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ORIGINAL STUDY

Is parathyroid hormone a viable solution for nonunion? a systematic review and pooled analysis

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We conducted a systematic review and pooled analysis of published studies to evaluate the clinical results of parathyroid hormone (PTH) in the treatment of nonunion and delayed union and assess whether there are any adverse effects of PTH. Four electronic databases (PubMed, Web of Science, EMBASE, and Cochrane library) were searched from 1950 to 2016. A total of 24 patients from 13 published studies were identified. The mean age of the patients was 57 years (range, 19-91 years). Mean duration of nonunion after initial treatment (surgical or conservative) was 8.4 months (range, 3-36 months). PTH was given to the patients for 1.5 months to 10 months (mean, 5.3 months) for various types of fractures. The union rates after using PTH was 96%. Mean time to union after PTH therapy was 7.3 months (range, 3-15 months). No patients reported any side effects during the entire period of PTH treatment.

Our study has helped to further elucidate the outcomes of PTH therapy in the treatment of nonunion. We believe that PTH is a viable option that is a promising, safe, and effective anabolic treatment for delayed union and nonunion.

Keywords : PTH ; parathyroid hormone ; delayed union ; nonunion.

INTRODUCTION

Each fracture has a failing risk which can lead to a nonunion. The rate of nonunion and delayed union in long bone fractures ranges between 5-10% *(13)*. For nonunion, a second intervention will undoubtedly be necessary, carrying additional risks and potential complications as well as increases in healthcare costs. The economic impact of treating nonunion is significant. The estimated direct cost for each tibial nonunion is approximately $7,500 and indirect costs related to lost productivity from time off from work during treatment can be as high as $17,000 *(4, 9)*. Therefore, any effective treatment that can solve this situation should be considered. Many strategies have been proposed to improve bone healing, surgical procedures, non-invasive locally effecting procedures and in the last years, pharmacological systemic treatments *(37)*.

Parathyroid hormone (PTH) is a naturally occurring 84 amino acid polypeptide. Its function is to increase serum calcium levels in response to systemic hypocalcaemia *(5)*. In addition to this classical effect, PTH and its amino-terminal fragments have been shown to increase bone mass, increase bone strength and reduce bone loss *(12)*. Teriparatide is a recombinant form of the

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biologically active component of human PTH and has been shown to stimulate osteoblasts, enhance bone connectivity, increase endosteal cortical thickness, and improve bone mineral content *(19, 23)*. Studies in both normal and delayed healing models have shown improvement in callus volume and mineralisation, bone mineral content, rate of successful union and strength at fracture sites *(41,44)*. Nevertheless, our current knowledge about the outcomes PTH therapy in human beings confined to a few case reports of single institution experience. Further understanding of PTH therapy would require a large database that would generate adequate power.

The current study was designed to evaluate the clinical results and adverse effects of PTH in the treatment of nonunion and delayed union with a review of literature and pooled analysis. On the basis of previous literatures *(42, 46)*, our hypothesis is that PTH therapy is a reliable option providing effective and safe results in different populations with varying comorbidities and fracture types.

PATIENTS AND METHODS

Search Strategy

We performed a systematic review of the available literature using multiple separate search strategies. A search was conducted with use of the following databases: PubMed, Web of Science, EMBASE, and Cochrane systematic reviews. The search term included a combination of medical subject headings (MeSH) and variations of keywords such as: "parathyroid hormone", "teriparatide", "fracture", "nonunion", and "delayed union". Two independent reviewers (SJK and JHK) separately completed the search, and the results were duplicated two times by each reviewer. The initial search was performed on January 15, 2016, and it was repeated on March 15, 2016, to ensure accuracy. No additional study was identified by repeating the search. A manual search was also performed from the references of the selected articles to identify any important reports that had been missed. The title, abstract, and full text were reviewed when the title or abstract suggested appropriateness of these publications and were discussed among the authors, and a decision was made regarding inclusion.

Study Inclusion

The inclusion criteria included (1) articles published from January 1, 1950 to July 15, 2015, (2) English-written articles in human species, (3) electronic publications that reported results of PTH, (4) both retrospective and prospective series, (5) only cases of PTH therapy in patients with nonunion, and (6) Only those articles that evaluated the outcomes.

