation through activating the osteoclasts [9]. Furthermore, PTH causes the proliferation and differentiation of osteoprogenitor cells along with bone matrix protein production [12, 13]. Few studies have been published on the administration of teriparatide for managing fractures non-union with no definitive conclusions. Consequently, the present study aimed to evaluate the effect of PTH administration on leg fractures.

Objectives

The current study aimed to evaluate the impact of PTH on the union of tibia/fibula in delayed union and non-union cases.

Methods

Study Setting and Population

This hospital-based study was carried out on patients with non-union or delayed-union of tibia/fibula fractures at Shahid Kamyab Hospital, Mashhad, Iran. The study population consisted of all patients with non-union or delayed-union fractures of tibia/fibula.

Inclusion Criteria

The inclusion criteria entailed the age of >18 years, fractures of the tibia/fibula, internal or external fixation surgery, at least 3 months have passed since the occurrence of fracture, being delayed union or non-union.

The Exclusion criteria were a history of radiotherapy at any time in any part of the body, chemotherapy, pregnancy, malignancies, having received immunosuppressive agents, anticonvulsant drugs, or digoxin, any evidence of infection, and glomerular filtration rate < 30.

Measurement

The patients with tibia/fibula diaphysis fracture at Shahid Kamyab Hospital, whose bone repair process based on clinical and radiological criteria, such as callus formation in three cortices in anteroposterior and lateral views took 3-6 months post-fracture (delay union), or no progress was made after 6 months (nonunion) were randomly enrolled in this study. Informed consent was signed in both case and control groups.

Complete blood count, erythrocyte sedimentation rate, Ca, P, magnesium, alkaline phosphatase, creatinine, and blood urea nitrogen were assessed as a baseline. Afterwards, in the test group, oral vitamin D (Vit D)-Ca was prescribed in combination with PTH injection at the dose of 8 IU/day (20 µg/day) for 3 months. The participants in the control group only received oral Vit D-Ca. All patients with specific risk factors, such as taking digoxin tablets or being affected by kidney failure were excluded from the study. After entering the study and receiving the hormone once a month, the individuals were evaluated based on the radiographic parameters by studying callus formation in both anteroposterior and lateral views.

Ethical Considerations

The present investigation was conducted according to the principles of medical ethics introduced by the Health Ministry, the Declaration of Helsinki, and legislation in the medical ethics committee of Mashhad University of Medical Sciences. The protocol of this study was approved by the ethics committee of Mashhad University of Medical Sciences.

Statistical Analysis

All the data were analyzed by the X2 test for qualitative variables and the t-test for quantitative variables using the SPSS software. P-value < 0.05 was considered significant.

Results

The mean and standard deviation of age in the intervention and control groups were 16.9±37.7 and 13.8±39.1 years, respectively. The age of the two groups did not have a statistically significant difference (P=0.73). In terms of gender, 24 cases were male and 6 cases were female. The two groups were not significantly different in terms of gender (P=1) (Table 1).

Table 1- Demographic information in Two Groups

Variables	Group		P Value
	Intervention	Control	
Age			0.73
Mean ± SD	39.1±13.8	37.7±16.9	
Gender			1.0
Male	24 (80)	24 (80)	
Female	6 (20)	6 (20)	

Moreover, in clinical findings, frequency of fracture type showed that in both groups 15 cases had open and 15 cases had closed fracture with no statistically significant difference (P=1). The frequency of fracture shape in the two groups demonstrated that in the intervention group, 5, 12, 6, and 7 cases had transverse, spiral, oblique, and combined fracture, respectively. In the control group, 7 transverse, 5 spiral, 11 oblique, and 7 combined fracture cases were recorded. The type of fractures was not significantly different between the two groups (P=0.18). In addition, the fixation methods in the test group were plate in 21, nailing in 3, and external fixator in 3 patients. In the control group, 13 plates, 7 nailing, and 4 external fixators were applied (P=0.26). Six cases of conditions contributing to delayed union, such as diabetes mellitus were found in the intervention group, while none was observed in the control group (P=0.27). A total of 17 cases in the test group and 24 patients in the control group were a smoker. According to the results of statistical evaluations, there was no significant difference between the two groups in terms of the latter factor (P=0.11). Furthermore, radiographic healing results were not significantly different between the two groups (Table 2).

