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Teriparatide (PTH 1-34) Seems not to Enhance Spinal Fusion in Humans: A Prospective Randomized Study on 33 Patients

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Abstract

Earlier studies have shown Positive Effects of Teriparatide (PTH 1-34) on fracture healing in animal models and in humans. The clinical and radiological effects of PTH on Posterolateral Lumbar Fusion (PLF) in humans are still unclear. The primary aim of this study was to determine whether PTH enhances fusion on computed tomography scans 6 months and more than 2 years after uninstrumented PLF. Secondary aims were evaluation of pain, function and quality of life at 3 and 6 months and >2 years postoperatively. Uninstrumented PLF surgery was performed on 33 patients with lumbar spinal stenosis at 1 or 2 levels. The patients were randomized postoperatively into a PTH group or a control group. In the PTH group, a daily dose of PTH for 28 days was initiated within 2 days postoperatively. At postoperative follow-up at 3, 6 months and >2 years, pain (Visual Analogue Scale [VAS]/ Numerical Rating Scale [NRS]), the Oswestry Disability Index (ODI) and quality of life (EQ-5D) were recorded. The grade of fusion was assessed with 3D computed tomography scans 6 months and 2 years postoperatively by two independent radiologists. The results for radiographic PLF, VAS/NRS, ODI, and EQ-5D were similar in both groups. Fusion in both groups had no influence on ODI. A daily dose of PTH subcutaneously over a 28-day period did not enhance posterolateral lumbar fusion or clinical outcome compared with controls in patients with lumbar spinal stenosis at 1 or 2 levels.

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Introduction

Teriparatide (human recombinant PTH 1-34) (PTH) is an anabolic drug used for treatment of osteoporosis. Animal studies have shown that intermittent injection of PTH accelerates fracture healing [1-3]. Other animal studies have suggested a positive effect of PTH on spinal fusion with regard to reduced fusion time, enhanced fusion mass and better segmental stability [4-7].

Whether these studies can be applied to humans is still debated. The hopes for improvement comprise two different issues: faster healing and reduced proportion of non-unions [8]. PTH improves early callus formation in distal radial fractures, thus showing a positive biological effect, even in humans [9]. The clinical benefit of the treatment is unclear. It seems probable that patients with distal radial fractures, proximal humeral fractures or cervical hip fractures do not benefit from additional medication with PTH analogues [10-12].

When PTH 1 to 84 was compared with placebo, it showed better healing in pubic bone fractures at 2 months in the experimental group as well as less pain and better walking ability [13]. However, that study has some methodologic shortcomings.

In conclusion, these studies suggest that PTH may improve fracture healing in humans, but the clinical importance for various diagnoses still needs to be elucidated and confirmed. The primary aim of this study was to determine whether PTH enhances fusion after uninstrumented Posterolateral Fusion (PLF) surgery for lumbar spinal stenosis with isthmic or degenerative spondylolisthesis at 6 months and after a minimum of 2 years after surgery. Secondary aims were to evaluate pain, function and quality of life at 3 and 6 months and after >2 years postoperatively.

