RESEARCH ARTICLE

Effect of teriparatide (PTH 1–34) on fusion mass and clinical outcomes the year after single-level instrumented posterolateral fusion.

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Abstract

BACKGROUND CONTEXT: Successful spine fusion requires formation and remodeling of new bone. For this reason, osteoporosis is a risk factor that affects fusion in spine surgery. Parathyroid Hormone (PTH) is an anabolic drug that increases activity of osteoblasts and osteoclasts. Some studies have demonstrate the PTH accelerates the lumbar posterolateral fusion in osteoportic patients, but the clinical and functional impact of these medication is not well known

PURPOSE: To study the influence of the treatment with Teriparatide in the fusion mass and clinical outcome in a group of patients with osteoporosis and a lumbar posterolateral fusion during a 1-year follow-up.

METHODS: Seventy-two patients underwent a L4-L5 instrumental posterolateral fusion using pedicle screws and bone graft. Patients were divided into 2 groups: Treated with teriparatide (20µg/day, post-surgery, during 1 year) n= 47, or not treated n=25. Patients were studied before surgery and 3 months, 6 months and 1 year after surgery. The following assessments were performed: quality of bone fusion mass and clinical outcome evaluated by visual analogue scale score (VAS) and Oswestry Disability Index (ODI).

RESULTS: Radiographically, a decrease on the volume of fusion mass is observed in all cases, but this decrease was significantly lower in the group of patients treated with PTH. All patients have a significant improvement in pain and function. No differences in the improvement were observed between both groups.

CONCLUSIONS: A decrease on fusion mass volume was observed in all cases, but patients on Teriparatide treatment had a better fusion mass volume development. However, these radiological differences did not influence on clinical outcome at 1 year follow-up, as both groups present the same improvement.

***Keywords*:** Teriparatide; Spinal fusion; Posterolateral arthrodesis; osteoporosis.

Introduction

Spine fusion is one of the most common orthopedic procedures [1]. Successful spine fusion requires formation and remodeling of new bone, processes in which osteoblasts and osteoclasts are involved. The most frequent complication of this procedure is pseudoarthrosis, occurring in 10% to 30% of the cases [2]. This fact presents derived problems for clinicians and patients that lead to pain and many times to need for re-operation. For this reason, investigations to prevent pseudoarthrosis are necessary.

Osteoporosis is a risk factor that affects fusion in spine surgery [3]. On the basis of preclinical data, some authors believe that anabolic agents may offer an advantage over antiresorptive medication in osteopo-rotic patients undergoing spine fusion [4].

Teriparatide [Parathyroid Hormone PTH (1-34)] is a genetically engineered analog of human parathyroid hormone that acts as an anabolic drug by increasing activity primarily in osteoblasts and secondarily in osteoclasts [5]. Due to these actions on remodeling, it seems logical to think that PTH administration could favor spine fusion, especially in osteoporotic patients, influencing the probability of a successful fusion.

PTH has demonstrated that it improves the fusion rate and fusion mass microstructure in animal studies [6-13] with no effect on biomechanical analysis [4].

In a previous work, Ohtori et al. [14] compared the effects of biphosphonates and teriparatide in clinical efficacy for bone union, after instrumental lumbar posterolateral fusion using local bone grafting, in 57 women with spondylolisthesis. Teriparatide was more effective than the administration of biphosphonates, although without significant differences in pain scores improvement between groups. In this study, both groups had an anti-osteoporotic treatment, with no control group.

In other work, Inoue et al. [15] demonstrated that teriparatide increased the insertional torque of pedicle screws during fusion surgery in patients with postmenopausal osteoporosis. These authors included two groups of patients, treated and untreated with teriparatide, but functional outcome of these patients was not reviewed.

The aims of this study was to analyze the influence of the treatment with teriparatide in the fusion process in a group of patients with osteoporosis and a uni-segmental posterolateral lumbar fusion during a follow-up of one year, compared with a control untreated group of patients, and its influence on the functional outcome.