The exclusion criteria included (1) animal studies, (2) PTH therapy in primary fracture healing *(3, 36)*, (3) articles without final outcomes (union) [10], (4) conference presentations, (5) cases with pseudofractures *(43)* or stress fractures (atypical femoral shaft fractures after bisphosphonate therapy) *(10,17)*, and (6) articles without the English language *(8)*. Due to the limited evidence available on the topic, case reports and case series were included in our study. Limits for the number of patients in each study or the minimum duration of follow-up were not used. A diagnosis of nonunion was made according to the established criterion: absence of healing at 3–6 months after an osteosynthesis (28, 40) or conservative treatment *(51)*.

Study Selection

A first search of the PubMed database yielded 50 articles and a second search of the Web of Science database with use of the same search strategy yielded 62 articles. The literature search is summarized (Figure 1). There were 110 articles that appeared in more than one of the four searches yielding a total of 220 unique articles. We selected most relevant articles from retrospective, cross sectional studies, clinical registries, or prospective studies. If there was any disagreement among authors regarding the inclusion of an article, the senior author (JHK) made the final decision. The full text of the 13 articles was obtained finally and then analyzed in detail. Owing to a lack of prospective randomized studies, most of the larger cohorts giving an answer or at least an insight to clinical problems were selected for this review. It

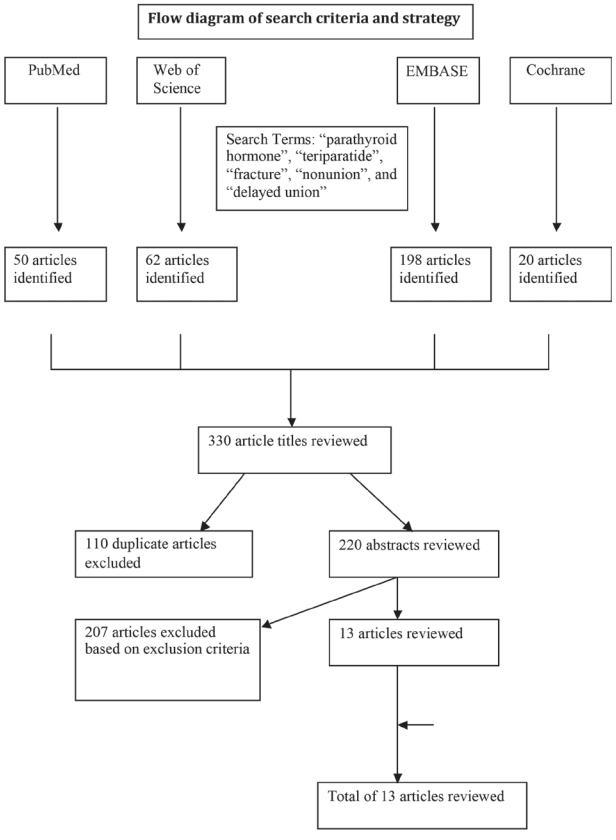

Fig. 1. —. Flow diagram of studies selected for inclusion in the review.

was not possible to conduct a meta-analysis due to the heterogeneity of the reports. An I2 value of 75% was indicated according to the test statistic for evaluating heterogeneity *(20)*. The Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline *(22)* was followed. Studies of PTH therapy in patients with nonunion predominantly started after the cases of Oteo-Alvaro et al. *(34)* and Chintamaneni et al. *(11)* in 2010, althouget alh there were a few prior studies with animal models *(1,44)*.

Data Extraction

Two authors (SJK. and JHA) independently extracted data onto Microsoft Excel. The following data were extracted: demographics including age, gender, comorbidity, mechanism of injury, types of fracture, fixation method, clinical and radiological outcomes following operative procedure, drug dosage, union rate, time to union, and other complications after PTH therapy. If there was a chance that the same patients (patients who were reported in 2 or more studies and treated by the same surgeon) had been included more than once in the present study, only the patients in the study with a larger cohort were included for data extraction.

