



Effect of PTH treatment on bone healing in insufficiency fractures of the pelvis: a systematic review

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- The aging of our society is associated with an increasing number of insufficiency fractures of the pelvis and the current standard of care is pain control and early mobilization. The aim of this study was to explore whether parathyroid hormone (PTH) treatment can support bone healing in these patients.
- We conducted a systematic review searching the databases PubMed, Embase and Cochrane. Our primary outcome was fracture healing, secondary outcome measures comprised pain, mobility and patient-reported outcome measures (PROMs).
- Eight articles were included in the qualitative synthesis, of which two were included in a meta-analysis. However, only three studies were comparative including one randomized controlled trial. Fracture healing and reported pain were assessed after eight weeks, and were significantly improved in the group being treated with PTH ($p < 0.01$) in the meta-analysis. All articles described a positive effect for PTH on fracture healing and pain.
- Our systematic review indicates that there is a positive effect of PTH treatment on healing and pain in patients with insufficiency fracture in the pelvic ring, but further research is necessary.

Keywords: insufficiency fracture; pelvic fracture; PTH

Cite this article: *EFORT Open Rev* 2021;6:9-14.

DOI: 10.1302/2058-5241.6.200029

Introduction

One of the major current epidemiological trends is an increase of life expectancy and thereby a growing

population of elderly patients.¹ As a consequence, the number of low-energy fractures of the pelvic ring is rising. Reading the literature, these fractures have several synonyms and can be described as insufficiency fractures, fragility fractures, osteoporotic fractures or stress fractures. What they all have in common are fractures caused by low-energy trauma or no known trauma.

The fracture is often located in the sacrum and can be either bilateral or unilateral. Bilateral fractures with an H-configuration in the sacrum are often seen in patients with no trauma and osteoporosis, whereas unilateral sacrum fractures more often are correlated with low-energy trauma.² However, the treatment is still of matter of debate, because the fracture is painful and the group of patients often fragile, with comorbidities which significantly increase the risk of complications.³

Osteoporosis is known to be a risk factor or even one of the major underlying reasons for low-energy fractures and the pelvis is a rather underestimated location for manifestation. Parathyroid hormone (PTH) is an important hormone in regulating the level of calcium in the blood and in modelling and remodelling the bone. PTH (34-1) is a fragment of the PTH and is also known as Teriparatide. Teriparatide is approved as a medical treatment for osteoporosis and has been proven to reduce the risk of non-traumatic fractures.⁴ In contrast to the classical approach of osteoclast inhibition in treatment of osteoporosis, Teriparatide has an anabolic effect on bone. If Teriparatide is given intermittently instead of continuously it stimulates bone formation by activating osteoblasts. PTH (1-84) has shown the same effect and has been used as an osteoporotic treatment as well.⁵ This suggests a positive influence on bone healing, and teriparatide has been used off-label for treatment of fractures, especially nonunions.⁶

It is hypothesized that teriparatide has the potential to supplement today's primary treatment, pain control and physiotherapy, for insufficiency fractures. The current literature is dominated by case reports or small studies, including fractures of all types.⁷⁻¹⁰

The purpose of this systematic review was to investigate whether PTH treatment for insufficiency fractures of the pelvis is more efficient than the current standard of care, physiotherapy and pain medication without PTH. Our research question for the review was: Does treatment with PTH (I) increase bone healing in insufficiency fractures (P) of the pelvis compared to standard treatment (C) observed on X-ray, computed tomography (CT) scanning, magnetic resonance imaging (MRI), or patient-reported pain (O)?

Methods

The study protocol, prior to data extraction and data analysis, was registered in Prospero, International Prospective Register of Systematic Reviews, CRD42018109854 (<https://www.crd.york.ac.uk/prospero/>). The study was conducted according to PRISMA guidelines. Patients who had sustained an insufficiency fracture of the pelvis were included. Studies describing PTH treatment before the fracture occurred as well as fractures in other regions than the pelvis were excluded. However, medical treatments for osteoporosis in patients' medical history other than PTH was not a reason for exclusion. But treatment with PTH was not combined with other types of osteoporosis treatments. Pathological fractures other than those caused by osteoporosis were excluded as well. Our intervention was medical treatment with PTH in patients who had sustained an insufficiency fracture seen on X-ray, CT scan or MRI; comparators were patients receiving standard treatment and no PTH.