Methods

Study design

This is a retrospective study on 313 patients. A homogeneous group of 72 patients with lumbar degenerative spondylolisthesis or spinal stenosis treated with a single-level lumbar spinal fusion and a minimum follow-up of 12 months was selected for the study. Each patient had a history of at least 6 months of low back pain. All the patients showed osteoporosis defined as lumbar or femoral t-score <-2.5 a history of osteoporotic fracture or multiple risk factors for fracture.

There were 60 females (83%) included in the study. The ages were in the range from 63 to 86 years, with a mean age of 76.4 years for both groups. The patient demographics were similar between the study cohorts (Table 1). All patients underwent instrumented posterolateral fusion at one level. All patients entering the practice were provided with an informed consent for data collection that was associated with their treatment.

Table 1

Baseline clinical and demographic characteristics of patients who underwent posterolateral lumbar fusion and were untreated or treated with PTH (1-34)

Parameters	With PTH (1-34) N=47	Without PTH (1-34) N=25	P
Age	74.7 ± 5.2 (63 - 84)	74.7 ± 6.7 (64 - 86)	0.986
Sex	39 female, 8 male	21 female, 4 male	1.000
Etiology	18 stenosis, 29 listhesis	7 stenosis, 18 listhesis, 1 review	0.336
BMI	27.5 ± 3.7 (20.3 - 39.0)	28.6 ± 4.0 (21.3 - 37.3)	0.247
LBMD	-1.9 ± 1.2 (-4.1 - 0.5)	-0.9 ± 1.7 (-3.4 - 2.0	0.040
FBMD	-2.1 ± 0.7 (-3.5 - 0)	-1.4 ± 1.4 (-3.5 - 1.9)	0.036
Previous OP treatment	38 none, 1 biphosphonates, 7 others	21 none, 1 biphosphonates, 3 others	1.000
Smoker	1 smoker 46 nonsmokers	0 smokers, 25 nonsmokers	1.000

BMI, body mass index; FBMD, femoral bone mineral density; LBMD, lumbar bone mineral density.

The protocols for human procedures used in this study were approved by the ethics committee of the Instituto de Investigacion Sanitaria Fundación Jiménez Díaz. Informed consent was obtained from each one of the participants

The patients were divided into 2 groups based on whether they were treated with teriparatide (20µg/day, post-surgery during one year) or not, according to a physician prescription.

Radiographical Outcome Measurements

Radiographical analysis was used to evaluate bone union. Patens were studied before surgery and at 3 months, 6 months and 1 year after surgery. A fusion scale was performed by our team with degrees from 1 to 5 (Figure 1). Three orthopedic surgeons blindly interpreted all imaging studies. As the material and quantity of bone graft was different for each patient, we calculated the difference in the fusion scale with respect of the situation 3 months after surgery, (3 months-6 months), (3 months-1 year) in order to calculate the evolution of the fusion mass.

