SPINE SOCIETY OF AUSTRALIA

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Dr Brian Richards

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Re: Vertebroplasty

Dear Dr Richards

I reply to your letter of 9th August requesting the Society's opinion regarding the use of the procedure of vertebroplasty. In formulating this response I have relied on expert opinion from two of our members who are spinal surgeons and epidemiologists as well as the results of an email survey (results in the enclosed appendix) of our membership and from written comments I have received from our membership.

The current situation is that vertebroplasty is used in three situations in this country.

- As a percutaenous procedure for osteoporotic vertebral fracture.
- As a percutaenous procedure for metastatic vertebral body infiltration.
- As an adjunct to open surgical fixation for vertebral body fracture due to osteoporosis or tumour.

Whilst some of our members perform reasonable numbers of this procedure, most spine surgeons refer patients to interventional radiologists for this procedure,

There is a widely (though not universally) held view that this treatment is effective and in a majority of cases causes near instant pain relief. There appears to be little doubt that vertebroplasty for metastatic disease is effective and that it may mean that open surgical intervention can be avoided. The situation with osteoporotic fracture is more complicated. Many patients with osteoporotic fractures will heal and become assymptomatic in a matter of months. As long as these patients can tolerate the pain without adverse health effects while healing occurs, vertebroplasty is probably not necessary and the risks of adjacent segment fracture and cement extravasation outweigh the benefits. However there remains two important groups of patient who do not follow this benign course. There is a group of patients who do not heal within a few months and go on to have slow further collapse of the fractured vertebral body. It is probable that this group of patients progress to non union of their fracture (healing does not occur). These patients probably would benefit from vertebroplasty. The

problem is identifying when a patient with persisting pain beyond a few months has this pain as a consequence of an ununited fracture or whether this may be due to other mechanical effects of their fall. Patients in this age group often have multiple other causes of back pain – such as multilevel degenerative discs, facet osteoarthritis, spinal stenosis and degenerative spondylolistheis or scoliosis. A persisting kyphotic deformity from a healed fracture can place stress on these degenerative structures and be the cause of pain. It can be difficult in these circumstances to determine if the fracture is the cause of pain. The existing approach of using bone oedema on an MRI is probably not sensitive enough to use this as the sole discriminator. It needs to be used in conjunction with clinical opinion from an expert clinician (usually a spine surgeon).

There is also a group of patients who, in the early phase after their fracture, have pain of sufficient severity for this to represent a health risk. It is well known that there are significant medical risks associated with a bedridden elderly patient. These include respiratory and cardiac complications, deep venous thrombosis, pressure sores and irreversible loss of muscle strength. Surgical management of acute painful injuries in this age group is well established as a means of preventing these complications. This is best illustrated by the well accepted practice of aggressive internal fixation of fractures of the femoral neck (also osteoporotic).

The existence of both these groups presents particular problems with proof of efficacy. In the first group the problem is one of proper patient selection (exclusion of patients with pain from other causes) and in the second group it is necessary to study pain in the acute phase (possibly daily or at least weekly for the first 4 weeks). Evidence that longer term outcome may be the same in treatment groups compared to conservative care (or even randomised sham operations) is missing the essential point of the problem in this group of patients. Vertebroplasty may allow such a patient to be avoid a number of weeks of hospitalization or to avoid some of the complications mentioned above. In these cases a few weeks or a month or so of pain relief may make a permanent difference to the outcome and may result in significant savings. It should also be clear that when the acute pain can be managed by other means (such as a brace – a biomechanically effective brace is estimated to cost $600) or analgesia and where there is little health risk that the potential benefits of vertebroplasty are likely to be outweighed by the extra risks of adjacent segment fracture and cement extravasation. The email survey of our members (see appendix) suggest that most feel that the minimum symptoms required before considering vertebroplasty was pain with a health risk.

