The Influence of Bone Graft Volume and Alendronate Treatment on Spine Fusion

a report by

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It has been estimated that worldwide more than 600,000 spinal fusion procedures are performed each year to treat patients suffering from debilitating back pain or injury. A successful fusion (arthrodesis) needs solid living bone tissue bridging adjacent vertebrae to provide long-term support. Bone grafting and stable internal fixation play the crucial roles in spinal fusion.

Bone graft materials have one or more basic biological properties:

- an osteoconductive matrix, which supports the ingrowth of new bone;
- osteoinductive proteins, which facilitate the recruitment and proliferation of undifferentiated stem cells; and
- osteogenic cells (osteoblasts or osteoblast precursors), which are capable of forming bone in the proper environment.

Autologous bone graft from the iliac crest fulfills all three criteria and remains the gold standard material for use in achieving a successful spinal fusion.

An appropriate equilibrium between bone resorption and formation is critical for successful fusion. Excessive bone graft resorption reduces the progenitive basis for new bone formation, which could be an underlying factor in cases of spine fusion failure. As a result, slowing down resorption of the bone graft and increasing the bone graft volume at the fusion site may facilitate fusion. Using a large amount of autograft materials can improve the rate of spine fusion in clinical practice. However, an attempt to improve the rate of spine fusion by adding larger amounts of bone graft may be counteracted by extensive bone graft resorption. Although a larger amount of bone graft brings about better fusion, in our study the use of excessively large amounts of bone graft seemed unnecessary. Only a certain amount of graft bone is involved in fusion process; the rest is absorbed.

Data analysis from 76 patients undergoing posterolateral instrumented lumbar or lumbosacral spinal fusion in the Spine Section of Aarhus University Hospital has shown that fusion rates are positively influenced by the quantity of bone graft placed at the fusion bed during the first six post-operative months (Laursen M, PhD thesis, Aarhus University Hospital, 2001). The amount of graft in ‘non-union’ segments was significantly smaller than in successful fusion segments. The median quantity of bone graft used in successfully fused segments was 24.4g (range: 13.5–53g), in contrast to a median of 14.7g (range: 12.5–23.4g) in non-fused segments. Therefore, approximately 24g of autogenous bone graft applied at each fusion segment is recommended when performing autografted posterolateral spinal spondylodesis surgery.

Alendronate (sodium 4-amino-1-hydroxybutyldene-1, 1 bisphosphonate trihydrate), a second-generation nitrogen-containing bisphosphonate, is well known as a potent inhibitor of osteoclastic bone resorption. It has been widely used clinically for the treatment of osteoporosis and calcium phosphate metabolic diseases. In addition, alendronate has also been shown to have a residual benefit on bone mass in post-menopausal women up to seven years after treatment withdrawal. Its residual effect is probably a consequence of a strong affinity to hydroxyapatite crystals in bone, where the mean terminal half-life of alendronate is up to 10 years.

Many patients who are already taking alendronate for osteoporosis or other disorders may also have indications for spinal fusion. Therefore, whether these patients should continue or stop taking alendronate before or after spinal fusion surgery is of clinical relevance. As a result, the safety of alendronate treatment or its residua on spinal fusion needs to be considered.

Alendronate’s Molecular Mechanisms of Action

Bisphosphonates bind to bone at sites of active bone remodelling to slow down rapid bone turnover or excessive osteolytic activity. The biological effects of bisphosphonates on calcium metabolism have been ascribed to their physico-chemical effects on hydroxyapatite crystals and their actions on cells, which include inhibiting osteoclast attachment to bone and disturbing osteoclast metabolism.

Although the detailed mechanism of action of alendronate is still unclear, it has been shown to inhibit farnesyl dipiphosphate (FPP) synthase, an enzyme of the mevalonate pathway in osteoclasts (see Figure 1). Inhibition of this enzyme prevents the biosynthesis of isoprenoid lipids that are essential for the post-translational farnesylation and geranylgeranylation of small guanosine 5’-triphosphate (GTP)ase proteins.
Influence of Alendronate on Bone Healing in Spinal Fusion

Several studies have been conducted to observe the influence of bisphosphonate on bone resorption or its effects on fracture healing. Treatment with alendronate before or during fracture healing, or both, does not impair bone mineralisation. In addition, alendronate may have a dose-dependent effect on osteoblasts. Based on the mechanisms of its action, alendronate treatment may facilitate autograft healing and incorporation processes in spinal fusion by preventing early resorption of autograft at the fusion bed and enhancing the proliferation and osteogenesis of BMSCs. Our group investigated its effect on bone healing in porcine anterior lumbar interbody fusion (ALIF) and posterolateral fusion (PLF) models. Data indicated that chronic administration of alendronate, at a dosage of 10µg/kg/week, alendronate had no deleterious effect and the effect of alendronate is dose-dependent. At a therapeutic dose of 1µg/kg/week, alendronate had no deleterious effect and the radiographic scores were equal to or better than those seen in the control group. However, at a supernormal dose of 10µg/kg/week alendronate resulted in radiographic pseudarthroses, probably due to an almost complete lack of osteoclasts and a significant reduction of osteoblasts. Data from Huang et al. suggest that disruption of graft resorption and incorporation by alendronate at a dose of 5µg/kg/day may lead to immature fusion mass and the lower fusion rate seen in the rat model.