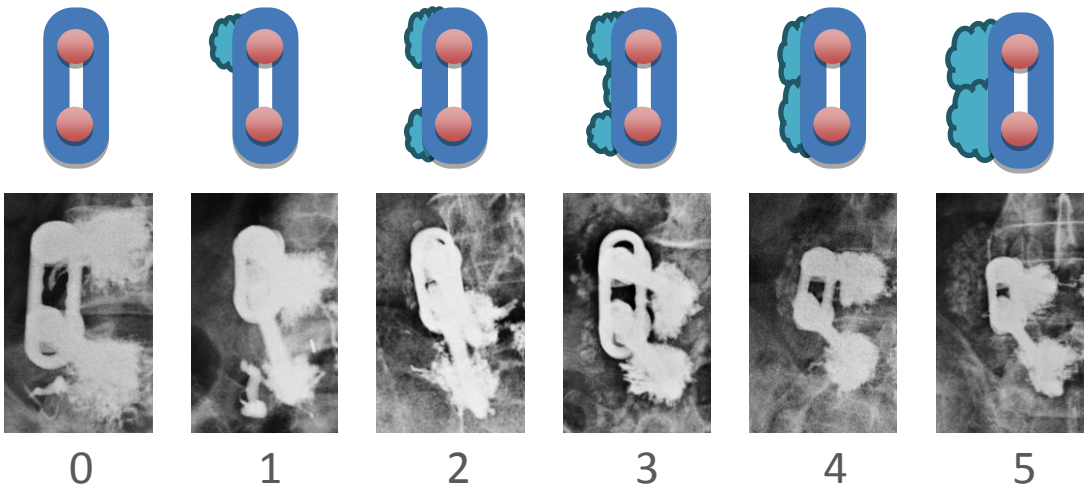

Figure 1. Fusion scale in posterolateral arthrodesis evaluated by radiography. Degrees of fusion were from 0 to 5 (no-fusion to total fusion). This scale was performed by L. Alvarez, one of the co-authors of this work.

Computed tomographic (CT) scans with contiguous 2.0-mm axial cuts perpendicular to the disc space (along with coronal reconstructions) were obtained at the 6 months follow-up in all cases. CT assessed the presence of contiguous bridging bone on at least 2 consecutive coronal and sagittal reconstructions and absence of a radiological cleft within the fusion mass. Noncontiguous bone formation. The presence of haloing around the screws was defined as pseudoarthrosis.

Patient Outcome Measurements

Functional outcome was evaluated by the change in pain, using the visual analogue scale (VAS) for low back pain and leg pain and the Oswestry Disability Index (ODI). During the subjects' hospital visits before surgery and at 3, 6, and 12 months after surgery, the ODI questionnaire was examined. The assessment was calculated as a percentage of total score compared with scores for answered questions. The questionnaires that the subject did not answer were excluded [16].

Surgical procedure

The surgery was as a conventional posterior decompression and fusion. First, the surgical area was incised to perform laminectomy when necessary. Fenestrated pedicle polymethylmethacrylate (PMMA) augmented screws were used in all cases. A curette and other surgical tools were used to prepare the facets and the transverses processes. Then, the local autogenous bones collected in the decompression process were broken into fine pieces and mixed with β-Tricalcium Phosphate in granules (PolyBone ®) or allograft in granules was placed over the transverse processes (15cc) per side.

Safety assessment

Safety was assessed through adverse events and clinical laboratory tests. Among the adverse events related surgery, incidental durotomy, wound infection, reoperation, and readmission were compared between both groups. Monitoring of serum calcium, urinary calcium, renal function or serum uric acid was performed in patients under Teriparatide treatment.

Results

Clinical and demographic characteristics

A summary of the patients' clinical and demographic characteristics is shown in Table 1.

Fusion assessment

A progressive decrease in fusion mass was observed in both groups of patients, treated and untreated with PTH (Table 2). Six months after surgery, fusion mass lost 0.35±0.8 points in our fusion scale (Fig. 1), with respect to the fusion mass three months after surgery, in the group treated with PTH, while the untreated group of patients lost 0.83±1.1 points ($p<0.0053$). One year after surgery fusion mass lost 0.53±0.8 points with respect the fusion mass three months after surgery in the group treated with PTH, while the untreated group of patients lost 0.85±1 points ($p<0.04$) This data indicates that decrease of fusion mass after surgery was significantly lower in the group of patients treated with PTH. Computed axial tomography corroborated the observed results with our fusion scale.

Table 2

Evolution of fusion of lateral mass volume in patients who underwent posterolateral lumbar fusion and were untreated or treated with PTH (1-34)

Parameters	With PTH n=47	Without PTH n=25	P
3 months–6 months	0.35 ± 0.8 (-2.5–2.5)	0.83 ± 1.1 (-1–3.5)	0.0053
3 months–1 year	0.53 ± 0.8 (-1–3.5)	0.85 ± 1.0 (-1–3.5)	0.0403

Treated patients received 20 µg PTH (1-34)/day after undergoing instrumental lumbar posterolateral fusion surgery. The radiographic fusion scale is described in Figure 1.