RESULTS

Search Results and Studies Included

A review of PubMed, Web of Science, EMBASE, and Cochrane literature searches revealed a total of 24 patients from 13 selected articles which have been reported from 2010 to 2015. Although complete data were not available, data such as age, gender, mean follow-up, underlying medical/surgical conditions, union rate and complications were collected. Duration of nonunion was not clearly identified in all the reports *(35)*.

Demography

There were 7 male patients and 17 female patients. The mean age of the patients was 57 years (range, 19–91 years). Demographic information is detailed in Table 1. There was no comorbidity in 6 (25%) patients (patients denied smoking, alcohol abuse, and had no history of metabolic disease or glucocorticoid use). The most common mechanism of injury was a fall (42%).

Treatments and outcomes

Types of fracture and respective operative procedures in each study are detailed in Table 2. The most common location of fracture was femur (46%). Five patients (21%) were treated conservatively. According to 12 available articles (one study *(35)* was not included), mean duration of nonunion after treatment (surgical or conservative) was 8.4 months (range, 3-36 months). PTH was given to the patients for 1.5 months to 10 months (mean, 5.3 months) for various types of fractures. There were two types of treatment regimens using teriparatide (a once-daily administration of

Table 1. — Data on the studies (DM, diabetes mellitus)

Author	Journal	Year	Country	Gender (M/F)	Age	Comorbidity	Mechanism of injury
Mancilla et al. (27)	Endocrine practice	2015	USA	F	64	Osteoporosis, hyperparathyroidism	Low energy fall
				F	19	None	Direct impact during soccer
				F	22	Seckel syndrome, osteoporosis, multiple fractures	Low energy fall
				F	31	Scoliosis	Fall while mountain hiking
				M	43	Hypogonadism, DM, vitamin D deficiency	Traffic accident
				F	64	Graves' disease, osteoporosis	Fall downstairs
Uemura et al. (49)	Orthopedics	2015	Japan	M	62	Smoker	Surgery
				F	42	Smoker	Surgery
Tachiiri et al. (46)	Arch Osteoporos	2014	Japan	F	72	DM	Surgery
				F	72	DM	Falling from bicycle
Giannotti et al. (15)	Eur J Orthop Surg Traumatol	2013	Italy	F	80	None	Accident
Mitani et al. (30)	Arch Osteoporos	2013	Japan	F	88	Colon cancer, gastric cancer, RA, steroid use	Fall from bed
Ochi et al. (33)	Arch Osteoporos	2013	Japan	F	74	RA	Fall from stairs
Tamai et al. (47)	Osteoporos Int	2013	Japan	F	25	DM, Charcot arthropathy	Climbing stairs
Bednar et al. (6)	J Spinal Disord Tech	2013	Canada	F	70	Atrial fibrillation, valvular heart disease, hypothyroidism, osteoporosis, lupus	Low energy fall
Lee et al. (21)	Osteoporos Int	2012	Korea	M	38	None	Traffic accident
				F	64	None	Traffic accident
				M	29	None	Traffic accident
Paridis et al. (35)	J Musculoskelet Neuronal Interact	2011	Greece	M	48	Smoker	Traffic accident
Oteo-Alvaro et al. (34)	J Shoulder Elbow Surg	2010	Spain	M	32	None	Ski accident
Chintamaneni et al. (11)	Osteoporos Int	2010	USA	M	67	Hypertension, Raynaud's phenomenon, glaucoma	Traffic accident
Rubery (42)	J Spinal Disord Tech	2010	USA	F	91	Hypothyroidism, breast cancer, diverticulitis	Traffic accident
				F	84	Hypertension, DM, breast cancer	Low energy fall
				F	82	Cardiomyopathy, arrhythmia, osteoporosis, congestive heart failure.	Low energy fall
Total				7/17	57		

recombinant type and a once-weekly administration of a chemically synthesized type). The union rates after using PTH was 96% (23/24 patients). The patient with the poorest response (nonunion at the final follow-up) had Seckel dwarfism *(27)*. Mean time to complete union after PTH therapy was 7.3 months (range, 3-15 months). No patients reported any side effects during the entire period of PTH treatment.

