

Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes

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Recommendations

Standards. The use of autologous bone or rhBMP-2 bone graft substitute is recommended in the setting of an ALIF in conjunction with a threaded titanium cage.

Guidelines. There is insufficient evidence to recommend a treatment guideline.

Options. 1) Recombinant human BMP-2 in combination with HA and tricalcium phosphate may be used as a substitute for autograft bone in some cases of PLF. 2) Several formulations of calcium phosphate exist and are recommended as bone graft extenders, especially when used in combination with autologous bone.

Rationale

Successful arthrodesis following lumbar fusion requires osseous bridging between the vertebral bodies, which is usually achieved by placing graft material between the

vertebral bodies, which then heal over time. The standard graft material is harvested autogenous bone, which may be limited by availability and may be associated with donor-site morbidity. Allograft bone may also be used for various applications; however, availability, cost, risk of disease transmission, and lack of osteoinductive capacity limit the utility of allograft in some applications. For these reasons, bone graft substitutes have been developed for application in the lumbar spine. These substitutes have variable mechanical properties and biological activities, and they may or may not be efficacious for specific situations. The purpose of this review is to examine the medical evidence regarding the use of bone graft substitutes in lumbar spinal surgery.

Search Criteria

An electronic search of the database of the National Library of Medicine from 1966 to November 2003 was performed using the search terms “bone graft substitute” as a key word and then again as the search focus. The search was repeated using search terms “bone substitutes,” “tricalcium phosphate,” “calcium phosphate,” “bone morphogenetic protein,” and “hydroxyapatite” combined with “spine” and “lumbar.” The search was limited to the English language and to reports on humans. The results of the searches were combined, and a total of 54 articles were

Abbreviations used in this paper: AGF = autologous growth factor; ALIF = anterior lumbar interbody fusion; AWGC = apatite and wollastonite-containing glass ceramic; BMP = bone morphogenetic protein; HA = hydroxyapatite; ODI = Oswestry Disability Index; PLF = posterolateral fusion; RCT = randomized controlled trial; rhBMP = recombinant human BMP.

identified and reviewed. The reference lists of each of these papers was reviewed, and further references were identified and subsequently submitted for review. The vast majority of references found included animal data and were therefore eliminated. There were also several papers dealing with cervical interbody fusion and scoliosis. Ultimately, six papers were identified as providing Class III or better data regarding the use of bone substitutes in lumbar fusion for degenerative disease. These papers are described in Table 1.

Scientific Rationale

Bone graft substitutes and extenders may be classified into two main categories, the first consisting of biological agents that induce the formation of bone from native tissues. The best known member of this category is rhBMP-2. Other examples of this category include other members of the BMP family and autogenous growth factor concentrates. The second class of bone substitutes comprises calcium phosphate salts of varying composition used to provide a scaffold for the growth of new bone. Members of this second category include β -tricalcium phosphate, hydroxyapatite, and wollastonite.

Recombinant rhBMP-2 is the best studied of all the biological agents. Three recent clinical series have described the use of this substance in humans undergoing fusion for lumbar degenerative disease. Burkus, et al.,^{2,3} investigated the use of rhBMP-2 as a substitute for autograft when used in combination with a titanium cage for an anterior lumbar interbody fusion. These investigators performed an RCI comparing rhBMP-2 with autograft in a group of 279 well-matched patients with lumbar degenerative disease.² Fusion status was assessed with both plain radiography (static and dynamic) and computerized tomography scanning studies reviewed by radiologists blinded as to bone graft material used. Clinical outcome measures used included the ODI for low-back pain, patient satisfaction, and visual analog scale scores for leg, back, and graft-site pain. Follow-up duration was at least 2 years, and the authors achieved greater than 90% follow up in both treatment groups. The authors reported significant improvements in ODI, back pain, leg pain, and patient satisfaction scores in both treatment groups. There was a slightly higher fusion rate in the rhBMP-2 group (94.5% compared with 88.7%, probability value not significant). There were advantages to the use of rhBMP-2 in terms of a slightly shorter operating room time (24 minutes) and slightly decreased blood loss (44 ml). There was also an advantage for the rhBMP-2 group in terms of donor-site pain. This study was well designed and used appropriate radiographic and clinical outcome measures. As such, it provides Class I medical evidence supporting the use of rhBMP-2 as a bone graft substitute in ALIF involving a titanium cage. The use of rhBMP-2 in this study was also associated with decreased donor-site pain and shorter operating room times.