Clinical assessment

Table 3 shows the values of ODI, lumbar VAS and lower limbs VAS pre-surgery and 3 months, 6 months and 1 year after surgery. ODI and VAS basal levels were statistically similar in both groups of patients. All patients had a significant improvement at 12 months after surgery in pain and function. This improvement was similar in both groups at 3 months, 6 months and 1 year after surgery. None of the patients presented a pseudoarthrosis that required a surgical review.

Table 3

Visual analogue scale (VAS) and Oswestry disability index (ODI) scores for the lower limbs and spine of patients who underwent posterolateral lumbar fusion and were untreated or treated with PTH (1-34).

Parameter	With PTH	Without PTH	Crude comparisons	Adjusted comparisons
ODI				
Baseline	58.0 ± 14.7 (n=42)	58.0 ± 14.7 (n=22)	0.996	0.748
3 months	31.3 ± 17.4 (n=37)	29.9 ± 24.8 (n=19)	0.810	0.950
6 months	30.7 ± 21.0 (n=36)	26.1 ± 18.2 (n=17)	0.442	0.063
1 year	27.1 ± 21.7 (n=34)	20.7 ± 19.7 (n=18)	0.303	0.515
Lower limb VAS				
Baseline	7.3 ± 3.1 (n=40)	7.9 ± 2.4 (n=22)	0.466	0.789
3 months	3.6 ± 3.4 (n=37)	4.2 ± 3.7 (n=19)	0.520	0.380
6 months	3.5 ± 3.2 (n=36)	2.7 ± 2.7 (n=17)	0.403	0.247
1 year	3.1 ± 3.1 (n=33)	2.4 ± 3.0 (n=18)	0.497	0.551
Spinal VAS				
Baseline	7.7 ± 2.2 (n=41)	8.6 ± 1.3 (n=22)	0.084	0.243
3 months	3.7 ± 2.9 (n=37)	3.4 ± 3.0 (n=19)	0.739	0.794
6 months	4.2 ± 2.8 (n=35)	3.2 ± 2.8 (n=17)	0.260	0.053
1 year	3.0 ± 2.5 (n=33)	2.9 ± 2.6 (n=18)	0.973	0.613

Treated patients received 20 µg PTH (1-34)/day after undergoing instrumental lumbar posterolateral fusion surgery. Multivariable linear regression was adjusted for BMI, body mass index; FBMD, femoral bone mineral density; LBMD, lumbar bone mineral density.

Discussion

Spinal fusion is a complex process that requires the concomitant actions of osteoblasts and osteoclasts in order to produce new bone formation and remodeling. With the great number of osteoporotic patients in the world population and also the great number of patients undergoing spinal fusion, an overlap between these two populations of patients is frequently produced. It has been demonstrated that patients with osteoporosis have high non-union rates compared with patients with osteoporosis [17]. For this reason, there have been studies trying to use the most classical treatments for osteoporosis, biphosphonates and PTH, in order to investigate if these treatments would help in the development of a better quality and quantity of bone mass during the fusion process after spinal surgery. With respect to the translational studies regarding the effects of biphosphonates on fusion rate, there are controversial results [4]. With regard to fusion mass quality biphosphonates treatment appears to decrease the process of remodeling. In the literature, the fusion masses of treated animals tended to have a higher percentage of cartilage (18-21).

Many translational works have addressed the issue of the effect of PTH on spinal fusion.

Normal rabbits have been used as an experimental model. O'Loughlin et al [6] found in a rabbit model of posterolateral lumbar fusion treated 6 weeks with 10µg/Kg/day of PTH that treated rabbits had a fusion rate of 81% compared with a fusion rate of 30% in untreated controls. Treated animals also showed a higher percentage of bone tissue and a significantly lower percentage of fibrous tissue and higher number of bone cells within the fusion mass. Lehman et al. [7] made an additional determination of fusion rate based on histology using the Emery score. They found that rats treated during 8 weeks with 10µg/Kg/day of PTH had a fusion rate of 86.7% compared with 50% in untreated controls. The average Emery grading score was 5.99±1.46 for the autologous group and 6.26±0.93 for the teriparatide group. However, these authors did not find significant differences in motion in flexion/extension, lateral bending and axial rotation. In other work, Lina et al [8] found that administration of PTH to male New Zealand white rabbits that underwent bilateral posterolateral intertransverse process arthrodesis results in increased fusion mass volume, but it did not improve biomechanical stiffness over use of autograft alone, and when delivered concurrently with bone morphogenetic protein, teriparatide provided no statistically significant improvement in biomechanical stiffness.

