Vertebroplasty and the Placebo Response¹

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Interpreting the Evidence

Extensive clinical experience and observational research indicate that vertebroplasty results in substantial and often dramatic improvement in pain from vertebral fractures (1,2). However, two sets of randomized controlled trials—one comparing vertebroplasty to a sham intervention without injection of cement and the other comparing vertebroplasty to conservative therapy—collectively pose interpretative puzzles and ethical conundrums (3,4). Herein, we argue that the most reasonable interpretation of the data from these trials is that vertebroplasty is effective in relieving pain not by virtue of injecting cement to stabilize fractures but by means of the placebo response. In other words, vertebroplasty has “placebo efficacy” but not “specific efficacy.”

The term “placebo efficacy” does not imply that there is anything fake about the effectiveness of an intervention that works by means of the placebo response. On the contrary, extensive scientific experiments elucidating placebo effects, especially with respect to pain, have demonstrated that the placebo response is a real neurobiologic phenomenon with potential for clinically meaningful benefit (5). What distinguishes placebo efficacy of a treatment from specific efficacy is that the treatment’s effectiveness derives from the patient’s response to the treatment *ritual*—the contextual factors associated with the treatment intervention—rather than its inherent pharmacologic or physiologic properties (6). After examining the import of the randomized trial evidence, we raise the question of whether the placebo response benefits of vertebroplasty outweigh the known risks. Answering this question proves difficult, however, because conceptual and ethical resources for evaluating the risk-benefit ratio of treatments that work by means of a placebo response are lacking or underdeveloped.

Two double-blind, randomized, placebo-controlled trials of vertebroplasty, with results published simultaneously, demonstrated that this procedure was no better than a sham intervention, without injection of cement, in relieving pain or improving function for patients with vertebral fractures at any of the measured time points (1 week to 6 months in one trial and up to 1 month in the other) (3,4). In one trial (3), which consisted of 78 patients, the median duration of pain at baseline for the vertebroplasty and sham groups was 9.0 and 9.5 weeks, respectively, and the mean overall pain severity was 7.4 and 7.1 on a standard 11-point numeric rating scale (with 0 representing no pain and 10 the worst pain ever). After 1 month, the overall pain severity decreased by an average of 2.3 points in the vertebroplasty group and 1.7 points in the sham group, an adjusted between-group difference of 0.6 point (95% confidence interval: −0.7, 1.8). In the other trial (4), which enrolled 131 patients, the mean duration of pain at baseline in the active and sham groups, respectively, was 16 and 20 weeks, and the average reported pain intensity in the 24 hours before the procedure was 6.9 and 7.2 out of 10. At 1-month follow-up, the mean pain intensity was 3.9 in the vertebroplasty group and 4.6 in the sham control group, an adjusted between-group difference of 0.7 (95% confidence interval: −0.3, 1.7). Differences in pain relief were neither statistically significant nor clinically meaningful in either of these two sham-controlled trials.

Although these results are consistent with those of two small open randomized controlled trials that found no difference in pain relief between vertebroplasty and usual care at 2 weeks and 3 months, respectively (7,8), a seemingly very different picture was presented in a large open randomized controlled trial of 202 patients with painful vertebral

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fractures, in which vertebroplasty was also compared with conservative medical therapy (9). The Vertos II trial (9) included participants with a mean duration of pain before the procedure of 5.6 weeks, which is shorter than that in the two sham-controlled trials; the baseline pain, however, was comparable (mean pain score in the active and placebo groups, respectively, was 7.8 and 7.5 on a visual analog scale of 0–10). At 1 month, pain was decreased to a mean of 2.5 points among patients receiving vertebroplasty and 4.9 points among those receiving conservative therapy, a mean between-group difference of 2.6 (95% confidence interval: 1.7, 3.4). In contrast to the sham-controlled trials, the between-group difference in pain at 1 month was both statistically significant and clinically meaningful, and these differences were maintained to 1 year.

