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# Cochrane vertebroplasty review misrepresented evidence for vertebroplasty with early intervention in severely affected patients

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## Abstract

The Cochrane vertebroplasty review of April 2018 was replaced with an updated version in November 2018 to address complaints of errors in analysis. The updated version continues to misrepresent the evidence supporting early intervention with vertebroplasty for patients with uncontrolled, severe pain and fracture duration <6 weeks. The VAPOUR trial is the only blinded trial of vertebroplasty restricted to this patient group. It showed the benefit of vertebroplasty over placebo, particularly when the intervention occurred within 3 weeks of fracture. The Cochrane vertebroplasty review has ignored the positive outcomes in the VAPOUR trial. Open randomised trials of fractures <6-week duration support the positive findings of the VAPOUR trial. This is not described in the Cochrane review. The VAPOUR trial is clinically heterogeneous from other blinded trials. Cochrane protocol stipulates that clinically heterogeneous trials be described separately, as independent evidence, and not combined in analysis with dissimilar trials. Failure to observe this represents a serious protocol breach in the Cochrane review.

## Complaint to Chief Editor of Cochrane

The Cochrane vertebroplasty review (CVR) of April 2018<sup>1</sup> was updated in November 2018<sup>2</sup> to address complaints to the Chief Editor of Cochrane<sup>3</sup> about errors in the report. The review does not accurately report the evidence for vertebroplasty in patients with severe symptoms and early fractures. The VAPOUR trial is the only blinded trial to specifically assess this patient group and found vertebroplasty more effective than placebo in alleviating severe pain. Readers of the review would be unable to discern this information from the way that the review has been presented. There is open randomised trial evidence supporting the findings of the VAPOUR trial that vertebroplasty is an effective remedy for severe pain when the intervention is performed early, mostly within the first 3 weeks. We are authors of the VAPOUR trial.

## New randomised evidence

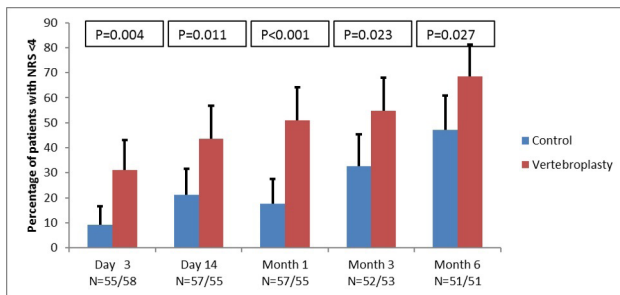
Three randomised trials comparing vertebroplasty with placebo<sup>4,5</sup> or usual care<sup>6</sup> have been published since the 2015 CVR.

The VAPOUR trial<sup>4</sup> enrolled patients referred for vertebroplasty with severe, uncontrolled pain

despite opiate analgesia. Eligible patients had fractures for a <6-week duration causing severe pain, uncontrolled by medical therapy including opiates. Vertebroplasty was offered without further delay. 79% of patients in the VAPOUR trial had the fracture duration ≤3 weeks at the time of intervention. This is the only blinded trial to enrol hospitalised inpatients. All patients required severe pain for enrolment, defined as the numeric rated score (NRS) of 7/10 or more. The primary outcome measured the proportion of patients who converted to a mild pain score (NRS <4/10) at 14 days. This favoured vertebroplasty over placebo at 14 days and at every other time point to 6 months (figure 1). Vertebroplasty reduced hospital stays and provided clinically significant reductions in the Roland Morris Disability score at 1, 3 and 6 months. Mean fracture duration at time of vertebroplasty was 2.8 weeks.

VERTOS4<sup>7</sup> recruited outpatients referred for radiography, not for vertebroplasty. Protocol<sup>7</sup> states 'all patients, 50 years of age or older, referred for an X-ray of the thoracic and/or lumbar spine, receive a short clinical questionnaire'. Patients who had a fracture, VAS pain ≥5/10 and pain duration ≤9 weeks (at the time of radiograph), were invited to provisionally enrol. The amended time of radiography is accessible with trial publication<sup>5</sup> via 'peer review' tab and clicking on 'protocol', which lists amendments. Consenting patients were then referred for physician assessment and MRI scanning, causing additional 1–3 week delay after radiography, so that fracture duration would extend to 12 weeks at the time of vertebroplasty although the full range is not reported. The IQR of fracture duration was 4.1–7.4 weeks, so <20% of patients had fracture duration ≤3 weeks, compared with 79% in VAPOUR. Primary outcome, mean pain, was equivalent in placebo and vertebroplasty groups at all time points. Mean fracture duration at time of vertebroplasty was 6.1 weeks.

