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## **Percutaneous Vertebroplasty for Painful Compression Fractures in a Small Cohort of Patients with a Decreased Expectation-Related Placebo Effect due to Dementia**

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# Percutaneous Vertebroplasty for Painful Compression Fractures in a Small Cohort of Patients with a Decreased Expectation-Related Placebo Effect due to Dementia

**BACKGROUND AND PURPOSE:** Although abundant literature has reported success with vertebroplasty for the treatment of painful compression fractures, none has accounted for a potential expectation-related placebo effect. We report the results of vertebroplasty for painful vertebral body compression fractures in a small cohort of patients with dementia with the assumption that this patient subgroup is subjected to a decreased placebo effect.

**MATERIALS AND METHODS:** All patients with objective evidence of dementia ( $N = 10$ ) who had undergone vertebroplasty at our institution were identified from a comprehensive prospectively constructed vertebroplasty data base. The patients' pain at rest and activity, mobility, and pain-medication use were analyzed at 2 hours postprocedure, 1 week, 1 month, 6 months, and 1 year.

**RESULTS:** Pain with activity decreased or resolved in 80%–100% of patients at each time point, whereas pain at rest decreased or resolved in 78%–100% of all patients at each time point. Improved mobility was reported in 80%–100% of patients at all time points. Pain medication was decreased or stopped in 67% of patients at 1 week and in 100% of patients at 6 months and 1 year.

**CONCLUSION:** Treatment of painful compression fractures in patients with dementia demonstrates a high rate of success regarding pain relief and mobility. This study offers additional evidence that vertebroplasty has true benefit.

Vertebroplasty has been implemented widely for the treatment of painful compression fractures. This practice is supported by hundreds of highly encouraging publications, including a small number of prospective studies with control groups,<sup>1–3</sup> 1 randomized controlled study,<sup>1</sup> and a recent ostensibly favorable consensus statement.<sup>4</sup> However, these promising results have not factored in the potential impact of expectation-related placebo response. A common misperception is that the placebo response in medical research is limited to 35% of patients reporting improvement.<sup>5,6</sup> In fact, the placebo response may far exceed that,<sup>6</sup> and the short and/or long-term clinical improvement reported with vertebroplasty might be overestimated. Without publication of a placebo-controlled trial, the contribution of an expectation-related placebo effect has not been investigated. Nonetheless, responsible implementation of vertebroplasty mandates that we attempt to determine the degree of perceived improvement due to vertebroplasty when patient expectations are minimized.

To address this issue, we analyzed the results of vertebroplasty in 10 patients with dementia, a population that has been shown to have a much reduced expectation-related placebo response.<sup>7</sup> The diminished expectation-related placebo response may result from a decreased or absent recollection of the procedure itself. We hypothesized that patients with dementia and painful vertebral compression fractures would represent an important clinical subgroup to define better the

importance of expectation-related placebo effect in vertebroplasty, and herein we present the outcomes of a small group of patients with dementia.

## Materials and Methods

### Selection Criteria

Institutional review board approval for a retrospective analysis of vertebroplasty results in patients with dementia was obtained. All patients with a known diagnosis of dementia were identified from a comprehensive prospectively acquired vertebroplasty data base of 791 patients. Our overall results from vertebroplasty have been previously published,<sup>8</sup> but no analysis of a subgroup of patients with dementia was performed in this publication. Initially, we screened all patients in whom the chart noted cognitive impairment of any type or degree. This screen yielded a cohort of 80 patients.

We aimed to achieve a high degree of specificity for patients with dementia rather than mild cognitive impairment to minimize the expectation-related placebo effect in the observed sample. Thus, we included only patients found to have a clinical diagnosis of dementia in the medical record with supporting evidence. This included formal neuropsychologic testing or a Short Test of Mental Status (STMS) administered by a neurologist with results consistent with dementia. For patients who had neuropsychologic testing, we documented the Mattis Dementia Rating Scale (DRS), a commonly used measure of dementia, as a rough indicator of dementia severity.<sup>9</sup> The neuropsychologic testing generally included objective measures of memory, language, attention, concentration, visuospatial functioning, and intelligence. Most patients with dementia have scores of  $<130/144$  on the DRS.<sup>9</sup> The STMS was designed and validated specifically for dementia assessment and is commonly used at our institution.<sup>10</sup> With this measure, a cutoff of 29/38 has reported sensitivity and specificity exceeding 90% as a screen for dementia.<sup>11</sup> Chart reviews of clinical

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visits, follow-up phone calls by radiology nursing, and neuropsychological testing were performed.

Exclusion criteria included the following:

1. Patients with a clinical diagnosis of dementia without any confirming objective evidence in the form of DRS, neuropsychologic testing, or a STMS.
2. Any patient with prior vertebroplasty. This criterion eliminated selection bias for patients with initial favorable clinical outcomes who might be encouraged by caregivers to undergo a subsequent procedure, even though the patients themselves might have no recollection of previous treatments.
3. Noncommunicative patients. There is evidence that the presence, but not the degree, of pain can be accurately determined in non-verbal patients with dementia.<sup>12-14</sup> This criterion has been applied to other studies of pain in patients with dementia.<sup>15</sup>

All patients had radiographic evidence of a compression fracture, including marrow edema on an MR image or radiopharmaceutical uptake on a bone scan. Clinically, the subjects had pain with movement as well as point tenderness over the compression site. One patient who was included had pain localized to the fractured level with fluoroscopic examination without radiopharmaceutical uptake or marrow edema. Patients with either single- or multilevel vertebroplasty were included.