Making sense of the results from these trials raises a host of interpretive questions. Dismissive editorial commentaries by practitioners of vertebroplasty contended that there were methodologic flaws in the sham-controlled trials (10–12). However, although the results of the sham-controlled trials appeared to conflict with extensive clinical experience, the methodologic criticisms have failed to withstand critical scrutiny (13–16). It is noteworthy that a recent “guideline and evidence report” of the American Academy of Orthopedic Surgeons (AAOS) has endorsed the validity of the sham-controlled studies (17). On the basis of their review of the evidence, the AAOS issued a “strong” recommendation against the use of vertebroplasty in the treatment of patients with vertebral fractures. (The review of evidence by the AAOS was completed before the results from the Vertos II trial were published, but this is unlikely to have altered their recommendation because it was not a double-blind, placebo-controlled trial.)

In light of the results from the sham-controlled trials, we suggest that the benefits of vertebroplasty seen in both the Vertos II trial and in clinical practice may be explained as reflecting a placebo response. However, it is important to address an alternative hypothesis. The observed results may be due, at least to

some extent, to response bias—biased patient-reported outcomes. Pain is a patient-reported subjective outcome; accordingly, response bias cannot be ruled out as a factor influencing results in an open trial of an invasive procedure versus conventional medical treatment. Conversely, response bias cannot be invoked to explain the results of the double-blind sham-controlled trials, as there is no reason to think that patients who were blinded to treatment type were more likely to produce biased outcome responses in one study arm or the other, and there were no significant outcome differences between the two study groups. On the other hand, participants who underwent vertebroplasty in the Vertos II trial may have been disposed to exaggerate their reported pain relief, either because they thought they should be getting better after receiving an invasive treatment or they wanted to please the investigators; those receiving conservative therapy might have been disappointed by not receiving vertebroplasty and therefore exaggerated their lack of pain relief.

It is difficult, however, to attribute dramatic and lasting pain relief with vertebroplasty in usual care as well as in clinical trials entirely to response bias. There are numerous examples of patients with severe pain and disability before vertebroplasty being able to return to normal activities of daily living shortly after receiving this procedure—an outcome that is highly unlikely to reflect biased appraisal of pain. A similarly dramatic improvement in pain was observed in some participants of both placebo-controlled trials who received the sham intervention (personal observations). These dramatic improvements are more likely to be due to the placebo response. Nevertheless, it is possible that response bias made some contribution, albeit unquantifiable, to the observed results of the Vertos II trial, suggesting that the genuine difference in pain relief between vertebroplasty and conservative therapy may not have been as large as reported.

The Placebo Response Hypothesis

We interpret the differential pattern of results in the two types of randomized

trials as reflecting a powerful placebo response in the open Vertos II trial owing to positive expectations of those patients who knew that they were receiving vertebroplasty. As described earlier, the degree of mean pain relief in the vertebroplasty arms of the two sham-controlled trials was much less than that in the open vertebroplasty group in the Vertos II trial and comparable to that of the patients in the conservative therapy group. This is likely due to the expectation differences among patients in the sham-controlled trials versus the open trial. Patients in the sham-controlled trials knew that they had a 50% chance of receiving either vertebroplasty or a sham intervention without injection of cement, thus diminishing expectations of benefit. It is also possible that the investigators in the open trial were more enthusiastic than those in the sham-controlled trials about the anticipated benefits from vertebroplasty and that this further encouraged the response to the placebo.

Evidence from a meta-analysis of randomized trials in which patients received placebo or no treatment supports this hypothesis (18). That study found a statistically significant effect of placebo in relief of pain; moreover, the effect size of placebo was substantially greater in studies with physical placebos, such as sham acupuncture and chiropractic interventions, than in those with pharmacologic placebos.

The placebo response hypothesis is further bolstered by reflecting on one of the leading explanatory accounts of the placebo effect—the “meaning model” developed by Howard Brody (19). Brody describes the meaning model as follows: “An encounter with a healer is most likely to produce a positive placebo response when it changes the meaning of the illness experience for that individual in a positive direction. The meaning of the illness experience most likely changes in a positive direction when these three things happen: The individual...receives an explanation for the illness that makes sense; the individual feels care and concern being expressed by the healer...; the individual feels an enhanced sense of mastery or control over the illness or its symptoms” (19).

All three components of the meaning model are exemplified by vertebroplasty. Patients in severe and lasting pain are desperate for relief. Attributing their pain to a diagnosed vertebral fracture gives them an understandable explanation of their suffering. More important, the recommendation for a procedure that injects cement into the spine to stabilize the fracture provides a plausible rationale for expecting reduced pain and improved function and thereby affords "an enhanced sense of mastery or control." The clinical attention associated with diagnosis and performance of the procedure demonstrates care and concern.

