ORIGINAL ARTICLE

Investigation of Bony Scar Tissue (Callus) formation in proximal femoral fracture and its relation to therapeutic application of PTH (1-34)

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ABSTRACT

Background: High Economic and social burdens of fracture complications have turned rapid recovery of fractures into a main objective for public health care. The role of parathyroid hormone (PTH) in osteoporosis treatment is generally accepted, but its effects on improving fractures remains controversial.
Aim: To analyze the effects of parathyroid hormone analogs in the healing process of bone fractures in patients with proximal femoral fractures.
Methods: This study is retrospective and was carried out via examination of hospital records of 40 patients who had proximal femoral fractures, and were hospitalized and treated in Kosar hospital, Iran during 2014-2015. Studied patients were divided into two groups each consisted of 20 members; the control group who only received normal treatment, and the experimental group who received normal treatment plus daily subcutaneous injections of the parathyroid hormone. Required data such as age, sex, area of fractures, underlying diseases, smoking history, the final condition of the fractured area, quality of callus formation after three months and a need for a reoperation were gathered. Afterwards, the role of demographic factors on final condition of the fractured area and the need for a reoperation were analyzed.
Results: After the three-month follow-ups were completed, it became clear that compared to the control, use of the parathyroid hormone significantly increased the pace of bony scar tissue (callus) formation (P<0/001) in the experimental group and also although higher percent of the experimental group patients (85%) succeeded in forming a proper callus compared to the control (60%), but this difference is not statistically significant (p=0/077). Also, the percentage of patients in need of reoperation was higher in the control (36.8%) compared to the experimental group patients (15%), but this difference was not statistically significant (p=0/118) also. There was also a statistically significant difference between different age categories and the final condition of scar formation (P=0/036).
Conclusion: The results of this study show that subcutaneous application of 20 mg per day of the parathyroid hormone can speed up the bony scar tissue formation and recovery of patients.
Key words: PTH hormone, Fracture, Proximal femur, Bone, Callus formation

INTRODUCTION

Femoral fractures are of special importance given their debilitating and often dangerous complications; different areas of this bone may fracture due to trauma or pathological reasons. Meanwhile, proximal femur fractures including neck, intertrochanteric and sub trochanteric are more commonplace among the elderly and osteoporotic patients. Osteoporosis leads to bone mass deterioration and microscopic decay of bone structure and as a result embrittlement and weakness of bones occurs[1].

Most of these fractures are treated by operations and insertions of screws and plates[2]. One of the complications that can threaten bone healing is that callus does not form and the chance of occurrence of this complication in osteoporotic patients is about 22%, while in non-osteoporotic people this incident happens to only 6.2% of patients[3,4]. Furthermore, in case cut out phenomenal happens as one of the delayed complications of proximal femoral callus formation[5], joint replacement and reoperation becomes mandatory, which apart from higher health costs, leads to dramatic limb function and therefore life quality decrease. Consequently, considering the importance of osteoporosis and complications such as bone fracture, the importance of post operation follow ups and use of medications are becoming the center of attention[6]. In therapeutic studies, bisphosphonates and parathyroid hormone analogs have shown the best results in bone fractures healing, restoration of function and increasing of bone mass[7].

The parathyroid hormone (PTH) is a molecule with great potential for reinforcement of bone restoration especially long bones. This potential is hidden in anabolic effects of PTH on bone. According to studies supervised by FDA, daily injections of PTH are an effective therapy for osteoporosis and can lead to increased bone mass and mineral density[8]. Animal[9,10] and human studies[11,12] have shown that application of PTH, leads to elevated bone mass of cancellous bone tissue and afterwards the rates of vertebral body and non-vertebral bone fractures decrease. Moreover, immunofluorescence studies have shown that during bone tissue restoration, the rate of PTH receptor expression on Chondrocytes and osteoblasts increases[13]. In addition, based on the evidence, by stimulating osteoprogenitor cells and by increasing bone matrix protein

synthesis, PTH plays a role in both cancellous bone tissue and cortical formation[14].