Our primary outcome was bone healing (evaluated on X-ray, MRI or CT scan). Our secondary outcomes were nonunions (no healing within six months of treatment on X-ray, MRI or CT scan), patient-reported outcome measures (PROMs), pain reported using a visual analogue scale (VAS) and mobilization.

We carried out a systematic search of the electronic databases PubMed, Embase and Cochrane for articles published between 1 January 2007 and 31 August 2018. Written language for the articles had to be English, German or a Scandinavian language and all articles were published. All data were found in the articles and no authors were contacted. The reference lists of the included studies were scanned, and no further studies were included.

Because of the small amount of data within this field we included randomized controlled trials, case-control studies and case reports. Systematic reviews were excluded because of risk of duplicated data.

The search strategy was: ((((((((((Teriparatide) OR "Teriparatide") OR "Forsteo") OR "Human Parathyroid Hormone") OR "hPTH") OR Forteo)) OR "Parathyroid hormone")) AND (((((((("stress fracture") OR "osteoporotic fracture") OR "insufficiency fracture")) OR "fracture") OR fracture)) AND (((((((("pelvis") OR "sacral") OR "sacrum") OR sacrum))) OR "pubic"))).

Articles from the three databases were extracted with the above-mentioned search strategy by PB. All articles were entered in Covidence (<https://www.covidence.org/home>). Duplicates were removed and two unblinded authors (PB and DH) individually screened all abstracts and sorted the articles according to eligibility criteria. Both authors read the included papers individually and excluded the articles which did not meet the inclusion criteria. After agreement between the two authors, data were extracted by both authors and compared to make sure the data extraction was correct.

For all studies and case reports age and gender were reported. If mean and standard deviation were not reported in the article, these were calculated based on the reported age in years. Fracture healing was reported as time to union. Pain was reported with the use of the visual analogue scale (VAS).

Risk of bias for each study was individually evaluated by the two authors. The risk of bias assessment tool RoB 2.0¹¹ was used for randomized trials. Risk of bias could be reported as low, some concern or high. The ROBINS-I risk of bias assessment tool¹² was used for non-randomized trials and risk could be classified as low, moderate, serious or critical. Additionally, the Cochrane Risk of Bias tool was applied for the studies included in the meta-analysis.

For meta-analysis, fracture healing was our primary outcome and pain was our secondary outcome. Forrest plots for both outcomes were prepared with Review Manager 5.3. A risk ratio was used for fracture healing, while difference in means was used for pain.

Results

After searching all three databases, 336 relevant studies were identified and retrieved for screening. After adjusting for duplicates, 299 studies remained, of which 280 had to be excluded. The remaining 19 studies all met the inclusion criteria, and the full text of each was examined in detail. Following the examination, an additional 11 studies were excluded (Fig. 1). Eight studies were included, one randomized controlled trial,⁸ two retrospective case-control studies,^{9,13} one case series^{10,13} and four case reports.⁽¹⁴⁻¹⁷⁾

In total, 132 patients could be included. The case reports and case series reported only on patients who were treated with teriparatide. In the randomized controlled study and

