ARTIGO ATUALIZAÇÃO / UPDATE ARTICLE

Osteogenic Protein-1 (OP-1) as a replacement for iliac autograft in lumbar posterolateral spinal fusion: overview and review of preclinical and clinical studies

Proteína osteogênica-1 (OP-1) como substituto do enxerto ósseo autólogo na artródeose póstero-lateral da coluna lombar. Revisão geral dos estudos pré-clínicos e clínicos

Proteína osteogénica-1 (OP-1) como sustituto del injerto óseo antólogo en la artrodesis posterolateral de la columna lumbar. Revisión general de los estudios preclínicos y clínicos

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ABSTRACT
Osteogenic Protein-1 (OP-1) is a commercially available alternative to autograft for use in lumbar posterolateral spinal fusion procedures. It is intended to minimize pseudarthrosis risk and obviate the difficulties and complications associated with autograft harvest. OP-1, also known as Bone Morphogenetic Protein-7 (BMP-7), has undergone extensive preclinical and clinical evaluation. In animal models, OP-1 has been associated with spinal fusion rates superior to those achieved using autograft in both primary fusions and pseudarthrosis repairs. Gene expression studies, also performed in animal models, have elucidated the biologic basis for these results. Human investigations have shown that OP-1 fusions rival those of autograft. Furthermore, safety and efficacy

RESUMO
A Proteína Osteogênica (P-1) é uma alternativa de auto-enxerto disponível para a utilização na artródeose lombar póstero-lateral. A redução do risco de pseudo-artrose e as complicações relacionadas com a retirada do enxerto do iliaco são os objetivos da sua utilização. A OP-1 é também uma proteína morfogénica-7 (BMP-7) e tem sido submetida a extensos estudos clínicos e pré-clínicos. Nos modelos animais a OP-1 tem sido associada com índices de artródeose superiores aos obtidos com a utilização de autoenxerto nas artródeses primárias e na reparação de pseudo-artrose. Os estudos de expressão gênica realizados em animais elucidaram os seus princípios biológicos básicos de atuação. Os estudos em humanos têm demonstrado que o resultado da artródeose com OP-1

RESUMEN
La proteína osteogénica (OP-1) es una alternativa de autoinjerto disponible para la utilización en la artródeose lumbar posterolateral. La reducción del riesgo de seudoartrosis y las complicaciones relacionadas con la retirada del injerto del iliaco son los objetivos de su utilización. La OP-1 es también una proteína morfogénica-7 (BMP-7) y ha sido sometida a extensos estudios clínicos y preclínicos. En los modelos animales, la OP-1 ha sido asociada con índices de artródeose superiores a los obtenidos con la utilización de autoinjerto en las artródeoses primarias y en la reparación de seudoartrosis. Los estudios de expresión gênica realizados en animales elucidaron sus principios biológicos básicos de actuación. Los estudios en humanos
studies have established OP-1 as a viable replacement for autograft bone in lumbar posterolateral spinal fusions. Most recently, the human clinical trial data with four-year follow-up has demonstrated that the safety and clinical benefit associated with OP-1 is durable over a relatively long time period. It is anticipated that OP-1 will benefit patients undergoing spinal fusion by lowering the rate of pseudarthrosis and by averting the well-established morbidity associated with autograft harvest.

INTRODUCTION
Posterolateral lumbar spinal fusion is a common element in the treatment of a variety of spinal disorders including trauma, deformity, and degenerative conditions, particularly those with instability, such as degenerative spondylolisthesis. The goal of the fusion procedure is segmental union between adjacent vertebrae. It is generally accepted among clinicians that solid bony union is necessary to achieve long-term stability. While there have been significant advances in understanding biologic processes that achieve fusion, many important details remain incompletely understood.

A bone graft or bone graft substitute is typically used to augment fusion procedures. This fusion-promoting material may be osteogenic, osteoinductive, osteoconductive, and/or osteopromotive. Osteogenic materials contain precursor cells necessary for bone growth, while osteoinductive materials induce local precursor cells to differentiate via a bone-forming lineage. Osteoconductive materials provide a structural scaffold onto which bone can be formed. Osteopromotive materials lead to the proliferation of bone forming cells.

