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18(5) 2023
Opinion

Spinal fusion: the function carried by osteogenic protein-1 & bone morphogenetic protein-7

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Statistics

Figures	00
Tables	00
References	00

Received: 04.05.2023; Manuscript No. jotsrr-23- 100635;
Editor assigned: 05.05.2023, PreQC No. jotsrr-23- 100635 (PQ);
Reviewed: 15.05.2022, QC No. jotsrr-23- 100635 (Q);
Revised: 18.05.2023, Manuscript No. jotsrr-23- 100635 (R);
Published: 23.05.2023,
DOI. 10.37532/1897-2276.2023.18(5).97

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Abstract

Due to its demonstrated osteoinductive effects, particularly in patients with spondylolisthesis, Osteogenic Protein-1 (OP-1), also known as Bone Morphogenetic Protein-7 (BMP-7), is a protein in the TGF-family of cellular proteins that has shown potential for use in patients undergoing spinal fusion. In order to promote bone development, OP-1 acts on Mesenchymal Stem Cells (MSCs), osteoblasts, and osteoclasts to start a variety of biological processes. The capacity of OP-1 to start ossification in posterolateral arthrodesis has been well supported by animal research. Early clinical trials with OP-1 produced promising results, leading the FDA to approve the treatment for long bone nonunions in 2001 and revision posterolateral arthrodesis in 2004 under a conditional Humanitarian Device Exemption.

Keywords: Osteogenic protein-1, Bone morphogenetic protein-7, ossification

INTRODUCTION

Recent larger clinical trials have not detected any appreciable safety issues or increases in adverse events linked to OP-1. Recent clinical trials have not, however, definitively shown that OP-1 is noninferior to autograft in revision posterolateral arthrodesis. The FDA's recent rejection of Premarket Approval (PMA) status in April 2009 leaves the future of OP-1 application in patients with spondylolisthesis questionable. To establish FDA approval for its usage in its current form, additional research on its effectiveness as a treatment and its immunological effects are necessary.

Treatment for symptomatic degenerative spondylolisthesis frequently involves posterior spinal arthrodesis. The term "spondylolisthesis" describes the sliding of one vertebrae in relation to nearby vertebrae, resulting in instability that frequently produces radicular symptoms like discomfort. However, nonunion is a well-recognized side effect of posterolateral spinal arthrodesis, with pseudoarthrosis rates influenced in part by the number and kind of united vertebrae. Up to 57% of patients undergoing spinal surgery may experience instability, ongoing pain, and neurological problems as a result of a lack of fusion, which may ultimately impair the operative outcome. Surgeons have integrated a variety of bone grafts, particularly iliac crest autografts, to lower the incidence of pseudoarthrosis.

However, 6% to 25% of individuals will experience morbidities after receiving an iliac crest autograft, including fracture, infection, hematoma, and chronic dysesthesias at the surgical site.3,4 Therefore, both patients and surgeons are drawn to the prospect of utilising a graft substitute that is comparable to or superior to autograft while removing donor site morbidity. Bioactive compounds like recombinant human bone morphogenetic protein, also known as Osteogenic Protein-1 (OP-1) or Bone Morphogenetic Protein-7 (BMP-7), have been made possible by breakthroughs in molecular biology.

A government investigation into the usage of Stryker Corporation's bone growth products is presently underway. Stryker Corporation is the supplier of the OP-1 Implant and OP-1 Putty. Three sales agents have admitted guilt since November 2008 for encouraging the use of OP-1 goods outside of the label. A federal investigation into the corporation was launched in March 2009 to look into allegations of misbranding of the OP-1 goods outside of their HDE certification. Representatives have claimed as part of plea agreements that they encouraged medical professionals to combine OP-1 products even though they were aware that doing so was against FDA guidelines and had led to unfavourable outcomes.

According to the prosecution, other company employees distributed leaflets with directions for combining bone products in ways that were not FDA-approved.

An FDA advisory panel has recommended against the Premarket Approval (PMA) of the OP-1 Putty, citing the latest trial. The FDA panel cited a number of reasons for its disapproval, including the use of post-hoc analysis to bias the study results and introduce type I errors; the radiographic marker of "bone" was not equivalent to "bridging bone," as the former could represent the formation of fibrous tissue; the patient population was representative of a "stiff population" at baseline; and, last but not least, the immunologic effects of antibody formation against the protein were unknown. These conclusions influenced the panel's decision as a whole to deny OP-1's current PMA certification. Any approval at this time would probably need a fresh clinical trial and additional research on its immunologic effects.

After the pilot and pivotal trials examining the use of OP-1 in patients having spinal fusion for grade I/II spondylolisthesis were finished, the product's proprietary owners (Stryker Biotech, Hopkington, MA, USA) requested authorisation for broader use. With an HDE, the FDA had approved restricted usage for tibial nonunions in 2001 and for revision posterolateral spinal fusion in difficult patients in 2004. Less than 4000 patients are presently treated annually with OP-1 Putty, which is marketed under the HDE. The key experiment conducted by Vaccaro et al., however, seems to make further approval challenging. As was previously mentioned, this randomised multicenter clinical trial was unable to show that OP-1 was superior to iliac crest autograft in terms of noninferiority.

Dr. Deepti Urist made the initial discovery of devitalized bone's capacity to trigger a cellular response and ultimately bone growth upon implantation in 1965. Urist found that this phenomena was caused by a collection of osteogenic proteins known as "Bone Morphogenetic Proteins" (BMPs), which were involved in a complicated chain of cellular processes that included cartilage creation, vascularization, bone production, and ultimately bone remodelling. Later research revealed that this chain of events was caused by pluripotent precursor cells differentiating along an osteogenic route.

A description of the molecular clones of BMPs, knowledge of their biochemical functions, and the elucidation of their amino acid sequence from a highly pure extract of bovine bone were all discovered by the year 1988.

These developments resulted in the identification of BMPs as members of the Transforming Growth Factor (TGF) family and the separation and expression of their human complementary DNAs (cDNAs). In the last 20 years, scientists have gained a deeper grasp of the molecular genetics of the TGF-superfamily and discovered a large number of members of the group that have varying degrees of inductive action towards bone or cartilage. OP-1 is one of the most well-known TGF-superfamily members with considerable current clinical applications.

OP-1 belongs to the TGF-superfamily, which is made up of several growth and differentiation factors with highly similar amino acid sequences in their C-terminal seven cysteine domains. Its members are all BMPs, with the exception of BMP.

TGF- components can all combine to create dimeric molecules. There are three intra-chain disulfide bonds in each of the family's molecular subunits, while a fourth bond holds the subunits together as a whole. Almost all members of the family are created as precursor molecules, and upon secretion from the cell, the pro-peptide is separated from the finished protein. In the form of homodimers or heterodimers, the bone matrix contains a variety of growth and differentiation factors.

Since their discovery in 1965, BMPs like OP-1 have attracted a lot of clinical attention due to their potential medical uses. The biochemical makeup of these TGF-family members and their physiological functions has provided insight into their function as bone development initiators. FDA approval for the use of OP-1 in long bone nonunions in 2001 and revision posterolateral arthrosis in 2004 under a conditional Humanitarian Device Exemption were spurred by promising results in animal studies and early clinical trials.