Nevertheless, there are still contradictions among results of studies done to analyze the effects of PTH therapy[15,16]. Also, prestigious journals have repeatedly emphasized on the need for further investigations, solid proofs gathering and increasing certainty[17]. Therefore, in this study we wanted to analyze the therapeutic effects of PTH (1-34) on patients with fractured femurs.

MATERIALS AND METHODS

In this retrospective study, statistical population was consisted of all the patients who underwent proximal femoral operation during 2014-2015 in Kosar Hospital, Semnan, Iran. Entrance criterion was being over 40 years of age and having the femur fracture confirmed by orthopedist. Exit criteria included: high-energy trauma fracture, cirrhosis, severe rheumatic disease and long-term intake of corticosteroid drugs. After taking all these considerations into account, 40 patients were chosen to participate in this study and were divided into two groups: control and experimental. Convenience and purposive sampling methods were adopted. In order to carry out this research, with the approval of hospital ethics committee and related wards and treating physicians, required information including: age, sex, fracture area, underlying diseases, smoking history, final condition of the fractured area, quality of callus formation after three months and necessity of a reoperation, all were extracted from records of patients who met the criteria. Then, the effects of demographic factors on final conditions of fractured areas and the need for reoperations were analyzed. In order to investigate the timing of callus formation, profile and full-face graphs of the fractured area which were taken during those three months, were classified into three levels of poor, medium and good, based on orthopedist opinion and by using potato-sorting method.

The experimental group patients, received daily subcutaneous injections of 20 mg PTH (1-34) -which is the short-chained injectable form of parathyroid hormone- in abdominal or groin skin, for three months. Other therapeutic factors such as type of operation, type of sutures and prescribed antibiotics were almost identical for both control and experimental groups and therefore interfering factors were eliminated. PTH (1-34) used in this study goes by the commercial name of Cinnopar, and was in 3 ml vials containing 750 µg active ingredient and the dose of the drug could be adjusted by using an adjustable screw that was implanted on top of the vial. Contraindications of this medicine include: hypercalcemia, bone cancer and metastasis, Paget's disease and allergy and side effects include: dizziness and imbalance, excitement and heart palpitation, joint pain, redness, edema, pain and inflammation at the site of injection.

Statistical analysis: Statistical processes were carried out using SPSS 16 software. Descriptive and inferential statistical methods were used for analysis of data. After calculating percentages, absolute and relative frequency tables were drawn, classified and compared. For statistical analysis, distribution of data (normal vs. non-normal) was examined using Kolmogorov–Smirnov test. If the data distribution was normal, One-way ANOVA test was used to compare means of more than two independent parameters and to compare means of two parameters Post hoc test was utilized. If the data did have a normal distribution, Kruskal–Wallis test was used for comparing means of three parameters and $P<0.05$ was considered as the significance level.

RESULTS

In the present retrospective study, 40 patients with femur fractures were divided into two groups. First group (experimental group), in addition to normal treatment of fracture, received subcutaneous injections of 20 mg of Cinnopar medicine and the second group (control) only received normal fracture treatment.

Average age of group one patients was 70.2 ±14.4 and average age of group two patients was 75.1 ±11.7. The youngest patient was 28 and oldest was 90 years old and from statistical point of view the two groups did not have a significant difference in age distribution (P=0/204), and 17 patients were male and 23 were female and there was no significant difference between the two groups in this regard too (P=0.749) (table 1). According to table 1, underlying diseases included: diabetes, ischemic heart disease and hyperlipidemia and there was no significant difference between the two groups in this regard. Moreover, as table 1 shows, the two groups had no significant differences in smoking history (P=0.661).

As indicated in table 2, patients were divided into four groups based on their Fracture areas: sub trochanteric, interochanteric, femur neck and sub & intertrochanteric combination. According to the following table, patients had no significant difference in distribution of their fracture areas (P=0/699).

In the present study, quality of scar formation was followed up for three months, radiological graphs were taken from fracture area monthly and based on orthopedist opinion and by using potato-sorting method were divided into poor, medium and good.

Table 3 demonstrates bony scar condition of control and experimental groups during these three months of radiologic follow- ups. (In the present study, one of the patients of the control group expired one day after operation and was excluded from statistical analysis). According to table 3, during the next three months [after the operation], especially during the second and third months, the experimental group had better scar formation progress compared to the control group, these results were statistically significant ($P=0.002$ ،$P<0.001$).

