Use of Teriparatide to improve fracture healing: What is the evidence?

Satish Babu, Nemandra A Sandiford, Mark Vrahas

Satish Babu, Core Surgical Trainee, St. George’s Hospital, London SW17 0QT, United Kingdom

Nemandra A Sandiford, Lower Limb and Tumor Reconstruction Fellow, University of British Columbia, Vancouver V5Z 1M9, British Columbia, Canada

Mark Vrahas, Orthopaedic Trauma Service, Massachusetts General Hospital, Boston, MA 02114, United States

Author contributions: All authors contributed to this manuscript.

Conflict-of-interest statement: We, the authors of this scientific paper, do hereby state that we have no conflicts of interest to declare.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

Correspondence to: Nemandra A Sandiford, FRCS (Trauma and Orthopaedics), Lower Limb and Tumor Reconstruction Fellow, University of British Columbia, 2329 West Mall, Vancouver V5Z 1M9, British Columbia, Canada. nemsandiford@hotmail.com

Telephone: +1-208-3069032

Received: February 12, 2015
Peer-review started: February 12, 2015
First decision: April 10, 2015
Revised: May 2, 2015
Accepted: June 1, 2015
Article in press: June 2, 2015
Published online: July 18, 2015

Abstract

Teriparatide is a recombinant form of the biologically active component of Parathyroid hormone. It has been shown to increase bone mass and prevent fractures in osteoporotic bone. It is licensed by the Food and Drug Administration for the treatment of Osteoporosis. Over the last decade, a growing body of evidence has accumulated suggesting a role for Teriparatide in the management of fractures. 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. However most of these results have been derived from animal studies. The majority of this research on humans has comprised low level evidence, with few randomised controlled trials, many case reports and case series. Nevertheless, the results from these studies seem to support research from animal models. This has led to a growing number of clinicians using Teriparatide “off license” to treat fractures and non-unions in their patients. This review presents a critical appraisal of the current evidence supporting the use of Teriparatide for fracture healing, delayed unions and non-unions and in the setting of osteoporotic fractures, the studies producing this evidence and their transferability to human beings.

Key words: Teriparatide; Fractures; Healing; Bone; Osteoporosis

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Teriparatide contains the biologically active component of Parathyroid Hormone. It is utilised in osteoporosis for its ability to increase bone mass and prevent fractures. Research suggests Teriparatide may improve callus volume, callus mineralisation, bone mineral content and successful union. However most research come from animal models. Human research, whilst supporting Teriparatide use, mostly comprises low level evidence such as case series. Currently many United States physicians use Teriparatide “off license” for fractures and non-unions. We suggest more, well designed, human randomised controlled trials are
required before Teriparatide can become a mainstream option in the conservative management of fractures and non-unions.

Babu S, Sandiford NA, Vrahas M. Use of Teriparatide to improve fracture healing: What is the evidence? World J Orthop 2015; 6(6): 457-461 Available from: URL: http://www.wjgnet.com/2218-5836/full/v6/i6/457.htm DOI: http://dx.doi.org/10.5312/wjo.v6.i6.457

INTRODUCTION
Parathyroid hormone (PTH) is a naturally occurring 84 amino acid polypeptide. Its function is to increase serum calcium levels in response to systemic hypocalcaemia. This effect is achieved by a promotion in osteoclast related bone resorption. 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.[1,2]

Structure-function studies of PTH have suggested that the N-terminal fragment of the PTH molecule [encompassing amino acids 1-34 and called PTH(1-34)] is the principal framework responsible for the observed biological activity.[3,4] Teriparatide is a recombinant form of these 34 amino-terminal residues of human PTH. It has a molecular mass of 4117.8 daltons.[5]. It is manufactured using a genetically modified strain of Escherichia coli and supplied as a solution for subcutaneous injection[6].

