Original Article

Bone Turnover in Vertebral Fractures: Does it Effect the Decision of Surgery?

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Abstract

Background and Aim: Instrumentation is commonly used in spinal surgery to stabilize the fracture. In the present study, we aimed to compare the early and late changes seen in bone production and degradation products in patients with traumatic spinal fracture who had been treated surgically or conservatively. **Materials and Methods:** Forty-three patients were admitted to the Neurosurgery Department with thoracolumbar or lumbar fracture in this prospective study. Patients were divided into two groups of surgically treated (n = 23) and nonsurgically/conservatively treated (n = 20) patients. The early and late changes seen in bone production and degradation products were compared in patients with traumatic spinal fracture who had been treated surgically or conservatively. **Results:** In conservatively treated patients, although osteocalcin level was slightly increased and deoxypiridinoline (DPD)/creatinine was slightly decreased after the treatment, the difference was not statistically significant (P = 0.08 and P = 0.539, respectively). There is no significant difference between admission time, posttreatment late period osteocalcin level, and DPD/creatinine ratio between the two group of patients (P = 0.215 and P = 0.236, respectively). **Conclusion:** We suggest that the healing and fusion processes in fractured vertebrae not only followed by the radiological examination but also by noninvasive biochemical changes seen in the serum levels of bone formation and resorption markers.

Keywords: *Deoxypiridinoline, osteocalcin, vertebral fractures*

Introduction

There are various reasons for spinal fractures including trauma, osteoporosis, tumor metastasis, and infections. The trauma-induced vertebral body fractures are directly proportional to the amount of kinetic energy loaded on the spine.[1] The diagnosis of traumatic spinal fractures is made using plain radiography, computed tomography (CT), and magnetic resonance imaging (MRI) images followed by the conservative or surgical treatment to establish the stability of fracture. Instrumentation from anterior or posterior is commonly used in spinal surgery to stabilize the fracture and to accelerate the bone turnover by filling the gaps occurred between bone cells.[2] The surgical procedure used for the treatment of spinal fractures since 1959 is performed through pedicles from a posterior approach.[3] Today, the pedicle screws used in the surgical procedures are bioinert and are made of a titanium metal of Ti6Al4V, which has the highest biocompatibility.[4]

Till date, the changes occurring in the bone metabolism after a fracture have been well documented. Healing and repair processes after long-bone fractures result in dramatic changes in bone destruction (resorption) and construction (formation) markers.[5-8] The level of bone degradation products increases immediately after a fracture while bone formation markers increase gradually.[9-14] Major bone formation markers are osteoblast-derived osteocalcin and bone-specific alkaline phosphatase, while the bone degradation products are urinary piridinoline (PYR), deoxypiridinoline (DPD), and serum C-telopeptide.[7,15,16]

Fracture healing process is divided into three different periods: period of inflammation, period of construction, and remodeling period. The changes occurring during bone degradation and production are more intense compared to those seen during the remodeling period.[7] However, very little is known about the changes occurring in bone metabolism after traumatic spinal fracture.

In the present study, we aimed to compare the early and late changes seen in bone

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production and degradation products in patients with traumatic spinal fracture who had been treated surgically or conservatively.

Materials and Methods

After obtaining the approval of local Ethics Committee, a total of 43 patients admitted to the Neurosurgery Department with traumatic thoracolumbar or lumbar burst fracture or unstable compression fracture with no neurological defects were included in this prospective study. Patients with osteoporotic vertebrae fracture, multiple organ injury, and/or additional musculoskeletal trauma were excluded from the study. Patients were divided into two groups of surgically treated (n = 23) and nonsurgically/conservatively treated (n = 20) patients. Both groups of patients did not receive vitamin D and bisphosphonate drugs during the treatment period.

After obtaining plain radiography, CT, and MRI images, the patients concluded to have spinal stability failure including anterior and middle colons according to the three-colon theory of Denis were assigned to undergo posterior pedicular surgery. Modified Rankin scale and the American Spinal Injury Association Impairment Scale were used for pre- and post-operative neurological examinations, respectively.[17] In surgically treated patients, preoperative 1 g of cefadroxil monohydrate sodium was administered and surgery was performed under general anesthesia in prone-positioned patients. Stabilization of the fracture was established using titanium screws on second upper and second lower intact vertebras, second upper and first lower vertebras, or the upper fractured and first lower vertebras. After establishing the posture alignment and distraction, fusion areas were decorticated. Laminectomy was performed in some cases. Posterolateral autograft and allograft were draped. Drainage was provided and surgical area was closed. Twenty-four hours after the surgery, patients were mobilized with using an orthotic corset device which was advised to be used for 3 months.[18]

