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Effectiveness of Parathyroid Hormone (PTH) Analogues on Fracture Healing: A Meta-Analysis

Mini-Abstract (50 words)

This meta-analysis evaluated the evidence for the use of parathyroid hormone (PTH) analogues to improve fracture healing. Eligible studies were prospective randomised controlled trials of adults with acute fractures treated with a PTH analogue. PTH improved functional outcomes but did not affect fracture healing rate or reduce pain.

Abstract

Purpose

This meta-analysis evaluated the evidence of Parathyroid Hormone (PTH) analogues in fracture healing. The use of PTH analogues to prevent osteoporotic fractures is well investigated and studies are emerging on extended indications. One such indication receiving increasing attention is the effect of PTH in fracture healing; however, the overall degree of efficacy remains inconclusive.

Methods

A systematic electronic database search of MEDLINE, EMBASE and the Cochrane Library was conducted for relevant articles in August 2019 with no date restrictions. Randomised controlled trials of adults with acute fractures treated with a PTH analogue we included. PTH was compared with a comparator intervention, placebo, or no treatment.

Results

PTH analogue treatment improved functional outcomes in a range of fracture types but did not affect the fracture healing rate or reduce pain. Most trials included in this review were in elderly patients with osteoporosis. There was no evidence that PTH treatment caused harm or impeded fracture healing.

Conclusions

Meta-analysis of published data supports the use of PTH analogues to improve functional outcomes but not fracture healing rate or pain for different fracture types. The evidence for PTH analogue use in fracture healing is less clear in younger, non-osteoporotic patient populations. Trial design was heterogeneous and of limited quality, justifying further original trials.

Keywords

Parathyroid Hormone: Teriparatide: Fracture Healing: Meta-Analysis: Osteoporosis

Declarations

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Conflicts of interest/Competing interests. Professor William Fraser has received unrestricted research grants, sat on advisory boards and given lectures on behalf of Eli Lilly, NPS and Nycomed. Dr Matt Gerlach, Dr Isabelle Piec, Prof Julie Greeves and Mrs Katharine Eastman have no conflicts of interest.

Ethics approval. This study was not a human or animal experiment so no ethical approval was required.

Consent to participate. This study used data already in the public domain, there was no requirement for consent to be taken.

Consent for publication. This study used data already in the public domain, there was no requirement for consent to be taken.

Availability of data and material. This study used data already in the public domain, data collection tools will be made available on request to the corresponding author.

Code availability. Software used was;

Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

RoB 2 tool [Computer program]. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; ***366****: l4898.*

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Introduction

Fractures are the most common large-organ trauma. All cause fracture rates in the UK were reported at 73.3 per 10,000 patients per year between 1988 and 2012 (1, 2). In England, fragility fractures alone cost £4.4 billion per year (3), the largest proportions of this is hip fractures that account for £1.5 billion and 1.3 million hospital bed days per year (4). Fracture healing is a complex, but critical physiological process to recondition bone and restore its function (5). Reducing fracture healing time is an important outcome because bone fractures, particularly those related to osteoporosis, are associated with high mortality, disability and the need for long-term institutional care and are exacerbated by prolonged recovery times (6).

There are no licensed drug treatments for fracture healing. The current mainstay of treatment is surgical fixation where indicated and a programme of rehabilitation. There are a number of drug treatments licensed for the prevention of osteoporotic fracture. Bisphosphonates and denosumab are anti-resorptive agents that prevent the breakdown of bone. Teriparatide (TPTD), a parathyroid hormone analogue, is the only anabolic treatment on the market in Europe for the prevention of osteoporotic fracture; it increases bone mass and reduces bone loss leading to an increase in bone formation (7-12). Teriparatide, one of two PTH analogues commercially available, is the 1-34 N-terminal amino acid sequence of the endogenous human parathyroid hormone. The second analogue is the full 1-84 amino acid parathyroid hormone, which is indicated as an adjunctive

treatment for chronic hypoparathyroidism. Another PTHrP analogue is available in the US called abaloparatide.

Investigations are ongoing to understand the potential for PTH analogues to expedite bone healing. Animal studies have supported this hypothesis (12-16), but the evidence in humans is less clear. Some studies show that PTH analogue administration has a beneficial effect on fracture healing (17, 18) while others show no effect on fracture healing rates or reduction in pain levels (19, 20). The six literature reviews published to date have focused on osteoporotic patients. The older reviews, that focus on case reports and series favour PTH treatment (21, 22), and conclude that whilst the evidence for TPTD is anecdotal it is sufficient to justify future prospective trials. Larger, prospective randomised trials have since been carried out. Reviews considering these trials concluded that the benefit of PTH analogue intervention in osteoporotic fracture healing was uncertain, however, the absence of adverse events justified further research (23, 24). Lou *et al* reported PTH analogues to be effective in accelerating fracture healing and improving functional outcomes in osteoporotic women only (25). Hong *et al* concluded the evidence supporting fracture healing indications was reasonably credible but more randomised controlled trials (RCTs) were required to verify differential effects in different populations (26).