Effects on Bone-Implant Interface Fixation in Spinal Fusion

Failure of pedicle screw internal fixation resulting in destabilisation is one of the most important factors underlying the non-union of spinal fusion or spoilage of an attempted deformity correction. The bone-screw interface has been indicated as the weak link in pedicle screw spinal fixation. The stability of instrumentation depends on the purchase of the pedicle screw in the pedicle and the vertebral body. The anchor strength of the bone–screw interface depends on the total volume of bone growth on the screw surface. Extensive bone resorption will reduce the holding strength of pedicle screws. Peri-prosthetic bone loss is the most common cause of orthopaedic implant failure. Peri-prosthetic bone loss after orthopaedic implantation arises through three mechanisms: surgical trauma, stress shielding and wear debris.

Surgical Trauma

Bone implant surgery stimulates osteoclast activity, leading to varying amounts of bone loss. Mechanical compaction, machinery and heating effects could damage the local blood supply and subsequently cause bone necrosis. The local bone and soft-tissue reaction to operative trauma also have an impact on bone loss. Knee resorption and a corresponding decrease in bone quality and density can occur after implant surgery.

Stress Shielding

An orthopaedic implant alters the mechanical loading of the host site and affects bone remodelling. Bone surrounding the implant adjusts its mineral density and structure to meet new mechanical demands. The implanted metal component leads to a disruption of the natural stress patterns that promote the maintenance of bone mass. This alteration of the local strain environment leads to bone loss due to disuse atrophy. This phase of bone loss occurs acutely and is confined mainly to the first six months after surgery, but may result in the loss of over 30% of peri-prosthetic bone mass. Deterioration of local bone structure will decrease the holding stress of implant fixation.

Wear Debris

Wear-debris-induced osteolysis occurs as a result of a host response to the implant particles. In this process, ingestion of particulate wear debris from the implant materials occurs at the interface between the implant and bone. Wear debris stimulates a foreign-body granulomatous response, leading to macrophage- and osteoclast-mediated bone resorption.
Unlike total joint replacement, in which polyethylene components are used and there is joint movement, wear debris and third-body wear are far less pronounced in peri-screw loosening. The metabolic equilibrium of the bone graft healing fusion mass is generally reached by one and half years after intertransverse fusion. The mechanical strength of the fusion will gradually come to rely on solid bony arthrodesis if non-union does not occur.

Screw insertions change the mechanical load environment for the bone tissue surrounding the screw, ultimately leading to changes in bone remodelling. The bone structures in contact with the screw surface become compacted by screw insertion, causing microfractures and bleeding. The superficial layer of bone surrounding the screws becomes more active in bone remodelling owing to mechanical compaction and avascularity. Necrotic bone appears to be removed by resorption during bone remodelling. Normal bone remodelling is characterised by bone resorption, linked to new bone formation by the so-called coupling phenomenon. The most effective approach to prevent implant loosening would be to have a positive balance between new bone formation and bone resorption in the active bone remodelling time period.

Bisphosphonate treatment has been reported to inhibit bone resorption in the area around the implant and to increase bone quality and density. Treatment with bisphosphonates shows a tendency to enhance screw-type implant fixation in ovariectomised rats. Alendronate does not inhibit early bone apposition to hydroxyapatite-coated implants. In humans, alendronate inhibits local bone loss after total joint arthroplasty. Venesmaa et al. found that alendronate, at a dose of 10mg daily for six months, significantly reduced peri-prosthetic bone loss and either limited the bone mineral density (BMD) decrease or increased BMD after total hip arthroplasty.

In the porcine PLF model, our results have shown that alendronate treatment resulted in increased biomechanical anchor strength with borderline significance at the bone–pedicle screw interface. The control group showed a lower maximum torque and lower initial angular stiffness than the alendronate-treated group (see Figure 2). Based on the results of histological evaluation, the treatment group had a higher percentage of bone growth on the pedicle screw surface (see Figure 3). The bone volume in the area between the screw threads was also higher in the alendronate-treated group; this was of borderline significance (Xue Q, PhD thesis, Aarhus University Hospital, 2004).

Summary

Increasing the bone graft volume at the fusion site and slowing down resorption of the bone graft facilitate fusion. However, using an excessively large amount of bone graft seems unnecessary. On the other hand, in spite of the absence of clinical data, patients who are already taking the conventional dosage of alendronate for osteoporosis or metabolic bone disorders may receive additional benefits without needing to change their medication regimen. These benefits may effectively prevent excessive autograft resorption, enhance apposition of new bone and improve bone–pedicle screw interface fixation. Data from all published reports are based on normal animals. Therefore, simulation of clinical settings using osteoporotic animals will be helpful in further understanding the effect of alendronate on spinal fusion. Finally, prospective, randomised clinical trials will be needed to confirm the benefit of alendronate treatment.

Key Messages

- Only a certain amount of autograft is involved in the fusion process; the rest is absorbed. We recommend placing approximately 24g of autograft at each intervention segment when performing autografted posterolateral spinal fusion surgery in humans.
- Animal studies indicate that patients who are already taking the conventional dosage of alendronate and have indications for spinal fusion can continue this treatment without impairing fusion.
- Prospective, randomised clinical trials will be needed to confirm the benefit of alendronate.