Rats have also been used as an experimental model. Using normal rats, Abe et al. [9] demonstrated that 4-6 weeks of treatment with 40 µg/Kg/day of PTH produced a significantly higher mineral apposition and a higher proportion of bone tissue, trabecular number and trabecular thickness when compared with controls in a spinal arthrodesis model. Using also normal rats, Ming et al [10] found that teriparatide at 23 µg/Kg/day for 4 weeks showed anabolic skeletal effects and significantly enhanced spinal fusion in rats, whereas teriparatide at 4 µg/Kg/day had also anabolic effects but did not significantly enhance spinal fusion rate. Other authors used ovariectomized rats as experimental model, in order spinal fusion was studied in an osteopenic model. Zhou et al. [11] evaluated the effects of PTH (1-34) in adjacent segment disk degeneration in an ovariectomized rat model in which posterolateral lumbar fusion was made. PTH was intermittently administered immediately after surgery ad during 8 weeks. Greater new formation in histology was observed in PTH-treated animals. PTH

also alleviated adjacent segment disc degeneration by preserving disk height, microvessel density, endplate thickness and the relative area of endplate calcification. Qiu et al. [12] also demonstrated that intermittent treatment with PTH (1-34) at 30 μg/Kg/day, during 6 weeks, enhances the quantity of the fusion callus and reduced the healing time of posterolateral spinal fusion with autologous iliac bone grafts in ovariectomized osteoporotic rats.

Other authors used as experimental model osteoporotic rats, where osteopenia was got through glucocorticoid treatment. Sugiura et al. [13] administered 5 mg/kg of methylprednisolone for 12 weeks to rats and then made a posterolateral spinal fusion with iliac crest autograft. They found that administration of 40 μg/Kg/day of teriparatide for 6 weeks accelerated bone remodeling predominantly by stimulating bone formation at the fusion mass and increasing the fusion rate and also improved bone microarchitecture of adjacent vertebrae.

At this point, it is important to note that, although used as translational models, the rat and rabbit are quadruped spine models, in contrast with the human bipedal spine. These differences relate to the paravertebral musculature and intervertebral disk and these differences exist with regards to the incorporation of bone graft in spine fusion.

On the basis of preclinical data some authors [4] believe that anabolic agents (PTH) may offer an advantage over antiresorptive medications (biphosphonates) in osteoporotic patients undergoing spine fusion.

In a work performed in humans, with alendronate, Nagahama et al. [22] demonstrated a higher fusion rate in treated patients after surgery, without any improvement in clinical outcome. It is important to note that the findings of this work are specific to interbody procedures and the environment in the interbody region differs from that of posterolateral spine because they are submitted to different loading forces and have different amounts of cancellous bone [23].

Park et al. [24] studied the effect of zoledronic acid on the volume of the fusion-mass in lumbar spinal fusion in 44 patients with degenerative lumbar spinal stenosis that underwent one or two-level posterolateral fusion. The mean volume of the fusion-mass level quantified by functional radiography and three dimensional computed tomography did not present significant differences between groups [autograph + zoledronicaci (ZA), allograft +ZA, the autograph alone or allograft alone]. VAS, ODI and short form 36 improved significantly after surgery, but there were not significant differences among the four groups.