The purpose of this meta-analysis was to determine the efficacy of PTH analogues on fracture healing, updating and broadening previously published reviews (21-26). Unlike the earlier reviews, this meta-analysis considers all fracture types and all controls (placebo, standard care and bisphosphonates) in addition to two recently published studies (19, 27). Consequently, more trials and a larger cohort of patients is considered than in previous reviews.

Methods

This meta-analysis protocol was reported according to the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA®) guidelines (28). This study was not a human or animal

experiment so no ethical approval was required. This systematic review is registered on Prospero (registration no. CRD42019131967). The PICO (Population, Intervention, Comparison and Outcomes) model was used to define the inclusion criteria. The Risk of Bias 2 Tool was used to evaluate the risk of bias (29) and RevMan 5.3.5 (Nordic Cochrane Centre 2019) software was used to perform meta analyses.

Literature Search Strategy

An electronic database search for relevant articles was conducted in August 2019 using the following databases: MEDLINE, EMBASE and The Cochrane Library. No date restrictions were applied. The search was performed using a combination of key words and MESH terms. The detailed search strategy is provided in online resource 1. In general, the Cochrane search strategy was used to identify randomised clinical trials (RCTs) with the addition of: (1) Parathyroid Hormone; (2) Teriparatide; (3) Forsteo; (4) Forteo; (5) NatPar; (6) PREOS; (7) Preotact; (8) PTH; (9) Fracture.

Reference lists from trials, conference abstracts and reviews were examined to identify additional eligible trials. For completeness, www.clinicaltrials.gov was searched for RCTs that were registered as complete but not yet published; no relevant trials were identified this route.

Trial Selection

A flow diagram illustrating the trial selection is shown in figure 1.

Results from the searches were combined and duplicates were removed. Two investigators (KL and MG) evaluated the title and abstract from each reference identified by the search. For inclusion, all trials were required to be prospective, randomised clinical trials in adult patients aged > 18 years old presenting with a fracture. Any type of fracture (delayed union, non-union or stress fracture) at any site (long bone, short bone, flat bone or irregular bone) were accepted. Trials where PTH analogues were used as an adjunctive therapy to operative or conservative treatments were included. Treatments included TPTD, PTH 1-84, abaloparatide or other PTH analogues with any route of

administration, dose or frequency. The outcomes included functional recovery, fracture union, pain, and adverse events.

All texts that were clearly irrelevant were excluded following abstract review, and full texts of the remaining articles were retrieved. Full texts that did not meet the inclusion criteria were excluded following further scrutiny. The reference lists of excluded articles were reviewed to identify any articles relevant to the subject area that met the inclusion criteria.

Any disagreement between authors regarding trial selection was resolved by means of consensus, involving a third investigator (WDF), according to *a priori* agreed criteria. Exclusion criteria were non-human studies, non-English language, and data sets with insufficient data to complete a review i.e. abstracts, review articles, editorials and letters.

Data Extraction

The results from each article were extracted using a standardised data collection form based on the pre-defined trial inclusion criteria. The main categories extracted from the articles were: author, year, title, trial overview, patient characteristics, type of fracture, duration of treatment, conclusions on primary outcomes and secondary outcomes where these related to fracture healing, pain, functional outcomes, adverse event or treatment discontinuations.

Quality Assessment of Included Articles

The quality of trial methods was independently rated by two investigators (KL and MG), who were not blinded to the article author, journal or institution, in accordance with Baker *et al* (30). A Risk of bias evaluation was completed (fig 2).

Data Analysis

The outcomes of the trials (bone healing rate, time to bone healing, functional recovery, pain and adverse events) were analysed. Forest plots were produced from meta-analyses performed by Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. Due to the variation within trial designs and

heterogeneity of results, not all data were suitable for meta-analysis. In these instances, analyses described in the eligible trials were extracted and reported in a systematic format as a narrative synthesis.

Odds Ratios (OR) were calculated for outcomes with dichotomous data including fracture healing rate (healing evaluated at set intervals), occurrence of adverse events and treatment discontinuations. The Mean Difference (MD) method was adopted for outcomes with continuous data including time to fracture healing, differences in pain (measured by visual analogue scale (VAS)) and functional outcomes (questionnaire scores or time as in the case of the 'timed up and go test'). Risk of bias was analysed using the *RoB 2 Tool* (29). This assessment reviews the risk of bias over 5 domains, bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported result.

Disease severity measurements such as bone mineral density were excluded from analysis.

Results

Literature Search Strategies

The literature search identified 5781 publications; 626 were excluded due to duplication and 5144 did not meet the inclusion criteria. Following full-text scrutiny, 11 trials on efficacy of PTH analogues in fracture healing were included in the analysis.

Fig 1 Flow diagram of the search strategy, Medline, EMBASE, Cochrane and other sources such as reference lists and clinical trials registers were reviewed. A total of 5781 articles were identified. After screening, 626 studies were excluded due to duplication and 5089 were excluded following abstract review. Sixty-six full text articles were scrutinised and 11 were selected for inclusion.