DISCUSSION

Few options exist for the treatment of delayed union and nonunion fractures and there have been no approved systemic drugs for nonunion. To the best of our knowledge, PTH is the only currently available anabolic agent to stimulate osteoblast activity. Nevertheless, its effect on delayed union or nonunion in human remains controversial. We therefore performed a systematic review of the literature to evaluate the clinical results and adverse effects of PTH therapy in the treatment of nonunion with a pooled analysis of the reported cases.

Every fracture has a risk of healing failure which can lead to a "non-union". Nonunions are common when the fracture gap is wide, or when there is too much interfragmentary movement, or when the surrounding soft tissues are heavily damaged or infected *(37)*. To facilitate maturation of the regenerated bone and reduce the treatment period, several experimental approaches have been describe including low-intensity pulsed ultrasound, electrical stimulation, and extracorporeal shock waves *(38,50)*. Other available alternatives include allogenic grafts, human demineralized bone matrix, and bone morphogenetic proteins *(26,39)*. However, these alternatives may require extensively invasive additional surgery and this invasive procedure could be life threatening for elderly patients with medical complications since such procedures are associated with a significant morbidity rate *(14)*. Until now, there have been no approved systemic drugs for nonunion *(30)*. As mentioned earlier, PTH is the only currently available agent that can stimulate osteoblast and bone marrow stroma cell activities to increase bone mass, improve bone quality, and reduce the risk of fracture. In our systematic review of the literature, the union rates after using PTH was 96%.

Animal experiments show a dramatic improvement of skeletal repair by teriparatide *(7)*. In 2010 Mognetti et al. *(31)* noted that 40 μg/kg per day of teriparatide stimulated callus mineralization until day 18 of bone healing and after 15 d of treatment the callus hardness approximated normal bone in closed tibial fracture models in mice. Andreassen et al. *(2)* demonstrated that PTH improves rate of callus formation and bone strength even in older bone in aged rats at 3 and 8 weeks post fracture. The lack of valid studies on fracture healing in humans is a direct consequence of the difficulties that are present in monitoring the healing process in human, both for the frequency of the controls and the difficulty in measure the healing process, radiographically or clinically *(37)*. The effects of teriparatide on normal primary fracture in human subjects have been examined *(3,36,52)*. In the present study, we have conducted a systematic review of the literature on the use of recombinant PTH to treat delayed union and nonunion in human subjects. Due to the limited available evidence on recombinant PTH used for nonunion, we relied considerably on case reports and case series in this study. However, on the strength of current available data, we believe that a conceivable positive effect of PTH on fracture healing is well-documented on animals, and very likely on humans. Further multicenter studies are needed to demonstrate objective long term results of PTH therapy in patient with nonunion before this method attains widespread use.

Potential known side effects of PTH therapy include headache, nausea, cramps, and hypercalcemia *(32)*. However, since its approval by the FDA in December 2002, teriparatide has been safely used by more than 600,000 patients *(29)*. Monitoring calcium excretion is not recommended in patients with no renal stones or normal basal urinary calcium *(29)*. There was also a concern that teriparatide might increase the risk for patients to develop osteosarcoma, as almost 45% of the rats treated with this drug at the highest-tested dose level developed this aggressive form of bone cancer. *(18)*. However, several literatures demonstrated that there have been no reports of osteosarcoma in any

Table 2. — Clinical outcomes of the studies (IM, intramedullary; EF, external fixation; IF, internal fixation; NA, not available)