In a recent work, Chen et al. [25] also studied, in seventy-nine osteoporotic patients with single-level degenerative spondylolisthesis, after spinal fusion, the effect of zoledronic acid administration. Patients were randomly assigned to receive either zoledronic acid infusion or saline infusion (controls). Functional radiography and CT scans were used to evaluate fusion status. Zoledronic acid shortened the duration of time to fusion: bridging bone bonding with adjacent vertebral bodies or either superior or inferior vertebral body was more frequently observed in zoledronic acid group at 3, 6 and 9 months after surgery, although at 12 months after operation fusion was not significantly different between groups. Zoledronic acid prevents the subsequent adjacent vertebral compression fractures and immobilization-induced bone loss in the hip. ODI showed the improved clinical outcomes compared with controls at 9 and 12 months post-surgery.

There are few works about the use of PTH as adjuvant of spinal fusion. Although the

next authors did not administer PTH to their patients, Kanaya et al. [26] described the association between levels of PTH and the outcome of bone fusion in patients who underwent/would undergo hemodialysis. Patients underwent posterolateral spinal fusion with instrumentation. The outcome of bone fusion was assessed 12 months after surgery. A significant difference in PTH levels was observed between the good fusion (mean PTH 235 pg/ml) and poor fusion (mean PTH 100 pg/ml) groups.

In 2012, Ohtori et al. [14] compared the clinical efficacy of teriparatide and biphosphonates for bone union after instrumented lumbar posterolateral fusion using bone grafting in women with postmenopausal osteoporosis. Twenty eight patients were treated with 17.5 mg of risendronate weekly and twenty nine patients with a daily subcutaneous injection of 20µg of teriparatide. Risendronate and teriparatide were administered for 2 months before and for 8 months after surgery. The rate of bone union was 82% in the teriparatide group and 68% in the biphosphonates group. The rate of bone union and the average of duration of bone union in the teriparatide group of patients were significantly superior to those in the biphosphonates group. Pain scores improved after surgery, but no significant differences were noted between the groups. The main difference of this work with our study is that these authors did not present a control group without any treatment.

Inoue et al. [15] published in 2014 another article examining the efficacy of preoperative teriparatide treatment for increasing the insertional torque of pedicle screws during fusion surgery in postmenopausal women with osteoporosis. The patients were divided in two groups: treated or untreated with PTH. In the treated group, patients received preoperative teriparatide therapy as either a daily (20µg/day) or a weekly (56.5µg/week) injection for a mean of 61 days and a minimum of 31 days. Authors conclude that teriparatide treatment prior to surgery was effective in increasing the insertional torque of pedicle screws during surgery in patients with postmenopausal osteoporosis. The main difference of this work with respect to ours is that these authors did not study the functional assessment of patients. In the present work we observed a decrease in the fusion mass that had not been previously described. Although a TAC was performed to patients at 6 months, there is not a follow-up with this technique and radiologic images can produce some degree of confusion. However, this image defect was similar for the two groups of patients. It would be desirable that the study of the evolution of fusion mass uses through more accurate techniques like TAC.

The results of our work demonstrated a significant lesser fusion mass decrease in osteoporotic patients submitted to posterolateral fusion treated with 20µg/day of PTH than in untreated patients. The absence of this radiological fusion, that is higher in the untreated group, may have some consequences in the future, so long term follow-up studies may be necessary.

In our work, all patients also improve their pain score, treated or untreated with PTH, without differences between groups. These finding indicates that posterolateral fusion surgery was the main cause of their functional improvement, and not PTH treatment.

We didn't have any case of clinical pseudoarthrosis, although in some case a complete bone bridge between the transverse processes was not observed. In all cases, we used PMMA augmented screws, that have demonstrated a better attachment to the osteoporotic bone [27,28].

Conclusions

According to our results and those of the other authors, it seems clearly that teriparatide treatment produces better results in bone fusion rate than the lack of treatment in osteoporotic patients submitted to posterolateral fusion surgery. However, the general state of the patients with respect to pain was similar between treated and untreated groups. It should be interesting to observe the follow-up of these patients with respect to pain score during a longer period of time in order to decide the obliged treatment of all these patients with teriparatide.

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