Common spinal fusion product shown to be harmful

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(Medical Xpress) -- The risk of complications associated with a bone growth factor commonly used in spinal fusion surgeries is estimated to be at least 10 to 50 times greater than previously reported in industry-sponsored studies, according to a comprehensive review published in The Spine Journal.

The review by journal editor Eugene Carragee, MD, professor of orthopedic surgery at Stanford, and colleagues documents a wide range of potentially harmful side-effects associated with the product, including male sterility, urinary problems, infection, bone and nerve injury and a possible increased cancer risk. (The journal has issued a news release summarizing the findings.)

The association of these complications with the bone growth product, some of them catastrophic, were never reported in early studies by orthopedists with significant financial ties to the product maker — studies which led to widespread use of the product, the reviewers reported in the June 29 online publication of the journal, which is devoted entirely to the subject.

The product, a bioengineered version of the protein BMP-2 (recombinant bone morphogenetic protein), is now used in more than 100,000 people per year undergoing spinal fusion surgery in the United States, Carragee said.

In an accompanying editorial, Carragee and four other experts indicated

in a careful critique that the early studies suggested “systematic bias.”

“It harms patients to have biased and corrupted research published,” they wrote. “It harms patients to have unaccountable special interests permeate medical research. It harms patients when poor practices become business as usual.”

The recombinant protein was approved in 2002 by the federal Food and Drug Administration to help heal the bone as part of a spinal implant procedure in which the vertebrae in the lower back are fused together. Early review articles suggested that the protein had inflammatory and growth stimulating properties, with the potential to have impact on the surrounding bone, urinary tract and other tissues, as well as increased cancer risk. However, between 2002 and 2009, orthopedic journals published 13 controlled studies involving 780 patients that validated its use and showed it to have a “near-perfect” or “perfect” profile, with no harmful side-effects, the authors write in the review.

Reassured of the product’s safety, orthopedists in the United States began using the protein off-label, or for uses unapproved by FDA, in other parts of the spine, including fusions in the cervical spine in the neck. Use of the product grewfrom about 1 percent of all spinal fusion procedures in the United States in 2002 to between 30 and 50 percent of these operations in 2007, according to the authors. The product, marketed by Minneapolis-based Medtronic Inc. under the brand names Infuse and Amplify, now represents revenue of about $900 million a year for the company, according to the Wall Street Journal.

By 2006, Carragee said reports of complications with the bioengineered protein began to turn up in the medical literature. In particular, serious problems, including reports of death, began to surface in patients undergoing cervical spine repair. In 2008, the FDA issued a “Public Health Notification” warning against use of the product in the neck, as

patients reported difficulty swallowing, speaking or breathing.

At the same time, the product became the subject of a Justice Department investigation, Congressional inquiries and whistleblower lawsuits involving former company employees, according to press reports.

A year ago, the journal's editors decided to investigate. They obtained the original, publicly available FDA data on the product and reviewed all the published spine literature on controlled BMP-2 trials between 1995 and 2010. They discovered that the early industry-sponsored studies had wide discrepancies with the FDA data and the non-industry studies, which showed an incidence of complications that were 10 to 50 times the original estimates.

For instance, when used in the lower spine, the reviewers found a 10 to 50 percent increased risk of complications, including male sterility, nerve inflammation, urinary problems, problems with bone reabsorption and movement of the implant. When used in the neck, the product was associated with a 40 percent greater risk of adverse events, some potentially life-threatening. The newer, high-dose version of the protein was associated with a greater risk of leg and back pain, nerve and infection problems, as well as a statistical increased risk of cancer, the authors reported.

The early studies, they reported, were published by some researchers who received at a minimum between $1 and $23 million annually from the product's manufacturer for consulting, royalty and other compensation, based on data reported by the company, to the journal or in public documents. These median payments ranged from $12 million to $16 million per study, the review authors reported.

The reviewers also concluded that the earlier studies were flawed in

design or analysis, as the studies claimed — inappropriately — that side effects were not statistically significant enough to report. The reviewers also found that the earlier studies had a built-in bias against the traditional treatment, in which a small piece of the patient's hip or spine bone is grafted onto the spine.

Dan M. Spengler, MD, former editor-in-chief of the Journal of Spinal Disorders, wrote in an accompanying commentary that the review "offers insight into the sometimes flawed processes that can occur in the development of a clinically applicable biological product."

"I don't think anybody understood these dollar amounts were in the amounts that they were," Spengler, a professor of orthopedic surgery at Vanderbilt, said in an interview. "It's one thing to receive BMP for study purposes. It's quite a bit different to receive $2 million a quarter. The readership needs to know it. Let the reader decide: Are you going to put your trust in articles by people who are this conflicted? The whole process needs to be looked at in a comprehensive way," including the nature of financial disclosures, the peer review process and industry sponsorship of studies.

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