Table 1: Distribution of control and experimental group patients according to demographic factors

p-value	Total	Number (%)		Variable		
		Group 2	Group 1			
0.204	18	7(38.9)	11 (61.1)	≤75		Age
	22	13(59.1)	9(40.9)	>75		
0.749	17	8(47.1)	9(52.9)	male		Sex
	23	12(52.2)	11(47.8)	female		
0.49	12	7(58.3)	5(41.7)	Yes	diabetic	Underlying diseases
	28	13(46.4)	15(53.6)	No		
0.525	22	12(54.5)	10(45.5)	Yes	Cardiac ischemia	
	18	8(44.4)	10(55.6)	No		
0.723	11	6(54.5)	5(45.5)	Yes	Hyperlipidemia	
	29	14(48.3)	15(51.7)	No		
0.661	6	2(33.3)	4(66.7)	Yes		Smoking
	34	18(52.9)	16(47.1)	No		

Table 2 Distribution of control and experimental group patients according to fracture areas

p-value	Total	Number (%)		Variable	
		Group 2	Group 1		
0.699	8	4(50)	4(50)	Sub trochanteric	Fracture area
	25	13(52)	12(48)	Intertrochanteric	
	1	0	1(100)	Femur neck	
	6	3(50)	3(50)	Sub & intertrochanteric combination	

Table 3: Distribution of control and experimental group patients based on scar formation quality during three months

Correlation coefficient (r)	p-value	Number (%)		Variable		
		Group 2	Group 1			
0.205	0.211	13(68.4)	9(45)	Poor	first month	Scar formation quality
		5(26.3)	11(55)	medium		
		1(5.3)	0	Good		
0.486	0.002	6(31.6)	0	Poor	Second month	
		9(47.4)	8(40)	medium		
		4(21.1)	12(60)	Good		
0.554	<0.001	0	0	Poor	Third month	
		12(63.2)	2(10)	medium		
		7(36.8)	18(90)	Good		

Table 4: Distribution of control and experimental group patients based on final condition of femur fracture area and need for a reoperation

Total	Re-surgery		Total	Final fracture status		Groups
	Needful	Needless		Lack of proper scar formation	Proper scar formation	
20	3(15)	17(85)	20	3(15)	17(85)	Group 1
20	7(36.8)	12(63.2)	19	8(40)	12(60)	Group 2
0.118			0.077			p- value

Table 5: Relationship between final condition of scar and three variants of sex, age category and smoking

p-value	Total	Number (%)		Variable	
		Needful	Needless		
0.051	17	10(58.8)	7(41.2)	≤75	Age
	22	19(86.4)	3(13.6)	>75	
0.056	18	16(88.9)	2(11.1)	male	Sex
	21	13(61.9)	8(38.1)	female	
0.137	6	3(50)	3(50)	Yes	Smoking
	33	7(21.2)	26(78.5)	No	

After three months of follow- ups, it was determined that 29 of patients succeeded in forming a proper callus (union) and 11 of them due to reasons such as non-union, screw and plate misplacement and death, failed to form sufficient scar in fractured area. According to table 4, although 85% of group one patients managed to form proper scars compared to control (60%), but this difference was not statistically significant (P=0/077). In addition, after three months of therapeutic and radiological follow-ups, based on clinical and radiological evidence, and based on orthopedist's opinion, some patient became candidates for reoperation. According to table 4, albeit 36.8% of the control group patients were in need of reoperation compared to experimental group (15%), but this difference was not statistically significant (p=0/118).

In the present study, as secondary objective effects of smoking, gender and age of the patients on final condition of the scar was examined. Based on the data, sex has no significant relationship with final scar condition (P=0/343), and though 76.5% of non-smokers managed to form scars

compared to smokers (50%), but there is no significant different between them (P=0/181). Moreover, according to our results there is a statistically significant difference between age category and final condition of scar (P=0/036) (Table 5).