In addition, vertebroplasty may further enhance the placebo response because of its invasive interventional nature. This physical intervention may suggest to patients and providers greater potency than pharmacologic treatments, which have already been tried and have failed to adequately relieve pain from the vertebral fracture. Finally, the clinical experience of practitioners administering a procedure such as vertebroplasty, with often dramatic short-term improvement, may itself engender a psychological response in clinicians comparable (but not identical) to the placebo response in patients (20). Sociologist of medicine Eliot Friedson described this dynamic as physicians being "placebo reactors" to their own treatments (21). This positive reaction of clinical experience, in turn, is likely to enhance placebo responses in patients.

Kyphoplasty and the Placebo Response

We have argued that the best explanation for the results of clinical trials evaluating vertebroplasty is that this procedure produces clinical benefit by means of the placebo response. It is also reasonable to suggest that this account may explain the results of randomized trials evaluating the closely related procedure of kyphoplasty. Kyphoplasty also delivers bone cement into the fracture but is preceded by balloon inflation of the vertebral body. To date, only one randomized controlled trial of kyphoplasty has been reported (22). This open trial randomized 300 patients to kyphoplasty

or usual medical care. The kyphoplasty group experienced significantly greater improvement in quality of life and decreased pain at all the measured time points from 1 month to 1 year. Compared with the medical care group, the reduction in pain in patients receiving kyphoplasty mirrored the results of the Vertos II trial, in which there was initially a considerably larger differential decrease in pain that tapered off over time. Given the lack of double-blind evaluation, results of that trial should be interpreted with caution. Moreover, the similarity between this procedure and vertebroplasty makes it probable that the results reflect a placebo effect. In view of the growing use of kyphoplasty, well-designed sham-controlled trials are needed to rigorously evaluate its efficacy.

The Legitimacy of Vertebroplasty

Assuming that the strong placebo response generated by vertebroplasty represents genuine therapeutic benefit, is vertebroplasty a legitimate treatment despite its lack of a specific efficacy? Does it have a favorable risk-benefit ratio, bearing in mind that the benefit derives from the placebo response, not from injection of cement? Addressing this question requires consideration of the risks of the procedure. Cement leakage has been reported to occur in almost 20% of patients receiving vertebroplasty (23), whereas investigators in the Vertos II trial reported that leakage outside the vertebral body occurred in more than 70% of their study participants (9). A subset of participants from the Vertos II trial were examined with chest computed tomography, and pulmonary cement embolism was detected in 26% of vertebroplasty recipients (24). Although these adverse effects have rarely been found to be of clinical significance (23), several cases of fatal pulmonary embolism and cardiac rupture have been reported in the literature (25).

It is currently not established whether vertebroplasty increases the risk of subsequent vertebral fracture, particularly in adjacent vertebrae. The best available evidence for addressing this issue is a single retrospective population-

based cohort study of patients with vertebral fractures from a large administrative database of a health insurer (26). The investigators reported a substantial increased risk of subsequent vertebral fracture after vertebroplasty or kyphoplasty: Compared with patients not receiving either of these procedures, the adjusted odds ratio for having a subsequent vertebral fracture within 90 days was 6.8 (95% confidence interval: 1.7, 26.9) (26).

Although typically performed without serious complications, vertebroplasty carries risk of substantial harm. Clinicians who continue to perform the procedure believe that it has a favorable risk-benefit ratio, on the assumption that the benefit derives from injecting cement into the spine. Is the risk-benefit ratio for vertebroplasty favorable if the benefit derives from the placebo response?