While autologous bone may be harvested from a variety of sites, the iliac crest is most commonly used for spinal applications, as first described by Abbott over six decades ago. Iliac crest autograft exhibits all four bone graft attributes described above and for many applications, is considered the “gold standard” among bone graft materials.

While autograft is commonly considered to be the material most likely to promote fusion, posterolateral spinal pseudarthrosis rates range from 5 to 35%3. The harvest of autograft also presents significant shortcomings. Harvest requires additional operative time and chronic donor site pain occurs in up to 25% of patients5-6. Poor bone quality or previous graft harvesting may limit the availability of donor bone. Infection,7 fracture, herniation,8 and injury to surrounding structures are other complications that are not infrequent9-10. The limitations and associated morbidities of autograft have provoked the need for bone graft alternatives (Table 1).

Osteogenic Protein-1 (OP-1), also known as Bone Morphogenetic Protein-7 (BMP-7) is a commercially available alternative to autograft. It has undergone extensive preclinical and clinical evaluations. OP-1 has demonstrated safety and efficacy in preclinical, short-term clinical, and recently in long-term clinical studies. As such, it may be a viable alternative to autograft, obviating the morbidity of bone graft harvest and reducing the risk of pseudarthrosis.
TABLE 1 - Perioperative and long-term complications of iliac crest bone graft harvesting. Data were obtained through a systematic literature review and represent a total of 1020 patients in eight previously published studies, as noted in table. The symbol, (*), represents data that was not reported in the respective study and therefore not included in the final calculations. Adapted from Table 3 as published in: Gupta AR, Shah NR, Patel TC, Grauer JR. Perioperative and long-term complications of iliac crest bone graft harvesting for spinal surgery: a quantitative review of the literature. Int Med J. 2001;8(3):163-6.

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Evaluation of bone grafts and alternatives for spinal fusion
Factors specific to the local biological and mechanical milieu may affect fusion success. For example, the anterior interbody environment, which heals under compression, differs significantly from the posterior elements of the spine, which may be required to heal under tension. In general, a bone graft material should be validated for each specific application being considered. This is often initiated at the preclinical level and then brought to the clinical setting when encouraging results are found.

While many bone graft materials contain a single component, such as allograft products, there are also multi-agent products available. For example, recombinant human bone morphogenetic protein (BMP) products are a combination of an osteoinductive protein and a collagen-based carrier. When a product has more than one component, each component must be specifically considered from both a scientific and regulatory perspective.

Not all bone graft materials are evaluated with the same level of scrutiny by the US Food and Drug Administration (FDA). One categorical difference is that some products are evaluated as implant devices, while others are evaluated as minimally manipulated human tissues. The highly publicized development of BMP for use in spinal surgery is one example. Randomized, prospective clinical studies regarding its use have been reported in the literature. It is only with this high level of scientific data that include radiographic and functional clinical outcomes. Indeed, more studies on noninvasive methods to assess spinal fusion are warranted.

Fusion success is the primary measure used to assess the efficacy of a bone graft material. This outcome, however, is often difficult to determine with certainty. The accuracy of using plain radiographs in assessing fusion success has been noted to be relatively poor. Clinical findings, such as loss of correction and back pain, are also unreliable. Although some investigators have stated their preference for the use of computed tomography (CT) imaging in the evaluation of fusion, there are no definitive studies documenting its accuracy in comparison to plain radiographs. The most reliable method of evaluation may be a combination of measures that include radiographic and functional clinical outcomes. Nonetheless, since the goal of bone graft augmentation is typically to achieve biologic union, success is characteristically measured by this outcome.

