

Retrospective radiological outcome analysis following teriparatide use in elderly patients undergoing multilevel instrumented lumbar fusion surgery

Arun-Kumar Kaliya-Perumal, MS^{a,b,c}, Meng-Ling Lu, MD^{a,b}, Chi-An Luo, MD^{a,b}, Tsung-Ting Tsai, MD^{a,b}, Po-Liang Lai, MD^{a,b}, Lih-Huei Chen, MD^{a,b}, Wen-Jer Chen, MD^{a,b}, Chi-Chien Niu, MD^{a,b,*}

Abstract

Elderly patients with chronic nonresolving symptoms due to degenerative spine pathologies are prone to have poor surgical outcomes and hardware-related complications, especially following multilevel instrumented lumbar fusion surgeries. With intention of analyzing if teriparatide can be an effective adjunct therapy to surgical management, radiological outcomes are studied. Sixty-two elderly patients were divided into 2 similar groups. Group 1 ($n=30$; mean age=69.83 years; fusion levels=137; screws=269) had taken teriparatide (20 mcg SC injection, once daily) for a duration of 7.4 ± 2.4 months following surgery and Group 2 ($n=32$; mean age=70.38 years; fusion levels=144; screws=283) did not take teriparatide. Radiological evaluation was done to determine the state of postero lateral fusion mass and to investigate the incidence of pedicle screw loosening at 1-year follow-up. Unilateral or bilateral bridging bone formation across the transverse process of adjacent vertebrae showing continuous trabeculation suggestive of solid fusion was obtained in 66.7% patients in the teriparatide group and 50% patients in the control group ($P=0.20$). 13.4% of the total no. of screws showed signs of loosening in the teriparatide group, compared to 24.4% in the control group ($P=0.001$). Percentage of patients achieving solid fusion following teriparatide use was found to be more than that of the control group. This difference may have clinical importance but was not statistically significant. However, teriparatide use was more significantly influential in reducing the incidence of subsequent pedicle screw loosening.

Abbreviations: AP = antero-posterior, BA = bronchial asthma, BMD = bone mineral density, CT = computerized tomography, DM = diabetes mellitus, MRI = magnetic resonance imaging, SC = subcutaneous, SD = standard deviation.

Keywords: fusion mass, posterolateral fusion, screw loosening, teriparatide

1. Introduction

Detriating osteogenesis potential and increased osteolysis leading to osteoporosis is prevalent in elderly population. The union rate and hardware-related complications remain a major concern in these patients, especially following multilevel spinal fusion surgeries. Developing an adjunct therapy that essentially supplements the mainstay surgical management is of great

importance to these patients. Multitudinous research to gain insight into use of teriparatide (1–34 recombinant human parathyroid hormone) for enhancing bone formation in osteoporosis is readily available in the literature.^[1–4] Its action as a direct anabolic agent in bone tissue, consistently increases bone mineral density and thus improves skeletal architecture.^[5] Since its availability in market, indications are unravelling and is being attempted in many conditions including fracture healing, dental stability, hypoparathyroidism, and hypocalcaemia.^[6,7] Another evolving field of interest is the role of teriparatide for enhancing bone graft union and osseo-integration of implants.^[8,9] It is said to accelerate bone graft union and reduce the incidence of pedicle screw loosening after lumbar spinal fusion surgeries.^[10,11]

We intended to study this effect and analyze if teriparatide can be an effective adjunct therapy to achieve solid posterolateral fusion mass and reduce the incidence of subsequent screw loosening after multilevel instrumented lumbar fusion surgeries in elderly patients.

2. Patients and methods

An open-labeled, nonplacebo controlled, retrospective, single center study is formulated by shortlisting 62 elderly patients (male 9; female=53) between the age group of 65 to 78 years (mean age \pm standard deviation [SD]=70.1 \pm 3.7), who underwent instrumented lumbar fusion for various degenerative pathologies over a period of time. All of them had received

Editor: Massimo Tusconi.

The authors have no funding and conflicts of interest to disclose.

^a Department of Orthopaedic Surgery, Spine Division, Bone and Joint Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan, ^b College of Medicine, Chang Gung University, Taoyuan, Taiwan, ^c Department of Orthopaedic Surgery, Melmaruvathur Adhiparasakthi Institute of Medical Sciences and Research, Melmaruvathur, Tamil Nadu, India.

* Correspondence: Chi-Chien Niu, Department of Orthopaedic Surgery, Spine Division, Chang Gung Memorial Hospital at Linkou, No. 5, Fusing Street, Gueishan, Taoyuan 333, Taiwan. (e-mail: niuchien@adm.cgmh.org.tw).

