Australian Government
Medical Services Advisory Committee

STAKEHOLDER MEETING MINUTES - FINAL

VERTEBROPLASTY

Friday 7 June 2019

Attendees

Meeting attendees included members of the Medical Services Advisory Committee (MSAC); clinicians with experience and expertise in geriatric medicine, interventional radiology and spinal surgery; representatives of the applicant; representatives from consumer organisations; and representatives from the Department of Health.

1. Meeting open – welcome and introduction

The MSAC Chair opened the meeting at 1:50 pm.

The Chair thanked participants for attending and clarified that the stakeholder meeting was not an MSAC decision-making forum, but would inform MSAC's future deliberations and advice to the Minister for Health by providing a better understanding of the issues raised by MSAC at its March 2019 consideration of Application 1466: Vertebroplasty for severely painful osteoporotic vertebral fractures of less than 3 weeks duration. MSAC's subsequent advice would then be considered by the Government.

The key objectives of the meeting were to seek a broader clinical perspective and patient input to inform the uncertainties in the application, and to ascertain the appropriateness of, and possible parameters for, an individual patient data (IPD) meta-analysis to further address those uncertainties.

The Chair reminded participants that this was a confidential discussion. The minutes of the meeting would be provided to all attendees for input/comment. The Chair noted that some invited clinical representatives were unable to attend the meeting because of attendance at other professional activities, and that representatives of some consumer organisations were also unable to attend. The Chair indicated that the minutes of the meeting would also be circulated to these invitees and they would be invited to submit their comments in writing.

The Chair advised that the final minutes would be published on the MSAC website, and would form part of MSAC deliberation should the application come back to MSAC for further consideration. The Chair indicated that these minutes would not attribute any of the discussion to any identified individual.

The Chair explained that participants would each have a chance to present a statement, and acknowledged that some participants had brought statements to present on behalf of others. Representatives of the applicant also tabled a written response to the PSD for participants to consider, which the Chair asked to be circulated to all attendees and invitees to the meeting.

Conflicts of interest

The Chair noted that conflicts of interest had been declared and recorded, but in the context of this meeting conflicts did not need to be managed by exclusion from discussions.

2. Background – recent MSAC consideration and key discussion points

The Chair provided an overview of MSAC's role and membership, and reiterated the strict management of conflicts of interest in relation to applications.

MSAC considered Application 1466 for vertebroplasty at its November 2018 and March 2019 meetings. MSAC deferred its advice regarding public funding to convene a stakeholder meeting for broader consultation. The relevant Public Summary Document (PSD) was ratified by MSAC, outlining MSAC's advice with supporting rationale and evidentiary basis. The PSD was circulated to attendees before the stakeholder meeting.

The Chair noted the differing and polarised views regarding vertebroplasty among stakeholders, which had been expressed to MSAC, publicly and in other forums.

The issues proposed for discussion were:

1. understanding the variance in views by relevant experts of the place of vertebroplasty
2. optimising patient selection (how, when and who)
3. obtaining patient input on outcomes of importance to them
4. refining questions to be addressed in a meta-analysis of relevant randomised trials based on IPD.

3. Summary of discussion

Expert views on the place of vertebroplasty

The Chair indicated that MSAC is interested in obtaining the views of a broader group of clinicians who treat the same fractures differently in different contexts.

The Chair noted that when items for vertebroplasty were previously listed on the Medicare Benefits Schedule (MBS), there was a wide variation in uptake of vertebroplasty across states. This variation was wider than expected by demographic statistics, suggesting that patients considered suitable for vertebroplasty in some states were not receiving vertebroplasty in other states. The Chair noted that usually if there is a high need for a service, it is taken up evenly around the country. Participants noted that other interventional procedures also show geographic variability in uptake, which is due to different referring practices, different skill sets among operators, and clustering of services in cities.