Since the date of the last MSAC review (28th November 2005) there have been a large number of publications regarding vertebroplasty. There are however 5 randomized controlled trials (RCT's) that are of interest. There is a single paper (Lau et al. 2008) that analyses mortality data with respect to osteoporotic vertebral fracture in a large US national database (medicare). There are two RCT's comparing vertebroplasty to conservative care, two randomized blinded placebo controlled trials comparing vertebroplasty to a sham procedure and one large trial comparing Kyphoplasty to conservative care.

The mortality study reported by Lau et al demonstrates that the mortality rate (as demonstrated by survivorship analysis) is higher for patients with osteoporotic vertebral compression fractures than the mortality rate of age matched population without vertebral fracture. Whilst no conclusion can necessarily be made about cause and effect, this data supports the widely held clinical belief that vertebral compression fractures impact on the health of affected patients. It is understood that a further paper from this group was presented at the recent American Academy of Orthopaedic Surgeons meeting and that an analysis of patients treated with vertebroplasty and

kyphoplasty had an improved mortality. This data is apparently in press and the abstract is not available. It may however represent important information.

The RCT's by Rousing et al (Rousing et al. 2009) and Voormolen et al (Voormolen et al. 2007) both concluded that the benefit from vertebroplasty was almost immediate with a moderately large effect size. However the benefit appeared to occur early and there was no statistical difference in average outcome between conservative care and vertebroplasty by 1 month. It was noted by Voormolen et al (Voormolen, Mali, Lohle, Fransen, Lampmann, van der Graaf, Juttmann, Jansssens, & Verhaar 2007) that a small subgroup of patients had persisting severe in the conservative care group.

The FREE study (Wardlaw et al. 2009) is a large study randomly comparing Kyphoplasty to conservative care. Kyphoplasty is a more complex procedure that involves inflating a balloon within the fractured vertebral body to attempt to reduce the deformity of kyphosis. A low pressure injection of bone cement is then performed into the resulting cavity. This paper showed improvement in both conservatively treated patients and in kyphoplasty treated patient though the improvement was greater in the kyphoplasty group and that this improvement was by and large maintained up to 12 month followup. Whilst kyphoplasty is a different technique to vertebroplasty, the final result is a fracture that is stabilized with cement. The difference is that to some extent the kyphotic deformity is reduced. Presumably the apparent longer term benefit in the kyphoplasty study is due to this mechanism and this would suggest that one of the reasons for persisting pain following an osteoporotic fracture (apart from fracture non union) may be the persisting deformity. This finding is consistent with the large body of evidence that suggests that kyphosis is a cause of spinal pain in many conditions due to the abnormal mechanics that it induces in the standing posture.

The two recently published randomized blinded placebo controlled trials of Kallmes(Kallmes et al. 2009) and Buchbinder (Buchbinder et al. 2009) have however cast some doubt on the efficacy of vertebroplasty for osteoporotic fracture. These have been the subject of much media attention and even public comment by our Prime Minister. Both papers used a control of an elaborate sham procedure that involved the insertion of a cannula under local anaesthetic down to the lamina of the vertebrae, the application of simulated pressure and an ampoule of bone cement was opened in the procedure room, thus exposing the patient to the strong smell of the volatile liquid component of the cement. Both papers reported no significant difference in outcome at 1 month and it has been widely reported that as these papers represent class 1 or 2 evidence that means that vertebroplasty is an ineffective treatment. As these papers apparently contradict wide clinical experience and as the procedure has reasonable biological plausibility, it is our view that these papers should be subject to substantial critical review.

The Society recently made a submission to the government HTA review process. In that submission we suggested that assessment of evidence did not simply mean assessment of 'levels of evidence' (such as levels according to the NHMRC) and that a formal process of assessing strength of evidence in combination with clinical expertise from content experts was required. This approach is internationally recognized – the GRADE process (Guyatt et al. 2008). We recommend this or a similar process be used to asses the evidence for vertebroplasty and particularly the strength of the papers of Kallmes et al and Buchbinder et al.

Both these papers have significant limitations.