The same group of authors performed a secondary analysis of these data and data derived from another clinical series.³ In this second paper, the authors asserted that the rhBMP-2 was associated with higher fusion rates than autograft bone in titanium cage-augmented ALIF. Interpretation of the data reported in this second paper must be performed with caution. Because much of the

data used for this secondary analysis were derived from uncontrolled cohort studies and because this was a reanalysis of previously published data, the data used to support rhBMP-2 as superior to autograft is considered Class III medical evidence. Given the fact that a Class I study established that rhBMP-2 and autograft bone were essentially equivalent with regard to the success of fusion, the impact of this second paper is minimal. The patients in the rhBMP-2 group experienced advantages in operating time, graft-site morbidity, and blood loss.²

Boden and colleagues¹ examined the role of rhBMP-2 in combination with β -tricalcium phosphate and HA as a bone graft substitute for PLF. They performed a pilot study involving 25 patients randomized to instrumentation-based PLF with autograft (five), instrumented PLF with rhBMP-2 plus carrier (11), or noninstrumented PLF with rhBMP-2 plus carrier (nine). Patients were followed for a mean of 17 months. Fusion was assessed with dynamic plain radiography, augmented by computerized tomography scanning in cases of uncertainty regarding fusion status. The ODI and portions of the SF-36 questionnaire were used to assess clinical outcomes. The authors reported fusion rates of 100% in both rhBMP-2 groups, compared with only 40% in the autograft group. The authors also reported improvements in functional outcome in the rhBMP-2 groups compared with the autograft group. They concluded that rhBMP-2 may be an effective alternative to autograft. Although this study was a randomized trial, there are several methodological concerns that limit the quality of its medical evidence. Its small population resulted in differences among the treatment groups. The autograft group had significantly fewer patients with education beyond high school, had a significantly larger percentage of patients with diabetes, more smokers, and more patients pursuing Workers' Compensation claims. In the autograft treatment group the fusion rate was only 40%, a much lower rate than that reported in numerous other studies. In this study, there was no significant advantage noted for the instrumented rhBMP-2 group in terms of operative time, blood loss, or hospital stay compared with the instrumented autograft group. Because of the small size of the study and the methodological concerns resulting from the small sample size, this study is considered to provide Class III medical evidence supporting the use of rhBMP-2, in combination with a carrier, in the performance of a PLF, with or without placement of instrumentation.

Other biological bone growth stimulators have been used for the treatment of lumbar degenerative disease in humans. Lowery, et al.,⁶ performed a retrospective review of 19 patients in whom AGF was used as a bone graft extender. Ultraconcentrated platelets derived from the patient's own blood combined with thrombin created a gel that was mixed with autograft bone (iliac crest graft in 14 and local autograft in five). Seven patients underwent 360° lumbar fusion procedures, eight were treated with PLF, and four underwent ALIF. All patients received supplemental pedicle screw instrumentation. All patients were considered to have successful fusion, and no graft-specific complications were identified. This study provides Class III medical evidence that the use of AGF as a graft extender is safe. Its efficacy as a graft extender has not been compared with autograft alone or other graft extenders.

TABLE 1
Summary of studies involving lumbar fusion and bone graft extenders and substitutes*