Patient Characteristics

The 11 articles selected for the systematic review included 1,452 patients, 91.8% (n=1,333) of whom were women. The mean age of patients was 72 years old. The anomaly was Almirol *et al.* who evaluated PTH analogues for lower extremity stress fractures in young female adults (n=14) with a mean age of 32 (± 5.8) and 31 (± 3.4) in treatment and control groups, respectively. Fracture sites in

the 11 articles were vertebrae (n=789, 3 trials) (27, 31, 32), femur (atypical) (n=13, 1 trial) (19), hip (n=343, 4 trials) (33-36), tibia (n=13, 1 trial) (37), humerus (n=40, 1 trial) (38) and radius (n=102, 1 trial) (18). Full details of patient characteristics are listed in table 1.

Trial Design

In all trials, patients were randomly assigned to treatment with a PTH analogue, standard care or a comparator drug. Randomisation approaches included sealed envelopes (34, 38), computer generated sequences (18, 33) and table based randomisation (35).

Two parathyroid hormone analogue regimes were used 20µg TPTD/day (18, 19, 31-38) and 56.5µg TPTD/week (27). Aspenberg *et al.* also included a 40µg TPTD/day dose but this was not used in analysis as it is not licensed in any territory (18). Comparator groups included: placebo, standard care (with the intention to initiate TPTD at 6-months), risedronate (17.5mg or 35mg /week, 75mg / month) or alendronic acid (70mg or 35mg /week). The full trial schedules are shown in table 1. The duration of PTH treatment varied from 1 to 24 months. Calcium and vitamin D supplements were administered in 9 of the 11 trials. Characteristics of trials selected for inclusion in this review are listed in Table 1.

	Trial	Number of Patients (women)	Mean Age Years ± SD	Treatment	Calcium and Vitamin D Supplementation	Treatment Duration	Follow-Up Durations Including Treatment	Fracture Type	Primary Outcome
1	Shigenobu *et al*. 2019 (27)	43 (38)	(n=24): 75.6 (n=19): 80.2 Overall: 78.1 (Range 61-93)	Teriparatide 56.6ug/wk Alendronic Acid 35mg/wk or Risedronate 17.5mg/wk or 75mg/mo	No	12mo	12mo	Vertebral Compression Fracture	Not stated
2	Greenspan *et al*. 2018 (19)	13 (13)	(n=7): 78.0 ± 3.3 (n=6): 69.8 ± 3.3	Teriparatide 20ug/d at fracture Teriparatide 20ug/d 6mo post fracture	Yes	6mo	12mo	Atypical femur	Radiological healing
3	Malouf-Sierra *et al.* 2016 (33)	171 (132)	(n=86): 77.2 ± 8.0 (n=85): 76.4 ± 7.5 Overall: 76.8 ± 7.7	Teriparatide 20ug/d Risedronate 35mg/wk	Yes	26wk blinded + 52wk unblinded	78wk	Post fixation low trauma pertrochanteric	Change from baseline in lumbar spine BMD at 78wk
4	Almirol *et al.* 2016 (37)	14 (14)	(n=6): 32 ± 5.8 (n=8): 31 ± 3.4	Teriparatide 20ug/d Placebo	Yes	8wk	12wk	Lower extremity stress fracture	Anabolic window in biomarkers for bone formation and resorption (P1NP and Yes OC Vs CTX and NTX)
5	Chesser *et al.* 2016 (34)	29 (29)	(n=15): 80.6 ± 8.8 (n=14): 78.6 ± 9.3	Teriparatide 20ug/d Standard Care	Yes	6wk	6mo	Trochanteric hip fracture	Pilot Study (Feasibility and acceptability of proposed methodology
6	Zhao *et al*. 2016 (31)	49 (49)	(n=24): 68.9 ± 5.37 (n=25): 68.7 ± 5.74	Teriparatide 20ug/d Alendronic Acid 70mg/wk	Yes	16mo	12mo	Osteoporotic vertebral compression fracture	Not stated
7	Bhandari *et al*. 2016 (35)	159 (117)	(n=78): 70 (Range 50-94) (n=81): 70 (Range 50-90)	Teriparatide 20ug/d Placebo	Yes	6mo	24mo	Femoral neck fracture followed be internal fixation surgery	Requirement for surgical revision at 12mo
8	Johansson *et al*. 2016 (38)	40 (40)	(n=19)^: 67 (Range 54-82) (n=20): 69 (Range 54-94)	Teriparatide 20ug/d Standard Care	No	4wk	3mo	Proximal humorous	Radiological healing and callus formation at 7wk
9	Kanakaris *et al.* 2015 (36)	30 (24)	(n=9): 75 ± 8.98 (n=11): 75 ± 9.18 (n=10): 75 ± 8.89	Teriparatide 20ug/d Alendronic Acid 70mg/wk Standard Care	Yes	6mo	6mo	Hip fractures	Not stated
10	Hadji *et al.* 2012 (32)	710 (710)	(n=360): 70.5 ± 8.8 (n=350): 71.6 ± 8.1	Teriparatide 20ug/d Risedronate 35mg/wk	Yes	18mo	18mo	Osteoporotic vertebrae	Greater than 30% reduction in worst back pain
11	Aspenberg *et al*. 2010 (18)	102 (102)	(n=34): 59.2 ± 9.6 (n=34): 62.8 ± 7.3 (n=34): 61.7 ± 8.6	Teriparatide 20ug/d Teriparatide 40ug/d Placebo	Yes	8wk	53wk	Distal Radius	Radiographic healing at 8wk