1. The most relevant is the low percentage of eligible patients who agreed to be randomized. In the paper by Kallmes et al this was 30% (131 out of 431) and in the paper by Buchbinder et al it was 36% (78 out of 219). The patient characteristics and the outcome of treatment in those that did not agree to be randomized is unknown. It is possible that the group who did not wish to be randomized had worse or less pain or pathology and that these patients may have been either more or less likely to respond to vertebroplasty. The group who did not wish to be randomized represents the majority of the sample and it is difficult to draw conclusions regarding the population of patients with osteoporotic crush fracture from the minority sample.

2. There is significant variation in the reported effect size of the active treatment. The paper by Buchbinder et al showed a very small effect size for the active treatment with a pain score change at 1 week of 1.5 (on a 10 point scale). Whereas the effect size measured by Kallmes was 2.7 at 3 days. In comparison the effect size measured by Rousing et al was 5.7 and 2.4 in the paper by Voormolen et al. The FREE kyphoplasty study had an early effect size of about 3.5. A similar variability in reported experience of the SSA members in the survey (see response to question 7 in appendix). Whilst a possible explanation for the small effect size seen in the Buchbinder paper is a placebo effect, these findings suggest a heterogeneous treatment effect. (Kravitz et al. 2004) this finding suggests that there are important subgroups within the studied population that have different outcomes, these subgroups could represent different patient populations and different experience and skill of the proceduralist.

3. The exclusion of patients with sufficiently severe pain to require hospitalization.

4. The use of bone marrow oedema to define the absence of fracture union.

5. Crossovers, the use of intention to treat analysis, loss of randomisation and power through post-hoc subgroup analysis.

6. Over 60% of patients in the Buchbinder study had experienced pain for greater than 6 weeks prior to the intervention and insufficient data on fracture union is provided to enable the reader to determine whether or not these studies examined the efficacy of vertebroplasty in treating osteoporotic fractures or persistent pain in united fractures.

Overall the conclusion is that whilst these studies cannot be dismissed, there are significant limitations. These studies show that there is a patient population that probably does not get benefit from the intervention; however it does not rule out that the possibility that many other patients may get benefit.

Conclusion:

Clinical experience with vertebroplasty suggests that the procedure can be beneficial for the appropriate group of patients. It is difficult to support the use of vertebroplasty in all cases of osteoporotic vertebral fracture. The procedure should be limited to those patients in the acute stage where pain cannot be controlled by conservative means and where the presence of continued pain would represent a risk to health, or in those

cases of chronic pain where it has been determined that the cause of pain is that of fracture non union, rather than other causes. This is a difficult determination and is best done by a clinical expert.

Recommendation:

The Spine Society supports the continued funding of vertebroplasty for osteoporotic vertebral fracture though would support the tightening of eligibility criteria. This could probably best be achieved by considering fractures that are acute (< 6 weeks) and chronic (> 6 weeks). And by requiring referral by a clinical treating specialist for interventional radiologists.

The eligibility criteria for vertebroplasty performed by an interventional radiologist should be:

- For acute pain (less than 6 weeks duration) - when referred by a treating specialist where conservative treatment has failed to relieve pain and where it is considered that the continuation of pain represents a risk to the health of the patient.

- For chronic pain (greater than 6 weeks duration) – when referred by an Orthopaedic surgeon or Neurosurgeon who is of the opinion that the persistence of pain is due to non union of the fracture.

Appropriate treating specialists to perform vertebroplasty are Orthopaedic Surgeons, Neurosurgeons and interventional pain specialists. For these practitioners the criteria should be:

- For acute pain (less than 6 weeks duration) - where conservative treatment has failed to relieve pain and where it is considered that that the continuation of pain represents a risk to the health of the patient.

- For chronic pain (greater than 6 weeks duration) – where the persistence of pain is thought to be due to non union of the fracture.

The Society also supports continued research into this important condition. It is felt unlikely that useful answers will be gained by further placebo controlled trials because of the problem of randomization, and that more useful information could be obtained by well designed cohort studies that are designed to better identify those patients who are likely to benefit from the procedure.

Sincerely

Dr Peter McCombe
President Spine Society Australia

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