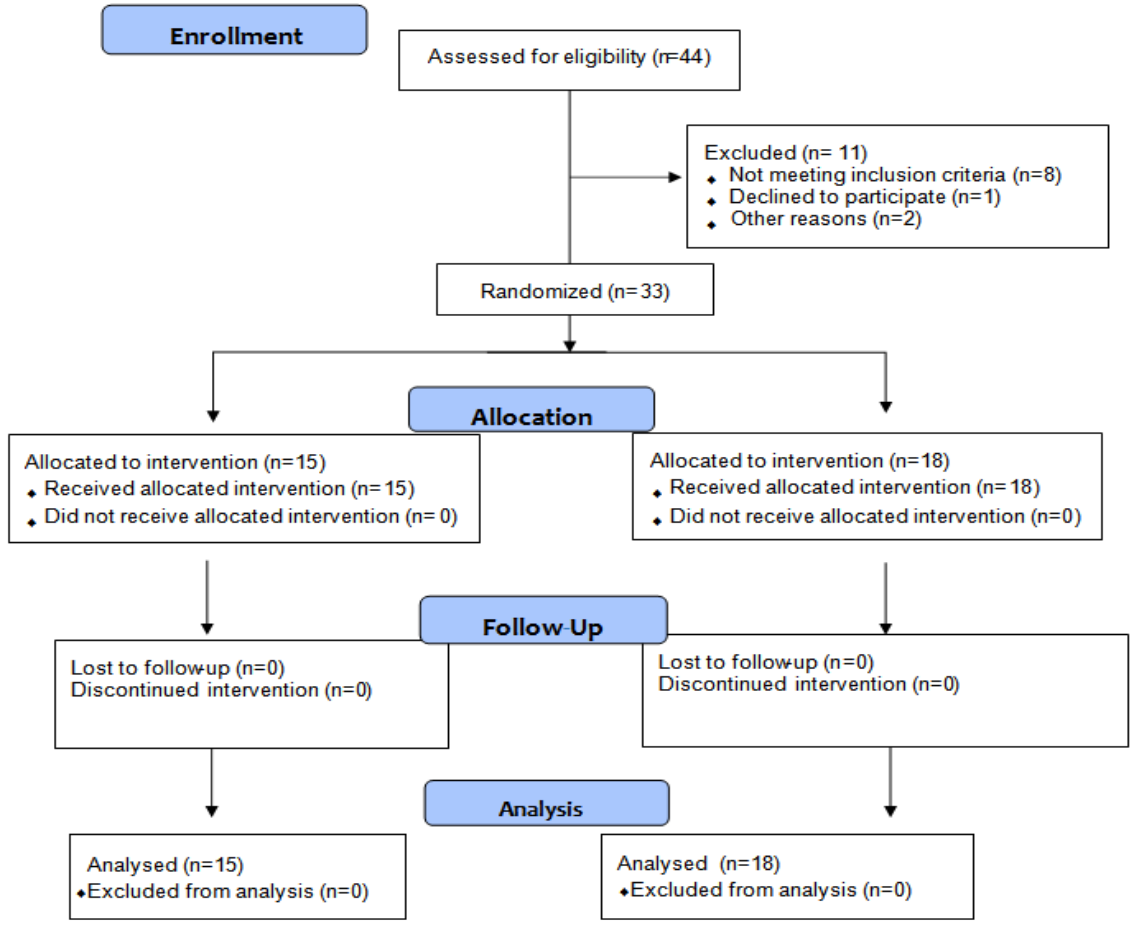

Figure 1: Oswestry Disability Index (median with corresponding 95% confidence interval) shows improved function postoperatively, but no statistically significant differences between the groups.

Methods

From 2012 to 2017, 33 patients with lumbar spinal stenosis and grade 1 to 2 spondylolisthesis underwent decompression and uninstrumented PLF over the affected segments. The groups were similar with regard to age, gender, smoking habits, weight and height (Table 1). Inclusion criteria were lumbar spinal stenosis with isthmic or degenerative spondylolisthesis including one or two segments. Both genders and all ages were accepted, but women had to be postmenopausal. Exclusion criteria were dementia or psychiatric disorder, known malignancy <5 years before surgery, calcium level above the reference value, signs of liver disease, creatinine level over the reference value, inflammatory joint disease, alcohol or drug abuse, oral corticosteroid medication and long-term treatment with non-steroidal anti-inflammatory drugs (≥ 3 months before surgery) (Figure 2).

The procedures were performed by four surgeons. Conventional decompressive surgery was performed along with a bone grafting procedure. An iliac bone graft was harvested from the posterior iliac crest with a biopsy drill. The iliac bone graft was mixed with minced laminar bone from the laminectomy. To achieve a standardized amount of bone graft on both sides at each level, a 5 ml syringe was used. The syringe was filled with bone and the bone then applied between the decorticated transverse processes on each side of each segment.