The Chair also presented MBS data from 2005–2011 showing that 3988 services for vertebroplasty to treat painful osteoporotic vertebral compression fractures were provided by 171 providers, but 71% of all services were provided by only 10 providers. The question was asked as to why this would have occurred for vertebral fractures, which are quite common, especially in the elderly, when centres of expertise are usually formed for uncommon conditions. Representatives of the applicant explained that it is largely related to confidence of proceduralists. They explained that 10 years ago most hospitals were not offering the procedure, and interventional radiology as a subspecialty has doubled in the last 10 years. Most major centres can do this procedure now.

Representatives of the applicant also related that their practice had increased to a high volume activity. The reasons for this was that there was a large elderly population in their area; they set up a specialist clinic and so developed expertise before other centres; and they actively educated GPs in their area. They commented that patients will be referred to operators who are known to have expertise in the procedure. They related that patients are willing to travel (even by flying) to access treatment within the strict 3 week timeframe set in their practice.

One clinician noted that the number of providers in the 2011 MBS data seems accurate based on professional organisation membership, and the proportions doing both diagnostic and interventional radiology is consistent with the pattern seen in practice. While many providers are generalists, some will develop a subspecialty interest and get a concentration of referrals, including from outside their hospital. The clinician was of the view that operators with moderate to high volume should be able to provide the procedure; operators doing the procedure only occasionally should be mentored. However, this cannot be enforced at the Medicare level, and relies on operator education and professional regulatory processes to enforce best practice.

Feedback was provided to the meeting that the surgical community believes there is a role for vertebroplasty. One clinician commented that about two-thirds of their patients are referred by neuro- or orthopaedic surgeons.

One clinician commented that there are large variations in care and opiate prescribing for patients with vertebral fractures. There is no widely disseminated model of care or pathway, so there is a role for guidelines for optimum management and medication. If vertebroplasty is not available, development of a pathway of care will be restricted. Most clinicians would use vertebroplasty selectively with other care options, but if they are not able to get experience with the procedure, they won't refer patients, who will then go down a different pathway that often includes aged care.

Patient selection

The Chair noted the importance of defined eligibility criteria to ensure that access to the service is limited to a specific group of patients. MSAC is seeking broader clinician input to further define the patient group with the greatest likelihood of clinical benefit, and how and when best to assess these characteristics to determine which patients are eligible for vertebroplasty.

Clinicians attending the meeting generally agreed that the typical patient for whom vertebroplasty would be considered is an elderly person with an acute fracture, presenting to the emergency department with severe pain that does not respond to analgesia. They typically have a CT scan and are then referred to a geriatrician for ongoing care. After admission, their pain remains unresolved with opiate analgesia, the patient is immobilised, and becomes increasingly confused and constipated because of the side-effect of opiates.

Representatives of the applicant explained that if a patient has been in hospital for a couple of days and is doing well in terms of pain and mobilisation, they will not be offered vertebroplasty. They also stated that vertebroplasty is only offered to patients whose pain does not improve with appropriate pain management (including opiates and/or other analgesics) because this is an indicator of an unstable fracture. They must also have an early fracture which has not yet healed, and severe osteoporosis or at least established osteoporosis. After the procedure, patients' pain is reduced very quickly from severe to mild, they are able to mobilise, can reduce or cease opiate use and be discharged much earlier.

It was noted that some people get substantial and sustainable benefit as shown in the VAPOUR trial; however, difficulties arise with patient selection. For the target group – those who are incapacitated and unable to mobilise – an assessment could be made after a short inpatient stay. However, in the community setting, where the intention of referral is to keep a patient out of hospital, the procedure may end up being undertaken for some people who would have recovered without vertebroplasty.