Fusion biology
Bone graft is incorporated into a developing fusion mass according to a defined series of biologic events including hemorrhage, inflammation, vascular invasion, remodeling. Surgical preparation of the fusion bed sets the stage for these events. Decortication is required to expose the marrow elements. Mesenchymal stem cells are then recruited to differentiate into chondroblasts and osteoblasts, as directed by local osteoinductive factors. These factors include the BMPs and other mitogens, such as platelet-derived growth factors (PDGF), interleukins, fibroblast growth factors, insulin-like growth factors (IGF), granulocyte colony-stimulating factors, and granulocyte-macrophage colony-
stimulating factors. Concurrently, capillary buds invade the graft to provide local blood supply. Angiogenic factors, such as vascular endothelial-derived growth factor (VEGF), are also released. The osteopromotive influence of these factors delivers a population of cells ready to form new bone.

**BMP discovery and development**

In 1965, Marshall R. Urist, MD (1914-2001) reported the osteogenic potential of demineralized rabbit bone when implanted in rabbit muscle. In the ensuing years, this osteogenic agent was isolated, now known as bone morphogenetic protein or BMP. BMPs are members of the transforming growth factor-b (TGF-b) super-family first identified by Urist for their ability to stimulate de novo formation of bone. These groundbreaking efforts introduced a revolutionary motif to orthopaedic surgery: the application of molecular biology in the development of novel treatment methodologies. In 1988, BMP genetic sequences were identified which led to the characterization of various BMP isoforms. Subsequently, it became possible to produce various BMP products with the use of recombinant gene technology.

**BMP osteoinduction**

The BMPs are cytokines that direct the osteoblastic differentiation of pluripotent mesenchymal stem cells. These proteins bind cell surface receptors and activate intracellular signal transduction cascades that change the protein expression of that cell. Pure BMP is very potent as subcutaneous injection of only 50 to 100 nanograms has been shown to promote heterotopic bone formation in rats. BMP represents 0.1% (by weight) of all bone protein and is most abundant in diaphyseal cortical bone. Immunolocalization studies have noted increased cellular expression of BMP as enchondral ossification progresses to early woven bone. BMPs are also found in the extracellular matrix (ECM), where they are inaccessible for osteoinduction until the bone matrix has been demineralized. Once exposed, however, they induce formation of cartilage and bone.

**Osteogenic Protein-1**

Osteogenic Protein-1 (OP-1) represents one of the two commercially available preparations currently approved for clinical practice. The potent osteoinductive properties of recombinant human BMP-7, also termed OP-1, have generated significant interest in its use as an autograft alternative.

**Preclinical studies**

The osteoinductive potential and safety profile of recombinant human BMP-7, also termed OP-1, have generated significant interest in its use as an autograft alternative. Fusion occurred more rapidly with OP-1 than with autograft alone. By 12 weeks the OP-1 levels demonstrated solid fusion compared to autograft levels, which required an average of 26 weeks to reliably fuse. All spines fused regardless of the grafting material, representing a limitation in the dog model for this comparison. Furthermore, both autograft and OP-1 were tested in the same spines, even though applied at different levels, which may have led to cooperative osteoinduction in these animals.

A similar dog model of posterolateral fusion was used by Cunninghan et al. to compare autograft and control-carrier putty alone. Autograft induced fusion in 63% of the specimens, carrier alone failed to induce any fusions, and OP-1 induced fusion in 100% of the specimens, as tested by manual manipulation and radiographic evaluation (Figure 1). These findings were statistically significant in both the autograft and the OP-1 groups, as compared to the carrier-alone group. Flexion stiffness was greatest in the OP-1 group and least in the carrier-alone group. Histological evaluation demonstrated small, distinct regions or “islands” of calcification in the autologous bone graft fusion masses, representing the original graft material (Figure 2A). There was little to no calcification observed in the carrier-alone fusion masses (Figure 2B). Bridging calcification was observed in the OP-1 augmented fusion mass (Figure 2C). These fusion masses were also noted to include more mature bone than the autograft fusions, indicating that the fusion process may have developed faster in the former.

