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ORIGINAL ARTICLE

Bone union after spinal fusion surgery using local bone in long-term bisphosphonate users: a prospective comparative study

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Abstract

Summary Bisphosphonates are the most commonly used drugs for osteoporosis and long-term use of bisphosphonates may affect fusion rate after spinal fusion surgery. There was significant delayed union after 6 months in long-term bisphosphonates users; however, there were no significant difference in fusion rate of long-term bisphosphonate users. Therefore, spinal fusion surgery should not be hesitated in long-term bisphosphonates users.

Purpose Bisphosphonates (BPs) are the most popular class of drugs for treatment of postmenopausal osteoporosis. Long-term use of BPs may also inhibit the spinal fusion process after posterior lumbar interbody fusion (PLIF). We compared bone fusion rates of long-term BPs users and non-users after undergoing spinal fusion surgery.

Methods A total of 97 postmenopausal women who were candidates for single-level PLIF were recruited from 2015 to 2016. Participants were divided into two groups, with 63 patients in a long-term BPs user group and 34 patients in a non-user group. Serum C-terminal cross-linking telopeptide (CTX) levels were checked for bone resorption markers. Bone fusion rates were calculated at 6 months and 1 and 2 years after the surgery. Clinical outcomes were measured using the Oswestry Disability Index (ODI) and visual analog scale (VAS).

Results Serum CTX level was dramatically decreased in the long-term BPs user group ($p < 0.05$). Fusion rates at 6 months after surgery were 42% in the non-user group and 26% in the long-term BPs user group ($p = 0.035$). However, fusion rates were 82% in the long-term BPs user group and 87% in the non-user group at 2 years after surgery ($p > 0.05$). There was no significant difference between the two groups in ODI or VAS.

Conclusions Even though there was significant delayed union after 6 months in long-term BPs users, at the 2-year postoperative follow-up, there was no significant difference in bone fusion rate between the two groups. Long-term BPs users showed fusion rates greater than 80% and clinical outcome improvements that were comparable to those in non-users. No significant effect on fusion rate after PLIF was found in long-term BPs users.

Keywords Spinal fusion · Bisphosphonates · Bone union · Long-term user

Introduction

Lumbar degenerative disease is common, with prevalence in the general adult population of 37% [1]. As the population ages, disability associated with lumbar degeneration is rapidly increasing and there is concomitant increase in prevalence of osteoporosis.

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Spinal fusion is a fundamental treatment option for a variety of degenerative disorders, tumors, infections, trauma, and deformities of the spine, because successful fusion can lead to pain relief and neurologic recovery. Spinal fusion surgeries have increased over the past several decades as the elderly population continues to grow [2–4]. Successful spinal fusion necessitates formation and remodeling of new bone, processes that rely on the osteoblast/osteoclast complex [5]. Although instrumentation and techniques have been improved, non-union after spinal fusion is the most frequently encountered complication and the rate of non-union after a single-level spinal fusion procedure has been reported be as high as 35%, which is caused by both systemic and environmental factors [6, 7]. Factors that influence fusion include the disease

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indicating fusion, types of graft used, fusion techniques, presence of instrumentation, smoking habits, alcoholism, and drugs the patients received [8–10].

Bisphosphonates (BPs), which are potent antiresorptive agents, are the most commonly used drugs for prevention and treatment of diseases related to increased bone resorption, such as osteoporosis [11–13]. BPs inhibit osteoclastogenesis in the bone marrow, decrease osteoclast activity at the bone surface, and shorten osteoclast life span by increasing apoptotic cell death [14]. Its mechanisms of action include inhibition of osteoclast activity, osteoclast inactivation, and apoptosis, thus reducing bone resorption [15]. The pharmacological action of BPs is understood to inhibit bone resorption by blocking osteoclasts from breaking down bone due to accumulation on bone surfaces [16]. The proposed mechanism involves oversuppression of bone turnover that limits the reserve capacity of bone to repair microdamage. Treating patients with BPs during bone hearing is controversial because osteoclasts are important for remodeling callus into cortical bone. Several studies about possible effects of BPs on fracture healing have been noted.