Representatives of the applicant emphasised that clinical success requires early intervention while the bone is still soft and not completely collapsed. They explained that the initial application was limited to fractures of <6 weeks duration, because after this time, in most patients, the fracture would have consolidated and vertebroplasty would be less effective. Patients with fracture duration of 3–4 weeks would benefit most. The application was subsequently limited to fracture durations of ≤3 weeks based on evidence from the VAPOUR trial in which 79% of patients had fractures of this duration. The applicant had provided MSAC with additional analyses of pain results limited to this subgroup of VAPOUR trial patients (n = 95), which also show that significantly more patients in the vertebroplasty arm achieved an NRS pain score of ≤4/10 after 14 days than in the sham arm, and the difference between the groups for this outcome was maintained out to at least 6 months.

Clinicians commented that it is important to treat people with acute, unresponsive pain as early as possible, but that 3 weeks may not be long enough to organise treatment for some patients. Some clinicians felt that some patients with fracture duration longer than 3 weeks (e.g. a slow-healing fracture at 6 weeks, or even some months) would still benefit. Prognostic factors include the site of the fracture and the degree of deformity. The view was expressed that experienced clinicians would be able to identify patients likely to have a better outcome. Representatives of the applicant reiterated that, although vertebroplasty should be offered within 3 weeks to avoid further deterioration, many patients will show improvement up to 6 weeks. However, it was pointed out that decisions will rely on what is able to be demonstrated by evidence.

One clinician commented that fractures will heal in 6–8 weeks, independent of age or presence of osteoporosis. However, in some patients pain keeps getting worse, which could be due to progressive vertebral fractures. The acuteness of the fracture event may be difficult to ascertain. Another clinician commented that patients with ongoing pain would need to have imaging and be reassessed. It is possible for the same vertebra to refracture.

Clinicians discussed whether use of vertebroplasty should be limited to thoracolumbar fractures (T11, T12, L1 and L2). Representatives of the applicant stated that there is enough evidence and biological plausibility that vertebroplasty is most effective in thoracolumbar fractures. This range of fractures would cover about 85% of hospitalised patients. Some clinicians expressed the view that lower thoracic vertebrae should be included. Representatives of the applicant stated that there is evidence to justify including T10–L3, but they would accept limiting it to the four bones in the thoracolumbar junction which have the best results.

One clinician commented that it is important to define the subset of patients for whom the procedure will be available. Although the risks of the procedure are comparatively low, in some patients it will fail and they will need surgery, which is difficult to do after vertebroplasty.

One clinician commented that persistent pain is related to deformity but there are no data that vertebroplasty is protective for spinal alignment; restoring vertebral height is not related to

spinal alignment. (Representatives of the applicant stated that the VAPOUR trial showed 36% restoration in vertebral height at 6 months in the vertebroplasty group.)

One clinician commented that vertebroplasty may also be appropriate to improve structural integrity in cancer patients with ongoing bone metastases.

The Chair noted that MSAC is also seeking clinicians' opinions on the suggestion raised during targeted consultation that eligibility of patients should be a combined decision between a spinal surgeon and an interventional radiologist.

Participants noted that, as observed for other procedures, requiring combined decision-making may place constraints on the number of procedures that are performed. One clinician commented that there is inherent conflict of interest in referral patterns; providers are financially incentivised to keep patients. Requiring specialty-specific referrals could lead to problems with under-referral. They also commented that pain specialists and geriatricians should not be excluded from referring. This was supported by another clinician who commented that collaboration between specialists should be part of specialist best practice, but it would not be appropriate for an MBS listing to specify who can and cannot collaborate.

Another clinician expressed the view that, in the past, vertebroplasty had been performed on a number of fractures for which the procedure was not suitable. They felt that assessment of fractures should be done by someone who regularly deals with fractures and trauma, and recommended spinal surgical review of fractures before performing vertebroplasty.

Another clinician commented that vertebroplasty is no different to orthopaedic surgery in that both are used to manage repair unstable fractures, but it seems that limitations are being discussed for vertebroplasty that are not placed on surgical interventions. Requiring that a neurosurgeon should agree to vertebroplasty being performed would be unusual. They also commented that there has been no comparison of vertebroplasty with surgical fixation of fractures.