After taking the pain under control, conservatively treated patients were mobilized following a 1–3 months of bed resting period with corset device and were advised to use the corset for 3 months.[15,19]

Preoperative blood and urine samples were obtained from all patients at the beginning of the study. In 23 surgically treated patients, blood and urine samples were obtained also at postoperative day 7 and postoperative late period (at month 4–6). On the other hand, postoperative blood and urine samples were obtained only at the late period in conservatively treated control patients. Serum samples obtained by the centrifugation of the venous blood samples in 30 min at 3000 g for 5 min and urine samples centrifuged at 500 g for 5 min were stored at −80°C until analysis.

Serum osteocalcin and urinary deoxypiridinium levels were measured by the solid-phase chemiluminescence immunometric method and using commercially available kits on an Immulite 1000 (Immulite, Diagnostic Products Corporation, LA, USA) analyzer. For the osteocalcin measurement, analytical sensitivity was 0.1 ng/ml with 3.17% of intraassay coefficient of variation and 4.68% of interassay coefficient of variation. For deoxypiridinium measurement, analytical sensitivity was 6 nM with 10% of intraassay coefficient of variation and 14% of interassay coefficient of variation.

Urinary creatinine level was measured by the method of Jaffe and using commercially available kits on Roche Modular (Roche Diagnostics, Switzerland) autoanalyzer. Urinary deoxypiridinium levels were divided by urinary creatinine levels and results were expressed as nM deoxypiridinium/mM creatinine.

Statistical analysis

Continuous data were given as mean ± standard deviation, while categorical data were presented as percentages (%). Shapiro Wilk's test was used to examine the normality of results. For the comparison of the variables in different measurement points, the Wilcoxon test was used when the group number was two. Two-way repeated-measures ANOVA (one-factor repetition) test was used for repeated measurements. Data were analyzed with IBM SPSS statistics 21.0 0 (IBM Corporation, New York, USA) and Sigma Stat 3.5 programs (Systat Software, Inc. USA). Statistical significance was considered as $P < 0.05$.

Results

Of the 23 patients treated with surgery, 11 (47.8%) were female and 12 (52.2%) were male with a mean age of 53.7 years (range, 22–67 years). The cause of traumatic vertebral fracture was falls in 14 patients, motor vehicle accident in 6 patients, and occupational accident in 3 patients. The level of traumatic fracture was Th12 vertebrae in 2 cases (8.7%), L1 vertebrae in 8 cases (34.8%), L2 vertebrae in 5 cases (21.6%), L3 vertebrae in 4 cases (8.7%), L4 vertebrae in 2 cases (8.7%),

Table 1: Demographic variables, causes of traumatic fracture, and level of the lesion

	Surgically treated group	Control group
Number	23	20
Gender (female/male)	11/12	14/6
Mean age (years)	53.7	56.1
Falls/motor vehicle accident/ occupational accident	14/6/3	12/6/2
Level Th12/L1/L2/L3/L4/	2/8/5/4/2/-	2/8/5/2/-/-
Multilevel fracture	2 cases	3 cases

Th12–L1 vertebras in 1 case (4.4%), and Th12–L2 vertebras in 2 cases (8.7%) [Table 1].

Of the conservatively treated patients, 14 (70%) were female and 6 (30%) were male with a mean age of 56.1 years (range, 31–64 years). The cause of traumatic vertebral fracture was falls in 12 patients, motor vehicle accident in 6 patients, and occupational accident in 2 patients. The level of traumatic fracture was Th12 vertebrae in 2 cases (10%), L1 vertebrae in 8 cases (40%), L2 vertebrae in 5 cases (25%), L3 vertebrae in 2 cases (10%), Th12-L1 vertebras in 1 case (5%), L1–2 vertebras in 1 case (5%), and L3–4 vertebras in 1 case (5%) [Table 1].

In surgically treated group, the postoperative complications of superficial wound infection or deep venous thrombosis were seen in a total of two cases. The patients were mobilized using an orthotic device.

In surgically treated group, a significant difference was found between the admission time, posttreatment early, and posttreatment late osteocalcin levels ($P < 0.001$). This difference was found to be caused by the increase seen in osteocalcin level in posttreatment late period compared to the admission time and posttreatment early period ($P < 0.001$ and $P < 0.001$, respectively). Although DPD/creatinine level was increased in this group of patients in the posttreatment early period, there was no significant difference between the admission time, posttreatment early, and posttreatment late periods ($P = 0.174$) [Table 2].