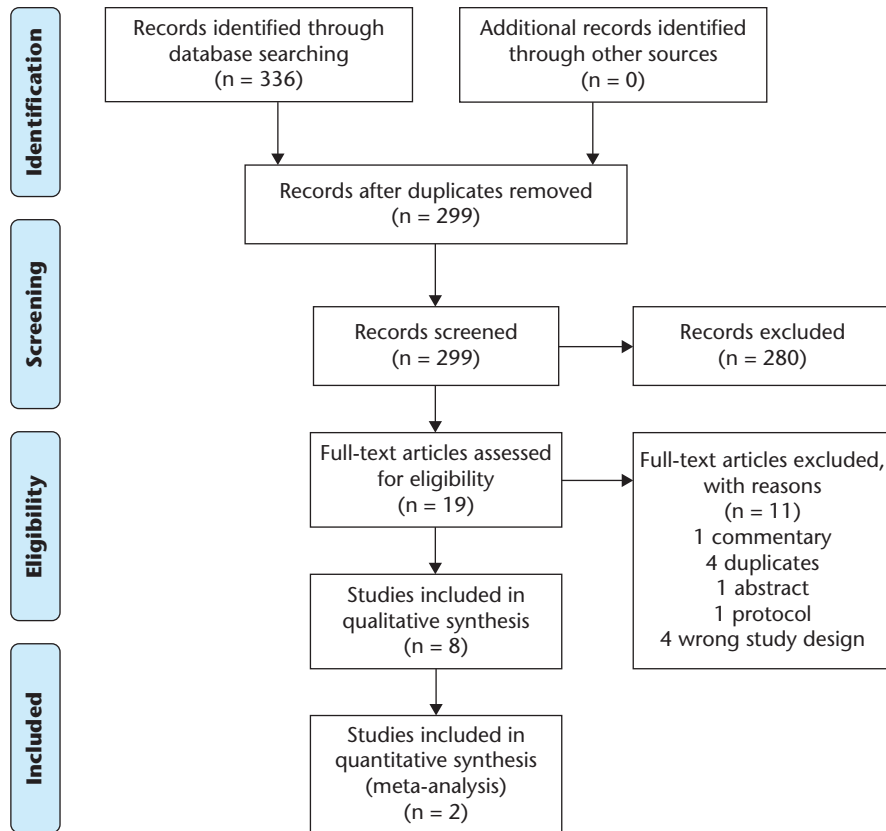


Fig. 1 Selection of studies.

Table 1. Included studies

	Study design	Total no. of patients (N)	PTH treatment
Baillieux, 2017 ¹⁴	Case	1	Forsteo 20 µg/day in 6 months
Hohenberger, 2017 ¹⁵	Case	1	Forsteo 20 µg/day in 12 months
Kasukawa, 2017 ¹⁰	Case serie	7	Forsteo 20 µg/day or Teribone 56.5 µ/week
Moon, 2012 ¹⁷	Case serie	2	Forsteo 20 µg/day in 8 weeks
Wu, 2012 ¹⁶	Case	1	PTH (1-34) daily
Peichl, 2011 ⁸	RCT	65	PTH (1-84) 100µg/day in 24 months
Na, 2017 ¹³	Case control	15	Forsteo (dose unknown)
Yoo, 2016 ⁹	Case control	41	Forsteo 20 µg/day

Note. PTH, parathyroid hormone; RCT, randomized controlled trial.

the two case-control studies, 58 patients received PTH and 74 patients did not (Table 1). Patient characteristics are listed in Table 2. Besides one exceptional case report, patient age ranges between 73 and 84 years, correlating with an age when these insufficiency fractures are expected to occur. Mainly women were affected, which indicates that insufficiency fractures are associated with osteoporosis.

Table 2. Demographics

	PTH group		Control group	
	Age Mean (SD)	Gender (m/f)	Age Mean (SD)	Gender (m/f)
Baillieux, 2017 ¹⁴	36	1/0		
Hohenberger, 2017 ¹⁵	79	0/1		
Kasukawa, 2017 ¹⁰	76.4 (+/-5.2)	0/7		
Moon, 2012 ¹⁷	76/82	0/1		
Wu, 2012 ¹⁶	73	0/1		
Peichl, 2011 ⁸	83.7 (+/-4.6)	0/21	82.4 (+/-3.8)	0/44
Na, 2017 ¹³	75.4 (+/-3.0)	0/5	77.1 (+/-5.22)	1/9
Yoo, 2016 ⁹	73.3 (+/- 9.7)	2/19	72.4 (+/-14.9)	3/17

Note. PTH, parathyroid hormone.