Table 1 Characteristics of randomised controlled trials included for review including numbers of and mean age of participants. The experimental treatments included teriparatide 20ug/d and 56.6ug/wk. Controls included standard care, placebo, or a bisphosphonate (alendronic acid or risedronate). Calcium, vitamin D supplementation, treatment duration, follow-up duration, fracture type and primary outcomes are also included.
d: day(s); wk: weeks; mo: months; PINP: N-terminal propeptide of type I collagen; OC: osteocalcin; CTX: Collagen-type I cross-linked C-telopeptide; NTX: collagen-type I cross-linked N-telopeptide. ^1 participant lost to follow -up, data not included in description of baseline characteristics.

Quality of Trials

The quality of trials was assessed by the risk of bias using the Sterne *et al* risk of bias tool (29). Overall 'low risk' and 'some concerns' were identified in seven trials. A high risk of bias was identified in four trials. The heterogeneous nature of the patient characteristics, treatments, comparators and outcomes of the trials was reflected in their risk of bias.

Fig. 2 Assessment of the risk of bias for trials selected for the Systematic Review. Adapted from the Cochrane risk of Bias Tool 2. Bias is assessed based on five domains — the randomisation process, blinding (deviations from the intended), missing data, outcome measurement and selective or multiple outcome reporting. The results of the five domains are reported in the consolidated overall risk of bias.

Reporting of Outcomes

The primary outcomes were clearly identified in nine of the 11 trials. Six trials reported a single primary outcome related to fracture healing outcomes, including radiological healing (18, 19, 38), differences in pain (32), the requirement for surgical revision (35) or changes in bone biomarkers (37). Identification of, and distinction between secondary, exploratory or post-hoc analyses was poor in nine trials. Three trials (19, 33, 37) clearly stated secondary outcomes and one identified outcomes as 'exploratory' (34). An overview of the outcomes and findings of each trial is described in table 2.

	Trial	Primary Outcome	Results	Additional Healing and Functional Outcomes Reported	Results
1	Shigenobu *et al*. 2019 (27)	Not stated	N/A	Radiological Healing (1,2,3, 6mo) Mean time to fracture healing Rowland-Morris Disability Questionnaire (RDQ) score EQ-5D score (2, 4, 8, 12,24wk) Change in pain (by VAS) (2,4,8,12, 24wk) Anabolic window in biomarkers for bone formation and resorption (P1NP Vs ALP and TRACP-5b)	TPTD group improved healing at 12wk (p<0.05), no difference at 24wk TPTD group had earlier fracture healing (p<0.05) TPTD group RDQ score improved at all timepoints (p<0.05) No significant difference between arms No significant difference between arms P1NP significantly higher in the TPTD arm at 12 and 24wk
2	Greenspan *et al.* 2018 (19)	Radiological healing	Cortical continuity on 2 of 4 cortexes at 6mo: immediate treatment = 3.1±0.1; delayed = 2.8±0.3 (p=0.1032)	SF-36 quality of life (6, 12mo) Pain assessment (6, 12mo)	No significant difference between arms
3	Malouf-Sierra *et al.* 2016 (33)	Change from baseline in lumbar spine BMD at 78wk	TPTD superior to RIS in the change of lumbar spine BMD at wk78 (mean difference 0.040 g/cm^2; 95%CI 0.025 to 0.55 g/cm^2; p<0.0001)	Timed Up and GoTUG test (6, 12, 18, 26wk Radiological healing (6, 12, 26wk) Mechanical failure (26wk) Ability to walk (6, 12, 18, 26wk) SF-36 Physical Function Component (6, 12, 18, 26wk)	Shorter TUG in TPTD vs RIS at all timepoints (p=0.021) No significant difference in the rate of radiographic healing (p=0.547) No significant difference in the rate of mechanical failure (p=0.577) No significant difference in the ability to walk or use of aids (p=0.8) No significant difference in SF-36 scores at any timepoint (p=0.205, 0.737, 0.435, 0.267 respectively)
4	Almirol *et al.* 2016 (37)	Anabolic window in biomarkers for bone formation and resorption (P1NP and OC vs CTX and NTX)	Significantly larger anabolic window in the teriparatide group (145.82±123.0) compared to placebo (5.99±48.4) (p=0.05)	MRI grade at baseline and wk 8	No difference between groups (p>0.13)
5	Chesser *et al.* 2016 (34)	Sample size calculation for full trial.	Detection of a one-point change is the SPPB at 12wk assuming 80% completion rate would require 405 patients.	EQ-5D score (12wk) SPPB (12mk)	Significance not calculated Significance not calculated
6	Zhao *et al.* 2016 (31)	Not stated	N/A	mJOA-BPEQ (6,12mo) Change in pain (by VAS) (6, 12mo) Biochemical makers of bone turnover (P1NP and TRACP-5b at 6, 12 mo) Kyphotic angle and anterior border heights of fractured vertebrae	TPTD group improved mJOA-BPEQ scores at 6 & 12 vs ALEN (p<0.05) TPTD group improved pain scores at 6 & 12 vs ALEN (p<0.05) Increased P1NP and CTX in TPTD group (p<0.05). No change in ALEN group Significantly larger anterior border height in the TPTD group vs ALEN (p<0.05). Significantly smaller kyphotic angle in the TPTD group vs ALEN (p<0.05)
7	Bhandari *et al*. 2016 (35)	Requirement for surgical revision at 12mo	There was no significant difference in the requirement for revision surgery at any time point	Radiographic assessment of fracture healing (10wk, 6,12mo) Pain control (12mo) Gait speed (12mo) Composite measure of fracture healing	No difference between groups at any timepoint No difference between groups Improved gate speed in the TPTD arm No difference between groups at 12mo
8	Johansson *et al.* 2016 (38)	Radiographic healing and callus formation at 7wk	No positive effect	Reduction in pain (by VAS) (8wk) Change in DASH scores	No difference between groups
9	Kanakaris *et al*. 2015 (36)	Not stated	N/A	Johansson Hip Rating Questionnaire (6wk, 3, 6mo) Non unions (6mo)	No meaningful statistical analysis due to small sample size
10	Hadji *et al*. 2012 (32)	Greater than 30% reduction in worst back pain	Greater than 30% reduction in worst back pain not seen at 6, 12 or 18 mo	Patients with worsening or worst or average back pain from 6 to 12, 18mo New vertebral fractures	More reports of worsening or 'worst' and 'average' back pain in the RIS arm vs TPTD arm (both p=0.04) Fewer new vertebral fractures in the TPTD group (p=0.01). Subjects in the TPTD group had less height loss at 18mo (p=<0.05)
11	Aspenberg *et al.* 2010 (18)	Shorten time to cortical bridging	The time to healing was shorted in the teriparatide 20ug group compared to placebo (9.1 vs 7.2 wks) (p=<0.001)	Patient-Rated Wrist Evaluation Score (total) Grip strength as a percentage of the uninjured hand	No difference in TPTD score Vs Placebo