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Medicine (2017) 96:5(e5996)

Received: 20 September 2016 / Received in final form: 23 November 2016 /

Accepted: 31 December 2016

<http://dx.doi.org/10.1097/MD.0000000000005996>

multilevel lumbar fixation (≥ 3 levels or 4 vertebral segments) with pedicle screw constructs and postero-lateral intertransverse fusion with a combination of local bone graft and allograft.

The prime indication for surgery was chronic unresolving low back pain, with or without neurological symptoms, associated with any one of the following conditions:

- a) Multisegmental spinal instability (spondylolisthesis \geq grade 1),
- b) Multilevel degenerative spondylosis with or without segmental instability, and
- c) Degenerative scoliosis with or without segmental instability.

We excluded:

- a) Those patients operated with oligo-level spinal fusions (≤ 2 levels or 3 vertebral segments).
- b) Those with 1 or more osteoporotic vertebral compression fractures among the fused levels.
- c) Those with previous surgery in the same level.
- d) Those in whom infection or tumor was an indication for surgery.
- e) Those with 1 or more potential data missing.

Selection was irrespective of individual bone mineral density (BMD) status, as BMD scoring was not done as a part of routine preoperative evaluation in patients undergoing multilevel spinal fusions. Our sample included elderly patients ≥ 65 years who are expected to have deteriorating osteogenesis potential. Associated medical comorbidities included diabetes mellitus (DM) and bronchial asthma (BA) in 25 and 8 patients, respectively. Surgeries were performed by a single surgeon using similar technique and implants. Thorough decortication of transverse process was done before laying down the bone graft. A mixture of fresh frozen allograft and local bone chips were used as graft. Local bone consisted of spinous process, lamina, and facets from the decompression site. Occasionally, additional interbody cages were used at insufficient discs especially at the caudal end of the construct to increase stability. Following surgery, patients were given an option of postoperative teriparatide use and opting to it was solely based on their own decision. In total, 30 patients who accepted for long-term daily use of teriparatide were in the experimental group and remaining 32 patients were in the control group.

Teriparatide (self-administered; 20 mcg SC injection) was started for those patients in the experimental group from the first postoperative day, once daily using delivery device. Mean duration of teriparatide administration was for 7.4 ± 2.4 months. The control group received similar standardized and accepted treatment protocols as those in the experimental group except for the use of postoperative teriparatide. All patients were instructed to take calcium and Vitamin D supplements every day following surgery. Clinical and radiological evaluation data of entire follow-up period was collected. Outcome analysis was done using radiological data which included antero-posterior (AP), conventional lateral view, and dynamic stress lateral view radiographs taken at 12 months' follow-up (Figs. 1 and 2).

Postero-lateral fusion was graded using Lenke's criteria. A detailed description of the criteria is available in their original work.^[12] They divide postero lateral fusion mass into 4 grades based on the appearance in an AP radiograph. Grade A represents definitive fusion with bilateral thick bony masses, Grade B represents probable fusion with unilateral thick bony mass and thin bony mass on other side, Grade C represents no probable fusion with thin bony mass on the one side and pseudoarthrosis on the other side, Grade D represents no fusion with

thin bony mass on both the sides showing obvious pseudoarthrosis or resorption of graft bilaterally.

We interpreted Grade 1 and Grade 2 of Lenke's criteria as solid fusion which is explained as unilateral or bilateral bridging bone formation across the transverse process of adjacent vertebra showing continuous trabeculation in an AP radiograph. Grade 3 and 4 will be interpreted as nonunion. Although most of the patients had long fixations, segmental Cobb's angle change involving the upper and lower ends of the construct as seen in dynamic (flexion and extension) stress lateral views will also be considered as nonunion. Screw loosening was determined when there was occurrence of radiolucency (Halo sign) around the pedicle screws in either AP or lateral view radiographs. Change in the screw position noticed in dynamic stress lateral view radiographs will additionally be considered as screw loosening, which may occur at the cephalic and caudal ends of the construct.

Evaluation of radiographs were blinded and performed by 3 surgeons. Their observations were taken only if at least 2 of them concurred. Results were tabulated and statistical analyses were carried out using Graph Pad Prism 5 (GraphPad Software Inc., San Diego, CA). Analyses were done using Unpaired T test for continuous variables and Fisher's exact test for categorical variables. Probability values of less than 0.05 were considered statistically significant. Written informed consent was obtained from all patients including acceptance of daily usage of teriparatide delivery device from those in the experimental group. This study was approved by the institutional review board of Chang Gung Memorial Hospital with IRB Registry No - 201600800B0 and was performed in accordance with the ethical standards stated in the most recent version of the 1964 Declaration of Helsinki.