Authors & Year	Class	Description	Comment
Lowery, et al., 1999	III	AGF used in combination w/ autograft & ceramic graft extender in 19 patients. Patients did well overall.	AGFs appear to be safe when used as a graft extender in lumbar fusions.
Boden, et al., 2002	III	Small pilot RCT comparing rhBMP-2 to autograft for PLF. Downgraded to Class III because of small size & significant discrepancies in the characteristics of groups (smoking, diabetes, Workers' Compensation).	rhBMP-2 used in combination w/ HA-TCP results in higher fusion rates than autograft w/ or w/o instrumentation. rhBMP-2 may be used as a bone graft substitute.
Burkus, et al., 2002	I	Multicenter RCT comparing rhBMP-2 w/ autograft in ALIF w/ specific (LT) cage. Results in terms of fusion & outcome equivalent w/ 91% FU.	rhBMP-2 is a viable alternative to autograft for ALIF w/ titanium cages.
Linovitz & Peppers, 2002	III	Series of 7 patients treated w/ interbody fusions using β 2-TCP (supplemented w/ venous blood only) in combination w/ structural autograft. Fusion considered present in all cases.	β 2-TCP may be used as a bone graft substitute in combination w/ structural allograft & venous blood in an interbody application.
Burkus, et al., 2003	III	Combined analysis of several series comparing rhBMP-2 w/ autograft for ALIF w/ specific (LT) cage. Claimed that rhBMP-2 group did better than ALIF group.	rhBMP-2 is a viable alternative to autograft for ALIF w/ titanium cages.
Kasai, et al., 2003	III	RCT comparing 3 groups treated w/ noninstrumented PLF using various mixtures of local autograft & AWGC (2:1, 1:1, 1:2). The 3 groups had comparable fusion rates. There was no control group.	AWGC appears to be effective as a bone graft extender when used w/ local autograft.

* FU = follow up; TCP = tricalcium phosphate.

The use of processed calcium phosphate salts as bone graft extenders in the setting of lumbar fusion for degenerative disease has also been reported. Kasai, et al.,⁴ recently reported their experience using a mixture of local autograft bone combined with varying amounts of AWGC. The ceramic was used as a graft extender and was combined with local autograft bone in a 2:1, 1:1, or 1:2 ratio. Thirty-five patients with degenerative disease and stenosis who underwent decompression followed by non-instrumented two-level PLF were randomized to one of three groups (defined by the ratio of AWGC to autograft). Fusion rates in the three groups were equivalent (82–83%). Because there was no control group (autograft alone), this paper provides Class III medical evidence supporting the safety of AWGC as a bone graft extender for noninstrumented PLF.

Linovitz and Peppers⁵ described their experience with the use of β -tricalcium phosphate ceramic as a graft extender at twelve levels in seven patients who underwent interbody fusion for degenerative disease of the lumbar spine. These patients underwent interbody fusion procedures that involved placement of allograft bone as a structural graft and the ceramic used as an osteoconductive matrix. No bone marrow aspiration was performed; the ceramic was mixed with venous blood instead. In all seven patients fusion was achieved at all operated levels when assessed with plain radiography 3 to 6 months following surgery. This paper provides Class III medical evidence supporting the use of β -tricalcium phosphate as a bone graft extender for interbody fusion procedures. Thalgot and colleagues^{7,8} performed retrospective analyses of patients treated with either ALIF or PLF with processed coralline HA. In two thirds of the patients treated with a PLF demineralized bone matrix was used in combination with the HA. Interestingly, in patients treated with a combination of HA and demineralized bone matrix there was a slightly lower fusion rate than in those treated with HA alone. All groups of patients had fusion rates comparable to historical controls. These papers provide Class III medical evidence with regard to the use of coralline HA as a bone graft extender or substitute.

Summary

Despite the large volume of animal data regarding the use of synthetic bone graft substitutes or extenders, there are very few data regarding the use of these substances for fusion in lumbar degenerative disease. The best available data indicate that rhBMP-2 is a viable alternative to autograft bone for interbody fusion procedures. This same substance may also be a viable alternative to autograft for PLF; however, definitive medical evidence is not yet available. There is little, if any, medical evidence to support the use of other biological agents at the present time. As promising new compounds are brought to market, well-designed cohort studies and randomized trials will be required to determine the actual usefulness of these compounds in clinical practice. It is important not to generalize the results obtained with one preparation or application to different preparations or applications.

The use of synthetic calcium phosphate ceramics as graft extenders appears to be reasonable in certain situa-

tions. The medical evidence available regarding their use is limited and of poor quality. Further study will be required to establish their utility for use in spinal fusion.

Key Directions for Future Research

As demonstrated by the trials used to evaluate rhBMP-2, clinical RCTs are feasible for the evaluation of bone graft substitutes. The existence of a true gold standard for comparison allows for high-quality data to be generated supporting or refuting the efficacy of any bone graft substitute. Prior to undertaking such trials, however, the efficacy and safety of any given product must be demonstrated across many animal species. The reader is reminded not to generalize results from one application to another (such as using ALIF data to support use in a PLF application) or to generalize results from one preparation to another (such as using rhBMP-2 data to support the use of AGF).

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