OHTAC Recommendation

Osteogenic Protein-1 for Long Bone Nonunion

April 8, 2005
The Ontario Health Technology Advisory Committee (OHTAC) met on April 8, 2005 and reviewed the health technology assessment report on osteogenic protein-1 (OP-1) for the treatment of long bone fracture nonunion. The review included a presentation by the Medical Advisory Secretariat of its health technology policy review and discussion by the committee.

About 5% to 10% of fractures do not heal within a normal time frame and are classified as delayed unions or nonunions. Nonunions can present complex orthopedic problems, and the multiple surgical procedures often needed are associated with patient morbidity and additional costs to the health care system. The estimated number of delayed unions or nonunions in the province would be between 3,863 and 7,725 per year.

The technique of autologous bone grafting is generally considered the gold standard in the treatment of nonunions because bone graft has several components that are critical in bone regeneration. However, harvesting the autologous bone graft is associated with postoperative pain at the donor site, bone fracture, potential injury to the surrounding tissues, and the risk of infection. To overcome the complications arising from graft harvesting, engineered materials that mimic at least one of the components of the autologous bone graft have been developed.

Osteogenic protein-1 (OP-1) is a growth factor, which is one of the components of the autologous bone graft. OP-1 plays an important role in bone formation by stimulating stem cells to differentiate into osteoblasts (bone cells). The first randomized controlled trial (RCT) of OP-1 on tibial nonunions has demonstrated equivalence between the gold standard autologous bone grafting and OP-1; the rate of clinical and radiological success in tibial nonunions was comparable to the autologous bone grafting when used in conjunction with intramedullary rod fixation. In addition, the rate of postoperative infection at the recipient site was significantly lower in those treated with OP-1 compared to those treated
with autologous bone grafting. Based on this trial, the FDA issued a Humanitarian Device Exemption to authorize the marketing of OP-1. This agent is currently available for clinical use. It comes in the form of a vial and is applied directly into the fracture site. The cost of each vial is approximately $5,000.

The review also located a number of other studies (total of 10), published mainly in peer-reviewed journals. The results of these studies show that another method, percutaneous autologous bone marrow grafting, is highly effective in the treatment of long bone nonunions. He reported success rate across these studies range from 75% to 95%. In a total of 301 fractures across all studies, 268 healed (89%) with a mean healing time of 2.5 to 8 months. However, all these studies are case series with no control group. No RCT has been conducted to compare the effectiveness of this method to the gold standard technique.

The method of percutaneous autologous bone marrow grafting involves aspiration and injection of bone marrow that could be performed under either local or general anesthesia. It is an outpatient procedure and has the advantage of treating long bone nonunions without exposing the patient to the risk of surgery and complications of graft harvesting. The bone marrow is harvested by needle aspiration from the patient’s pelvic bone and is then injected percutaneously into the fracture site under fluoroscopic control. Bone marrow contains stem cells, which are unspecialized cells that can differentiate and produce mature osteoblasts, which are capable of producing bone. Clinical use of stem cell transplants for hematopoietic conditions, such as various blood cell cancers was established over a decade ago.

Comparing the three available technologies in terms of their clinical and economic outcomes, percutaneous autologous bone marrow grafting is expected to produce the most favourable outcomes. The existing evidence
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regarding its clinical effectiveness should be supported by a larger scale clinical trial.

OHTAC Recommendations:

• Based on level one evidence, OP-1 is as effective as autologous bone grafting and offers the advantages of eliminating donor site morbidity and reducing the risk of infection at the recipient site. Therefore, OP-1 is a reasonable alternative to autologous bone grafting in the treatment of long-bone nonunions and the decision to use it should be left to the discretion of treating physicians.

• That the MOHLTC seek the advice of Ontario clinical and academic experts regarding the appropriateness and feasibility of conducting research in Ontario into the effectiveness of autologous bone marrow as an alternative treatment for nonunion fractures, based on the review presented to OHTAC.