Patient input

The Chair acknowledged the importance of obtaining input from patients or patient representatives about what outcomes are important to them, especially over time and in relation to analgesic use and functionality.

Consumer feedback provided to the meeting indicated that consumers would like clear information about the evidence that demonstrates which patients are most likely to benefit from the treatment. This includes advice on the intricacies of when to treat, preferred cement volume and how many times a patient could have the procedure. Giving consumers a voice about what they choose to do will be an important consideration if the procedure is listed on the MBS. If there is controversy around when patients should be treated, it is important that patients know their options based on the evidence.

It was noted that, if use of vertebroplasty is limited to thoracolumbar fractures, it would be important for consumers to understand why some patients would be excluded despite some evidence for effectiveness in other sites. A representative from the Royal Australian and New Zealand College of Radiologists commented that the College has a recognised history of developing educational resources and website guidance for clinicians and consumers. They would be willing to collaborate with the applicant to develop resources, including advice for referrers. It was agreed that this would be useful. From the consumer point of view, such resources are highly valued, but it was noted that consumers should be included in

developing them. The resources must also clearly show the steps of informed consent that the patient or their decision-maker need to go through.

The Department gave feedback from consumers which came through the newly established HTA Consumer Evidence and Engagement Unit of the Department. They described an elderly female patient with a history of vertebral fractures who had been given opiates by her GP. She decided to change GPs and was given a different medication, after which she regained function and decided not to have any further intervention. The Department also mentioned feedback that had been submitted to the review of vertebroplasty in the UK from the National Osteoporosis Society (UK) noting they would be hesitant for external time pressures to rush people into a procedure before they had received an adequate trial of optimal analgesia.

The meeting heard from a patient who had vertebroplasty following a fall in 2006. The procedure was only offered after 12 months of severe pain, and was performed on the T6 vertebra in 2007. The procedure relieved the patient's pain but the patient had further fractures of T7 and T12 in 2008. The patient has had very little pain in that area since then. The patient has been told that there are more fractures present but has been told not to have further vertebroplasty procedures. It was noted that this patient had experienced great relief 12 months after a fall, but that this is outside the timeframe covered by the application being considered by MSAC.

One clinician noted difficulties raised by the way private health funds treat admissions involving non-MBS reimbursable procedures. They described the situation where a patient is in hospital for 8 days with neurological problems, is found to have an osteoporotic fracture and is very difficult to mobilise. The private health fund would deny payment for the whole admission if one of the procedures used during the admission is not MBS funded. To work around this, the patient would be forced to return home for 5 days to create a clear gap between the neurological event and the non-refundable procedure.

IPD meta-analysis

The Chair asked for input on whether an independent meta-analysis based on IPD would be possible and of value. Considering that the available randomised trials show a small variation in effect size, and the totality of evidence shows a small effect favouring vertebroplasty, would such a meta-analysis be able to give more clarity and confidence about the clinical meaningfulness of the effect and which patients would most benefit?

To support this, the Chair advised that MSAC is seeking advice on the perceived clinical effect of vertebroplasty and the durability of that effect. In particular, MSAC is seeking input to better specify the questions and themes for further investigation of vertebroplasty in a meta-analysis (if that is considered appropriate).

MSAC had already proposed several assessment themes:

- the size of effect of vertebroplasty on different types of outcomes and ways of measuring them
- potential harms of vertebroplasty
- sources of clinical heterogeneity in predicting and estimating the extent of any treatment effect modification.

Representatives of the applicant were strongly of the view that an IPD meta-analysis of the four randomised trials would be of no value because there is insufficient clinical overlap between the VAPOUR trial and other trials. In their opinion, the VAPOUR trial assessed a different set of patients with vertebral fracture and used a different technique to the other randomised trials.