It was licensed for use by the FDA in the treatment of patients with Osteoporosis in 2002. This licences encompasses postmenopausal females, individuals with glucocorticoid-induced osteoporosis and men with hypogonadal or idiopathic osteoporosis at high risk of fracture.

The current recommended dose is 20 μg once daily and treatment is not recommended for a duration exceeding 2 years. Apart from this recognised application, there is a growing body of evidence suggesting its ability to accelerate fracture healing and heal nonunions. The purpose of this review is to summarise the current evidence for the use of Teriparatide for fracture healing, delayed unions and non unions and in the setting of osteoporotic fractures, the studies producing this evidence and their transferability to human beings.

ANIMAL MODELS OF NORMAL FRACTURE HEALING
Numerous studies using small animal models have demonstrated that PTH enhances fracture healing. In 1999, Andreassen et al[7] showed that PTH increased callus formation and ultimate load to failure for tibial fractures in adult rats. Intermittent administration of PTH(1-34) at 60 and 200 μg doses produced increases in callus volume of 42% and 72% respectively and increased ultimate load to failure by 132% and 175% respectively after 40 d. In the same year, Holzer et al[8] found histological evidence of increased callus area and improved bone strength after daily PTH(1-34) administration in rats.

In 2004, Andreassen et al[8] also found that intermittent PTH increased fracture strength and callus volume 8 wk after fracture in rats. The following year KomatsuBara et al[9] showed, amongst other things, that intermittent Teriparatide at 30 μg/kg before and after osteotomy accelerated the fracture healing process in rats up to 12 wk after osteotomy. In 2010 Mognetti et al[10] 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. They also found that the formation of callus was accelerated.

The beneficial effect from PTH is not only limited to the periods during which treatment is given. Alkhairy et al[11] administered daily Teriparatide at 5 or 30 μg/kg doses to rats with fractures and compared this to controls. After 35 d both doses produced significant increases in bone mineral content, density and total osseous tissue volume. Analysis 49 d after discontinuing treatment in the 30 μg/kg group showed a sustained increase in bone mineral density and torsional strength when compared to controls. This implies a sustained anabolic effect throughout the remodelling phase of fracture-healing[11]. No change in osteoclast density was seen possibly suggesting that treatment enhanced bone formation but not resorption[11]. A sustained increase in mechanical strength and bone density was also observed by Andreassen et al[8].

Several authors have also suggested that PTH used in conjunction with other therapies may be beneficial in fracture healing. Gardner et al[12] showed a symbiotic relationship between PTH and mechanical loading in mice. They divided mice into 4 groups: (1) a control who received sham loading and vehicle injection; (2) a group which received daily loading; (3) one which received daily subcutaneous PTH injections (30 μg/kg per day); and (4) a group which received loading and PTH.

After 2 wk group 4 showed increased osteoblast and osteoclast activity and was the only group with a significantly larger callus mineral density and bone volume fraction. In contrast the PTH only group had more osteoid in the callus compared to controls (indicating increased early osteoblast activity) and a significantly higher bone mineral content and total bone volume compared to controls. The loading only group exhibited greater osteoclast activity.

A major criticism of the above studies is that they were all carried out in rodents. These animals and humans metabolise PTH differently and therefore legitimate questions have arisen about the transferability
of these results to human beings. Studies in animals genetically closer to humans have also been performed. Manabe et al\textsuperscript{[13]} examined the effect of intermittent Teriparatide on cynomolgus monkeys who have an intracortical remodelling system similar to humans. They used the relatively low doses of 0.75 $\mu$g/kg and 7.50 $\mu$g/kg in their studies. They found a higher ultimate stress and elastic modulus in the femora of the group receiving 7.50 $\mu$g/kg. They also observed lower total area and percent bone area of the femur in PTH treated monkeys as well as a dose dependent decrease in callus porosity with PTH treatment\textsuperscript{[13]}. These actions potentially accelerate fracture healing by restoring the mechanical properties of osteotomised femur.