None of the studies reported any nonunions, but all studies reported time to union. Neither studies nor cases used PROMs in assessment of treatment. Mobilization was described in five studies in different manners. Peichl et al used a timed ‘up and go’ (TUG) test to estimate functional outcome, otherwise mobilization was described as walking with or without walking aids. Peichl et al reported significantly better performance in the TUG test in the PTH group after 12 weeks.⁸

Fracture healing was reported in either weeks or months and was confirmed by X-ray or CT scan performed

Table 3. Fracture healing and VAS score

	Fracture healing		VAS Mean (SD)	
	PTH group	Control group	PTH group	Control group
Baillieul, 2017 ¹⁴	26.0 weeks			
Hohenberger, 2017 ¹⁵	12.0 weeks			
Kasukawa, 2017 ¹⁰	32.0 weeks		12.9 after 12 weeks	
Moon, 2012 ¹⁷	12.0 weeks		2 after 2 weeks	
Wu, 2012 ¹⁶	12.0 weeks			
Peichl, 2011 ⁸	7.8 weeks	12.6 weeks	3.2 (+/-1.0)*	6.5 (+/-0.8)*
Na, 2017 ¹³	21.6 weeks	30.0 weeks	3.2#	3.67#
Yoo, 2016 ⁹	10.6 weeks	13.6 weeks	3.4 (+/-1.8) *	4.8 (+/-1.8)*

*At 8 weeks, # last follow up

Note. PTH, parathyroid hormone; VAS, visual analogue scale.

at follow-up in out-patient clinics. Although follow-up regimes were not identical or were carried out at different time points, all patients were examined three months after the start of treatment using CT or X-ray. Time for fracture healing and VAS are listed in Table 3, showing usual average healing time periods below 10 weeks with PTH administration. Na et al is an exception, however, in this study the primary period of normal treatment without teriparatide was included.¹³

The two case-control studies were assessed for risk of bias using the ROBINS-I assessment tool. Both studies were overall classified with serious risk of bias. In both studies the domain ‘bias in selection of participants into the study’ was classified as serious risk. The rest of the domains were classified with low or moderate risk of bias.

The randomized study was assessed using RoB 2.0 and was classified as with some concern. The five remaining studies are case series and case reports. In all articles, the authors have described gender, age, type of PTH treatment, but selection of patients was always biased in the case reports because the report was based on a good result after treatment – fracture healing and pain relief.

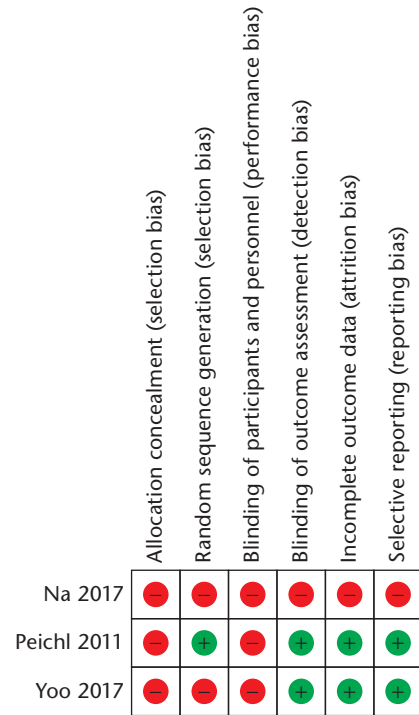


Fig. 2 Risk of bias summery.

Meta-analysis

Three studies compared PTH treatment with controls, but Na et al¹³ were excluded because the patients receiving PTH treatment were enrolled based on unsuccessful union after a period with standard treatment. They were excluded to reduce the risk of bias (Fig. 2).

Two studies were included in our meta-analysis.^{8,9} Fracture healing was analysed using the frequency of union eight weeks after initiating treatment observed at CT or X-ray. All fractures in the PTH group were healed after eight weeks, but not all in the control group ($p < 0.00001$) (Fig. 3). Both studies reported pain with VAS at eight weeks. The patient-reported VAS was significantly lower in the PTH group compared with controls (Fig. 4).