In conservatively treated patients, although osteocalcin level was slightly increased and DPD/creatinine was slightly decreased after the treatment, the difference was not statistically significant ($P = 0.08$ and $P = 0.539$, respectively) [Table 3].

There was no significant difference in admission time and posttreatment late period osteocalcin level and DPD/creatinine ratio between the two group of patients ($P = 0.215$ and $P = 0.236$, respectively).

Discussion

Traumatic vertebral fractures are treated conservatively or surgically. After an initial neurological examination, the plain radiography, CT, and MRI images are used to determine whether anterior, middle, or posterior colon is affected as well as to assess the kyphotic angle of the fracture and involvement of bony structures in the channel, all of which are used to guide the treatment choice.[17] On the other hand, it is well known that regional osteopenia is seen in the area surrounding the fracture site. Histopathological studies have reported increased bone turnover induced by regional osteopenia.[20] The healing of traumatic bone fractures is composed of 3 stages: inflammation, regeneration, and remodeling stages. For the fracture healing process, the changes occurring during bone degradation (resorption) and production (formation) are more intense compared to those seen in the remodeling period in all bone fractures.[7,15] Many neurosurgeons advocate using the fusion surgery from the posterior in unstable vertebral fractures to complete the healing process with no deformation and to ensure stability. All transpedicular implants are used to provide vertebral reduction until the fracture heals and fusion occurs.[18,21]

There are several advantages of surgical procedures performed from the posterior. Most importantly, the screw implemented through pedicles encloses all three colons defined by Denis, holding the vertebrae from its most strong region and ensuring the stability. This most commonly used surgical method is easy, simple, safe, and

Table 2: Osteocalcin level and deoxypyridinoline/creatinine ratio in surgically treated group of patients

Surgically treated patients	Mean±SD Median (Q_1–Q_3)			*P**
	Admission time	Posttreatment early period	Posttreatment late period	
Osteocalcin (ng/ml)	4.91±3.98	3.87±3.00	8.37±3.00	<0.001
	3.3 (2.82-4.95)	2.85 (1.72-5.27)	7.55 (5.72-11.6)	
DPD/creatinine (nM DPD/mM creatinine)	12.08±7.06	25.44±41.79	13.30±17.25	0.174
	10.6 (7.63-16.36)	12.63 (10.26-17.20)	8.00 (7.20-9.77)	

*Two-way repeated-measures ANOVA (one-factor repetition). DPD – Deoxypiridinium; SD – Standard deviation

Table 3: Osteocalcin level and deoxypyridinoline/creatinine ratio in conservatively treated group of patients

Conservatively treated patients	Mean±SD Median (Q_1–Q_3)		*P**
	Admission time	Posttreatment late period	
Osteocalcin (ng/ml)	4.02±4.67	6.30±3.21	0.080
	2.70 (1.62-4.00)	5.25 (4.72-6.25)	
DPD/creatinine (nM DPD/mM creatinine)	15.54±25.74	11.15±18.46	0.539
	8.90 (6.87-15.42)	7.00 (5.62-9.07)	

*Wilcoxon test. DPD – Deoxypiridinium; SD – Standard deviation

useful. By this way, it is aimed to decrease the existing neurological injury, to improve the posttraumatic deformity and kyphotic tilting, to provide pain control and bone fusion, and to allow early mobilization and termination of bedriddenness. Moreover, this approach also decreases the long-term immobilization-induced adult respiratory distress syndrome, pneumonia, deep vein thrombosis, and pulmonary embolism and thromboembolic complications risks.[17,19,22] However, this surgical method also has some disadvantages including instrumentation failure, pseudoarthrosis, infection, spinal cord injuries, loss of kyphotic correction, and neurological decompression failure.[23-25]

The implementation techniques are long-segment or short-segment pedicular screw surgical techniques. In some clinical series, it has been emphasized that the pedicle screws implemented to the second upper and second lower vertebrae from the fractured vertebra provide a better fusion and a rigid spinal region in an unstable spine. It has also been reported that the screw placed to the two intact upper vertebras can biomechanically protect from the implant failure induced by segmental kyphosis. Neuwirth has also preferred to place pedicle screw to the second upper vertebra from the injured vertebra.[22-24,26] Similarly, in our study, surgical stabilization by long- and short-segmental screws and pedicular screw application to the second upper vertebrae were used. Surgery was completed by applying another pedicle screw to one or two segments below the fractured vertebrae or by stabilizing to the upper fracture itself and the first lower vertebrae.

