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Concern over the use of recombinant bone morphogenetic protein in spinal fusion surgery: are stem cells an alternative?

Spinal fusion comprises the joining of two or more segments of the spine by a bony union, which immobilizes these segments. Indications for spinal fusion include many common degenerative, traumatic, neoplastic and congenital conditions. The gold-standard material used to promote fusion is autologous bone, harvested from local bone or from the patient's own iliac crest.

Spinal surgeons have long recognized a need for strategies that enhance bone fusion, as there are potential complications of non-union and donor site morbidity. The osteoinductive recombinant bone morphogenetic proteins (BMPs) BMP-2 (Infuse, Medtronic, Minneapolis, MN, USA) and BMP-7 (OP1, Stryker, Kalamazoo, MI, USA) were designed to enhance bone fusion. A recent meta-analysis demonstrated fusion rates are 12% higher with BMP use compared with iliac bone crest bone graft.[1] In the case of BMP-2, however, there are reports of adverse effects, as well as questions regarding the validity of much of the safety and efficacy data obtained from early industry sponsored trials.[2]

The Food and Drug Administration of the United States issued a warning advising against the use of BMPs in cervical spine surgery in 2008, following reports of ectopic bone formation, wound complications and soft tissue swelling in the neck.[3] It is estimated that BMPs are used in over 50% of spinal fusion surgeries in the United States, predominantly in the lumbar spine, and often in an 'off-label' physician directed fashion, despite only being approved for use anterior lumber interbody fusion surgery.[4] Current concerns with BMPs include complications such as ectopic bone formation or resorption, radiculitis, neuropathic pain, retrograde ejaculation and an increased incidence of cancers, including that of the skin, thyroid, pancreas and prostate.[1,2] Of further concern is that there was an under-reporting of complications in early studies.[5]

Debate within the spinal surgery community has resulted in the recent publication of two independent meta-analyses of BMP-2 data, commissioned by the Yale Open Data Access Project, and sponsored by Medtronic. Fu *et al*. demonstrated no difference between BMP-2 and autologous iliac crest bone graft in terms of fusion rates, pain and disability outcome measures, and adverse events.[6] This analysis also found a low but statistically significant increase in cancer associated with BMP-2 use. The second analysis by Simmonds *et al*. demonstrated higher fusion rates with BMP-2 but this did not correlate with clinically significant reductions in pain and disability.[1] This second report found inconclusive evidence of an increased cancer incidence.

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The indications for BMPs in spine surgery continue to be refined and the relative risks and benefits need to be carefully considered taking into account the surgical approach, the availability of autologous bone for grafting and the relative risk of non-union in the patient. BMPs were purported to be equal or better than iliac crest bone graft (ICBG) in terms of fusion rates, and have been considered a valid alternative to avoid the donor site morbidity associated with ICBG harvesting. Despite the Yale Open Data Access reports identifying lower degrees of efficacy and higher adverse events than originally reported, similar clinical outcomes, fusion rates and adverse events between BMP-2 and ICBG have been demonstrated in anterior lumbar interbody or posterolateral fusion. BMPs continue to be an option for these indications; however, in view of the concerns regarding increased cancer risk and other complications, a detailed informed patient consent process should be mandatory. With regard to posterior interbody fusion, surgeons should be circumspect with BMPs, principally because of the increased risk of ectopic bone formation in peri-neural tissues and subsequent radiculopathy. BMPs are probably best used here in patients at high risk of non-union or where alternative graft options are unavailable. We recommend against the use of BMPs in the cervical spine.

Cell therapies, using stem cells and other progenitor cells, are suited to enhance spine fusion because, like BMPs, they demonstrate osteoinductive properties. Furthermore, some stem cells are osteogenic. The earliest uncommitted clonogenic populations of bone marrow stromal cells, designated mesenchymal progenitor cells (MPCs), can be isolated and culture expanded using magnetic cell sorting in combination with antibodies which identify various cell surface receptors. MPCs isolated in this manner can generate cell banks of purified cells from a single donor, which retain extensive proliferative capacity and differentiation potential, and can be used in an allogeneic fashion. Numerous preclinical studies have demonstrated that, following transplantation to the graft during surgery, these allogeneic MPCs enhance interbody and posterolateral fusion in the lumbar spine without adverse effects.[7,8]

MPCs secrete numerous growth factors, including BMPs and other cytokines involved in bone fusion, in a more physiological fashion when compared with the administration of a supra-physiological dose of BMP. A recent preclinical study demonstrated a more rapid and robust cervical fusion by the addition of MPCs to tricalcium phosphate graft material contained within an interbody cage.[9] In addition, MPCs possess potent anti-inflammatory and immune-modulatory properties that could impart additional clinical benefits. Several phase-2 studies utilizing allogeneic MPCs to enhance interbody and posterolateral fusion have now commenced.[10,11] To date, there have been no cell-related adverse events

in these clinical trials; however, whether MPCs will remain free from the complications now evident with BMPs remains to be seen.

Cell therapies could offer a safer alternative to the use of the BMPs. The potential offered by stem cell therapies to promote fusion should be of great interest to spinal surgeons.

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