A study by Yang *et al*<sup>6</sup> is an open randomised trial which recruited patients with acute, severe pain and fracture duration <3 weeks duration at the time of the procedure. Vertebroplasty was immediately offered as acute pain treatment without further delay. A total of 135 patients were randomised to vertebroplasty or conservative care. The primary outcome, mean pain, was lower in the vertebroplasty group at all time points to 12 months. Mean fracture duration was 1.1 weeks.



**Figure 1** Primary outcome of the VAPOUR trial. Primary outcome is the proportion of patients in each group with mild pain (NRS<4/10) having enrolled with severe pain at baseline. NRS  $\geq 7/10$  was an inclusion requirement. Lines above each column represent 95% CIs. The positive primary outcome was rejected by the CVR. CVR, Cochrane vertebroplasty review; NRS, numeric rated score.

The VOPE trial is unpublished, but its authors have kindly shared trial data and manuscript. Forty-six outpatients from an orthopaedic outpatient clinic with vertebral fracture and back pain  $\leq 8$  weeks duration were randomised to vertebroplasty (22) or placebo (24). The placebo involved a bone biopsy of the vertebral body with an 11G needle. Vertebroplasty injected 2–4cc PMMA, half that of the VAPOUR trial. Patients were younger (mean age 70 vs 80), with mild osteoporosis (T score  $-2.4$  vs  $-4.3$ ) and less severe pain (7.5/10 vs 8.6/10) than patients in the VAPOUR trial. There is no mention of opiate use. The authors report ‘we found in our study a significant higher VAS in the SHAM group throughout the follow-up period ( $p=0.001$ ) when applying ANOVA statistical model on our data’, but there was no significant difference between groups at any single time point, although the trial was not powered to detect this. The unpublished VOPE manuscript concludes ‘When reviewing the evidence at hand, we believe PVP should be offered to patients with acute VCFs in severe pain and immobilised after optimal conservative treatment including pain medication’. This concurs with the findings of the VAPOUR trial. Mean/median fracture duration not available.

### Clinical differences between VAPOUR and the other blinded trials

VAPOUR adopted a different clinical approach to other blinded trials. Rather than waiting for the pain to abate before offering vertebroplasty, VAPOUR offered earlier intervention in patients whose pain remained severe despite the use of opiate analgesia. VAPOUR patients were older, had higher pain score at entry and a substantial proportion had been hospitalised before enrolment,

compared with other blinded trials which enrolled younger patients with less comorbidities and less severe symptoms, none of whom were hospitalised (table 1).

VAPOUR provides the only blinded evidence of vertebroplasty for hospitalised patients with severely painful vertebral fractures. Hospitalisation usually occurs due to uncontrolled pain and loss of independence within the first 3 weeks of fracture, when pain is maximal. Kallmes *et al*<sup>8</sup> excluded inpatients by the protocol. VERTOS4 excluded inpatients, confirmed by private author correspondence. VOPE exclusively recruited from an outpatient clinic. Buchbinder *et al*<sup>9</sup> did not report any hospital inpatients and this is consistent with the methods of the trial; trial design assessed outcome via posted questionnaires with no provision for inpatient follow-up, small enrolment (38 vertebroplasty patients) and few patients with fractures  $\leq 3$  weeks duration (fracture duration IQR 4–13 weeks). VAPOUR found a 6-day reduction in hospitalisation in the vertebroplasty group and all attending physicians were blinded, so patient discharge related to improved pain and functional status.

