Does alendronate disturb the healing process of posterior lumbar interbody fusion? A prospective randomized trial

Clinical article

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Object. Bisphosphonate medications are widely used for the treatment of osteoporosis, but they might disturb the healing process of spinal fusion. The object of this prospective randomized controlled study was to evaluate the effect of bisphosphonate medication on spinal fusion through radiographic, clinical, and biological assessments.

Methods. A total of 40 patients with osteoporosis who were candidates for single-level posterior lumbar interbody fusion were randomly assigned to the alendronate group (alendronate sodium 35 mg/week) or the control group (vitamin D, alfalcacidol 1 μg/day). Pedicle screw fixation and carbon polyetheretherketone cages were used for all the patients. Bone graft material was prepared as a mixture of local bone and β-tricalcium phosphate in a ratio of 2:1. Functional radiography and CT scans were used to evaluate fusion status and cage subsidence. The incidence of vertebral compression fractures (VCFs) occurring after surgery (subsequent VCFs) was assessed by means of MR imaging. Bridging bone formation was graded into 3 categories: Grade A (bridging bone through bilateral cages), Grade B (bridging bone through a unilateral cage), or Grade C (incomplete bony bridging). A solid fusion was defined as less than 5° of angular motion in flexion-extension radiographs and the presence of bridging bone through the cage (Grade A or B). Clinical outcome was evaluated by means of the Oswestry Disability Index. Bone metabolic markers (serum bone alkaline phosphatase, serum and urine Type I collagen cross-linked N-telopeptides) were measured to investigate the biological effects of alendronate on spinal fusion.

Results. Bridging bone formation (Grade A or B) was more frequently observed in the alendronate group at all postoperative assessment periods. At 1-year postoperative follow-up, a solid fusion was achieved in 95% of the patients in the alendronate group and 65% of those in the control group. Cage subsidence (> 2 mm) was observed in 5% of the alendronate group and 29% of the control group. No vertebral fractures were observed in the alendronate group, whereas 24% of patients in the control group showed subsequent VCFs. There was no statistically significant between-groups difference in clinical outcomes, but poor clinical results in the control group were associated with pseudarthrosis and subsequent VCFs. Biochemical analysis of bone turnover demonstrated that alendronate inhibited bone resorption from the early phase of the fusion process and also suppressed bone formation after 6 months postoperatively.

Conclusions. Favorable mechanical circumstances provided by alendronate overcame its detrimental biological effect on the healing process of spinal fusion. The authors recommend that osteoporosis patients undergoing spinal fusion take bisphosphonates throughout the postoperative period. (DOI: 10.3171/2010.11.SPINE10245)

Key Words • bisphosphonates • alendronate • spinal fusion • posterior lumbar interbody fusion

Abbreviations used in this paper: BAP = bone alkaline phosphatase; BMD = bone mineral density; MPR = multiplanar CT reconstruction; NTX = cross-linked N-telopeptides of Type I collagen; ODI = Oswestry Disability Index; PLIF = posterior lumbar interbody fusion; VCF = vertebral compression fracture.
Alendronate and fusion

In the treatment of osteoporosis, bisphosphonates are the first-line medications to inhibit osteoclast-mediated bone resorption,11,12,28 and have been shown to increase vertebral strength2,12 and prevent VCFs.3

Successful bone graft healing is achieved through appropriate coordination between bone formation and resorption. Bisphosphonates are increasingly used in the elderly population, but they might modify bone graft healing and result in deteriorating spinal fusion. To our knowledge, no previously published clinical studies have investigated the influence of bisphosphonates on spinal fusion.

The objective of this prospective randomized controlled study was to evaluate the effect of alendronate on the healing process in patients who have undergone PLIF. Toward that end, radiographic, clinical, and biological assessments were used.