Table 2 An overview of results of randomised controlled trials included in the review. Results are presented for primary outcomes and corresponding results, secondary and post-hoc outcomes, and corresponding results for each of the trials.

d: day(s); wk: weeks; mo: months; RDQ: Rowland-Morris Disability Questionnaire; EQ-5D: EuroQol-5D, VAS: Visual Acuity Score; PINP: N-terminal propeptide of type I collagen; ALP: Alkaline Phosphatase; TRACP-5b: Tartrate-resistant acid phosphatase 5b; TPTD: Teriparatide; SF-36: Short Form 36; JOA-BPEQ: Japanese Orthopedic Association Back Pain Evaluation Questionnaire; BMD: Bone mineral density; RIS: Risedronate; TUG: Timed Up and Go; OC: osteocalcin; CTX: Collagen-type I cross-linked C-telopeptide; NTX: collagen-type I cross-linked N-telopeptide; ALEN: Alendronate; SF-12 PCS: Short Form-12 Physical Component Summary; SF-12 MCS: Short Form-12 Mental Health Component Summary; DASH: Disabilities of the arm, shoulder and hand;

Radiological Assessment of Fracture Healing

Radiological assessment of fracture healing was used in nine trials and was the primary outcome in three trials (18, 19, 38). Four trials used plain film radiographs (19, 33, 35, 38) and one trial used magnetic resonance imaging (MRI) (37). Two trials used a combination of X-Ray and computed tomography (CT) (18, 36). Kanakaris *et al* reported radiological non-union at 6 months as an outcome but did not describe the radiological method used (36).

The criteria used to grade the scans and the detail to which it was described differed greatly between the trials. Radiological healing was categorised as two outcomes — fracture healing rate (healing at set time points) and fracture healing time (days). Shigenobu *et al* used a non-standard method and did not provide adequate description of this method (27); consequently, this trial was excluded from the analysis of radiological fracture healing.

The fracture healing rate between the PTH analogue and comparator or control groups was examined in four trials (334 patients) at the first reported timepoint. The forest plot of the Odds Ratios (95% CI) across trials is shown in Figure 3. There was no difference in the fracture healing rate when PTH analogues were compared with comparator and control groups (OR 0.96, 95% CI 0.57 to 1.61, p <0.87).

Fig 3 Forest plot evaluating the change in fracture healing rate between Experimental (PTH analogues) and Control groups. Data are Odds Ratio (95% CI, Confidence Intervals). M-H: Mantel-Haenszel test. There was no difference in the fracture healing rate when PTH analogues were compared with comparator and control groups (OR 0.96, 95% CI 0.57 to 1.61, p <0.87). Data are from the first reported timepoint: Almirol *et al* at 8 weeks (37); Bhandari *et al* at 10 weeks (35); Malouf-Sierra *et al* at 12 weeks (33); Kanakaris *et al* at 6 months (36).