The same research group subsequently modified this rabbit posterolateral lumbar fusion model to test OP-1 under more rigorous conditions, specifically evaluating the ability of OP-1 to overcome the inhibitory effect of nicotine on lumbar fusion. Eighteen rabbits underwent L5–L6 posterolateral intertransverse fusion with either autograft and control-carrier putty alone. Autograft induced fusion in 63% of the specimens, carrier alone failed to induce any fusions, and OP-1 induced fusion in 100% of the specimens, as tested by manual manipulation and radiographic evaluation (Figure 1). These findings were statistically significant in both the autograft and the OP-1 groups, as compared to the carrier-alone group. Flexion stiffness was greatest in the OP-1 group and least in the carrier-alone group. Histological evaluation demonstrated small, distinct regions or “islands” of calcification in the autologous bone graft fusion masses, representing the original graft material (Figure 2A). There was little to no calcification observed in the carrier-alone fusion masses (Figure 2B). Bridging calcification was observed in the OP-1 augmented fusion mass (Figure 2C). These fusion masses were also noted to include more mature bone than the autograft fusions, indicating that the fusion process may have developed faster in the former.

A dog model of posterolateral fusion was used by Cook et al. to compare autograft to OP-1. Nine dogs underwent posterolateral fusion and each animal spine was augmented with all four implant substances: OP-1 with collagen carrier, collagen carrier alone, iliac crest autograft, and no implant. Fusion occurred more rapidly with OP-1 than with autograft alone. By 12 weeks the OP-1 levels demonstrated solid fusion compared to autograft levels, which required an average of 26 weeks to reliably fuse. All spines fused regardless of the grafting material, representing a limitation in the dog model for this comparison. Furthermore, both autograft and OP-1 were tested in the same spines, even though applied at different levels, which may have led to cooperative osteoinduction in these animals.

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the number of successful fusions. After five weeks, all attempted fusions were explored and those cases found to have pseudarthroses present (94%) underwent attempted pseudarthrosis repair with no graft, autograft, or OP-1. After an additional five weeks, fusions were again assessed with manual palpation, radiology, and histology. Fusion rates of 10% (no graft), 42% (autograft), and 82% (OP-1) were observed. OP-1 was also compared to a hydroxyapatite bone graft substitute and autograft bone in a sheep interbody fusion model27. A posterolateral approach was used to perform interbody fusion in 30 sheep, which were instrumented with pedicle screws. The spines underwent mechanical testing and histological evaluation at six months post-operatively. The OP-1 animals demonstrated greater bone formation than either the autograft or the hydroxyapatite animals. Both comparisons were found to be statistically significant. The maturity and stiffness of the OP-1 fusions were confirmed histologically and by mechanical testing. The maturity of the fusion mass, as assessed by bone scintigraphy, showed less activity in the OP-1 group, signifying a more mature fusion mass.

The potential toxicity of OP-1 was evaluated by implanting OP-1 into the subarachnoid space during lumbar laminectomy in a dog model of spinal fusion27. Laminectomies (L2 level) and durotomies were performed in 30 dogs. OP-1 was implanted within the dural sac, followed by dural closure in 26 of these animals. OP-1, together with local laminectomy bone, were used to perform a posterolateral fusion in each of the 26 animals. The four control animals underwent durotomy with closure, as well as autologous posterolateral fusion using local laminectomy bone alone. Fusion assessment was carried out at 16 weeks post-operatively by palpation, CT imaging, and histology. Eighty percent of the OP-1 animals and 25% of the autograft animals achieved solid fusion. Two of the 26 animals in the OP-1 group were suspected to have developed epidural hematomas with associated paraplegia. The OP-1 animals also developed bone formation adjacent to the neural elements, causing mild spinal cord compression without clinical evidence of lower extremity weakness. Inflammation was observed adjacent to the newly-formed bone, but not within the spinal cord itself. No neuronal cell death was observed.