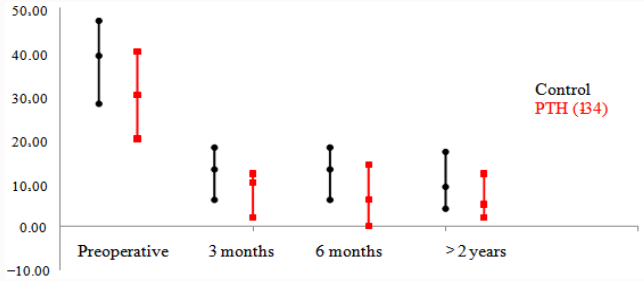

Figure 2: CONSORT 2010 flow diagram.

All patients were randomized postoperatively, using sealed envelopes, to the control group or the PTH group (daily dose of 20 µg PTH over 28 days). The PTH medication was started 1 to 2 days postoperatively and was self-administered subcutaneously by the patients. The control group did not get any placebo medication. Follow-up of all patients occurred at 3 and 6 months and >2 years postoperatively when Visual Analogue Scale (VAS)/Numerical Rating Scale (NRS), Oswestry Disability Index (ODI), EQ-5D (User Guide 2018) and adverse events related to the surgery or the PTH medication were recorded [13,14].

The original primary outcome was radiographic findings, using a 3D Computed Tomography (CT) scan, of complete and bilateral fusion at 6 months. When planning the study, we assumed that, in

successful cases, fusion could be expected at 6 months, but we soon realized that the chosen time may have been too short. Therefore, we added, and approved through an amendment, a second CT scan after a minimum of 2 years. The assessments of the radiographs were performed by two blinded and independent radiologists, first separately and then, in the case of different evaluations, a consensus was reached between them to reach a final verdict.

Secondary outcomes were pain evaluated with VAS/NRS where 0 meant no pain and 10 was maximum pain. Function was evaluated using ODI where 0 equated with no disability and 100 was the maximum disability possible. Quality of life (EQ-5D) was measured where the maximum was [1].

Power analysis

When we planned, the study there was a lack of reliable data in the literature concerning the degree of radiologically verified bony fusion after PLF. Several studies had used standard radiographs, others early-generation CT scans or the patients had been operated on with instrumentation, which made the radiological assessments of whether a segment was fused or not dubious. Furthermore, the expected time to complete PLF radiologically was not known. Thus, it was impossible to perform a normal power analysis. We assumed that 100 patients would be a sufficient number to show whether PTH had a positive effect or not.

The inclusion of patients took longer than expected, and we finally decided to limit the study to 33 patients. However, if PTH had a positive effect on PLF and the radiologists could tell the right treatment in 80% of cases (α=0.05 and 80% power), 26 patients were needed.

Statistics

The chi-squared test was used to compare the radiologic assessment with the given treatment. Parametric unpaired data were tested with Student's two-tailed t test. Non-parametric data were tested with the Mann-Whitney U test.

Ethics, conflicts of interest and registration

The study was approved by the Regional Ethics Committee in Linkoping (2011/347-31) and the Swedish Medical Products Agency (EudraCT number 2011-002917-12). The authors declare no conflicts of interest. It complied with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and was registered at ClinicalTrials.gov (NCT02090244).

Results

Radiographic PLF rates were similar in both groups (Table 1). Secondary outcomes, ODI (Figure 1), EQ-5D (Table 2) and VAS/NRS (Table 3) showed similar results for the PTH group and controls. Fusion in both groups had no positive effect on VAS/NRS (P=0.87) or ODI (Table 4). No postoperative complications, reoperations or adverse events related to the surgery or the PTH medication were seen during follow-up.

Discussion

This study could not show that PTH had any positive effect on fusion after uninstrumented lumbar PLF surgery. We could not detect any positive effects on pain, function or quality of life. Fusion in both groups had no influence on pain and function. The primary aim of our study was to determine whether or not there was complete and continuous bone bridging between the transverse processes on thin slice CT scans. Methods and definitions of bone union differ between studies. Radiography including profile views at flexion and extension has been used but it seems more accurate to use CT scans.