Spinal fusion is the most common surgical option for spine diseases, and most patients who require spinal fusion are elderly with bone fragility due to osteoporosis [17, 18]. As BPs are well-known first-line medications for prevention or treatment of osteoporosis, a significant proportion of patients requiring spinal fusion might also be taking BPs [11]. The reported fusion rates of elderly patients in previous studies have been over 90% [19, 20]. BPs might affect the process of spinal fusion, but such effects have not been clarified sufficiently in cases of spinal fusion surgery. Several animal and clinical studies on spinal fusion have shown positive effect similar as fracture healing, and postoperative administration of BPs is recommended after spinal fusion surgery.

As BPs inhibit bone metabolism, the long-term use of BPs before spinal fusion surgery may affect the biological process of spinal fusion and lead to non-union. To the best of our knowledge, no previously published clinical studies have investigated the influence of preoperative long-term BPs usage on spinal fusion. The objective of this study was to compare fusion rates between long-term BPs users and non-users after single-level posterior lumbar interbody fusion (PLIF) surgery.

Materials and methods

Study design and participants

We hypothesized that the fusion rate after single-level PLIF surgery of long-term BPs users would be comparable to that of non-users. This study was approved by our Institutional Review Board, and informed consent was obtained from each patient.

The inclusion criteria were a diagnosis of single-level spinal stenosis, degenerative spondylolisthesis, or spondylolytic spondylolisthesis with symptoms of low back pain and/or leg pain for at least 3 months, which was not adequately controlled by nonoperative treatments including bed rest, bracing, non-steroidal anti-inflammatory drugs, and physical therapy. Exclusion criteria included severe spinal deformity, previous spine surgery, infection, trauma, and tumorous conditions.

A total of 97 postmenopausal women who were candidates for single-level PLIF were recruited from January 2015 to August 2016. A 2-year follow-up period was planned. Participants were divided into two groups; there were 63 patients in the long-term BPs user group and 34 patients in the non-user group. One patient from each group was lost during the postoperative follow-up period, making the final number of patients from the long-term BPs user group and the non-user group 62 and 33 patients, respectively (Fig. 1). Long-term BPs users were patients who used alendronate for more than 2 years under the diagnosis of postmenopausal osteoporosis. BMD of lumbar spine and proximal femur were measured by dual-energy X-ray absorptiometry (DXA) before surgery. The criteria for osteoporosis were less than 70% of the young adult mean BMD value (or less than 80% of the young adult mean BMD value in postmenopausal women) or the presence of a vertebral fracture related to bone fragility.

Surgical procedures: single-level posterior lumbar interbody fusion

One orthopedic spine surgeon from our Institute performed all the operations. All patients were operated on in a prone position through a midline skin incision under general anesthesia. Transpedicular screws and a polyetheretherketone (PEEK) cage were used in each patient. After transpedicular screws were inserted, a total facetectomy was performed using a high-speed drill, osteotome, and Kerrison rongeurs. The ligamentum flavum was removed, and the exiting nerve roots were exposed. A complete discectomy and curettage of the endplate was performed. Then, the anterior third and contralateral side of the disc space was filled with local bone graft harvested from the posterior elements. An appropriately sized PEEK cage packed with excised local bone was inserted into the disc space. Finally, the pre-lordosed rod was seated and compression was applied.

Outcome measures

All patients completed self-assessment questionnaires and provided demographic and clinical information, including age, body mass index (BMI), smoking history, diagnosis, and BMD. Serum C-terminal cross-linking telopeptide (CTX) levels were checked for bone resorption markers, which could be decreased dramatically in long-term BPs users. To minimize diurnal variation