[Figure 1](#)

Representative posteroanterior plain radiographs of attempted single-level lumbar intertransverse spine fusions in New Zealand white rabbits grafted with (A) autograft, (B) control-carrier alone, and (C) OP-1 five weeks following surgery. Adapted from Figure 1 as published in: Grauer JN, Patel TC, Erulkar JS, Troiano NW, Panjabi MM, Friedlaender GE. 2000 Young Investigator Research Award winner. Evaluation of OP-1 as a graft substitute for intertransverse process lumbar fusion. Spine. 2001; 26(2):127-33.

[Figure 2](#)

Low magnification images of toluidine blue-stained sagittal sections of L5 and L6 transverse processes and intertransverse regions from New Zealand white rabbits grafted with (A) autograft, (B) carrier-alone, and (C) osteogenic protein (OP)-1. Adapted from Figure 4 as published in: Grauer JN, Patel TC, Erulkar JS, Troiano NW, Panjabi MM, Friedlaender GE. 2000 Young Investigator Research Award winner. Evaluation of OP-1 as a graft substitute for intertransverse process lumbar fusion. Spine. 2001; 26(2):127-33.

Gene expression studies

As discussed above, OP-1 induces solid intertransverse process fusion more reliably than autograft in a New Zealand white rabbit model. This animal model has been used to evaluate the effects of both iliac crest autograft and OP-1 on cytokine gene expression within the developing fusion mass31. The purpose of this study was to characterize the biologic events responsible for the superiority of OP-1 versus autograft, with respect to spinal fusion. The reverse-transcription polymerase chain reaction (RT-PCR) was used to assay gene products for glyceraldehyde-3-phosphate dehydrogenase (GAPDH), type I collagen, BMP-2, BMP-4, BMP-5, BMP-7, PDGF, VEGF, and IGF-b from the intertransverse fusion masses of rabbits. This study demonstrated, for the first time, that spinal fusion induced by a single BMP is associated with an enhanced expression of osteoinductive and angiogenic growth factors. In the first two weeks of fusion development, the pattern of expression for most genes examined was found to be remarkably similar for the autograft and the OP-1 groups. This highlights one of the most important results of this study; the application of a single recombinant protein to the fusion bed results in nearly the same gene expression as the application of autologous bone that contains both osteogenic precursors as well as critical growth factors.

Temporal differences in gene expression between the two above-mentioned groups were observed33. Gene expression in the OP-1 group was more active in the later periods of observation, typically at the 35-day time point, as compared to expression in the autograft group. The application of OP-1 to the fusion site induced a cascade of osteoinductive events that maintained activity for as long
as OP-1 remained at the fusion site. It has been estimated that OP-1 is active at the rabbit fusion site for up to five weeks following surgery. This appears to be corroborated by gene expression data showing that OP-1 stimulates the expression of genes involved in the arthrodesis process more effectively and for longer duration than transplanted autologous bone. The increased gene expression of particular osteogenic, chondrogenic, and angiogenic growth factors at the later stages of fusion may be responsible for the improved rate of solid fusion with OP-1 versus autograft alone.

There has also been an interest in studying the role of angiogenic factors in the fusion mass, particularly as specific risk factors for pseudarthrosis. Vascularization is essential to the development of intertransverse process posterolateral spinal fusion34. VEGF is a critical angiogenic factor and has been shown to be responsible for the cartilaginous neovascularization necessary for endochondral ossification and bony healing35. It is anticipated that the application of osteoinductive factors such as OP-1 may promote spinal fusion in the presence of risk factors for pseudarthrosis. Indeed, it has already been shown that systemic nicotine in a rabbit model inhibited the expression of specific cytokines involved in neovascularization and osteoblast differentiation36.

In 2004, White et al.33 demonstrated the increased peak expression and late-over-expression of VEGF and other angiogenic factors following arthrodesis with OP-1 versus autograft. Nicotine is known to inhibit angiogenesis and OP-1 has been shown to increase the expression of angiogenic factors. It has been hypothesized that OP-1 osteoinductive activity may be able to overcome the inhibitory effects of nicotine, as well as other osteogenic inhibitors, including non-steroidal anti-inflammatory drugs. Therefore, the application of OP-1 to spinal fusions may be of value not only in avoiding the complications of autograft harvesting, but also in stimulating spinal fusion in the presence of pseudarthrosis risk factors.