Barnes et al\textsuperscript{[14]} have recommended a cautious approach to the use of PTH preparations in human subjects. Dosages used in many animal studies exceed the recommended equivalent human dosage for treatment of an equivocal condition\textsuperscript{[14]}. Current recommended dosages of between 20 and 40 $\mu$g/kg per day for humans are much lower than dosages used in animals\textsuperscript{[14]}. Other authors have found conflicting results. In addition to the results obtained by Manabe et al\textsuperscript{[13]}, Nakajima’s group have found higher bone mineral content, bone mineral density and ultimate load to failure in rat models on days 28 and 42 after fracture using 10 $\mu$g/kg doses of Teriparatide\textsuperscript{[15]}. Increases in bone mineral density, bone mineral content and osseous tissue volume have also been reported with doses of 5 $\mu$g/kg\textsuperscript{[11]}.

**ANIMAL MODELS OF DELAYED HEALING**

Arguably the most useful clinical application of Teriparatide would be in those situations where sub-optimal fracture repair mechanisms are expected such as, smoking, diabetes, corticosteroid treatment, metabolic bone disease and states of relative oestrogen deficiency as well as patient with osteoporosis. Between 5% and 20% of the 7.9 million fractures that occur every year in the United States exhibit some degree of impaired fracture healing\textsuperscript{[16]}.

As our population ages, the effect of PTH on aging bone has become increasingly relevant. Andreassen et al\textsuperscript{[17]} analysed the effect of intermittent doses of 200 $\mu$g/kg of Teriparatide on callus formation and bone strength in aged rats at 3 and 8 wk post fracture. At 21 d after fracture, those treated with Teriparatide exhibited an ultimate load to failure increase of 160%. After 56 d this increased to 270%. External callus volume increased by 208% and 135% after 21 and 56 d respectively. Bone mineral content increased by 190% after 3 wk and 388% after 8. This group noted differences in the healing mechanism of these older rats compared to their younger counterparts. They observed callus production to be slower in older rats when comparing young and old controls. The callus volume in the older group at 56 d was similar to the young controls at 20 d\textsuperscript{[17]}. However when comparing PTH-treated animals both young and old rats had similar callus volumes at 20 and 21 d respectively. Callus volume remained unchanged from day 21 to 56 in old PTH-treated rats but this volume declined after 20 d in younger rats. These results suggest that PTH improves rate of callus formation and bone strength even in older bone.

Investigators examining the role of PTH in osteoporotic bone have commonly used ovariectomised animals to mimic menopause and relative oestrogen deficiency. In 2008 Nozaka et al\textsuperscript{[18]} examined the effects of hPTH(1-34) in 4 groups of rats which received a sham operation and vehicle, sham and human PTH(1-34), bilateral ovariectomy and vehicle and bilateral ovariectomy and hPTH(1-34). Recombinant hPTH(1-34) was administered once a week at a dose of 100 $\mu$g/kg.

They assessed the effect of each of these regimens on osteotomey and non-osteotomey cancellous bone in the tibia. They observed that ovariectomy caused a significant decrease in cancellous bone volume compared with the sham group (33.2% decrease). PTH treatment significantly increased cancellous bone volume and osteoid surface in the sham group (81.5% and 75.4% respectively) and ovariectomised cohort (81.1% and 57.3%) compared with respective vehicle groups\textsuperscript{[18]}. In the ovariectomised group PTH suppressed bone resorption parameters, including eroded surface, osteoclast surface and osteoclast number compared with vehicle. PTH treatment was shown to significantly increase the percentage of union in both sham (45.6% increase) and ovariectomised (59.0% increase) groups compared with respective vehicle groups\textsuperscript{[18]}.

Histological analysis revealed that PTH treatment was associated with decreased adipocyte volume and number in the bone marrow of ovariectomised animals compared to controls. These findings suggested that intermittent PTH administration promoted osteoblastogenesis and decreased adipogenesis at the site of cancellous bone osteotomy resulting in increased bone union in normal and ovariectomised rats\textsuperscript{[18]}. Similar results have also been reported by Kim and Jahng\textsuperscript{[19]}.