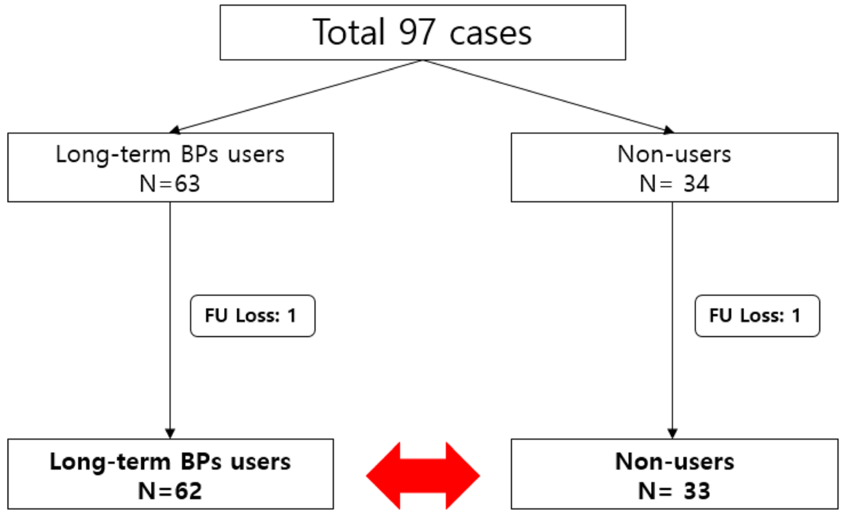

Fig. 1 Trial profile

of bone metabolic markers, the samples were obtained in the morning. Bone fusion rates were calculated 6 months and 1 and 2 years after the surgery using dynamic radiographs and computed tomographic (CT) scans. Clinical outcomes were measured using the Oswestry Disability Index (ODI) and visual analog scale (VAS). Serial evaluation measures were performed at the immediate postoperative period, and at 1 and 2 years postoperatively.

Radiologic assessment

Dynamic radiographs, including flexion and extension views, and high-quality thin slice (1- to 3-mm) CT scans were obtained at 6 months and at 1 and 2 years after surgery to allow the surgeon to assess the degree of stability and to determine whether fusion had occurred. The CT scans were examined by two different orthopedic surgeons. The parameters of interest included segmental angular motion, presence or absence of bridging bone, and cage subsidence. The flexion radiographs were taken with the patient in the standing position, trying to bend forward as far as possible, whereas the extension radiographs were taken with the patient maximally arching the back. Bone formation on CT scans was graded into three categories: grade A, with bridging bone bonding with both adjacent vertebral bodies; grade B, with bridging bone bonding with either superior or inferior vertebral body; or grade C, with incomplete bony bridging (Fig. 2). Fusion was defined as a bridging bone between the vertebral bodies either within or external to the cage. A solid fusion was defined as less than 5° of angular motion on flexion-extension radiographs at the fusion level and the presence of grade A or B bone formation on CT scans [18].

Statistical analysis

Differences in mean VAS and ODI scores between the baseline and each postoperative period were assessed with paired *t* tests. Demographic data, clinical data, radiologic data, and the incidence of adverse events were compared with the Mann-Whitney *U* and Fisher's exact tests. The level of significance was set at $p < 0.05$. All statistical analyses were performed using SPSS ver. 20.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic data

Age, BMI, smoking history, and diagnosis were not significantly different between the two groups (Table 1). The mean age of the non-user group was 62.5 years and that of the long-term BPs user group was 65.8 years. The mean BMI of the non-user group was 24.1 kg/m^2 and that of the long-term BPs user group was 23.8 kg/m^2. One patient in each group had a history of smoking. The other covariates that are known to be risk factors for non-union were similar between the two groups.

The mean BMD of the non-user group was −2.3 in the spine and −1.8 in the hip; those of the long-term BPs user group were significantly different ($p < 0.001$), at −2.7 in the spine and −2.1 in the hip. Long-term BPs users had used alendronate (alendronate sodium [Fosamax] at a dosage of 35 mg/week) for at least 2 years (average, 32 months). The serum CTX level was dramatically decreased in the long-term BPs user group (0.43 ± 0.14 vs. 0.11 ± 0.12 ng/ml, $p = 0.002$). The serum vitamin D level was not different significantly between the two groups (22.79 ± 13.06 vs. 23.98 ± 13.7 ng/ml, $p = 0.392$). Also, the serum calcium level was not different significantly between the two groups (9.68 ± 0.84 vs. 9.75 ± 0.88 mg/dl, $p = 0.223$).

The spinal pathologies were degenerative spondylolisthesis in 29 patients, spondylolytic spondylolisthesis in 11 patients, and spinal stenosis in 22 patients in the long-term BPs user group; degenerative spondylolisthesis in 15 patients,

Fig. 2 Three-category grading system for bridging bone formation based on sagittal computed tomography. **a** Bridging bone bonding with both adjacent vertebral bodies. **b** Bridging bone bonding with one vertebral body. **c** Incomplete bony bridging

spondylolytic spondylolisthesis in eight patients, and spinal stenosis in 10 patients in the non-user group. In both groups, the most common diagnosis was degenerative spondylolisthesis.