Majority of stable thoracolumbar spinal injuries are treated without surgery. When there are no neurological deficit, vertebral fracture patients with stable explosion and simple compression are mobilized in hyperextension in early period using a corset.[27-29] These nonsurgical patients were included in the control group and they had been mobilized with a corset after a resting period varying from 1 to 3 weeks. Patients were asked to use the corset for 3 months[15,19] because previous studies have showed increased serum and urinary levels of bone production and degradation products in patients with osteoporosis;[7] osteoporotic patients were not included in the study.

Similar to other bone fractures, bone resorption markers of serum C-terminal telopeptide and urinary PYR and DPD can also be measured as biochemical changes that occur in vertebral fractures. As is known, the formation products produced and released by active osteoblasts are bone-specific alkaline phosphatase, type 1 collagen amino- and carboxyl-terminal and osteocalcin, all of which can be measured in serum and plasma.[15,30,31] Osteocalcin is a noncollagen protein and serum osteocalcin level increases in cases with increased bone turnover. It is synthesized by osteoblasts during the bone matrix mineralization phase. After synthesized, it moves in the bone matrix as well as moves out to the circulation.[32] Increased osteocalcin level at a late period indicates that osteoblast differentiation is in a late period or that the mechanical stress induced by walking or physical activity maintains the osteoblast differentiation.

Hitherto, there are no reports on long-term changes in bone resorption and formation markers in patients with vertebral fracture. Our study investigated the early and late changes in these markers in vertebral fracture patients treated conservatively or by surgery.

The deoxypirinidoline crosslink formed for the stabilization of collagen fibers during the bone formation is more specific to the bone tissue than other crosslinks.[33] In bone degradation, these crosslinks are excreted unchanged in the urine. During the bone healing period, degradation products were found to start to increase in our patients 1 week after the surgery. Ohishi *et al*.[7] have found in their study that bone degradation products have started to increase within the 1st week in nonoperated and operated patients. The authors have attributed these findings to the necrosis in the early period. This increase was also found to decrease from the 4th week. Similarly, in our study, bone degradation products were found to increase and decrease in similar time periods. However, they have reported simultaneous increase in bone formation products as well as a marked increase in osteocalcin level at week 24. All these above-mentioned pattern of changes is similar to that seen in hip fractures.[7] In our study, osteocalcin level was found to increase in both groups between months 4 and 6 with a statistical difference in surgically treated group. We believe that fusion surgery may facilitate the increase of these bone formation products. However, it should also be mentioned that there was no difference between the two groups in terms of posttreatment late osteocalcin levels ($P = 0.215$).

Two different previous studies have reported lower level of bone formation markers in patients with delayed healing of tibial shaft fracture compared to those with complete healing,[11,13] indicating that bone formation products always increase along with the bone healing process. During the normal fracture healing process, bone-specific alkaline phosphatase is associated with the osteoblastic activity in the early period while increased osteocalcin level at the late period is associated with the mineralization of bone. Therefore, different from the bone-specific alkaline phosphatase, osteocalcin may somewhat indicate the fractures with poor healing.[15] From a pathological perspective, under the microscope, fibrous or avascular granulation tissue as well as necrotic bone or serous fluid was seen in the bodies of unhealed vertebras.[34,35] In the light of these pathological findings, Ohishi *et al*.[15] have suggested that fracture healing is impaired due to the decrease in the number of osteoblasts and in mineralization activity in unhealed or incompletely healed vertebras which

are associated with osteocalcin defect in the advanced stages of healing process. All these findings indicate that serum osteocalcin level may be a follow-up marker during the healing of fractured vertebrae in patients who have had fusion surgery.

As seen, increases and decreases in bone resorption and formation products are seen during the remodeling phase in bone healing process. This is also true for vertebral fractures. However, we believe that the most appropriate option is the surgery for posterior pedicular stabilization in unstable vertebras to minimize the risk of alignment disorders such as kyphotic angulation, bending, and breakdown induced by the healing process of deformed vertebrae.

Conclusion

We have been using it for decades for the surgery of spinal fractures, and we still prefer that the transpedicular screw that is applied posterior is the ideal technique because it is the easiest, safest, and quickest to heal as it is nowadays all over the world. We also believe that these processes can be followed biochemically through assessment of bone formation and degradation biomarkers, not only by radiological techniques, but also in follow-ups in the process of healing and fusion in conservative or surgically treated vertebral fractures. We believe that these biochemical markers should be supported in other clinical trials to be routinely used in the healing process.

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Conflicts of interest

There are no conflicts of interest.

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