Methods

Patient Population

Forty patients (38 women and 2 men) who were candidates for single-level PLIF were recruited for this study. The patients’ mean age was 68.6 years (range 47–85 years), and all had symptoms of low-back pain and/or leg pain, which had not been adequately controlled by nonoperative treatment including pain medication (nonsteroidal antiinflammatory drugs) and nerve root blocks. Spinal pathologies included degenerative spondylolisthesis, isthmic spondylolisthesis, and foraminal stenosis. Patients who had severe spinal deformities such as degenerative scoliosis were not included in this study. Bone mineral density of lumbar spine and proximal femur were measured by dual-energy x-ray absorptiometry before surgery. The criteria for osteoporosis were less than 70% of the young adult mean value (or less than 80% of the young adult mean value in postmenopausal women) or the presence of a vertebral fracture related to bone fragility. Osteoporosis was diagnosed in all 40 patients according to these criteria. Those who were older than 85 years old or had been treated with osteoporosis medication before surgery were not included in this study. The study protocol was fully approved by our hospital’s institutional review board.

Patients were randomly assigned to the alendronate group (alendronate sodium [Fosamax] 35 mg/week) or the vitamin D control group (alfacalcidol [Onealfa] 1 μg/day). The randomization procedure involved opening 1 of 40 envelopes for each of the 40 patients. The contents of the envelope allocated the patients to the alendronate group or the control group. All the patients received an explanation of the study protocol and agreed to participate in the study. To avoid bias of surgical techniques, surgeons were also blinded to the treatment protocol of osteoporosis.

Four patients were lost to follow-up because of cerebral hemorrhage, gastrointestinal adverse event due to alendronate, deep wound infection, or withdrawal from participation (Tables 1 and 2). A total of 36 patients were observed for 1 year postoperatively (19 in the alendronate group, 17 in the control group). The alendronate group included 18 women and 1 man (mean age 70.2 years) and the control group included 16 women and 1 man (mean age 67.4 years). The mean preoperative BMD measurements and T-scores, respectively, of the lumbar spine were 0.762 g/cm² and −2.6 in the alendronate group and 0.823 g/cm² and −1.9 in the control group. The mean preoperative proximal femur BMD measurements and T-scores, respectively, were 0.729 g/cm² and −1.9 in the alendronate group and 0.710 g/cm² and −2.2 in the control group. The mean preoperative ODI scores were 20.3 in the alendronate group and 21.6 in the control group. No significant between-groups differences were detected in age, BMD, or ODI score. The spinal pathologies were degenerative spondylolisthesis in 15 patients, isthmic spondylolisthesis in 1 patient, and foraminal stenosis in 3 patients in the alendronate group; and degenerative spondylolisthesis in 14 patients, isthmic spondylolisthesis in 1 patient, and foraminal stenosis in 2 patients in the control group. The operative level was L3–4 in 1 patient, L4–5 in 14 patients, and L5–S1 in 4 patients in the alendronate group; and L2–3 in 1 patient, L3–4 in 3 patients, L4–5 in 12 patients, and L5–S1 in 1 patient in the control group.

Surgical Technique

Patients were placed in a prone position under general endotracheal anesthesia. The spinous processes were exposed through a midline incision, and the paraspinal muscles were reflected to the tips of the transverse processes. Pedicle screws were inserted at the intersection of a horizontal line joining the midpoint of the transverse processes and a vertical line through the midpoint of the superior articular process under fluoroscopy. Bilateral total facetectomies were performed to decompress the nerve roots. Discectomy was then performed using ring curettes and rongeurs. All the disc material was removed to ensure proper endplate preparation. After completion of the discectomy, a distractor was used to open up the disc space. The bone graft material was a mixture of local bone harvested from the lamina and facet joints and β-tricalcium phosphate (OSferion; Olympus Corp.) in a ratio of 2:1. Bone graft material was packed as tightly as possible into the anterior and lateral part of the disc space, then carbon polyetheretherketone cages (Brantigan I/F cage Jaguar; DePuy Spine, Inc.) filled with bone graft material were inserted bilaterally. Each cage was placed 3–4 mm from the posterior vertebral margin to prevent nerve root impingement. The mean amount of graft material used was 11.5 g (range 8–15 g). Finally, rods were applied to pedicle screws and the screws were tightened to apply the compressive load to the cages and graft bone.14