VAPOUR performed vertebroplasty earlier than other blinded trials. The mean fracture duration at the time of vertebroplasty in VAPOUR, VERTOS4, Buchbinder *et al* and Kallmes *et al* was 2.8, 6.1, 12 and 23 weeks, respectively. 79% of patients in VAPOUR had intervention within 3 weeks compared with  $<20\%$  in other blinded trials (table 1). VAPOUR subgroup analysis by fracture duration suggested better vertebroplasty outcome in the  $<3$ -week group although there were insufficient patients in the 4–6 week group for statistical significance. All patients in Yang *et al* had a fracture duration  $<3$  weeks and the results strongly favoured vertebroplasty.

VAPOUR used different vertebroplasty techniques to trials<sup>8,9</sup> by authors of this CVR. The ‘vertebral fill technique’ illustrated in trial publication<sup>4</sup> braced the whole vertebral body, not just the fracture line, requiring three times the PMMA volume of the 2009 trials (table 1). Dismissing technical differences between VAPOUR and their trials,<sup>3</sup> CVR authors reference level 4 evidence<sup>10</sup> from chronic fracture treatment to assert that PMMA volume does not affect the outcome. Patients with early fractures and uncontrolled pain are likely to have fracture instability and plasticity. The ‘vertebral fill’ technique is designed for this patient group to prevent further collapse and restore vertebral height. Calibrated radiographs at 6 months demonstrated 36% vertebral height improvement with vertebroplasty compared with placebo. This is an entirely different vertebroplasty approach to the trials of the CVR authors.

The positive findings of VAPOUR are limited to patients with severe pain caused by fractures  $<6$  weeks duration and are not

**Table 1** Baseline values in the four blinded vertebroplasty trials which have been published

Trial	Kallmes <i>et al</i> <sup>8</sup>	Buchbinder <i>et al</i> <sup>19</sup>	VERTOS4	VAPOUR
Enrolment (no)	131	78	176	120
Inpatients	0	Not reported	0	59%
Fracture duration range	$<12$ months	$<12$ months	$<12$ weeks	$<6$ weeks
Mean fracture duration (IQR) weeks	22.5 (10–36)	11.7 (3.8–13)	6.1 (4–7.4)	2.6 (1–3)
Fracture duration $\leq 3/52$	0	$<20\%$	$<20\%$	79%
Mean pain score	7.0 (1.9)	7.3 (2.2)	7.8 (1.5)	8.6 (1.2)
T-score mean (SD)	Not reported	Not reported	$-2.4$ (1.0)	$-4.3$ (1.0)
PMMA volume cc (SD)	2.6	2.8 (1.2)	5.1 (1.8)	7.5 (2.8)

Mean fracture duration for VERTOS4 derives from conference proceedings. Mean fracture duration data for Buchbinder *et al* and Kallmes *et al* are derived from Staples *et al*. PMMA volume Kallmes *et al* is via author correspondence. The VAPOUR trial is clinically heterogeneous to the other trials.

generalisable to patients with older fractures or non-severe symptoms.

### Trials of vertebroplasty for fractures <6 weeks duration

One blinded<sup>4</sup> and three open<sup>6 11-13</sup> randomised trials for fractures <6 weeks duration are published. VAPOUR, VERTOS2 and Yang *et al* showed clear benefits from vertebroplasty in pain reduction.

Rousing *et al*<sup>12 13</sup> failed to meet its primary endpoint (pain reduction at 3 months), but was underpowered to detect this (47 patients randomised). Baseline pain differed between groups ( $p=0.02$ ), and 28% of patients did not have baseline pain measured. Vertebroplasty significantly reduced NRS pain at 1 day and 1 month and shortened duration of hospitalisation.

Meta-analysis<sup>14</sup> of 25 patients from twin non-acute blinded trials<sup>8 9</sup> who underwent vertebroplasty within 6 weeks of pain onset, found no benefit for vertebroplasty. The analysis was underpowered, and the parent trials had fundamental clinical differences to VAPOUR (table 1).

There is no analysis of outcomes from the subgroup of patients in VERTOS4 with fractures <6 weeks duration.

### Protocol breaches

CVR protocol<sup>15</sup> states 'Prior to meta-analysis, studies will be assessed for clinical homogeneity with respect to study population, type of therapy, .... Clinically heterogeneous studies will not be combined for analysis but will be individually described'.