Author	Fracture type	Operative procedure	Duration of nonunion (month)	PTH therapy (month)	Dose	Time to union after PTH	Complication
Mancilla et al. (27)	Femoral shaft	IM nailing	3	9	20 μg/day	9	No side effects
	Tibial shaft	IM nailing	8	7	20 μg/day	7	No side effects
	Tibial and femoral shafts	EF	15	NA	20 μg/day	Non-union	No side effects
	Tibial shaft	IF	3	3	20 μg/day	3	No side effects
	Femoral shaft	IM nailing	36	5	20 μg/day	5	No side effects
	Subtrochanteric femur	IM nailing	12	8	20 μg/day	8	No side effects
Uemura et al. (49)	Ulnar shaft	Ulnar shortening osteotomy and IF with non-locking plate	10	10	20 μg/day	10	No side effects
	Ulnar shaft	Ulnar shortening osteotomy and IF with non-locking plate	6	6	20 μg/day	6	No side effects
Tachiiri et al. (46)	First metatarsal bone	Osteotomy and fixation with a locking plate	4	4	56.5 μg/week	4	No side effects
	Olecranon fracture	Tension band wiring	4	4	56.5 μg/week	4	No side effects
Giannotti et al. (15)	Distal femoral fracture	OR/IF with lateral femoral locking plate	7	3	20 μg/day	3	No side effects
Mitani et al. (30)	Femur neck fracture	CR/IF with Hansson hook-pin system	11	10	56.5 μg/week	10	No side effects
Ochi et al. (33)	Periprosthetic femoral fracture after TKA	OR/IF with periarticular locking plate, reoperation	9	6	56.5 μg/week	6	No side effects
Tamai et al. (47)	Ankle joint	Ankle arthrodesis	13	3	20 μg/day	3	No side effects
Bednar et al. (6)	Type III odontoid process fracture	None (collar brace)	3	6	20 μg/day	6	No side effects
Lee et al. (21)	Femur shaft fracture	Retrograde IM nailing	8	9	20 μg/day	15	No side effects
	Distal femoral fracture	OR/IF with lateral femoral locking plate	6	3	20 μg/day	11	No side effects
	Femur neck fracture	CR/IF with cannulated screws	10	3	20 μg/day	15	No side effects
Paridis et al. (35)	Two level, comminuted fracture (pertrochanteric and middiaphyseal)	IF with a hip sliding screw and a dynamic compression plate, reoperation	NA	2	20 μg/day	12	No side effects
Oteo-Alvaro et al. (34)	Diaphyseal humeral fracture	IM nailing with 2 elastic nails	6	5	20 μg/day	5	No side effects
Chintamaneni et al. (11)	Body of the sternum	None	6	9	20 μg/day	9	No side effects
Rubery (42)	Type III odontoid process fracture	None (collar brace)	5	1.5	20 μg/day	7	No side effects
	Type III odontoid process fracture	Halo vest	4.5	2.5	20 μg/day	7	No side effects
	Type III odontoid process fracture	Halo vest	4	4	20 μg/day	4	No side effects
Total			8.4	5.3		7.3	

patients treated with teriparatide *(16,48)*. Balancing the proven benefits of teriparatide shown by clinical trials with the theoretical risk for teriparatide-induced osteosarcoma, the FDA mandated both a black-box warning and a company postmarketing surveillance program *(45)*. In our pooled analysis, No patients reported any side effects during the entire period of PTH treatment.

Another major concern about PTH therapy is cost-effectiveness. Definitely, teriparatide is expensive and may produce a smaller increase in quality-adjusted life year. However, a recent cost-effectiveness analysis from Sweden suggested that teriparatide may be cost-effective compared with no treatment *(25)*. It could become more cost-effective with reductions in teriparatide price, restriction of use in high-risk women, or if short courses of teriparatide could provide the same fracture reduction efficacy as those reported in longer clinical trials *(24)*.

Limitations of this systematic review

Our study has some limitations. First, there is a potential for publication selection bias since most of the studies included in our review are case reports or small case series. This means that the authors of each study are unlikely to publish negative results and as a result of this, reports are likely biased toward patients that healed their nonunion. Second, due to the limited available data on recombinant PTH, we have combined the evidence for teriparatide *(PTH (1–34))* and PTH (1–84) in our analysis, which limits our ability to differentiate the efficaciousness of these 2 peptides. Third, as a case series, our report represents an observational study that reports data from a subject group without a comparison population. Hence, in the hierarchy of evidence, it represents level IV evidence.

CONCLUSION

In conclusion, we believe that PTH is a possible alternative to surgical intervention in difficult cases of nonunion or delayed union. Administration of PTH can induce stable consolidation of the bone in nonunion and delayed healing of bone fractures. Overall, PTH therapy is very well tolerated and safe in most patients. Additional randomized placebo-controlled trials are needed to determine the potential benefit of PTH as an adjunct to treat nonunion and its efficacy in broader populations with varying comorbidities and fracture types.

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