It is difficult to answer this question because we lack any well-developed approach for thinking about risk-benefit assessment for treatments that work by virtue of the placebo response. From a psychological perspective, the placebo response derives from patient expectations. Will the positive expectations underlying the placebo response to vertebroplasty be diminished, or vanish entirely, if patients are informed that this procedure has been shown to be no better than a fake intervention without the injection of cement? In other words, does the efficacy of vertebroplasty depend on false beliefs of patients (and physicians) regarding its mechanism of action? In an interesting and puzzling fashion, issues of informed consent intersect with risk-benefit assessment of treatments that work by virtue of the placebo response. The process of disclosing information about treatments will have an effect on patient expectations about the benefit from the procedure that may, in turn, influence the magnitude of a placebo response. What information is disclosed about an invasive procedure and how it is disclosed are all the more important in this context. The evidence relating to vertebroplasty has negative and positive aspects: It is no better than a sham intervention but substantially superior to

conservative therapy. When the full picture is described to patients in language that they can understand, along with an explanation of the positive benefits that may accrue from the placebo response, expectations for benefit from vertebroplasty may be no less in magnitude (or not substantially lower) than those for the procedure understood as relieving pain by virtue of stabilizing vertebral fractures. However, this is an empirical question, the answer to which is currently lacking.

There is also an issue of professional integrity of physicians that must be addressed. If vertebroplasty has placebo efficacy, but not specific efficacy, then it is the treatment ritual, not the injection of cement, that produces pain relief. Can a physician of integrity inject cement into the spines of patients for the purpose of a credible treatment ritual aimed at promoting a placebo response? Do physicians become quacks if they recommend invasive treatments with only placebo efficacy? Quackery, however, involves recommending treatments lacking in any scientific rationale that are harmful or without benefit. As noted earlier, placebo efficacy is backed by substantial scientific evidence (from laboratory experiments and clinical trials) that the placebo response is a real neurobiologic phenomenon with potential therapeutic value, especially with regard to pain relief. Therefore, it is not necessarily quackery to recommend or perform an invasive procedure for the purpose of generating a therapeutically meaningful placebo response despite dissonance with the prevailing view in biomedicine that treatments are worthless if no better than a placebo intervention. Indeed, taking seriously the therapeutic potential of the placebo response requires giving up the dogma that superiority to placebo is the minimal test of treatment value (27,28). We suggest that the question of professional integrity relating to placebo efficacy reduces to the related issues of whether a given treatment has a favorable risk-benefit ratio because it promotes a placebo response and whether the benefit can be sustained by truthful disclosure to patients, consistent with informed consent.

It seems premature to answer definitively the question of whether vertebroplasty is a legitimate treatment with which to promote clinically meaningful placebo responses based on a favorable risk-benefit ratio. There is too much uncertainty about the benefits of vertebroplasty in the context of appropriate informed consent disclosure. Without greater confidence in the benefits, it is difficult to assess whether the benefits outweigh the known risks. Nevertheless, the risks of vertebroplasty described herein arguably set a high bar for justifying the procedure on the basis of promoting a beneficial placebo response.

In conclusion, our interpretation of the evidence for vertebroplasty has distinctive implications for clinical practice and health policy. If the benefits of vertebroplasty derive from the placebo response, it is difficult to justify the continuing use of this procedure in clinical practice. The reason for this is not that benefit from the placebo response is lacking in therapeutic value; rather, it is doubtful that the placebo response benefits from vertebroplasty are sufficiently large to justify the risks. Moreover, although it is unknown what the outcomes would be for patients who are candidates for vertebroplasty and informed about the evidence that this procedure is no different from a sham intervention without injection of cement, they are likely to be lower than the benefits observed in clinical practice or in the Vertos II trial. Hence, on the basis of the placebo response hypothesis, the risk-benefit ratio of vertebroplasty does not appear favorable. Finally, whether continued evaluation of vertebroplasty within clinical trials might be justified is debatable—indeed, we are not in consensus on this issue.