The operative level was L3/4 in five patients, L4/5 in 42 patients, and L5/S1 in 16 patients in the long-term BPs user group; and L3/4 in two patients, L4/5 in 22 patients, and L5/S1 in 10 patients in the non-user group.

Radiologic assessment

Bridging bone formation was assessed by CT and graded into three categories. In the long-term BPs user group at the 6-month observation, one patient was classified as grade A (2%), 35 patients were classified as grade B (56%), and 26 patients were classified as grade C (42%). In the non-user group at the 6-month observation, one patient was classified as grade A (3%), 22 patients were classified as grade B (67%), and 10 patients were classified as grade C (30%). In the long-term BPs user group at the 1-year observation, 20 patients were classified as grade A (32%), 35 patients were classified as grade B (57%), and seven patients were classified as grade C (11%). In the non-user group at the 1-year observation, 14 patients were classified as grade A (42%), 16 patients were classified as grade B (48%), and three patients were classified as grade C (10%). In the long-term BPs user group at the 2-year observation, 37 patients were classified as grade A (60%), 19 patients were classified as grade B (30%), and six patients were classified as grade C (10%). In the non-user group at the 2-year observation, 22 patients were classified as grade A (67%), nine patients were classified as grade B (27%), and two patients were classified as grade C (6%). Grade C was less frequently observed in the non-user group during all postoperative periods.

Table 1 Demographic data

	Control ($n = 33$)	BP user ($n = 62$)	
Age (year)	62.5 ± 13.5	65.8 ± 15.3	ns
BMI (kg/m^2)	24.1 ± 4.5	23.8 ± 3.9	ns
Smoking	1	1	
Diagnosis			
Spinal stenosis	10	22	ns
Degenerative listhesis	15	29	
Lytic listhesis	8	11	
BMD (t-score)			
Spine	− 2.3 ± 0.4	− 2.7 ± 0.3	$p < 0.001$
Hip	− 1.8 ± 0.3	− 2.1 ± 0.4	$p < 0.001$
Level			
L3/4	2	5	ns
L4/5	22	42	
L5/S1	10	16	
Vitamin D (ng/ml)	22.79 ± 13.06	23.98 ± 13.7	ns
Calcium (mg/dl)	9.68 ± 0.84	9.75 ± 0.88	ns
CTX (ng/ml)	0.43 ± 0.14	0.11 ± 0.12	$p = 0.002$

BP, bisphosphonate; *BMI*, body mass index; *BMD*, bone mineral density; *CTX*, C-terminal cross-linking telopeptide; *ns*, not significant

In dynamic radiographs, including flexion and extension views, 19 patients showed more than 5° of angular motion in the non-user group at 6 months after the surgery; seven and five patients showed more than 5° of angular motion at 1 and 2 years after the surgery, respectively. Forty-six patients showed more than 5° of angular motion in the long-term BPs user group at 6 months after the surgery; 14 and 10 patients showed more than 5° of angular motion at 1 and 2 years after the surgery, respectively (Fig. 3).

Union was significantly delayed at initial 6 months in the long-term BPs user group relative to the non-user group. In the non-user group, 14 patients (42%) showed union at 6 months after the surgery, whereas 16 patients (26%) in the long-term BPs user group showed union ($p = 0.035$). However, there were no significant differences between the groups in fusion rates at 1 and 2 years after surgery. Twenty-six patients (79%) in the non-user group and 48 patients (77%) in the long-term BPs user group showed fusion at 1 year after surgery. Final