3. Results

Sixty-two elderly patients (age=65–78 years; mean=70.11 years; male=9, female=53) are divided into 2 groups based on teriparatide administration following surgery. Group 1 or the experimental group (n=30; mean age \pm SD=69.8 \pm 3.8 years) was those in whom teriparatide was administered and Group 2 (n=32; mean age \pm SD=70.4 \pm 3.6 years) was the control group. Mean age and sex ratio in the groups are similar (Table 1). Considering their age, patients in both groups are presumed to have poor BMD. The presence of concomitant medical comorbidities in Group 1 (DM=14; BA=4) and Group 2 (DM=11; BA=4) was matched. The demographic variation in characteristics of the groups is statistically insignificant (Table 1).

Surgical parameters of the experimental group (fusion levels=137; pedicle screws=269) and the control group (fusion levels=144; pedicle screws=283) had no statistically significant variance. Duration of teriparatide administration averaged 7.4 ± 2.4 months in the experimental group. Follow-up data were available for a mean duration of 25.4 months for those in the experimental group and 27 months for those in the control group. Even though follow-up was done for a longer duration, analyzing outcome further after 1 year may not be related to teriparatide use. Considering the duration of administration of teriparatide, radiological outcome analysis was decided to be done at 1 year follow-up. None of our patients missed the 1st year follow-up and required x-rays were available in our database for all the patients.

Radiological outcome analysis was done using AP, lateral, and dynamic stress lateral view radiographs taken at 12 months follow-up. Two or more observers concurred stating that there



Figure 1. Radiological outcome illustration of a random case from the teriparatide group. (A) Preoperative AP view radiograph. (B) Preoperative lateral view radiograph showing degeneration involving L1–L5 segments. (C) MRI images showing severe degeneration of disc levels and canal stenosis from L1–L5. (D) 12 months follow-up AP view x-ray which was considered as solid fusion (Lenke Type 1). AP = antero-posterior, MRI = magnetic resonance imaging.

was unilateral or bilateral bridging bone formation across the transverse process of adjacent vertebrae showing continuous trabeculation confirming solid fusion in 20 patients (66.7%) of the teriparatide group and 16 patients (50%) in the control group. Nonunion was noted in 10 patients (33.3%) of teriparatide group and 16 patients (50%) in the control group. The 16.7% advantage procured with teriparatide use was not statistically significant ($P=0.20$) (Table 2). Screw loosening was calculated comparing the number of screws showing signs of loosening to total number of screws in each group. The incidence of screw loosening was 13.4% in the teriparatide group and 24.4% in the control group. This difference was statistically significant with $P=0.001$ (Table 2).

4. Discussion

Elderly patients with chronic unresolving symptoms due to degenerative spine disease are prone to have poor surgical outcomes. They also predispose for more hardware-related complications, especially following long spinal fusions. Considering the possibility of poor outcomes, treating these conditions cannot be ignored but rather a potential solution needs to be developed which effectively supplements the mainstay surgical management. Teriparatide seemed to be a promising solution for this difficult problem. It is said to play a reasonable role in treatment of osteoporosis.^[1–4] Apart from being used in

osteoporotic individuals, insights into its action on many other conditions are unraveling.^[6] Animal studies yielded promising results for teriparatide usage to enhance postero-lateral fusion mass in rat models.^[13] In human studies relating to teriparatide, most authors studied its effect only in osteoporotic individuals.^[10,11] In our sample, patients were between 65 and 78 years of age and are more susceptible to have poor BMD. Patients had comorbidities such as DM and bronchial asthma that have negative influence over BMD.^[14–16] DM is said to reduce BMD at a higher rate in elderly women, even if the baseline BMD was high.^[14] Patients with bronchial asthma are also prone to have reduced BMD.^[15]

All available potentially confounding variables were matched among both the groups of our sample. We followed similar standardized surgical technique of posterolateral fusion and instrumentation. Along with postero-lateral fusion, additional interbody cages were used especially at very insufficient discs often seen in the caudal end of the construct. Thorough decortication of transverse process was done before placing the graft. This promotes fusion by exposing the underlying cancellous bone rich in vascular supply.^[16] This step also allows the graft to access the pluripotent stem cells of the bone marrow.^[16] Since a large amount of graft is required for long fusions, there usually is a lack of host bone. We preferred fresh frozen allografts along with local bone chips for this purpose. These allografts can yield greater quantity of bone that gets



Figure 2. Radiological outcome illustration of a random case from the control group. (A) Preoperative AP view radiograph. (B) Preoperative dynamic stress (extension and flexion) lateral view radiographs showing degeneration from L3–S1 segments. (C) MRI images showing severe degeneration of disc levels and canal stenosis from L3–S1. (D) 12 months follow-up AP view x-ray showing bilateral signs of pseudo-arthritis interpreted as nonunion (Lenke Type 4). AP = antero-posterior, MRI = magnetic resonance imaging.

completely incorporated. Donor site morbidity can be significantly overcome by using allografts. Teriparatide could be a supplement for enhancing osteogenesis and bio-integration of allografts.^[17]