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References

1. Alvarez L, Alcaraz M, Pérez-Higueras A, et al. Percutaneous vertebroplasty: functional improvement in patients with osteoporotic compression fractures. *Spine (Phila Pa 1976)* 2006;31(10):1113–1118.
2. Diamond TH, Bryant C, Browne L, Clark WA. Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy. *Med J Aust* 2006;184(3):113–117.
3. Buchbinder R, Osborne RH, Ebeling PR, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009;361(6):557–568.
4. Kallmes DF, Comstock BA, Heagerty PJ, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009;361(6):569–579.
5. Benedetti F. Placebo effects: understanding the mechanisms in health and disease. Oxford, England: Oxford University Press, 2009.
6. Miller FG, Kapchuk TJ. The power of context: reconceptualizing the placebo effect. *J R Soc Med* 2008;101(5):222–225.
7. Voormolen MH, Mali WP, Lohle PN, et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures—the VERTOS study. *AJNR Am J Neuroradiol* 2007;28(3):555–560.
8. Rousing R, Andersen MO, Jespersen SM, Thomsen K, Lauritsen J. Percutaneous vertebroplasty compared to conservative treatment in patients with painful acute or subacute osteoporotic vertebral fractures: three-months follow-up in a clinical randomized study. *Spine (Phila Pa 1976)* 2009;34(13):1349–1354.
9. Klazen CAH, Lohle PNM, de Vries J, et al. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. *Lancet* 2010;376(9746):1085–1092.
10. Noonan P. Randomized vertebroplasty trials: bad news or sham news? *AJNR Am J Neuroradiol* 2009;30(10):1808–1809.
11. Bono CM, Heggeness M, Mick C, Resnick D, Watters WC 3rd. North American Spine

- Society: newly released vertebroplasty randomized controlled trials—a tale of two trials. *Spine J* 2010;10(3):238–240.
12. Clark WA, Diamond TH, McNeil HP, Gonski PN, Schlaphoff GP, Rouse JC. Vertebroplasty for painful acute osteoporotic vertebral fractures: recent Medical Journal of Australia editorial is not relevant to the patient group that we treat with vertebroplasty. *Med J Aust* 2010;192(6):334–337.
 13. Kallmes D, Buchbinder R, Jarvik J, et al. Response to “randomized vertebroplasty trials: bad news or sham news?”. *AJNR Am J Neuroradiol* 2009;30(10):1809–1810.
 14. Buchbinder R, Osborne RH, Kallmes D. Invited editorial presents an accurate summary of the results of two randomised placebo-controlled trials of vertebroplasty. *Med J Aust* 2010;192(6):338–341.
 15. Carey TS. ACP Journal Club. Vertebroplasty was not effective for painful osteoporotic vertebral fractures. *Ann Intern Med* 2009; 151(12):JC6–JC9.
 16. Carragee EJ. The vertebroplasty affair: the mysterious case of the disappearing effect size. *Spine J* 2010;10(3):191–192.
 17. American Academy of Orthopaedic Surgeons. The treatment of symptomatic osteoporotic spinal compression fractures. Guideline and Evidence Report. September 24, 2010:69–85. <http://www.aaos.org/Research/guidelines/SCFguideline.pdf>. Accessed December 1, 2010.
 18. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010;(1):CD003974.
 19. Brody H. The placebo response. New York, NY: Cliff Street Books, 2000.
 20. Miller FG, Kallmes DF. The case of vertebroplasty trials: promoting a culture of evidence-based procedural medicine. *Spine (Phila Pa 1976)* 2010;35(23):2023–2026.
 21. Freidson E. Profession of medicine. Chicago, Ill: University of Chicago Press, 1988.
 22. Wardlaw D, Cummings SR, Van Meirhaeghe J, et al. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. *Lancet* 2009; 373(9668):1016–1024.
 23. Eck JC, Nachtigall D, Humphreys SC, Hodges SD. Comparison of vertebroplasty and balloon kyphoplasty for treatment of vertebral compression fractures: a meta-analysis of the literature. *Spine J* 2008;8(3):488–497.
 24. Venmans A, Klazen CA, Lohle PN, et al. Percutaneous vertebroplasty and pulmonary cement embolism: results from VERTOS II. *AJNR Am J Neuroradiol* 2010;31(8): 1451–1453.
 25. Nussbaum DA, Gailloud P, Murphy K. A review of complications associated with vertebroplasty and kyphoplasty as reported to the Food and Drug Administration medical device related web site. *J Vasc Interv Radiol* 2004;15(11):1185–1192.
 26. Mudano AS, Bian J, Cope JU, et al. Vertebroplasty and kyphoplasty are associated with an increased risk of secondary vertebral compression fractures: a population-based cohort study. *Osteoporos Int* 2009; 20(5):819–826.
 27. Miller FG, Colloca L, Kaptchuk TJ. The placebo effect: illness and interpersonal healing. *Perspect Biol Med* 2009;52(4):518–539.
 28. Miller FG, Colloca L. The legitimacy of placebo treatments in clinical practice: evidence and ethics. *Am J Bioeth* 2009;9(12):39–47.