Representatives of the applicant emphasised that clinical success depends on using enough cement to fully support the bone. They explained that, in their practice (and in the VAPOUR trial), they use the vertebral fill technique (using enough cement to fill the vertebral body top to bottom, side to side, and at least two-thirds of the way back) under radiological guidance, stopping if cement begins to leak from the fracture. Published data shows progressive increase in volume of the vertebral bodies from T5 to L5 such that L5 has four times the volume of T5. The two randomised trials published in 2009 used much lower volumes of cement, mainly because fractures in those trials were of longer duration than in the VAPOUR trial and would already have healed or consolidated to a greater extent. It would be impossible to tell from IPD whether adequate cement had been injected. It would not be possible to compare the effects of a specific volume of cement because the amount of cement required depends on the size of the vertebral body, which varies, and on the fracture morphology (e.g. the presence of a fracture cleft). Adjustment for varying fill volume across multiple different vertebral levels each of different size would be impractical in an IPD meta-analysis.

Representatives of the applicant also stated that data from the VAPOUR trial should not be combined with the more recent (2018) VERTOS IV trial. Patients in the VERTOS IV trial were referred from radiology centres if a fracture was found on X-ray. They were given a questionnaire about their level and duration of pain. Those with pain scores >5/10 and duration of <9 weeks were assessed by a clinician to determine their suitability for vertebroplasty, meaning duration before treatment was extended to up to 12 weeks. Patients in the VERTOS IV trial were all outpatients, half did not have osteoporosis, most had not tried opiates, and only 17 of 180 randomised patients had fracture durations of <3 weeks. The procedure used in the VERTOS IV trial used slightly less cement than in the VAPOUR trial but the higher frequency of extravasation indicates that fractures being treated were older (mean 6 weeks) than in the VAPOUR trial. The procedure was also performed without sedation in the VERTOS IV trial.

Another meeting attendee indicated that there would need to be sufficient clinical overlap across patients enrolled in the trials for an IPD meta-analysis to be meaningful. Some clinicians suggested that the difference in cement volume and fracture duration between trials without having these differences defined to the individual patient level would mean that the trials could not be meaningfully meta-analysed.

A question was raised about the effect of vertebroplasty on early mobilisation, and why there seemed to be reduced or no incremental treatment effect in terms of analgesic use and quality of life outcomes between the two groups in the VAPOUR trial, given the apparent large benefit of vertebroplasty in the patient stories. Representatives of the applicant explained that the trial did not measure early mobilisation but used hospital discharge as a proxy, finding that hospitalised patients in the trial were discharged a median of 5.5 days earlier. They noted that the EQ-5D questionnaire is not specific for osteoporosis and is insensitive to vertebral fractures, and more than half the patients were unable to complete the timed-up-and-go test at baseline. Results showed that pain was reduced in patients who were taking less analgesia.

Roland-Morris Disability scores lagged a little behind pain scores, but showed clinically significant benefits at 1–6 months in the vertebroplasty group.

The issue was raised that, without standardised data on analgesic use, it is hard to determine the effect of vertebroplasty. Representatives of the applicant explained that the initial intention was to measure all opiate types and doses and convert them to a morphine equivalent. However, because patients were hospitalised, often confused and taking multiple medications together, collecting detailed information on opiate type and dose was not possible. They also commented that it is not possible to supervise or standardise opiate treatment regimens in a trial; it is impractical, hospitals would not allow it, and private insurance health funds would not pay for the entire admission.

Representatives of the applicant were asked about the implications of vertebroplasty on subsequent fractures of adjacent vertebral bodies. They explained that even if vertebroplasty is not done, adjacent vertebrae can be affected in up to 10–20% of patients. There is reliable trial data that there is no excess risk of adjacent fracture after vertebroplasty.

Representatives of the applicant were asked about the risks of extravasation of cement during the procedure. They are confident that the risk of cement migration is known and is low. They explained that the new purpose-built kits for vertebroplasty use very high viscosity material that does not leak. They also do the procedure under radiological guidance to ensure that the procedure is stopped before leakage occurs.