Table 2- Clinical information in Two Groups

Variables	Group		P Value
	Intervention	Control	
Fracture Type			1.0
Closed	15 (50)	15 (50)	
Open	15 (50)	15 (50)	
Fracture Shape			0.18
Spiral	12 (40)	5 (16.6)	
Oblique	6 (13.3)	11 (36.6)	
Transverse	5 (16.6)	7 (23.3)	
Combined	7 (23.3)	7 (23.3)	
Fixation Type			0.26
Plate	13 (43.3)	21 (69)	
Nail	7 (23.3)	3 (10.3)	
External Fixator	4 (13.3)	3 (10.3)	
Plate+ External Fixator	6 (20)	3 (10.3)	
Radiography			0.11
Union	16 (61.5)	19 (63.3)	
Non Union	10 (38.5)	11 (36.6)	
Special disease			
affected	6(19.2)	0(0)	
Not affected	24(80.8)	30(100)	0.27
smoking			
yes	17(58.7)	24(80)	
no	13(41.3)	6(20)	0/11

Discussion

The effects of teriparatide have been examined on normal fracture healing, delayed union, and non-unions in human subjects. We found the mean±SD of age in the intervention and control groups as 16.9±37.7 and 13.8±39.1 years, respectively (P=0.73). In terms of gender in the two groups, 24 cases were male and 6 cases were female (P=1). In addition, in clinical findings, fracture type (P=1), fracture shape (P=0.18), fixation method (P=0.26), and graphical result (P=0.11) did not have a statistically significant difference between the two groups. Lou et al. [14] showed high efficacy for PTH in improving the healing of fracture in a study by. However, the results of Shi et al. [15] were not in line with the mentioned findings. This difference may be due to different types of fractures evaluated in these two investigations. Aspenberg et al. examined the impact of a placebo, compared to teriparatide administered

as 20 and 40 µg/day up to 2 months to a population of female patients with distal radius fractures. These patients aged 45-85 years and their fractures were treated conservatively. This was a well-designed level 1 study. They found that the median time to the first radiographic evidence of healing was 9.1, 7.4, and 8.8 weeks in the placebo, 20 µg teriparatide, and 40 µg teriparatide groups, respectively. This difference between the groups was not statistically significant (P=0.15) [16]. The results of the latter authors were similar to our findings in terms of the inefficiency of this medication in tibial fracture healing.

In another study, Peichl et al. evaluated the influence of PTH 1-84 on pelvic functional outcome and fracture healing in postmenopausal women. Sixty patients were divided into two groups of control and intervention that received 100 µg/day of PTH 1-84 for 3 months starting within two days after hospital admission. All individuals received a Ca-Vit D supplement. These researchers observed that the median time from fracture to the first sign of complete cortical bridging in the pelvic fracture verified by computerized tomography scan was 7.8 weeks in the treatment group and 12.6 weeks in the control group. Furthermore, they revealed that at the primary endpoint of 8 weeks after commencement of the study all fractures in the treatment group (100%) and four fractures in the control group (9.1%) had healed. Significant improvements in functional outcome assessed by visual analogue scale in the treatment group were 7.6 at the beginning of the study to 3.2 in week 8, in comparison with controls with 7.7 at first to 6.5 in week 8. Statistically significant enhancements were also noted in timed up and go test times of the test group [17]. However, these results were different from our findings, which could be attributed to distinct study groups in two investigations.

In delayed union studies, Bukata et al. reported 145 cases with spine fracture who were treated with 20 µg/day of teriparatide for up to 3 months. They observed that 50% of the cases demonstrated delayed fracture healing and 88% had a failed previous union attempt and presented with a non-union. They were elderly or had significant medical comorbidities. Regardless of the fracture site, 141 people reported pain resolution at the fracture site within 12 weeks of starting teriparatide, and the fracture united in 93% of the patients [18]. Moreover, cases have been reported of almost normal fracture healing in elderly patients with established osteoporosis after starting treatment with teriparatide [19]. These results were in line with our findings concerning teriparatide consumption in patients with a fracture in different sites. Therefore, most studies in this field have been consistent with the results of the current study indicating the need for new therapeutic approaches in such patients.

Conclusion

Teriparatide constitutes the active portion of the PTH molecule and is a commercially available agent approved by the Food and Drug Administration for the treatment of osteoporosis. However, in this study, we did not find any positive effect for this hormone in 3 months on fracture status neither in the clinical nor paraclinical evaluation.

Conflicts of interest:

The authors declared no competing interests.

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