Improvements in rates of fracture healing have also been demonstrated in animals receiving corticosteroid therapy. Bostrom et al\textsuperscript{[20]} examined the effect of the PTHrP analog RS-66271 and hPTH(1-34)-NH$_2$ on fracture healing in the ulnae of steroid treated rabbits. Experimental group animals received a dose of 0.01 mg/kg of hPTHrP. After 6 wk, nine of the ten ulnae from the PTHrP treated rabbits achieved radiographic union compared to two in the control group\textsuperscript{[20]}. In another arm of the study 100% of treatment group rabbits achieved union by 6 wk compared to 20% of controls after 10 wk. The ulnae of PTHrP treated rabbits showed greater radiographic intensity, larger callus dimensions and volume, greater stiffness (64%) and mechanical strength\textsuperscript{[20]}.

**STUDIES IN HUMANS**

The effects of Teriparatide on normal fracture healing,
delayed union and non-unions in human subjects have also been examined. Aspenberg et al [21] examined the effect of placebo compared to Teriparatide administered in 20 and 40 μg doses given daily to a population of female patients with distal radius fractures [21]. These patients were all between 45 and 85 years of age and their fractures were being treated conservatively. This was a well designed level 1 study. They found that median time to the first radiographic evidence of healing was 9.1 wk in the placebo group compared to 7.4 and 8.8 wk in the groups treated with 20 μg and 40 μg of Teriparatide respectively. This was not statistically significant (P = 0.15).

There was no significant difference between the placebo and 40 μg groups (P = 0.523). Post hoc analysis demonstrated a significant difference between the placebo group and those patients treated with 20 μg daily. The authors advised interpreting this result with caution however.

Peichl et al [22] evaluated the effect of PTH 1-84 on pelvic fracture healing and functional outcome in postmenopausal women. Sixty five patients were divided into two groups; one control and one which received once daily 100 μg of PTH 1-84 starting within two days after admission to hospital. All individuals received calcium and vitamin D supplementation. The median time from fracture to the first sign of complete cortical bridging of the pelvic fracture (verified with CT scanning) was 7.8 wk for the treatment group compared with 12.6 wk for controls.

At the primary end point (8 wk 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 VAS score) in the treatment group (7.6 at the start of the study to 3.2 at week 8) compared with controls (7.7 at origin to 6.5 at week 8). Statistically significant improvements in timed up and go test times were also noted in the treatment group. The authors of this study noted that although this molecule is not identical to Teriparatide, the time frame to healing that has been noted is similar to that observed in the treatment of patient with pelvic fracture nonunions with Teriparatide at the standard dosage [22].

DELAYED UNION

Bukata et al [23] reported on a series of 145 patients with fractures of the spine or other extremities that were treated with 20 μg of Teriparatide. Half of the patients in this study demonstrated delayed fracture healing and 88% had failed a previous attempt at union, presented with a non-union, were elderly or had significant medical comorbidities. Regardless of fracture site, 141 people reported resolution of pain at the fracture site within 12 wk of starting Teriparatide and the fracture united in 93% [23]. Indicators of healing (pain resolution and bridging of the fracture site by radiograph or CT scan) were noted to occur sooner in fractures that were predominantly trabecular bone (vertebrae, sacral ala, metadiaphyseal long bones) compared with fractures of diaphyseal bone or fusion sites [23]. Cases have been reported of almost normal fracture healing in elderly patients with established osteoporosis after starting treatment with Teriparatide [24].

NON-UNIONS

Several published case reports have suggested a beneficial effect of Teriparatide on non-unions. Chin-tamaneri et al [25] reported on a 67-year-old male who sustained a fracture of the body of the sternum as a result of a motor vehicle accident. This subsequently failed to heal resulting in a painful atrophic non-union. A trial of 20 μg per day of Teriparatide was initiated and showed significant healing of the non-union within 3 mo and complete healing and symptomatic resolution after 9 mo [25].