The fracture healing time between the PTH analogue and comparator / control groups was examined only by Greenspan *et al* and, therefore, not suitable for analysis by forest plot (19). Using standard care as a comparator, the fracture healing time was confirmed by radiograph and defined as cortical continuity in 2 of 4 cortexes. Fracture healing time was shorter in the TPTD treated group (13.6 vs 12.3 weeks p=<0.001).

Pain

Pain was reported as an outcome in nine of the 11 trials, eight of which used an 11-point visual analogue scale (VAS) (0 = no pain, 10 = greatest pain imaginable) (18, 27, 31-35, 38). Two trials (n=78) published sufficient data for meta-analysis (31, 34). The results are shown in figure 4. PTH analogue-treated groups reported less pain compared with comparator / controls in the trials that were suitable for meta-analysis (MD -4.55, 95% CI -7.47 to -1.63, p= 0.002). The Short Form 36 (SF-36) questionnaire (19) was also used for pain reporting.

Fig 4 Forest plot evaluating the differences in pain between patients treated with PTH analogues and comparators / controls following fracture. Data are Mean Difference (95% CI, Confidence Intervals). PTH analogue-treated groups reported less pain compared with comparator / controls in the trials that were suitable for meta-analysis (MD -4.55, 95% CI -7.47 to -1.63, p= 0.002).

Seven trials reported insufficient data on pain for inclusion in the meta-analysis. Two trials reported no significant differences in pain but did not publish the data (19, 27). Three trials reported no significant differences in pain between treatment and control, but these data were not included in the forest plot because they were published as a percentage change rather than as raw data (18, 32, 35). Another trial reported a significant reduction in pain during the 'timed up and go' test, but the results were reported as a time change (33). One trial did not report standard deviations (38) so was excluded from the meta-analysis.

Functional Outcomes

Nine trials reported functional outcomes (18, 27, 31-36, 38), and three of these used multiple assessment methods (27, 32, 34). In total, 13 different methods of assessment were used, including a mixture of physical tests and questionnaires.

Validated functional multi-activity assessments were used in nine of these trials, and speed gait was used in one (Bhandari *et al* (35)). Four trials used self-reported functional scores and published data detailed enough to be included for meta-analysis; the results are shown in Figure 5. These analyses show a statistically significant improvement in functional outcome for participants treated with PTH analogues (MD -1.59, 95% CI -1.97 to -1.21, p= <0.00001). Of the remaining trials, two reported no significant difference in functional outcomes but did not publish the data (32, 38), Bhandari *et al*

and Shigenobu *et al* did find a significant improvement in functional outcomes in the PTH analogue group vs control (27, 35) and Aspenberg *et al* reported an improvement at the week 13 timepoint only (18) but none of these trials published sufficient data for a meta-analysis.

Fig 5 Forest plot evaluating the differences in functional outcomes between patients treated with PTH analogues and controls during fracture healing. Controls included standard care (34, 36) and bisphosphonates (31, 33). Data are Mean Difference (95% CI, Confidence Intervals). PTH analogues improved functional outcomes (MD -1.59, 95% CI -1.97 to -1.21, p= <0.00001).

Biochemical Markers of Bone Turnover

Three trials reported biochemical markers of bone formation and resorption (27, 31, 37). All trials demonstrated significant increases in serum N-terminal propeptide of type I procollagen (P1NP) following PTH analogue treatment vs placebo (37) and vs bisphosphonates (27, 31), and no significant change in CTX, resulting in a greater anabolic window. Insufficient data were included for meta-analysis.

Adverse Events

Eight trials reported adverse events, and five (1182 patients) provided enough data for a meta-analysis (figure 6). There was no statistical difference between PTH analogue treated groups and comparators / controls (OR 0.74, 95% CI 0.45 to 1.02, p= 0.07).

Fig 6 Forest plot evaluating the difference in adverse events between patients treated with PTH analogues and controls for fracture healing. Controls included standard care (34), placebo (18, 35) and bisphosphonates (32, 33). Data are Odds Ratio (95% CI, Confidence Intervals). M-H: Mantel-Haenszel test. There was no difference between PTH analogue treated groups and comparators / controls (OR 0.74, 95% CI 0.45 to 1.02, p= 0.07).

Four trials (1023 patients) reported treatment discontinuation of PTH analogues as an outcome measure. The results are described in figure 7. There was no statistical difference between PTH analogue treated groups and comparators / controls (OR 1.13, 95% CI 0.72 to 1.77, p= 0.58).

Two trials did not report serious adverse events (SAE's), but did report no significant difference in mild or minor adverse events (37, 38).

Fig 7 Forest plot evaluating the difference in treatment discontinuations between patients receiving PTH analogues and comparator / controls for fracture healing. Data are Odds Ratio (95% CI, Confidence Intervals). M-H: Mantel-Haenszel test. There was no statistical difference between PTH analogue treated groups and comparators / controls (OR 1.13, 95% CI 0.72 to 1.77, p= 0.58).

Choice of Comparator group

Sub-analysis was performed on the comparator groups as six trials used placebo (18, 35, 37) or standard care (19, 34, 38) and four used a bisphosphonate (27, 31-33). One trial had both a standard care arm and a bisphosphonate arm so was included in both analyses (36).