A subsequent gene expression study by the same group was specifically designed to evaluate the processes by which OP-1 overcomes the inhibitory effects of nicotine in repairing established rabbit spinal pseudarthroses37. This was motivated, in part, by the prior study that established a correlation between OP-1 fusion outcomes and enhanced levels of cytokine gene expression. The expression of these cytokines is decreased in nicotine-exposed rabbit pseudarthroses38. Tissue was isolated from nicotine-exposed New Zealand white rabbit lumbar pseudarthroses following attempted no graft, autograft, and OP-1 pseudarthrosis repairs. RT-PCR was used to assess the expression of angiogenin, angiopoietin, intracellular adhesion molecules (ICAM), PDGF-b, VEGF, BMP-2, BMP-7, type I collagen, and osteonectin. Gene expression levels in the OP-1 group were higher than those of the autograft group, which were higher than the no graft group for the majority of the genes studied. These differences in gene expression were statistically significant. In the rabbit pseudarthrosis model, gene expression data supported the hypothesis that successful pseudarthrosis repair is related to the induction of osteogenic and angiogenic cytokines by OP-1.

Human trials of OP-1

Multiple human clinical trials have assessed the effects of OP-1 on posterolateral spinal fusions38-41. Johnsson et al.41 randomized 20 patients with degenerative spondylolisthesis at L5-S1 (up to Grade 2) to receive either OP-1 or iliac crest autograft for single-level posterolateral fusion. The hypothesis, based on the animal studies discussed above, that the OP-1 group would have more rapid and stronger fusions was not met. In part, due to the limited number of patients in this study, there was no statistically significant difference found between the autograft and OP-1 groups with regard to fusion. No adverse events related to OP-1 were observed, while one of the ten patients that underwent iliac crest autograft harvesting developed persistent harvest site pain.

Subsequently, an FDA-approved human pilot study evaluated the safety and efficacy of OP-1 as an adjunct to iliac crest autograft for non-instrumented posterolateral fusions in patients with degenerative spondylolisthesis44. This challenging clinical model was selected because of the associated development of pseudarthrosis in this particular population. The inclusion of only non-instrumented fusions allows for unambiguous evaluation of the bony fusion (Figure 3). Twelve patients with spinal stenosis received a mixture of iliac crest autograft and OP-1 in the intertransverse process space after laminectomy and partial facetectomy, as required for adequate decompression. Evaluation included the use of the Oswestry index, as well as static and dynamic radiographs. Independent, blinded radiologists were used to determine fusion status. The stringent radiographic criteria used to define fusion success were those provided by the FDA for use in clinical trials: the presence of bridging bone, five degrees or less of angular motion, and 2mm or less of translation were required. Oswestry scores improved by at least 20% in 9 of 12 patients (75%) following fusion. Bridging bone was seen in 10 of 11 (91%) patients on PA radiographs, but only 6 of 11 (55%) patients with complete radiographic follow-up qualified as achieving solid fusion. This was not found to be statistically significantly different when compared to historical controls. With regard to safety, no adverse events related to OP-1 were found, specifically including no systemic toxicity, no ectopic bone formation, and no recurrent stenosis. This pilot subsequently led to an FDA HDE approval for OP-1 in the United States.