Rubery and Bukata [26] have also report 3 cases of painful delayed unions of type II odontoid fractures which united and led to resolution of pain after treatment with Teriparatide.

CONCLUSION

Teriparatide constitutes the active portion of the Parathyroid Hormone molecule and is a commercially available, Food and Drug Administration (FDA) approved agent for the treatment of Osteoporosis. Emerging research over the last decade has shown a potential application in fracture management. Widespread evidence obtained from studies utilising small and large animal models indicate Teriparatide can improve fracture healing. Significant improvements in callus volume, callus mineralisation, bone mineral content, strength and rate of successful union at the fracture site in both normal and delayed healing models has been demonstrated. Research in humans has been relatively sparse with only two randomised controlled trials having been conducted to date. These are interspersed within a sea of anecdotal case reports. However the results of the human studies are in line with their animal counterparts and it seems that inferences can therefore be made despite obvious differences in PTH metabolism between the species.

Currently Teriparatide is being used “off license” for the management of fractures and non-unions by physicians who are confident of its beneficial effect. Well designed randomised controlled trials are required to comprehensively analyse the actions of Teriparatide in human subjects (in both normal and delayed healing models). This will allow conclusive decisions to be made on whether or not to incorporate this product as a standard option for conservative management of fractures and non-unions.

REFERENCES

1. Dempster DW, Cosman F, Parisien M, Shen V, Lindsay R.
Anabolic actions of parathyroid hormone on bone. Endocr Rev 1993; 14: 690-709 [PMID: 8119233 DOI: 10.1210/edrv-14-6-690]

2 Turner CH, Wang T, Hiranu T, Burr DB, Hock JM, Hotchkiss CE, Brommage R and Jerome CP (1999). In primates, treatment with PTH (1-34), LY333334, increases bone strength at trabecular bone sites without compromising the strength of cortical bone. J Bone Miner Res 1999; 14 Suppl 1: S414 abstract

3 Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, Hodson AB, Erikson EF, Ish-Shalom S, Gentian HK, Wang O, Mitlak BH. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001; 344: 1434-1441 [PMID: 11346808 DOI: 10.1056/NEJM200105103441904]

4 Hodson AB, Bauer DC, Dempster DW, Dian L, Hanley DA, Miller PD, Olszynski WP, Orwell E, Euen CK. Parathyroid hormone and teriparatide for the treatment of osteoporosis: a review of the evidence and suggested guidelines for its use. Endocr Rev 2005; 26: 688-703 [PMID: 15769003 DOI: 10.1210/er.2004-0006]

5 Berg C, Neumeyer K, Kirkpatrick P. Fresh from the Pipeline: Teriparatide. Nat Rev Drug Discov 2003; 2: 257-258 [DOI: 10.1038/nrd1068]

6 Andreassen TT, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1-34) treatment increases callus formation and mechanical strength of healing rat fractures. J Bone Miner Res 1999; 14: 960-968 [PMID: 10352105 DOI: 10.1359/jbmr.1999.14.6.960]

7 Holzer G, Majeska RJ, Lundy MW, Hartke JR, Einhorn TA. Parathyroid hormone enhances fracture healing. A preliminary report. Clin Orthop Relat Res 1999; (366): 258-263 [PMID: 10627743 DOI: 10.1097/00003086-199906000-00033]

8 Andreassen TT, Willick GE, Morley P, Whitfield JF. Treatment with parathyroid hormone hPTH(1-34), hPTH(1-31), and monocyclic hPTH(1-31) enhances fracture strength and callus amount after withdrawal fracture strength and callus mechanical quality continue to increase. Calcif Tissue Int 2004; 74: 351-356 [PMID: 15255072 DOI: 10.1007/s00223-003-0093-6]