Important clinical and technical differences between the VAPOUR trial and the other blinded trials are listed in table 1. Different degrees of pain, osteoporosis, hospitalisation status, earlier intervention and technical differences in PMMA administration are key contrasts between the trials. Despite this heterogeneity, VAPOUR has been combined for analysis with these trials, breaching Cochrane protocol. This error in analysis renders the conclusions of the CVR unsupported.

CVR (April 2018) Analysis 8.1/2, not specified by protocol, wrongly included all VERTOS4 patients in subgroup of fractures <6 weeks duration despite half having fractures >6 weeks, rendering the analysis nonsense. Rather than removing incorrect data from the subgroup, the November version opted to retain these data but to change the designation of the subgroup.

The subgroup previously defined as 'fracture duration  $\leq 6/52$ ' was replaced by a subgroup of 'acute fractures' defined as any blinded trial using the word 'acute' in publication. 'Acute' fractures were extended to 12 weeks rather than 6 as previously. Manipulation of a subgroup analysis to arbitrarily fit the data, for the purpose of the authors, is data dredging.

The VERTOS4 trial, initially reported on April analysis 8.1/8.2 as  $\leq 6$  weeks, is now reported on November analysis 8.1/8.2 as  $\leq 9$  weeks which is still incorrect. Nine weeks is the duration limit for radiography, not for vertebroplasty which was undertaken up to 12 weeks after fracture.

### Misreporting of VAPOUR and VERTOS4

VAPOUR published its primary outcome online<sup>16</sup> before the trial commenced and this has never been altered despite the assertions of the CVR. The advantage of a pre-specified clinical improvement over mean group scores was described by Farrar *et al*<sup>17</sup> who wrote 'differences between groups, as summarised by a change in mean values over time, can be difficult to apply to clinical care. ... group mean differences could reflect large changes in a few patients, small changes in many patients, or any combination of these outcomes. Determination of the proportion of patients who have a clinically important improvement in their pain would provide a more interpretable result with direct clinical implications'.

CVR rejects Farrar *et al*'s advice, dismissing the primary outcome to focus on mean NRS. Re-defining minimally important difference (MID) NRS as 1.5, (again breaching CVR protocol<sup>15</sup> which defined it as 1), the authors describe NRS reduction as clinically insignificant when the between group difference is <1.5. Katz<sup>18</sup> describes this methodology of applying MID to assess group differences as invalid.

MID is not measured from groups but from individual patients and should be applied as such. In order to use MID to compare group outcomes, it should be measured from individual patients. The proportion of patients in each group who achieve it can then be compared. Its manner of use to directly interpret group outcomes in CVR creates non-sensical conclusions. For example, 31% more patients in the vertebroplasty group than the placebo group achieved clinically important pain reduction at 1 month and mean NRS difference between groups of 1.4 favoured vertebroplasty (table 2). CVR authors describe<sup>4</sup> this outcome as clinically

**Table 2** NRS pain outcomes VAPOUR trial

Measure	Vertebroplasty	Placebo	Treatment effect difference (95% CI)	P value
	No. (%)	No. (%)		
<b>NRS pain &lt;4/10</b>				
At 3 days	18 (31)	5 (9)	22 (8 to 36)	0.004
At 14 days*	24 (44)	12 (21)	23 (6 to 39)	0.01
1 month	28 (51)	10 (18)	33 (17 to 50)	<0.001
3 months	29 (55)	17 (33)	22 (4 to 41)	0.02
6 months	35 (69)	24 (47)	22 (3 to 40)	0.03
<b>Absolute reduction NRS pain</b>				
At 3 days	3.5±2.6	1.8±2.3	1.8 (0.8 to 2.7)	<0.001
At 14 days	4.2±2.7	3.0±3.0	1.2 (0.1 to 2.3)	0.03
1 month	4.6±3.0	3.2±2.7	1.4 (0.4 to 2.5)	0.01
3 months	5.4±3.5	4.1±3.1	1.3 (0.0 to 2.6)	0.05
6 months	6.1±3.3	4.8±3.1	1.3 (0.0 to 2.6)	0.04

\*Primary endpoint was the proportion of patients with an NRS pain score <4 at 14 days. Mean absolute reduction in NRS pain was a secondary pain outcome. CVR describes these changes as clinically meaningless.