The quality of the bone graft could have an effect on the fusion rate. We used a mixture of a fresh iliac bone graft mixed with fresh

Table 1: Radiographic fusion at 6 months and after >2 years.

Treatment	Number of patients	6 months			>2 years		
		Unilateral	Bilateral	Total	Unilateral	Bilateral	Total
PTH (1 to 34)	15	3	2	5	2	6	8
Controls	18	4	0	4	6	6	12

No statistically significant differences between the PTH group and controls were seen (P values at 6 months and >2 years were 0.48 and 0.44, respectively)

Table 2: Quality of life (EQ-5D).

Treatment	Number of patients	Preoperatively, median (range)	3 months, median (range)	6 months, median (range)	>2 years, median (range)
PTH (1-34)	15	0.60 (0.09 to 1)	0.84 (0.73 to 1)	0.87 (0.66 to 1)	0.79 (0.66 to 1)
Controls	18	0.64 (0.2 to 0.73)	0.80 (0.72 to 1)	0.80 (0.62 to 1)	0.77 (0.62 to 1)

The results were similar for both groups

Table 3: Pain (visual analogue scale/numerical rating scale) at rest and during activity.

Treatment	Preoperatively, median (range)	3 months, median (range)	6 months, median (range)
PTH (1 to 34) group (n=15)			
At rest	37 (0 to 63)	0 (0 to 35)	0 (0 to 49)
Activity	66 (45 to 91)	16 (0 to 68)	10 (0 to 74)
Controls (n=18)			
At rest	20 (0 to 74)	6 (0 to 60)	3 (0 to 50)
Activity	63 (0 to 85)	24 (0 to 85)	25 (0 to 60)

The results were similar for both groups without any statistically significant differences

Table 4: Fusion versus Oswestry Disability Index at >2 years irrespective of treatment.

Fusion	Number of patients	Median (range)
Yes	20	4 (0 to 26)
No	13	9 (0 to 33)

The results were similar for both groups (P=0.22)

Table 5: Patient characteristics were similar except for a higher proportion of women in the control group.

Treatment	Number of patients	Gender (female/male)	Age (years), median (range)	Weight (kg), median (range)	Height (cm), median (range)	Smoker
PTH (1-34)	15	7/8	75 (50 to 85)	80 (53 to 114)	170 (153 to 183)	
Controls	18	13/5	72 (59 to 84)	80 (52 to 105)	162 (155 to 179)	1

laminar bone. Others have used local autograft from the laminectomy mixed with fresh-frozen femoral head allografts [15]. Some clinical studies in humans suggest positive effects of PTH on PLF, but the study designs differ and it is not possible to get a clear overall picture of whether or not PTH enhances bony fusion [15-18]. Many earlier studies are retrospective, often involving PLF in combination with instrumentation. Some studies compare PTH with other osteogenic agents (bone morphogenetic protein) but without untreated controls. Instrumented fusions may make it difficult to analyse and get a proper picture of the fusion mass on CT scans. To our knowledge, there is only one clinical study focusing on the effect of PTH on uninstrumented lumbar fusions [15]. They did not see any positive effect after 90 days of PTH treatment.

There are several weaknesses in this study. The number of patients was small. The length of time during which medication was given may have been too short, but an argument against this is that in a previous study, we were already able to see more callus in distal radial fractures after 5 weeks [9]. The optimal treatment time is still not clear. Furthermore, we still do not know whether a standard dose of 20 μg or a dose of 40 μg of teriparatide is optimal. Finally, our patients were not blinded to the treatment. Placebo injection pens are not commercially available and this study was performed without support from the manufacturer. A 28-day treatment with (PTH 1-34) seems not to enhance fusion or clinical outcome after uninstrumented lumbar PLF surgery.