Radiographic Assessment

Radiographic outcomes were assessed in a blind fashion. Throughout the radiographic assessment, the reviewer was informed of only the number assigned to the patient. Fusion status was radiographically assessed by means of functional radiography and CT scans obtained 3, 6, 9, and 12 months postoperatively. The parameters included segmental angular motion, presence or absence of bridging bone, and cage subsidence. All the patients were examined under fluoroscopy to evaluate angular motion.
of the fusion level during flexion and extension. A flexion radiograph was obtained with the patient in a standing position trying to bend forward as far as possible, and an extension radiograph was obtained with the patient maximally arching his or her back. Angular motion between flexion and extension was measured using computer graphic software (DrABLE-EX; Fujitsu Corp.). Coronal and sagittal multiplanar CT reconstruction (MPR) was obtained through the cages by 3-mm contiguous slices. Bridging bone formation was graded into 3 categories, as follows: Grade A (bridging bone through bilateral cages), Grade B (bridging bone through unilateral cage), or Grade C (incomplete bony bridging) (Fig. 1). A solid fusion was defined as less than 5° of angular motion in flexion-extension radiographs at the fusion level and the presence of bridging bone (Grade A or B) through the cages on the coronal MPR scans. Cage subsidence was defined as more than 2 mm vertical migration from baseline on coronal or sagittal MPR scans. Occurrence of subsequent VCF was assessed by MR imaging (T1-weighted, T2-weighted, and STIR images) 12 months postoperatively.

**Clinical Assessment**

The ODI was used to evaluate clinical outcome. The data were collected before surgery and at 3, 6, 9, and 12 months postoperatively.

**Laboratory Assessment**

All of the patients started treatment with either alendronate sodium or alfacalcidol 1 week after surgery. To evaluate the biological effects of alendronate, bone turnover was analyzed 1, 3, 6, and 12 months after surgery using bone metabolic markers. Bone formation was assessed by measuring the serum level of bone alkaline phosphatase (BAP). The level of Type I collagen cross-linked N-telopeptides (NTX) was measured in serum and urine to evaluate bone resorption. Because of diurnal variation in bone metabolic markers, the serum samples were obtained in the morning and the urine samples were collected from the second morning void. The biochemical data for each postoperative period were shown as a percentage change compared with the preoperative baseline.

**Results**

**Radiographic Assessment**

Bridging bone formation was assessed by CT (coronal and sagittal MPR scans), and graded into 3 categories. As shown in Fig. 2, in the alendronate group at the 1-year observation, bridging bone formation was observed bilaterally (Grade A) in 12 patients (63%) and unilaterally (Grade B) in 6 patients (32%); incomplete bony bridging

**TABLE 1: Demographic and clinical characteristics of the alendronate group**

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<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Fusion Level</th>
<th>Diagnosis</th>
<th>Preop ODI Score</th>
<th>Preop VCF†</th>
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<th>Final Angular Motion (°)</th>
<th>Final Bridging Bone Formation</th>
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* Mean values: age 70.2 years; preoperative ODI Score 20.3; final ODI Score 9.3; final angular motion 2.5°.
† Preop VCF refers to preexisting VCFs (before surgery).
‡ The Final Subsequent VCF refers to VCFs that occurred after surgery.
Alendronate and fusion

**TABLE 2: Demographic and clinical characteristics of the control group***

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<th>Case No.</th>
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<th>Fusion-Level</th>
<th>Diagnosis</th>
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* Mean values: age 67.4 years; preoperative ODI Score 21.6; final ODI Score 14.6; final angular motion 3.2°.

(Grade C) was observed in 1 patient (5%). In the control group, Grade A bridging bone formation was seen in 8 patients (47%), Grade B in 3 (18%), and Grade C in 6 (35%). Incomplete bridging bone formation (Grade C) was less frequently observed in the alendronate group at all postoperative periods.

One year postoperatively, solid fusion was observed in 18 (95%) of 19 patients in the alendronate group and 11 of 17 patients (65%); the alendronate group had a significantly higher fusion rate than the control group (p = 0.025, Mann-Whitney U-test).

Cage subsidence was observed in 1 patient (5%) in the alendronate group and 5 patients (29%) in the control group. There was a tendency for lower risk of cage subsidence in the alendronate group, but the difference was not statistically significant (p = 0.056, Mann-Whitney U-test).