9 Komatsu Suke T, Mori S, Mashiba T, Nonaka K, Seki A, Akita Y, Yamanoto K, Cao Y, Manabe T, Norimatsu H. Human parathyroid hormone (1-34) accelerates the fracture healing process of woven to lamellar bone replacement and new cortical shell formation in rat femora. Bone 2005; 36: 678-687 [PMID: 15781066 DOI: 10.1016/j.bone.2005.02.002]

10 Mognetti B, Marino S, Barberis A, Martin AS, Bala Y, Di Carlo F, Boivin G, Barbos MP. Experimental stimulation of bone healing with teriparatide: histomorphometric and microhardness analysis in a mouse model of closed fracture. Calcif Tissue Int 2011; 89: 163-171 [PMID: 21701938 DOI: 10.1007/s00223-011-9503-3]

11 Alkhia K, Ntim A, Bostrom MP, Einhorn TA, Ejersted C, Oxlund H. Increases in callus formation and mechanical strength of healing fractures in old rats treated with parathyroid hormone. Acta Orthop Scand 2001; 72: 304-307 [PMID: 11486014 DOI: 10.1080/00016470152846673]

12 Nozaka K, Miyakoshi N, Kasukawa Y, Masekawa S, Noguchi H, Shimada Y. Intermittent administration of human parathyroid hormone enhances bone formation and union at the site of cancellous bone osteotomy in normal and ovariectomized rats. Bone 2008; 42: 90-97 [PMID: 17997377 DOI: 10.1016/j.bone.2007.08.041]

13 Kim HW, Jang JS. Effect of intermittent administration of parathyroid hormone on fracture healing in ovariectomized rats. Iowa Orthop J 1999; 19: 71-77 [PMID: 10847519]

14 Bostrom MP, Gamradt SC, Asnis P, Vickery BH, Hill E, Avnur Z, Waters RV. Parathyroid hormone-related protein analog R5-66271 is an effective therapy for impaired bone healing in rabbits on corticosteroid therapy. Bone 2000; 26: 437-442 [PMID: 10773582 DOI: 10.1016/S8756-3282(00)00251-9]

15 Aspenberg P, Gentien HK, Johansson T, Nino AJ, See K, Krohn K, Garcia-Hernandez PA, Recknor CP, Einhorn TA, Dalsky GP, Mitlak BH, Frielinger A, Lakshmanan MC. Teriparatide for acceleration of fracture repair in humans: a prospective, randomized, double-blind study of 102 postmenopausal women with distal radial fractures. J Bone Miner Res 2010; 25: 404-414 [PMID: 19594305 DOI: 10.1359/jbmr.090731]

16 Peichl P, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J Bone Joint Surg Am 2011; 93: 1583-1587 [PMID: 21915572 DOI: 10.2106/JBJS.I.01379]

17 Bukata SV, Puzeas JE. Orthopedic uses of teriparatide. Curr Osteoporos Rep 2010; 8: 28-33 [PMID: 20425088 DOI: 10.1007/s11914-010-0006-3]

18 Resmini G, Iolascon G. 79-year-old post-menopausal woman with humerus fracture during teriparatide treatment. Aging Clin Exp Res 2007; 19: 30-31 [PMID: 18182890]

19 Chintamani S, Finzel K, Gruber BL. Successful treatment of sternal fracture nonunion with teriparatide. Osteoporos Int 2010; 21: 1059-1063 [PMID: 19859645 DOI: 10.1007/s11917-009-1061-4]

20 Rubery PT, Bukata SV. Teriparatide may accelerate healing in delayed unions of type III odontoid fractures: a report of 3 cases. J Spinal Disord Tech 2013; 26: 151-155 [PMID: 20561918 DOI: 10.1097/BSD.0b013e1819a8b7a]

P-Reviewer: Kvar F, Madadi F S-Editor: Ji FF L-Editor: A E-Editor: Wu HL