The following opinions were expressed:

- because different trials emphasised different approaches to measuring outcomes, an IPD could provide ‘a level playing field’ in terms of defining outcomes
- there may be a role for analysing these trial data to determine if there is a subgroup of patients with fractures in the delayed phase who might benefit from vertebroplasty
- analysis of IPD could help to show if there was any trend in size of the treatment effect of vertebroplasty by fracture duration
- IPD could be useful to look at whether other factors related to particular patient characteristics might modify the size of this treatment effect.

Other issues raised

In addition to the tabled written response to the PSD and other comments above during the meeting, representatives of the applicant also made the following points:

- there has been no consideration of complications of conservative care and opiate treatment
- none of the randomised trials were powered to compare the effect of fracture duration between subgroups within each trial, so instead compared outcomes across trials with respect to their differences in enrolment by facture duration
- among the four blinded randomised trials available, the VAPOUR trial, with 79% of patients with fracture duration of <3 weeks, shows positive results, but the three other trials with 20% of patients with fracture duration of <3 weeks show negative results; this would seem to confirm that vertebroplasty is effective for short-duration fractures

- recruitment for blinded randomised trials is difficult, but despite this, the VAPOUR trial was completed and was properly powered to detect an effect; concentration of patients in one centre in this type of trial is to be expected
- the VAPOUR trial results are supported by positive results from an open randomised trial reporting data for patients with fracture duration of <3 weeks (Yang eta l, 2016)
- the VAPOUR trial was purpose-built for this application, so the applicant disagrees with MSAC's opinion that its results cannot be generalised
- the VAPOUR trial is an independent blinded randomised trial with positive outcomes; however, the applicant considers that it is not clear from reading the Cochrane review that there has been a positive trial.

Representatives of the applicant were asked about the criticism raised in the Cochrane review of potential unblinding in the VAPOUR trial. Representatives of the applicant explained that patients were asked to guess which procedure they had (vertebroplasty or sham) and to give reasons for that guess. Reduction in pain was the only reason that patients gave for their responses. It was acknowledged that the observed responses to the questionnaire after the procedure could reflect that patients had a better pain response, but was there potential for patients to guess which treatment they had based on smell or sensation etc.? Representatives of the applicant explained that the cement they use is mixed in a closed system so there would be no detectable smell in either procedure. They also explained how they simulated the vertebroplasty procedure in the sham group, and noted that patients were under conscious sedation so would be very unlikely at the time to be aware of which procedure they had.

One clinician commented that there is respect among his colleagues for the MSAC process. They feel it is fair and rigorous, and prevents adoption of low value practice and wastage of health funding. However, there is some concern that the process is quite arduous, and the difficulty of obtaining the evidence required may discourage people from submitting applications for services that may be beneficial. The clinician suggested that MSAC needs to have procedural consistency in dealing with differences of opinion between professional groups. They commented that vertebroplasty is an established technique, and related that clinicians were achieving good results with it when it was previously funded. Clinicians were surprised when the 2009 randomised trials showed no benefit. The clinician commented that the VAPOUR trial compensated for problems in the early trials, and showed that with strict patient selection criteria, results can be positive. They expressed their disappointment that so far results of the VAPOUR trial had been combined with, and effectively 'drowned out' by, the other trials. Other clinicians agreed that there is no rationale for combining data from the VAPOUR trial for patients in the acute phase with data from other trials in patients with chronic fractures.

One clinician commented that it is difficult to perform trials and generate evidence for interventional radiology procedures that are continually evolving, and which have heterogeneous techniques and many variables. Device companies will not fund these trials. They commented that the VAPOUR trial controls for heterogeneity with consistent patient selection criteria, consistent technique and limited centres. They expressed the concern that withholding funding until further evidence arises will lead to many patients suffering a great degree of morbidity.

4. Meeting close

The Chair invited each attendee to make any further comment. Participants were then thanked for their valuable insights and it was hoped that they found the meeting productive.

The meeting closed at 4:10 pm.