Static and dynamic radiographs are used for radiological assessment of spinal fusion by many authors, but computerized tomography (CT) is considered more accurate.^[18] Most of the

radiographic criteria developed to assess fusion mass consider movement in dynamic radiographs as a main component for assessment.^[19] Dynamic radiographs include flexion and extension lateral views. They lack reliability as the absence of motion does not confirm fusion, especially in the case of long instrumented levels.^[20] Based on AP radiographs, we considered Grade A (definitive fusion; bilateral thick bony mass) and Grade

Table 1

Demographic comparison.

| | Teriparatide group | Control group | Statistical analysis |
|--|--------------------|------------------|----------------------|
| No. of patients | n=30 | n=32 | |
| Age, y, mean age±SD, range | 69.8±3.8 (65–78) | 70.4±3.6 (65–77) | P=0.56 |
| Sex | M=4, F=26 | M=5, F=27 | |
| DM | 14 | 11 | P=0.32 |
| BA | 4 | 4 | P=0.92 |
| Total no. of fusion levels | 137 | 144 | P=0.73 |
| No of levels in each patient | 4.6±0.8 (3–6) | 4.5±0.7 (4–6) | |
| Total no of screws | 269 | 283 | P=0.76 |
| No of screws in each patient | 8.9±1.6 (7–12) | 8.8±1.5 (7–12) | |
| No of patients with interbody cages at caudal insufficient discs | 7 | 9 | P=0.66 |
| Follow-up, mean | 25.4 mo | 27 mo | P=0.65 |

Some values are presented as “mean±standard deviation (range).”

A probability value (P) < 0.05 was considered statistically significant.

BA=bronchial asthma, DM=diabetes mellitus, SD=standard deviation.

Table 2**Results.**

| | Teriparatide group | Control group | Statistical analysis |
|---|--------------------|-----------------|----------------------|
| Fusion, 1 y, – evaluation by radiography | | | |
| | No. of patients | No. of patients | |
| Solid fusion | 20 (66.7%) | 16 (50%) | $P=0.20$ |
| Nonunion | 10 (33.3%) | 16 (50%) | |
| Screw loosening—evaluation by radiography | | | |
| | No. of screws | No. of screws | |
| 1 y | 36 (13.4%) | 69 (24.4%) | $P=0.001^*$ |

Values are presented as "total number (percentage)."

* A probability value (P) < 0.05 was considered statistically significant.

B (probable fusion; unilateral thick bony mass) described by Lenke et al^[12] as solid fusion. Fusion masses that did not favorably appear to have definitive or probable fusion were considered as nonunion. We also considered change in segmental Cobb's angle, visualized in dynamic stress lateral view radiographs as an additional criterion to interpret as nonunion. Formation of a radiolucent zone (halo sign) around the pedicle screws seen in conventional AP/lateral view radiographs and change in screw position seen in dynamic stress lateral view radiographs were considered definitive indicators for screw loosening.^[21]

Teriparatide is said to have potential to increase the quality of lumbar spine bone marrow and pedicle cortex and thus reduces the incidence of pedicle screw loosening.^[11] It is even believed to increase the insertional torque of pedicle screws when administered from at least 1 month prior to surgery.^[22] Long-term teriparatide use can be associated with significant improvement in bone microarchitecture and trabeculation.^[23] It is also said that; more than 6 months of daily injection facilitates effective bone union following postero-lateral fusion.^[24] Considering this, we administered teriparatide for a mean duration of 7.4 months and none of the patients had any drug induced complications. Most of the similar studies in literature included only short segment postero-lateral fusions. Our study is foremost to discuss the effect of teriparatide on multilevel posterolateral fusions in elderly patients. According to our preliminary results, the percentage of patients achieving solid fusion following teriparatide use was found to be more than that of the control group. This difference may have clinical importance but was not statistically significant. Besides that, use of teriparatide effectively reduced the incidence of subsequent screw loosening which proved to be statistically significant.

5. Conclusion

Our study evaluates the radiological outcome following postoperative teriparatide administration in patients undergoing multilevel instrumented lumbar fusion surgery. Even though percentage of solid fusion was more among patients who used teriparatide, the difference was not statistically significant. However, teriparatide was more significantly influential in reducing the incidence of subsequent pedicle screw loosening. This can be considered supplementary to its wide evolving range of benefits.

6. Limitations

Being a retrospective study, there are few methodological shortcomings that may have influenced our outcome. The lack

of preoperative BMD data, variation in surgical indications, and differential treatment durations of teriparatide administration may have biased the sample. Use of CT as an evaluation tool to assess bone graft union could have been more empirical. Considering the selected sample size, the study may be underpowered to draw potential conclusions. These limitations need to be considered and results be interpreted with caution.

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