Vertebroplasty: a promising but as yet unproven intervention for painful osteoporotic spinal fractures

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Medicare funding could jeopardise the research needed to establish the benefits and risks of this procedure

Recent publications and regulatory decisions about the therapeutic use of vertebroplasty, or injection of bone cement into diseased vertebrae such as osteoporotic fractures, call for a closer look at the evidence. New drug treatments are not considered to have proven efficacy until, at the very least, they have been evaluated in randomised controlled trials. Even then, their safety is not guaranteed, particularly for uncommon adverse effects, or those for which there is a long delay between exposure and clinical manifestation. Adverse effects that have a high prevalence may also be difficult to detect, as exemplified by the much-delayed recognition of the association between myocardial infarction and strokes and rofecoxib.[1] In Australia, drugs must also be shown to be cost-effective compared with existing subsidised treatments before they are accepted into the Pharmaceutical Benefits Scheme.

The Medical Services Advisory Committee (MSAC) recently recommended vertebroplasty for interim public funding for restricted indications, including painful osteoporotic vertebral compression fractures confirmed by diagnostic imaging and not controlled by conservative medical therapy.[2] While technology appraisals of vertebroplasty by health policymakers in a variety of settings, including Australia, have recognised that there is inadequate high-quality evidence on which to base a reimbursement decision, many have subsequently recommended public funding.[3] Making these reimbursement decisions in the face of limited evidence raises some concerns.

Firstly, while uncontrolled studies have suggested that vertebroplasty may be an efficacious treatment for painful osteoporotic spinal fractures not responsive to conservative management, uncontrolled studies tend to overestimate treatment benefit for a variety of reasons.[4] They fail to take into account the natural history of the condition, which is that it improves over time; they make no allowance for the statistical artefact of "regression to the mean"; and they do not adjust for the placebo response, which is likely to be accentuated with an invasive procedure.[5] At present, the best available evidence for efficacy of vertebroplasty are data from two controlled before–after studies that compared volunteers who were offered the treatment with those who refused it.[6,7] This constitutes level III-2 evidence in the National Health and Medical Research Council (NHMRC) hierarchy of levels of evidence, which ranges from I for the highest level to IV for the lowest level.[8] While these studies showed an early benefit of vertebroplasty over conservative treatment, it is likely that they too have overestimated the treatment effect,[9] particularly as volunteers who agree to have a new therapy are known to have a better outcome than those who refuse it. Patient self-selection bias in one study meant that, in comparison to those who refused treatment, those who agreed were considerably more disabled at baseline and so had more potential to improve.[6] Participants in the other study were treated relatively early after presentation with an acute vertebral fracture, and most of them were admitted as inpatients, so the results may not be relevant to patients who have had pain for longer than a few weeks.[7]

Of more concern than questionable efficacy is the potential for harm. The risk of subsequent vertebral fracture once a spinal fracture has occurred in patients not exposed to vertebroplasty is very high — the risk within a year of a single vertebral fracture has been estimated to be about 20% in those with untreated osteoporosis and about 10% in those treated with bisphosphonates.[10] Several uncontrolled studies have now suggested an increased incidence of vertebral fractures after vertebroplasty, particularly in vertebrae adjacent to treated levels or if cement has leaked into the adjacent disc,[11,12] while the two controlled before–after studies have yielded conflicting results in this regard.[6,7] Yet, like heart attacks and strokes with rofecoxib, in the absence of rigorous controlled trials that are powered to detect an increased incidence of an already prevalent condition, this may take time to become evident. Furthermore, while the risk of immediate complications (such as cement leakage into the spinal canal, adjacent disc and venous circulation) from the procedure when it is performed by experienced operators, is estimated from published case series to be low, it is likely that the incidence of immediate complications will be higher in routine use, where there is likely to be a learning curve, and there are no restrictions on who can perform the procedure.[13]

Now that proponents of vertebroplasty have the imprimatur of MSAC approval, promotion of this procedure to the medical community and the public has intensified. For example, a recent "advertorial" in *Australian Family Physician* claimed that vertebroplasty is a safe, effective, and cost-effective procedure when performed in an appropriate technical environment by adequately trained interventional radiologists.[14] Yet, as outlined above, the available evidence is weak and does not justify these strong claims.

The way forward is to gather the necessary evidence. To this end, a multicentre, randomised, double-blind, placebo-controlled trial of vertebroplasty for painful osteoporotic spinal fractures has been funded by the NHMRC and is currently underway in Australia. In addition to gathering evidence on short-term efficacy, all trial participants are being followed up for 2 years so that the question of long-term safety and, in particular, risk of future fractures can be assessed. However, public funding of vertebroplasty through Medicare has the potential to seriously undermine the success of this and other trials by not only providing easy access to an unproven treatment, but also by lending implicit support to its use. This may result in a situation where the true effects of this treatment may never be established. At present, the trial has recruited almost a quarter of the required sample and, at the current rate of recruitment, is expected to be complete within 4 years. A second randomised, double-blind, placebo-controlled trial of vertebroplasty for osteoporotic spinal fractures is in progress in the United States. These trials will provide pivotal evidence on the value of vertebroplasty.

At present, vertebroplasty, while promising, is of unproven safety, effectiveness and cost-effectiveness. Thus, the promotion and routine use of this procedure outside of the research setting remains unjustified and premature, and the onus remains on the proponents of vertebroplasty to prove their claims. *Primum non nocere*, or first, do no harm.

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