CVR, Cochrane vertebroplasty review; NRS, numeric rated score.

irrelevant and consistent with the negative results of their trials. This assertion is false.

The treatment effect is directly measured by the primary outcome of the VAPOUR trial. It is likely to be larger in clinical practice where conservatively managed patients do not benefit from the placebo effect. Patients who were 80-year-olds, who have severe pain despite opiate analgesia are difficult to manage and have no other treatment option except increased opiate dose with all the attendant negative side-effects in this age group. More than half of the placebo group of the VAPOUR trial reported moderate or severe pain at 6 months and 76% were still using analgesic medication.

Mean VERTOS4 fracture duration at the time of vertebroplasty was 43 days, as reported in the conference proceedings used by CVR authors, not 29 as listed in the CVR. The fracture duration would extend to 12 weeks, not 9, as reported in CVR. Early intervention is a critical factor in the outcome, so these reporting errors are important. Despite advice in our letter of complaint to Cochrane,<sup>3</sup> they remain uncorrected in the updated November version of the review.

### Undisclosed conflict of interest

There is ongoing disagreement<sup>19–22</sup> between the authors of the VAPOUR trial and the CVR. It is unlikely in this context for the CVR author group to provide an independent assessment of the VAPOUR trial.

The review coincided precisely with Medicare vertebroplasty funding application<sup>23</sup> based on identical clinical inclusion criteria to the VAPOUR trial. CVR's first author belongs to the Medicare Services Advisory Committee (MSAC) which determines application outcomes. This author was excluded from committee involvement due to conflict of interest, but not from the Cochrane review. CVR became a late-breaking centrepiece of evidence before the MSAC committee. Medicare funding was previously removed based on trials<sup>8,9</sup> by authors of this CVR and provides part of the legacy of their trials.

Responding to our complaints, the Cochrane Chief Editor advised that 'Cochrane does not have a non-financial conflict of interest policy', an apparent weakness in the Cochrane model.

The author group of CVR includes first authors of two key trials, one of whom is co-ordinating editor of the Cochrane musculoskeletal section charged with editing the CVR. Cochrane author advice recommends that editors can write reviews but should clarify the editorial pathway to overcome this potential conflict of interest. This did not occur in the CVR. The safeguard against potential author bias is ensuring strict adherence to protocol, which has been breached in this review.

### Faulty risk of bias assessment

Risk of bias is judged more harshly for VAPOUR than other blinded trials despite independent randomisation, data collection and analysis. Invalid blinding is inferred from more vertebroplasty patients correctly guessing their intervention than placebo patients, although they overwhelmingly nominated pain relief, not lack of blinding, as a reason for their guess.

Cochrane's tool for assessing risk of bias<sup>24</sup> stipulates: 'Evidence of correct guesses exceeding 50% ....can simply reflect the patients' experiences in the trial: a good outcome, or a marked side effect, will tend to be more often attributed to an active treatment, and a poor outcome to a placebo', as in the VAPOUR trial. Judgements of reporting bias and placebo bias are other examples of disproportionate use of risk of bias assessment against VAPOUR compared with other blinded trials by CVR.

### Conclusion

The Cochrane review ignores positive evidence supporting the use of early vertebroplasty to manage the most severely affected patients. It uses inappropriate meta-analysis technique and fails to address the differences between trials, the role of the different type of procedure used and the clear evidence of vertebroplasty superiority in patients with fracture <3 weeks including hospitalised patients with severe pain.

To deny this advantage of vertebroplasty sidelines a procedure that can provide better health outcomes to a specific group of patients and permits publication of guidelines from a biased review, by authors with undisclosed conflicts of interest.

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**Competing interests** WAC, PB, THD, PG and VG are authors of the VAPOUR trial. WAC was an investigator in Kallmes2009 and VERTOS4 trials. THD was an author in Kallmes 2009 trial. WAC, THD and PG were expert advisers to the Medicare Services Advisory Committee in application 1466 for Medicare funding of vertebroplasty in Australia.

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