References

1. Chalidis B, Tzioupis T, Tsiridis E, Giannoudis PV. Enhancement of fracture healing with parathyroid hormone: Preclinical studies and potential clinical applications. Expert Opin Investig Drugs. 2007;16(4):441-9.
2. Kostenuik P, Mirza FM. Fracture healing physiology and the quest for therapies for delayed healing and nonunion. J Orthop Res. 2017;35(2):213-23.
3. Seebach C, Skripitz R, Andreassen TT, Aspenberg P. Intermittent parathyroid hormone (1-34) enhances mechanical strength and density of new bone after distraction osteogenesis in rats. J Orthop Res. 2004;22(3):472-8.
4. Lawrence JP, Ennis F, White AP, Magit D, Polzhofer G, Drespe I, et al. Effect of daily parathyroid hormone (1-34) on lumbar fusion in a rat model. Spine J. 2006;6(4):385-90.
5. O'Loughlin PF, Cunningham ME, Bukata SV, Tomin E, Poynton AR, Doty SB, et al. Parathyroid hormone (1-34) augments spinal fusion, fusion mass volume, and fusion mass quality in a rabbit spinal fusion model. Spine (Phila Pa 1976). 2009;34(2):121-30.
6. Abe Y, Takahata M, Ito M, Irie K, Abumi K, Minami A. Enhancement of graft bone healing by intermittent administration of human parathyroid hormone (1-34) in a rat spinal arthrodesis model. Bone. 2007;41(5):775-85.
7. Qiu Z, Wei L, Sochacki KR, Bishop C, Ebraheim M, Yang H. Effect of intermittent PTH (1-34) on posterolateral spinal fusion with iliac crest bone graft in an ovariectomized rat model. Osteoporos Int. 2013;24(10):2693-700.
8. Aspenberg P. Special Review: Accelerating fracture repair in humans: A reading of old experiments and recent clinical trials. Bonekey Rep. 2013;2:244.
9. Aspenberg P, Johansson T. Teriparatide improves early callus formation in distal radial fractures. Acta Orthop. 2010;81(2):234-6.
10. Aspenberg P, Genant HK, Johansson T, Nino AJ, See K, Krohn K, et al. 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(2):404-14.
11. Bhandari M, Jin L, See K, Burge R, Gilchrist N, Witvrouw R, et al. Does teriparatide improve femoral neck fracture healing: Results from a randomized placebo-controlled trial. Clin Orthop Relat Res. 2016;474(5):1234-44.
12. Johansson T. PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures. A randomized, controlled study of 40 patients. Acta Orthop. 2016;87(1):79-82.
13. 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;93:1583-7.
14. Fairbank JC, Pynsent PB. The oswestry disability index. Spine (Phila Pa 1976). 2000;25(22):2940-52.
15. Jespersen AB, Andresen ADK, Jacobsen MJ, Andersen MO, Carreon LY. Does systemic administration of parathyroid hormone after noninstrumented spinal fusion surgery improve fusion rates and fusion mass in elderly patients compared to placebo in patients with degenerative lumbar spondylolisthesis? Spine (Phila Pa 1976). 2019;44(3):157-62.
16. Ohtori S, Inoue G, Orita S, Yamauchi K, Eguchi Y, Ochiai N, et al. Teriparatide accelerates lumbar posterolateral fusion in women with postmenopausal osteoporosis: Prospective study. Spine (Phila Pa 1976). 2012;37(23):E1464-68.
17. Ohtori S, Orita S, Yamauchi K, Eguchi Y, Ochiai N, Kuniyoshi K, et al. More than 6 months of teriparatide treatment was more effective for bone union than shorter treatment following lumbar posterolateral fusion surgery. Asian Spine J. 2015;9(4):573-80.
18. Ebata S, Takahashi J, Hasegawa T, Mukaiyama K, Isogai Y, Ohba T, et al. Role of weekly teriparatide administration in osseous union enhancement within six months after posterior or transforaminal lumbar interbody fusion for osteoporosis-associated lumbar degenerative disorders: A multicenter, prospective randomized study. J Bone Joint Surg Am. 2017;99(5)365-72.