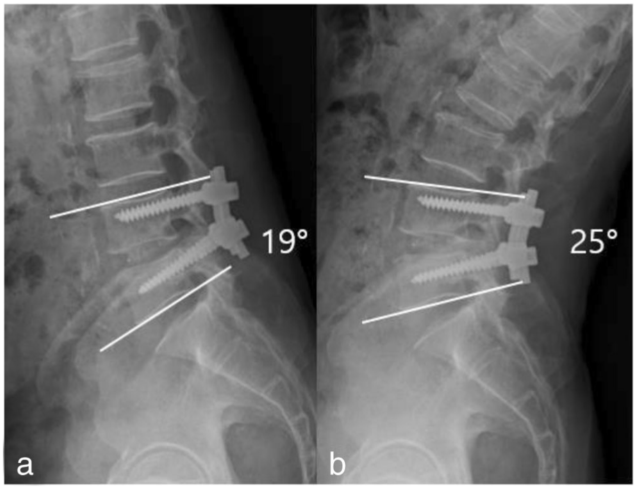

Fig. 3 Measuring angular motion with dynamic plain radiographs. **a** Flexion radiograph and **b** extension radiograph, showing more than 5° of angular motion

fusion rates at 2 years after surgery were 82% (52/62) in the long-term BPs user group and 87% (28/33) in the non-user group (Fig. 4) (Table 2). A total of 14 cases were diagnosed as non-union at 2 years after surgery; there were four cases (12%) of non-union in the non-user group and 10 cases (16%) in the long-term BPs user group, with no significant difference between the groups.

Clinical data

The VAS score in the long-term BPs user group was 6.3 immediately after surgery, and 1.6 and 1.0 at 1 and 2 years after surgery, respectively. In the non-user group, the VAS score was 6.4 immediately after surgery, and 1.5 and 1.1 at 1 and 2 years after surgery, respectively. The ODI score in the long-term BPs user group was 32 immediately after surgery, and 8 and 5 at 1 and 2 years after surgery, respectively. In the non-user group, the ODI score was 31 immediately after surgery, and 6 and 4 at 1 and 2 years after surgery, respectively.

Table 2 Fusion rates

	POD 6 months	POD 1 year	POD 2 years
Control	14/33(42%)	26/33 (79%)	29/33 (87%)
BP users	16/62 (26%)	48/62 (77%)	52/62 (83%)
	$p = 0.035^*$	ns	ns

Ns, not significant; *BP*, bisphosphonate

Clinical outcomes based on VAS and ODI score showed good results in both groups, with no significant statistical differences.

Discussion

In this study, long-term preoperative use of BPs had significant inhibitory effect on spinal fusion at initial 6 months. However, there was no significant difference in bone fusion rate between the two groups 2 years after the surgery. CTX level and BMD were significantly lower in long-term BPs users. Long-term BPs users had fusion rates greater than 80% and clinical outcome improvements that were comparable to those in non-users.

The CTX is one of several known serum tests that measures a breakdown product of bone resorption [21, 22]. The CTX specifically measures a specific crosslink peptide of type I collagen in bone. Type I collagen is the structural organic component of bone and accounts for 98% of the total protein in bone. The serum CTX is considered to best correlate to bone turnover [23]. Lower values represent varying degrees of suppression of normal bone turnover, also called bone remodeling. BPs-induced ONJ is a rare but real entity caused by the antiosteoclastic effects of BPs which inhibit bone turnover. The serum morning fasting CTX bone turnover marker is a straightforward and useful tool to assess the bone turnover suppression by BPs.

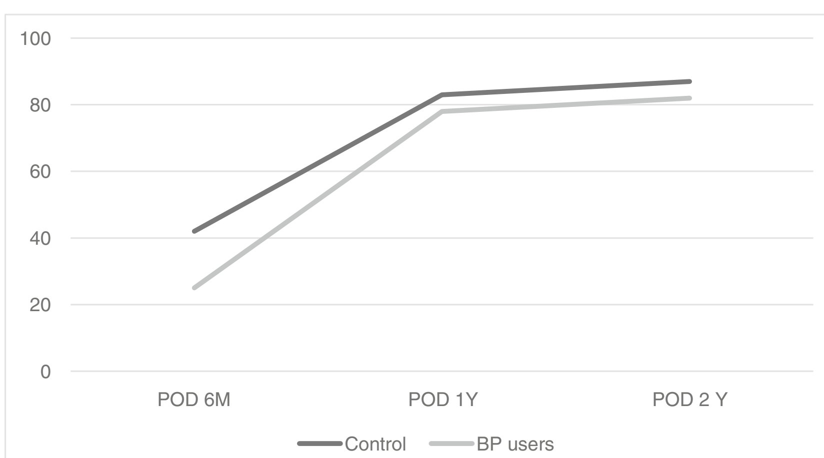

Fig. 4 Fusion rates. There was significant delayed union 6 months after surgery in the long-term BPs user group (42 vs 26%, $p = 0.035$). However, there was not a significant difference between the groups in fusion rates at 1 and 2 years after surgery

