Editorial

Bone morphogenic proteins are a good choice for select spinal surgeries and merit further research

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Autologous bone graft with bone obtained from the iliac crest has long been used in spinal fusion surgery (1). Reports of morbidity associated with harvesting iliac crest bone graft (ICBG) have led to an ongoing quest for bone graft substitutes. Ever since Urist introduced the use of bone morphogenic protein (BMP) in 1960, BMPs have been the subject of debate and various research projects (2). BMP-2 (Infuse, Medtronics) has been FDA approved for anterior lumbar interbody fusion. BMP-7 [Osigraft (OS) and OP1 Putty, Stryker] has only been granted a Humanitarian exemption for revision posterolateral fusion in compromised patients.

Delawi *et al.* recently published a multicenter randomized trial investigating BMP-7 (OS, Stryker) *vs.* ICBG (3) for one level instrumented posterolateral fusion of the lumbar spine for degenerative or isthmic spondylolisthesis (grade 1 to 2). The strength of their study comes from the following two study design features: randomized trial and the use of CT scan to assess bone bridging. They found that the overall fusion rate using OS was significantly lower (54%) than that of ICBG (74%) and that it cannot be recommended for fusion in posterolateral instrumented fusion. The clinical outcome (Oswestry disability index, ODI), however, was comparable in both the groups (84% in OS group compared to 86% in ICBG group). The OS group had a significantly higher number of smokers although they did not find this to be of any significance through a regression analysis.

Vaccaro *et al.* in their study comparing OP1 Putty (Stryker) and ICBG for degenerative listhesis, used CT scan and also radiological angulation/translation criterion to assess fusion (angulation <5 degree and translation <3 mm as fusion success) (4). Using the radiological angulation/translation criterion, they found similar fusion rates of 69.3% *vs.* 68.4% for angulation and 74.8% *vs.* 75.7% for translation by 36 months. Clinical outcomes at 2 years using ODI were also comparable; 74.5% in the OP1 group *vs.* 75.7% in the ICBG group. The CT scan performed at 24 months and greater than 36 months showed varying results. At 2 years, bridging bone at the graft site was seen in 61.7% in the OP1 group compared to 83.1% in the ICBG group (P<0.001). At the last follow up (over 36 months), CT showed comparable fusion rates (74.8% in the OP1 group compared to 77.4% in the ICBG group).

Based on the above observation, assessing bridging fusion by CT scan at 1 year (as was done in the Delawi study) may be too early since it seems that the process continues beyond 1 year. The slightly higher fusion rates based on the CT scans in the study by Vaccaro *et al.* (61.7%) compared to the Delawi *et al.* study (54%) could be due to several reasons (3,4). The fusion assessment time period was different, as mentioned above. Only degenerative listhesis was included in the Vaccaro study while the Delawi study also included isthmic cases. What was most interesting to note was the type of BMP-7 used in the studies. Vaccaro *et al.* used OP1 putty in their study while Delawi *et al.* used OS. OS is predominately available in Europe. OP1 Putty (which is the same as OS in constituent) is available in the United States but has an additional component, carboxymethylcellulose (CMC), which may be a factor in enhancing adhesion (5-7). Currently, there is no literature that directly compares the effectiveness of OS to OP1 putty (with CMC). Studies have shown that CMC improves bone formation. Research into

the effectiveness of OP1 and CMC should be conducted to further evaluate and validate its effectiveness in fusion procedures.

Delawi *et al.* included only grade 1 and 2 listhesis patients in their study. The results (clinical and radiological) were not categorized with respect to degenerative or isthmic type. It would have been interesting to see if the fusion rates and clinical outcomes differ with respect to the type of listhesis. This may have been a factor, especially in isthmic spondylolisthesis where high sheer stress at times requires robust circumferential fixation techniques.

Iliac crest autografts do have drawbacks with higher rates of complications including: nerve, arterial and urethral injury, pelvic fractures, gait disturbances, hematoma, infection and chronic pain at the harvest site, in addition to chronic neuralgia (8).

One potential advantage of using OS is avoidance of morbidity associated with harvesting ICBG, although Delawi *et al.* reported no difference in the two groups. We agree with the Delawi *et al.* suggestion that the degree of pain attributed to the donor site is probably over-estimated. Also, the technique of harvesting autograft also plays a role with associated morbidity (9,10).

It is important to note that Delawi *et al.* did not report any adverse events with the use of BMP-7. Although they reported that reoperation rates were higher in the OS group (ten cases compared to two), this was not associated with use of OS. There has been controversy in the use of BMP-2. Tannoury *et al.* explored the complications of bone morphogenetic proteins in depth, concluding that its use should be reserved for patients with no other alternative (9). The Yale University Open Data Access (YODA) studies, however, indicated the efficacy of BMP-2 to be equivalent or superior in achieving fusion as compared to autologous bone graft. BMP-2 is used most often in spine surgery as an off-label use.

Concerns of carcinogenesis remain at the forefront when discussing BMP complications, with cancer appearing at the top of the list of adverse effects; media coverage on OP1's rare carcinogenic effects has skewed public opinion negatively, influencing patients' decisions about its use (11). Although previous research may have indicated a correlation between BMP use and increased incidence for malignancy, its association has been highly exaggerated by the media. Current literature suggests no statistical significance between BMP treatment and cancer (12). Two recent studies by Dettori *et al.* and Malham *et al.*, found no significant association between BMP and the risk of cancer (12,13).

New fusion techniques are constantly evolving, with advancements in technology, biomaterials and instrumentation that may lead to alternatives for standard therapies. These alternatives may include off label uses of medications, such as the current off label use of BMPs in spine surgery. My personal experience has been that many of our patients prefer that we use OP1 instead of an iliac crest autograft because it eliminates the need for them to undergo an additional incision and procedure with possible complications.

Delawi *et al.* did an evidence based study comparing the effectiveness of BMP-7 use with ICBG, the current gold standard. Although Delawi *et al.* could not prove statistical non-inferiority, this study does suggest areas of further research. BMPs show promise as a means for interbody and onlay fusion in spine surgery. Further research studies may uncover more promising data showing the benefits of BMP use in selected patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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