DISCUSSION

Generally bone has a good capacity for recovery and since renewal of bone continues during adulthood, healing occurs without scars[18]. If healing process of bone fracture lasts for more than 3 months, it is considered a delayed healing. If the healing does not occur during three months and there are no signs of an improvement, fractured is considered a non-union[19]. By stimulating differentiation and proliferation of osteoblasts and osteoclasts, the parathyroid hormone plays a major role in bone restoration[20]. According to other studies osteoporosis has been cured with full length PTH (84-1) and teriparatide which is an N-terminal PTH (1-34,)[21]. Currently, teriparatide (PTH, 1-34) is the only anabolic therapy for osteoporosis which is approved by FDA[22,23]. PTH can improve the quality of bones in people who are at high risk of fractures and also can prevent fractures[24]. At the end of the present study it was revealed that 29 patients managed to form an appropriate scar and 11 patients due to complications such as non-union, screw and plate misplacement and death failed to form sufficient bony tissue scar at the fractured area. Statistical analysis have shown that 85% of experimental group patients and 60% of the control group succeeded in forming a proper callus, even though numerically the experimental group excelled in this regard, but there was no statistically significant difference between the two groups. This result is in accordance with Aspenerg *et al*. who stated that administrating parathyroid hormone for bone fractures of upper body limbs especially wrist, does not yield significant positive results[25]. Yet, Peich *et al* stated that administrating 20 mg of the parathyroid hormone subcutaneously per day resulted in the proper bone scar (union) formation after eight weeks in all 21recipients (experimental group), while only 4 of 44 control group patients achieved union and their results were significantly different[26].

Furthermore, analysis of radiologic graphs which were taken from femur fractures monthly indicated that the pace of proper scar formation in the experimental group was significantly higher and this leads to faster recovery and fracture healing in Cinnopar receivers. According to Lou *et al*. who reviewed related papers from 1966 to 2015, suggested that using teriparatide for a minimum of four month results in improved recovery of patients and is beneficial for fracture healing[27]. Moreover, Hong *et al*. stated that PTH therapy led to faster recovery and healing and reduction of pain for fracture patients (experimental group), compared to placebo and control groups[28]. Nevertheless, Shi *et al*., results contradict results of the present study. This contradiction can be the result of the limitations of their study. For instance, in that study, patients who received other drugs, or even different doses of this drug were also included in the analysis[29] and also Lou *et al*. just included patients with osteoporosis and only fracture healing time and changes in limb function were evaluated[27]. In addition, at the end of the three- month follow-ups of the present study, 15% of the experimental group and 36,8% of the control group were considered in need of another operation for repairing the fractured area by orthopedist, though from statistical point of view this difference was not significant which aligns with Lwata *et al*., report. Lwata *et al*., divided 98 patients with vertebral compression fractures (VCF) in to two groups randomly; first group was treated with teriparatide 20 mg per day (TDP group, consisted of 38 patients) and second group was treated with Alenderonate 35mg per week (BP group, consisted of 60 patients). After 27 month follow-ups they stated that scar formation was significantly faster in TPD group, correction angle was steeper and elevation and healing of vertebrates was better and the need for a reconstructive surgery was less compared to BP group[30], it seems that differences between our results and Lwata *et al*. was due to smallness of our study population and limitations we faced for long-term follow-ups.

As for the secondary objective of the present study, it was revealed that only 59.1% of patients over 75 years of age succeeded in forming a proper scar before three month follow-ups, while 88.9% of patients under 75 years old succeeded in forming a proper scar. This difference is statistically significant and this data aligns with WHO statement about the prevalence of osteoporosis and its complication with age[31]. Clark *et al*., also stated that age-related changes affect many biological functions involved in the fracture healing process and have negative effects on cellular and molecular activities of different stages of healing process[32].

Generally, one of the limitations of the present study was that sample size was not big enough for some analysis and also in this research assessment of general condition of patients during the three month was not possible. It is suggested that in order to investigate the discrepancies found among some studies and also for statistical analysis of bone fracture complications, quality of recovery and refunctioning of limbs, clinical study with a bigger sample size be carried out.

CONCLUSION

According to the results of the present study, using PTH (1-34) speeds up the bone healing process and patient recovery and reduces possible need for a reoperation. Furthermore, for high risk patients therapeutic use of this medicine is beneficial for preventing complications such as non-union and screws and plates displacement.

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