No subsequent VCFs occurred in the alendronate group, but 4 patients (24%) in the control group developed VCFs; the incidence of subsequent VCFs was significantly higher in the control group (p = 0.027, Mann-Whitney U-test). In addition, 3 of the 4 patients who developed subsequent VCFs showed incomplete bony bridging and cage subsidence.

**Clinical Assessment**

The mean ODI score in the alendronate group con-

![Fig. 1. Computed tomography evaluation of bridging bone formation. Coronal multiplanar reconstructed CT was used to evaluate bridging bone formation. Bridging bone formation was graded into 3 categories, illustrated in panels A, B, and C, respectively: Grade A (bridging bone through bilateral cages), Grade B (bridging bone through unilateral cage), or Grade C (incomplete bony bridging).](image-url)
sistently decreased until 12 months after surgery \( (p < 0.0001) \) vs preoperative baseline, 2-way repeated-measure ANOVA; Fig. 3). In the control group, the mean ODI score decreased until 3 months postoperatively, but thereafter reached a plateau. At 1 year after surgery, there was a tendency toward better clinical results in the alendronate group, but the between-groups difference in ODI scores was not statistically significant \( (p = 0.460, \) 2-way repeated-measure ANOVA). However, 3 (10.5\%) of the patients in the alendronate group and 4 (23.5\%) of the patients in the control group had poor clinical outcomes (less than 20\% improvement in ODI score). Of the 4 patients with poor clinical outcomes in the control group, 2 were diagnosed with pseudarthrosis and 3 had developed VCFs postoperatively (subsequent VCFs).

**Laboratory Assessment**

Figure 4 shows the percentage change of the bone metabolic markers (BAP, serum and urine NTX). In the alendronate group, as shown in Fig. 4A, the serum level of BAP was elevated by 52\% at 1 month after surgery and 14\% at 3 months after surgery, but thereafter decreased to below the preoperative baseline (−19\% at 6 months and −38\% at 12 months after surgery). In the control group, however, the serum level of BAP was elevated above the preoperative baseline at all postoperative periods. Thus, alendronate decreased bone formation after 6 months postoperatively.

In terms of bone resorption, the mean serum NTX level in the alendronate group was below the preoperative baseline throughout the postoperative period (Fig. 4B). The mean urine NTX level also decreased to below the preoperative baseline after 3 months (Fig. 4C). In the control group, the mean serum and urine levels of NTX were elevated by 16\% and 38\%, respectively, 1 month postoperatively; the levels returned to the preoperative baseline 6 months postoperatively. These data suggest that alendronate inhibited bone resorption from the early phase of the fusion process.

**Fig. 2.** Bridging bone formation. Bridging bone formation (Grade A or B) was more frequently observed in the alendronate group at all postoperative periods. At 12 months postoperatively, 18 (95\%) of 19 patients in the alendronate group and 11 (65\%) of 17 patients in the control group had bridging bone formation. The fusion rate was significantly higher in the alendronate group than in the control group \( (p = 0.025, \) Mann-Whitney U-test).
Spinal instrumentation and fusion is an established surgical treatment for degenerative spinal deformities (degenerative scoliosis and kyphosis), spinal instability (degenerative and isthmic spondylolisthesis), and neuroforaminal lesions (foraminal stenosis). The aging of the population leads to an increasing number of elderly candidates for spinal fusion. Elderly patients have potential risks for failed spinal fusion associated with malnutrition, lower activity for osteoinduction, medical comorbidities, and osteoporosis. Placing instrumentation in an aged spine is challenging because of poor fixation due to osteoporosis and the resultant risks of pseudarthrosis and progression of instability and deformities.