Sub-Analysis of Fracture Healing Rate, Pain, Adverse Events and Treatment Discontinuations Using Placebo or Standard Care as a Comparator

Consistent with the overall evaluations, there was no difference in the fracture healing rate, (OR 0.45, 95% CI 0.27 to 0.73, p=0.001) or adverse events (OR 0.53, 95% CI 0.21, 1.31, p=0.17) between the PTH analogue and placebo or standard care. Unlike the overall evaluations, functional outcomes were not improved with PTH analogue treatment in this sub-analysis (MD 0.38, 95% CI -1.97, 2.72, p= 0.75). These results are shown in figure 8.

Fig 8 Forest plots evaluating the difference between PTH analogue treatment and placebo or standard care. (a) Forest plot evaluating the difference in healing rate at first reported time point. Data are Odds Ratio (95% CI, Confidence Intervals). M-H: Mantel-Haenszel test. There was no difference between the healing rate between PTH analogue treated group and placebo or standard care (OR 0.97, 95% CI 0.53 to 1.75, p=0.91). (b) Forest plot evaluating the difference in functional outcomes. Data are Mean Difference (95% CI, Confidence Intervals). There was no difference in functional outcomes between the PTH analogue treated group and placebo or standard care. (MD 0.38, 95% CI -1.97, 2.72, p=0.75). (c) Forest plot evaluating the difference in adverse events. Data are Odds Ratio (95% CI, Confidence Intervals). M-H: Mantel-Haenszel test. There was no difference in adverse events between the groups (OR 0.53, 95% CI 0.21, 1.31, p=0.17).

Sub-Analysis of Fracture Healing Rate, Pain, Adverse Events and Treatment Discontinuations Using a Bisphosphonate as a Comparator

Result of sub-analysis of trials comparing PTH analogues with bisphosphonates were consistent with the overall evaluations. Functional outcomes were improved (MD -0.87, 95% CI -1.27, -0.46, p=<00001) and no difference was identified in fracture healing rate (OR 0.93, 95% CI 0.32 to 2.72, p=0.90), the rate of adverse events (OR 0.78, 95% CI 0.56, 1.09, p=0.15) or treatment discontinuations (OR 1.17, 95% CI 0.73, 1.89, p=0.52). These results are shown in figure 9.

Fig 9 Forest plots evaluating the difference between PTH analogue treatment and bisphosphonate treatment.

(a)Forest plot evaluating the difference in healing rate at first reported time point. Data are Odds Ratio (95% CI, Confidence Intervals). M-H: Mantel-Haenszel test. There was no difference in healing rate between groups (OR 0.93, 95% CI 0.32 to 2.72, p=0.90).
(b) Forest plot evaluating the difference in functional outcomes. Data are Mean Difference (95% CI, Confidence Intervals). Functional outcomes were improved in the PTH treated group (MD -0.87, 95% CI -1.27, -0.46, p=<00001).
(c) Forest plot evaluating the difference in adverse events. Data are Odds Ratio (95% CI, Confidence Intervals). M-H: Mantel-Haenszel test. There was no difference in adverse events between the groups (OR 0.78, 95% CI 0.56, 1.09, p=0.15).
(d) Forest plot evaluating the difference between treatment discontinuations. Data are Odds Ratio (95% CI, Confidence Intervals). M-H: Mantel-Haenszel test. There was no difference in treatment discontinuations between the groups (OR 1.17, 95% CI 0.73, 1.89, p=0.52).

Discussion

This systematic review and meta-analysis reviewed the effect of PTH analogue treatment in fracture healing. The currently available PTH analogues — PTH (1-34) and PTH (1-84) — have been licensed in the UK since June 2003 and April 2017 for the treatment of hypoparathyroidism and the prevention of fractures in osteoporotic women. PTH (1-84) was licensed for osteoporosis treatment prior to 2017 by Nycomed and its sister company NPS Pharmaceuticals, but this formulation was withdrawn due to 'production difficulties'.

Several case reports and case series have suggested that PTH analogues are also efficacious in fracture healing (39-49) and a number of trials have begun to explore this indication, predominantly with TPTD in osteoporotic fractures (23, 25). Previously published literature reviews of these treatments have reached conflicting conclusions; the efficacy of TPTD is reported as uncertain (11 trials, 1602 patients (23)), effective in reducing fracture healing time (5 trials (inc. 1 using PTH (1-84), 251 patients (25)), or not effective in reducing time to union, union rate, or reduction in pain (5 trials, 380 patients (24)). The most recently published review, which included PTH(1-84) (26), concluded that the evidence to support the use of PTH analogues to improve fracture healing was reasonably well established. Previous reviews (26, 50) report that PTH analogues are not harmful to fracture healing and there is no evidence that they have a higher incidence of adverse events compared with control arms. This updated review considers eleven trials; the intervention arms

were PTH analogues (TPTD 20 µg / day or TPTD 56.5 µg / week) given post fracture trialled against a variety of comparators.

In this review we found that PTH analogue treatment improves the functional outcomes of patients, but there was no evidence of improved fracture healing rate compared with comparators although one trial did show reduced time to fracture healing (19). A reduction in pain is reported but while statistically significant, the clinical relevance is questionable (51). There was no difference in SAEs or treatment discontinuations.