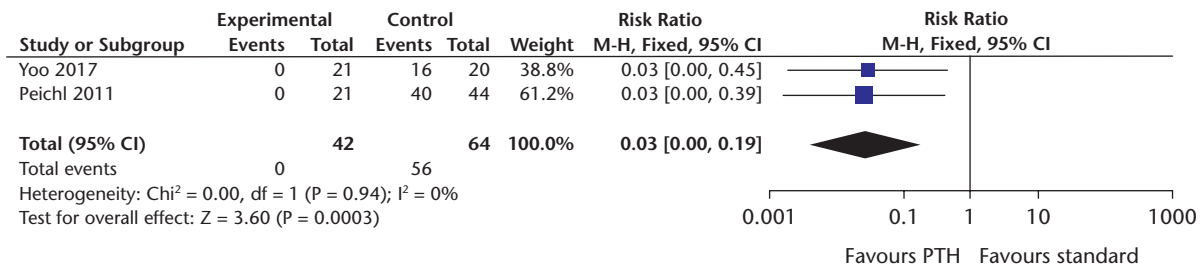


Fig. 3 Meta-analysis – healing after eight weeks.

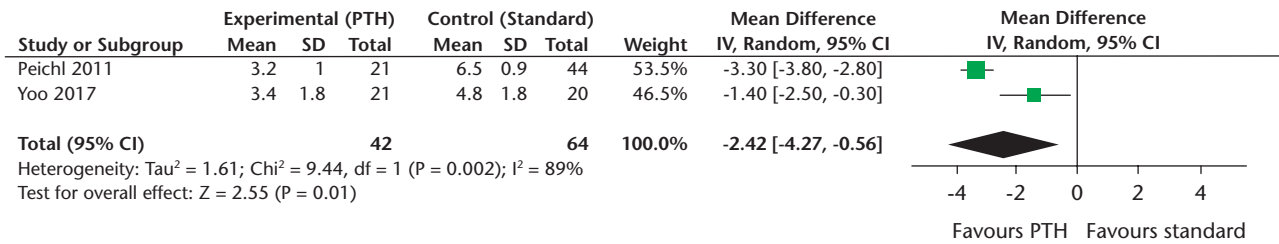


Fig. 4 Meta-analysis – pain after eight weeks.

Na et al only had five patients in the PTH group and 10 patients in the control group, but time to union was also significantly shorter in the PTH group. They did not find a significant difference in VAS between the two groups at the last follow-up.

Discussion

The results of the systematic review indicate that PTH treatment effectively supports healing in insufficiency fractures of the pelvis. After eight weeks the number of healed fractures was already significantly increased, and pain perception significantly decreased in the group receiving PTH injections compared with the current standard of care. However, considering the significant bias associated with the included studies, no final conclusions can be drawn.

The standard treatment for most patients diagnosed with insufficiency fractures of the pelvic ring is pain relief and mobilization as tolerated. It is of utmost importance that the patient’s pain is sufficiently treated because a longer period of bedrest increases the risk of complications such as infections, cardiovascular diseases and reduced muscle strength.¹⁸ Several studies show a high one-year mortality, which matches mortality seen in patients with hip fractures. Dodge et al³ found a one-year mortality of 17%. Out of 77 patients with low-energy pelvic fracture five patients died in hospital, four because of pneumonia and one of myocardial infarction. Morris et al¹⁹ reported a mortality of 7.6% in the hospital and a one-year mortality of 27%. The study included 148 patients with a mean age of 83 years.

A way to stabilize the fracture to achieve early pain control and mobilization is surgical treatment, and different methods are used and described in the literature. Even though these are low-risk procedures they are all invasive. In the literature, treatment with percutaneous iliosacral screws and sacroplasty are described, but not in combination with or compared to PTH treatment.^{20–23} Considering the alternatives to pain medication and physiotherapy, PTH administration has the advantage of treating the original cause and being non-invasive.

The side effects of teriparatide treatment have also been investigated, and studies conclude that the treatment is safe.^{24,25} PTH treatment is administrated with daily subcutaneous injections and can be cost-intensive for the patient. It must be noted that metabolic bone diseases, hypercalcemia and bone cancer are contraindicative to therapy with PTH.

Conclusion

The results indicate that there is a positive effect of PTH administration on fracture union and pain relieve after eight weeks. However, considering study bias and the small cohorts no final conclusions can be drawn.

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ICMJE CONFLICT OF INTEREST STATEMENT

HS reports receiving payments for lectures for Arthrex, outside the submitted work. The other authors declare no conflict of interest relevant to this work.

FUNDING STATEMENT

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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