Regarding prevention and treatment of osteoporosis, Donaldson et al. estimated that at least 72% of white women over 65 years of age in the US and 93% of those over 75 years of age would be recommended for pharmacological treatment. Bisphosphonates are the current gold standard for osteoporosis treatment and have been reported to increase bone quality and prevent implant loosening. Xue et al. investigated the influence of alendronate on pedicle screw fixation in a porcine posterolateral lumbar fusion model. Through biomechanical and histomorphometric analyses, they suggested that alendronate improved bone-screw interface fixation by inhibiting bone resorption. In a prospective randomized clinical trial of external fixation for hip fracture, Moroni et al. measured extraction torque of fixation pins implanted in cancellous bone and demonstrated that bisphosphonates enhanced a screw-type implant fixation in osteoporosis. Regarding fracture risk in osteoporosis, Black et al. conducted a prospective randomized controlled study to investigate the efficacy of alendronate in prevention of vertebral fractures. In this study involving 2027 women with osteoporosis and pre-existing vertebral fractures, subsequent vertebral fractures occurred in 8.0% of the alendronate treatment group and 15.0% in the placebo group. The authors concluded that alendronate reduced the risk of vertebral fractures in osteoporosis patients. In addition, Imai et al. used a quantitative CT-based finite element model to assess vertebral strength in postmenopausal women. Alendronate treatment increased vertebral strength by 10.2% from the baseline at 3 months after administration. Thus, evidence suggested that bisphosphonates had biomechanical advantages to increase vertebral strength and to improve implant fixation stability. These advantages could also decrease risks for failure of stabilization and correction, pseudarthrosis, and subsequent vertebral fractures at sites adjacent to or remote from the fusion level.

On the other hand, it remains unclear how bisphosphonates influence the healing process of spinal fusion. Several studies have suggested that bisphosphonates may improve bone healing and reduce the risk of pseudarthrosis.

**Discussion**

Spinal instrumentation and fusion is an established surgical treatment for degenerative spinal deformities (degenerative scoliosis and kyphosis), spinal instability (degenerative and isthmic spondylolisthesis), and neuroforaminal lesions (foraminal stenosis). The aging of the population leads to an increasing number of elderly candidates for spinal fusion. Elderly patients have potential risks for failed spinal fusion associated with malnutrition, lower activity for osteoinduction, medical comorbidities, and osteoporosis. Placing instrumentation in an aged spine is challenging because of poor fixation due to osteoporosis and the resultant risks of pseudarthrosis and progression of instability and deformities.

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**Fig. 3.** Oswestry Disability Index. The mean preoperative ODI scores were 20.3 in the alendronate group and 21.6 in the control group (p = 0.588, unpaired t-test). The ODI in the alendronate group consistently decreased until 12 months after surgery. In the control group, the ODI decreased until 3 months postoperatively, but thereafter reached a plateau. At 12 months after surgery, there was a tendency toward better clinical results in the alendronate group, but the intergroup difference in ODI scores was not statistically significant (p = 0.460, 2-way repeated-measure ANOVA).

**Fig. 4.** Percentage change of bone metabolic markers. A: The mean BAP level was elevated in the alendronate group was elevated by 52% at 1 month and by 14% at 3 months after surgery, but thereafter decreased to below the preoperative baseline (~19% at 6 months and ~38% at 12 months after surgery). In the control group, however, the mean BAP level remained elevated above the preoperative baseline during the entire postoperative period. B: The mean serum level of NTX (a bone resorption marker) remained below the preoperative baseline throughout the postoperative period in the alendronate group. In the control group, the mean serum level of NTX was elevated by 16% at 1 month, and the level returned to the preoperative baseline at 3 months after surgery. C: The mean urine NTX level decreased to below the preoperative baseline after 3 months in the alendronate group. In the control group, the mean urine NTX level was elevated by 38% at 1 month after surgery, and the levels had returned to the preoperative baseline 6 months postoperatively.
eral animal studies have been attempted to investigate the effects of bisphosphonates on spinal fusion.1,5,15,19,2,28,30,31,33 Huang et al.15 investigated the effects of alendronate on spinal fusion using a rat posterolateral lumbar fusion model. Radiographic and histomorphometric data showed that alendronate increased the size and density of the fusion mass but decreased the chance of a solid fusion. They suggested that alendronate inhibited bone graft incorporation and recommend that patients undergoing spine arthrodesis should not take alendronate until a solid fusion is achieved. Bransford et al.7 used manual palpation and radiographic assessment to determine whether zoledronic acid enhances fusion rate in a rabbit intertransverse fusion model. They demonstrated that zoledronic acid increased the size and bone mineral content of the fusion mass and led to an increased fusion rate and recommended that bisphosphonate treatment should be maintained to enhance successful spinal fusion. Thus, the use of bisphosphonates during the healing process of spinal fusion is controversial, and it remains unclear which favorable mechanical circumstances or elimination of detrimental biological effect is a priority for successful spinal fusion. Only prospective, randomized, and controlled clinical trials can answer this question.