In 2005, Vaccaro et al.41 reported the two-year follow-up data on these patients who underwent non-instrumented fusion with iliac crest autograft supplemented with OP-1 for the treatment of degenerative spondylolisthesis. The early follow-up results were found to be maintained at two years. Of the 12 patients enrolled in the pilot study, complete clinical and radiographic data was available for 9 and 5 patients, respectively. Eight of nine patients (89%) showed at least a 20% improvement in their pre-operative Oswestry score. While bridging bone on the PA radiograph was reported in seven of ten patients (70%), only five of ten patients (50%) were found to have met the stringent FDA criteria for a solid fusion (Figure 4). The excellent safety results previously reported were found to be maintained at two years, with no adverse events, including no systemic toxicity, no ectopic bone formation, and no evidence of recurrent stenosis.
Vaccaro et al.\textsuperscript{41} later evaluated the safety and efficacy of OP-1 alone by comparison to iliac crest autograft for posterolateral spinal arthrodesis. In this prospective, randomized, controlled, multi-center study conducted under an FDA-approved investigational device exemption, 36 patients with degenerative lumbar spondylolisthesis and spinal stenosis underwent decompression, consisting of laminectomy and partial (medial) facetectomy. Non-instrumented posterolateral fusion was performed with a 2:1 randomization to OP-1 or autograft, respectively. Static and dynamic radiographs were examined by independent, blinded radiologists to determine fusion status. Fusion success was designated if all three of the following criteria were met: bilateral bridging bone between the transverse processes, less than or equal to 5 degrees of angular motion, and less than or equal to 2 mm of translation. At a minimum of one-year follow-up, complete clinical data was available in 32 patients and complete radiographic data was available in 29 patients. Clinical success, defined as at least a 20% improvement in Oswestry index was achieved in 18 of 21 (86%) OP-1 patients and 8 of 11 (73%) autograft patients. Successful posterolateral fusion occurred in 14 of 19 (74%) OP-1 patients and 6 of 10 (60%) autograft patients. No adverse events related to OP-1 were observed, including no systemic toxicity, no ectopic bone formation, and no recurrent stenosis. The authors concluded that successful radiographic fusion was obtained with OP-1 at a rate similar to that obtained with autograft, despite the challenging fusion environment of the posterolateral spine in patients with degenerative spondylolisthesis.

Vaccaro et al.\textsuperscript{41} reported on the durability of these results at a minimum of 24 months following attempted fusion. In this investigation, 31 of 36 and 30 of 36 patients had complete clinical and radiographic data available for analysis, respectively. Clinical success, defined as at least a 20% improvement in the preoperative Oswestry score was achieved by 17 of 20 (85%) OP-1 patients and 7 of 11 (64%) autograft patients. Solid fusion was reported in 11 of 20 (55%) OP-1 patients and in 4 of 10 (40%) autograft patients. An excellent safety profile was also maintained, with no adverse events reported. Since the use of OP-1 without autograft was associated with a radiographically solid fusion in 55% of the patients at 24 months, which is comparable to the historical fusion rates for non-instrumented arthrodesis in this challenging clinical scenario, the authors concluded that OP-1 may be considered a viable alternative to autograft. Since there may be a possibility of fusion success progressively deteriorating over time, these patients continued to be followed in order to determine whether these favorable results were maintained over a still longer term.

In 2006, Kanayama et al.\textsuperscript{42} reported the results of their prospective, randomized comparison of OP-1 to local autograft mixed with ceramic bone substitute in instrumented, posterolateral lumbar fusions. Nineteen patients with degenerative spondylolisthesis at L3–L4 or L4–L5 underwent posterolateral fusion with pedicle screw instrumentation. Randomization to either OP-1 alone (nine patients) or to local autograft with hydroxyapatite-tricalcium phosphate (HA-TCP) granules (ten patients) was performed. Plain radiography and CT imaging were used to evaluate the fusions. Stringent FDA radiographic criteria for fusion success were used, requiring less than 5 degrees of angular motion, less than 2 mm of translation, and evidence of bridging bone. At a minimum of one year following initial surgery, the patients who showed radiographic evidence of fusion underwent surgical exploration of the fusion site with instrumentation removal. Fusion mass tissue was sampled and evaluated histologically. The fusion rate was reported to be 78% (7 of 9) in the OP-1 group and 90% (9 of 10) in the control (i.e. autograft with HA-TCP) group. Histological evaluation of the fusion masses in 16 patients demonstrated new bone formation macroscopically in all 16 cases. Solid fusion was observed in 57% (4 of 7) of OP-1 patients and 78% (7 of 9) of autograft with HA-TCP patients. Histological evaluation demonstrated viable bone in 6 of 7 OP-1 patients and in all nine controls. The authors concluded that in human posterolateral lumbar spine fusions, OP-1 reliably-induced viable amounts of new bone, but the fusion success rate evaluated by surgical
expansion was only 57% (4 of 7). This rate is comparable to that previously reported by Vaccaro et al. who used OP-1 as an adjunct to autograft and is also comparable to historical controls that used iliac crest autograft alone.