Several animal studies have demonstrated that BPs treatment after fracture surgery would increase callus formation and delay callus remodeling, but without influencing the strength of bone healing [24–26]. BPs reduced osteoclast activity, but more and more clinical results showed that they did not have adverse effects on bone healing [27]. In a randomized study of patients with osteoporotic distal radius fractures treated with volar locking plate fixation, the early initiation of BPs did not affect fracture healing or clinical outcomes.

Some reports about fracture healing and BPs did not show a significant inhibition of fracture healing, although the maturation and remodeling of callus was significantly delayed. Based on these results, it is thought that BPs treatment might modify bone graft healing and the remodeling process of spinal fusion [28]. Previous studies that have evaluated the effect of BPs on fusion rate after spinal fusion surgery have been scant and have only been conducted on animal models, and their results have been contradictory, finding no effect, delays in fracture healing, or even enhanced fracture healing [29–35]. Mashiba et al. also reported decreased bone remodeling but no significant differences in bone strength with BPs [36]. Fracture healing was impaired during the early stages of healing after the long-term administration of pamidronate [37].

Understanding the effects of antiresorptive drugs on spinal fusion outcomes in patients with osteoporotic conditions is clinically important. The effect of BPs on bone fusion after spinal fusion surgery remains controversial. As bone remodeling is a vital part of graft incorporation and fusion, BPs can have a significant effect on the process of fusion [11]. The effect of BPs on spinal fusion consolidation in humans has not been determined yet; therefore, only limited data are available on the effect of BPs on spinal fusion. Approximately 50% of systemically absorbed BPs is deposited in the bone tissues from which it is extricated slowly [38]. Animal studies have shown that BPs had no adverse effect on fracture healing, with the suppression of bone healing on early stages and the formation of larger callus and more mechanically stable regenerated bone mass finally [39–41].

The skeletal half-life of BPs is very long and it is associated with residual effect [42, 43]. Therefore, it is possible that the suppressive effect of BPs on bone resorption might be cumulative over time. Recent reports of excessive suppression of physiologic bone turnover have raised concerns about the long-term use of BPs [44, 45]. Long-term use of BPs may cause several complications such as atypical femoral fractures (AFF) and osteonecrosis of jaw (ONJ). Negative effect of excessive suppression of physiologic bone turnover with long-term BPs use plays an important role in the pathogenesis of AFF and ONJ. Although the risk of AFF and ONJ is higher with long-term BPs use, it is extremely rare.

In the case of preoperative administration, it is possible that the residual bone-bound BPs in an autograft may affect the fusion process even without a recent administration of BPs. The effects of BPs on inhibiting bone remodeling and endochondral ossification during the bone graft healing process have been the major reasons for hesitation in using BPs in patients undergoing spinal fusion surgery [9]. However, in our study, spinal fusion was impaired in the early stage, but no significant inhibitory effect of spinal fusion was shown in preoperative long-term BPs users.

More than 6 months of daily injection of teriparatide after spinal fusion surgery in women with postmenopausal osteoporosis showed superior results in the rate of fusion, duration of fusion, and pedicle screw loosening compared with the BPs-treated patients [46–48]. Since there is delayed union 6 months after the surgery in long-term BPs users, postoperative teriparatide administration may enhance fusion rates.

This study has several limitations. Our sample size is relatively small; however, it has strength in that it is a prospective comparative study. Second, our study only dealt with single-level fusion surgeries. As multilevel surgery is one of the risk factors for delayed union, the result would be different with our study. Further studies are needed about fusion rates of multilevel fusion surgeries in long-term BPs users.

Conclusion

Spinal fusion surgery should not be hesitated or avoided in long-term BPs users. However, it needs to be paid attention due to low fusion rate on early stage.

Compliance with ethical standards

Conflicts of interest None.

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