To our knowledge, the current investigation represents the first randomized controlled clinical trial to examine the effect of bisphosphonate on the healing process of spinal fusion. Radiographic results showed that alendronate enhanced bridging bone formation more frequently at all postoperative periods and, finally, increased the fusion rate. Cage subsidence and subsequent vertebral fractures were successfully prevented by the use of alendronate. There was no statistically significant difference between the alendronate group and the control group with respect to clinical outcomes, but poor clinical results were associated with pseudarthrosis and subsequent VCFs at adjacent or remote sites above the fusion level. In contrast, subsequent biochemical vertebral compression analysis using bone metabolic markers demonstrated that alendronate inhibited bone resorption from the early phase of the fusion process. Bone formation was also suppressed in the alendronate group after 6 months postoperatively. In the healing process of spinal fusion, bone formation might be downregulated by a consequence of osteoclast inhibition or a direct inhibitory effect on osteoblast activities.16 From a biological standpoint, alendronate disturbed the healing process of spinal fusion. However, overall results of the current investigation demonstrated that favorable mechanical circumstances provide by alendronate overcame its detrimental biological effect on the healing process of spinal fusion. Thus, alendronate treatment is advantageous for osteoporosis patients who require spinal fusion, and we recommend that treatment with this agent be continued after such surgery.

Several limitations of this study should be addressed. Some criticism may arise regarding the control arm. From a scientific standpoint, the controls should receive placebo or no medication. However, osteoporosis was diagnosed in all of the patients in this study, and there was a heightened risk of pathological fractures without medication. Because of the ethical issues related to the use of a placebo in this situation, we treated the patients in the control group with vitamin D, which has been used clinically and has shown some relatively weak evidence for prevention of osteoporosis-related fractures.15,22

The methods for assessment of fusion status should be addressed. Flexion-extension radiography has been widely used, but the definition of a solid fusion remains controversial.4,6,12 Pedicle screw fixation provides immediate stability to the operative segments and might lead to overestimation of fusion status. In the current study, we employed fluoroscopy to monitor micromotion during flexion and extension and measured segmental angular motion using computer graphic software. As recommended by Cook et al.? Fogel et al.,12 and Shah et al.,25 thin-slice helical CT was used for assessment of bridging bone formation through the cages. Based on the combination of these data, we believe that the current radiographic assessment is reliable to diagnose a solid fusion. Our control group demonstrated a low radiographic fusion rate (65%) compared with previous reports, which might be related to the method of radiographic assessment. We also believe that the use of strict and consistent criteria for fusion status was a key to obtaining reliable data in this randomized controlled study.

A small sample size might be a weakness of this study. Although the study was statistically underpowered, we observed significant differences in the radiographic fusion rate and prevalence of subsequent vertebral fractures between the 2 groups. Sampling larger number of patients might indicate the difference in occurrence of cage subsidence and other parameters.

The accuracy of bone metabolic marker analysis might be a concern. To minimize diurnal variation in bone metabolic markers, we obtained serum samples in the morning and urine samples from the second morning void. These consistent methods for serum and urine sampling should contribute to accurate biochemical assessment.

Conclusions

The current prospective randomized and controlled study investigated the effect of alendronate on the healing process in PLIF. Bone metabolic marker analyses suggested that the healing process of spinal fusion was biologically disturbed by alendronate administration. However, radiographic results demonstrated that alendronate increased the fusion rate and successfully prevented cage subsidence and subsequent vertebral fractures above the fusion level. Our conclusion is that the favorable mechanical circumstances provided by alendronate overcome its detrimental biological effect on the healing process of spinal fusion. We recommend that patients with osteoporosis who undergo spinal fusion should take bisphosphonates throughout the postoperative period.

Disclosure

Dr. Minami received study support from Banyu Pharmaceutical Co., Ltd. The remaining authors report no other conflicts of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Nagahama, Kanayama. Acquisition of data: Nagahama. Analysis and interpreta-
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