Most recently, the long-term safety and efficacy results of OP-1 putty as an alternative to autogenous bone for non-instrumented posterolateral fusion were appraised, using the patient group previously assessed at two-years follow-up. Radiographic and clinical outcomes, as well as the respective complication rates of the OP-1 putty and control groups were compared. The primary efficacy endpoint was the overall fusion success rate, a composite measure derived from radiographic and clinical parameters. The safety of OP-1 putty was confirmed by comparing the nature and frequency of all adverse events and complications that were prospectively observed in either of the groups.

In this long-term, prospective, randomized, controlled, multicenter clinical pilot study, 36 patients with degenerative spondylolisthesis underwent laminectomy and single-level non-instrumented fusion. They were randomized to receive either OP-1 (24 patients) or autogenous iliac crest bone graft (12 patients). At a minimum of four-years follow-up, complete radiographic data were available for 22 of 36 patients (16 OP-1 and 6 autograft). Blinded radiologists reviewed static and dynamic radiographs to determine fusion mass morphology. The presence or absence of continuous bridging bone across the transverse processes was noted. Digital calipers were used to measure motion on dynamic radiographs. Radiographic evidence of a solid arthrodesis was present in 11 of 16 (69%) OP-1 patients and in 3 of 6 (50%) autograft patients.

In this four-year follow-up investigation, complete clinical data were available for 25 of 36 patients (18 OP-1 and 7 autograft). Clinical success was defined as at least a 20% improvement in Oswestry scores and was achieved by 14 of 19 (74%) OP-1 patients and 4 of 7 (57%) autograft patients. This clinical benefit was corroborated by improvements in short-form (SF-36) scores.

Overall success rates were found to be 63% in the OP-1 group and 33% in the autograft group. There was no evidence of local or systemic toxicity, ectopic bone formation, or other adverse events potentially related to the use of OP-1.

In this long-term follow-up study, OP-1 exhibited excellent rates of radiographic fusion, clinical improvement, and overall success that were consistently maintained for at least 48 months following fusion. Since the efficacy and safety profile of OP-1 were at least comparable to that of the autograft controls, OP-1 may represent a viable bone graft substitute for fusion applications.

The FDA, under a HDE, has approved OP-1 as a substitute for autogenous bone when performing revision posterolateral lumbar fusion. The use of OP-1 is considered to be approved for patients who have already experienced a failed attempt at posterolateral fusion and are considered to be at risk for repeated pseudarthrosis. Animal studies and early human clinical trials have shown the efficacy of OP-1 as both an alternative and an enhancer to autologous bone graft or spinal fusion. To date, no serious adverse side effects of OP-1 have been noted in these trials. Continued work is under way to optimize the dose and carrier. OP-1 may replace or augment autograft bone in the wide spectrum of spinal pathology encountered in clinical practice.

CONCLUSION

OP-1 has been designed to replace autograft in spinal fusion. In multiple animal models, OP-1 has produced impressive fusion results, superior to that of autograft, for both primary fusions and pseudarthrosis repairs. Gene expression studies in animal models have established the biologic rationale for these effects. In clinical human investigations, the fusion results with OP-1 alone rival that of autograft. The safety and efficacy evaluations of OP-1 have established it as a viable replacement for autologous bone. In this role, it is expected to benefit patients, by both obviating the well-established morbidities associated with autograft harvest and by reducing the risk of spinal pseudarthrosis.

REFERENCES


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