Treatment durations varied from one (38) to 18 months (32), however, fracture healing endpoints were determined as 12 months or earlier. The optimum treatment duration for fracture healing is yet to be defined, but the three trials treating for 8 weeks or less did not show any difference in radiological healing, supporting a longer duration of treatment with PTH analogues.

The sensitivity of the radiological methods used in the trials may have affected outcomes. Most used plain-film x-ray, that might not have been sensitive enough to differentiate different phases of healing. One trial reported significant improvements in radiological healing using CT (18). The reproducibility of serial CT scans in the clinical setting would be difficult to justify given the radiation dose required to maintain image quality, despite dynamic protocols that keep the radiation dose to a minimum. Typically, CT scans are only used to assess cortical bridges in traumatic fractures that appear to be healing on plain film radiographs. MRI, the primary tool for diagnosing and following up insufficiency fractures, could be a safer alternative but this was only used in one trial (37). Metal artefact reduction sequences that allow assessment of marrow signal next to prothesis make this suitable for patients undergoing internal fixation, which is a large proportion of the patient population considered in this review.

The value of reporting time to radiological healing as an outcome is questioned as it is an estimate taken from radiological assessment at set intervals and assumes a normal distribution of healing. Earlier reviews have estimated the standard deviation of these values and incorporated them into meta-analysis. We did not analyse time to radiological healing in this review as the multiple

estimations (particularly where the p value is reported as <0.05 rather than the precise value) required to calculate these limits their reliability. Greenspan *et al* (19), Johansson *et al* (38) and Aspenberg *et al* (18) described radiological outcomes as the primary outcome of the trial, and they all used plain film x-ray. The intervals of analysis varied greatly between all of the trials and there was no common analysis point between the trials using radiological outcomes as a primary endpoint. The assessment criteria were different for all trials; Almirol *et al* (37) used the validated Freidricson scale (52). Other assessment criteria included healing graded on continuity of the cortices, but definitions were inconsistent with trials reporting this as either 'normal' or 'better' (38), or as 'cortical continuity in 2 of 4 cortices' (19) . Zhao *et al* investigated vertebral fractures and reported kyphotic angle changes as part of this assessment criteria, but this is not considered as a metric for fracture healing and was excluded from this analysis (31).

Rarely was sufficient information reported to enable repetition of the analysis. One such example is Bhandari *et al* (35); these authors set a statistical significance level at the one-side 10% level (a two-sided 20% level) rather than the conventional two-side 5% level, i.e. allowing p-values four times the size of convention to be declared sufficient evidence of a beneficial effect. Consistent with the 10% one-sided significance level, would be the use of an 80% confidence interval but this is reported at 90%. The methods section does not discuss the rationale for the non-standard statistical significance levels (35).

A sub-analysis was performed comparing PTH analogues with either no intervention (placebo or standard care) and treatment with bisphosphonates, but the reduced number of trials and smaller sample of patients reduced statistical power. These results suggested no difference in fracture healing rate, adverse events or treatment discontinuations between any of the groups, but PTH analogues did improve functional outcomes compared with bisphosphonates. We did not undertake sub-analysis by fracture type due to the heterogeneity in the pattern of fractures and the methods of evaluation used in trials.

The majority of the trials included in this review included elderly patients. Only one trial examined a younger population (n=13) (37). There is evidence to suggest that age is a complicating factor in fracture healing and can lead to delayed union (53, 54). This is an area that is still being explored in human subjects, but animal models (mice and rat) show age-related changes that compromise bone regeneration (53). This limits the relevance of the findings of these trials in a younger population.
The variability in trial design compounds the complexities of comparison. The lack of a standard comparator arm is one such factor. The National Institute of Clinical Excellence (NICE)[1] does not recommend any standard treatment for fractures, yet there are placebo, standard care, oral bisphosphonate and TPTD weekly arms. Fracture locations, primary outcomes and time points at which these are measured vary considerably between the trials further limiting any comparisons.
The trials in this review mainly involve osteoporotic women, but there is no evidence that the results should not be relevant to men since no gender differences in fracture healing has been shown between the sexes (54).
This review selected all fracture types to maximise the inclusion of all RCTs of PTH analogues and fracture healing, but this approach increased the heterogeneity of the results. The quality of some the selected trials was limited, and often contained insufficient data to enable meta-analyses; authors were contacted for further detail but no responses were received.

Conclusion

Meta-analysis of published data supports the use of PTH analogues to improve functional outcomes across a range of fracture types with no additional incidence of adverse events compared with bisphosphonates and standard care. The hypothesis that PTH improves fracture healing rate or reduction of pain was not proven, but the low-quality and heterogeneity of trial designs justify further investigation as there is no evidence that PTH treatment caused harm or impeded fracture healing.

[1] https://www.nice.org.uk/

Only one pilot study has been performed in a young patient population and a high quality well powered randomised controlled trial is required to confirm the benefit of PTH analogues in this patient cohort. In addition, further work is required to establish the optimum duration of treatment, which probably exceeds 8 weeks.

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