### Outcome Measures

Outcome measures were assessed preprocedure, 2 hours postprocedure, and at 1 week, 1 month, 6 months, and 1 year. These measures included pain at rest and activity, mobility, and pain medication use. Lack of successful follow-up at 1 time point did not preclude subsequent follow-up. Pain medication included narcotics and/or non-narcotics. Mobility and narcotic use were not assessed 2 hours postprocedure, because a longer interval would have been required to assess a meaningful response. Follow-up was achieved with a standardized phone call by radiology nursing.

Although pain generally was assessed with a 10-point visual analog scale (VAS) in the data base, the inability of patients with dementia to consistently assign numbers to a VAS precludes a quantitative analysis of pain in this cohort. We recorded pain as worse, no change, improved, or resolved. This approach allowed the response of each patient to be compared with only his or her baseline pain, avoiding the direct comparison of VAS ratings among multiple patients who could assign different pain ratings to a given degree of pain.

Self-reported pain from patients with dementia typically was aided by the observation of close caregivers. It is generally thought that pain in patients with dementia is best assessed by self-report with supplemental information such as observations by caregivers when necessary, but the accuracy of self-assessment of pain alone is still questioned.<sup>14,16</sup> Studies have shown that relatives and caregivers can reasonably assess pain in patients with mild-to-moderate dementia.<sup>14,17</sup>

Similarly, at each time point, mobility was reported as the percentage of patients reporting increased, unchanged, or decreased mobility, and medication use was reported as the percentage of patients with increased, unchanged, decreased, or no pain medication use.

## Results

### Patient Population

From the initial screened cohort, 16 patients with known dementia were identified. Five of these were excluded due to the absence of confirming neuropsychologic testing or STMS, and 1 patient was excluded due to complete lack of follow-up. The 10 remaining patients consisted of 5 men and 5 women with an average age of 80 years (range, 65–90 years). There were 6 patients with a clinical diagnosis of Alzheimer disease, 1 with Lewy body dementia, 1 with “mixed” vascular and Alzheimer dementia, and 2 without a specific diagnosis. Eight patients had neuropsychologic testing, with a mean calculated DRS score of 106 (range, 71–133), 1 patient had a neuropsychologic test confirming dementia with no calculated DRS score, and 1 patient had a diagnosis of Alzheimer dementia with a STMS score of 23/38. A single patient had a DRS score of >130, but the overall results of the neuropsychologic testing were confirmatory of dementia.

All 10 patients had undergone lumbar vertebroplasty between February 2002 and October 2006. Eight patients had a single-level vertebroplasty, and 2 patients had 2-level vertebroplasty. The compression fractures resulted from osteoporosis in 8 patients, trauma in 1 patient, and a neoplasm in 1 patient. Four patients also had untreated fractures. The average time from the initial fracture was  $2.0 \pm 1.4$  months. The average cement volume was  $3.5 \text{ cm}^3$ . Conscious sedation was used in all patients. Nine patients used pain medication before the vertebroplasty. One patient did not initially use pain medication and remained free of medication throughout the study. Before the procedure, 4 patients were confined to a bed, 3 had restricted mobility, and 3 were ambulatory. Three patients died within the 1-year follow-up interval. One patient died 1 month postprocedure, and 2 patients, 1 year postprocedure.

### Vertebroplasty Response

Most patients demonstrated decreased pain with rest and activity at all follow-up time points. Pain with activity decreased or resolved in 80%–100% of patients at each time point. Complete resolution of pain with activity was seen in 50% (3/6) of patients at 6 months, though this decreased to 25% (1/4) at 1 year. Similarly, pain at rest decreased or resolved in 78%–100% of all patients at each time point. Complete resolution of pain at rest was seen in 83% (5/6) of patients at 6 months, though this decreased to 50% (2/4) at 1 year. The pain with activity or at rest for all follow-up time points is summarized in Table 1.

Improved mobility was reported in 80%–100% of patients at all time points. Mobility was unchanged or worse in 20% (1/5) of patients at 1 month and in no patients at other time points. Pain medication was decreased or stopped in 67% (4/6) of patients at 1 week, 100% (6/6) of patients at 6 months, and 100% (3/3) at 1 year. The mobility and medication use are summarized in Table 2.

## Discussion

In this study, we report outcomes among a small cohort of patients with dementia with painful vertebral compression fractures, each of whom was treated with percutaneous verte-

Table 1: Pain at rest and with activity at all follow-up time points						
Pain	Result	Post-Op (%)	1 Week (%)	1-Month Follow-Up (%)	6 Months (%)	1 Year (%)
At rest	Improved or resolved	78 (7/9)	88 (7/8)	80 (4/5)	100 (6/6)	100 (4/4)
	Resolved	33 (3/9)	38 (3/8)	40 (2/5)	83 (5/6)	50 (2/4)
	Improved	44 (4/9)	50 (4/8)	40 (2/5)	17 (1/6)	50 (2/4)
	No change	11 (1/9)	13 (1/8)	0 (0/5)	0 (0/6)	0 (0/4)
	Worse	11 (1/9)	0 (0/8)	20 (1/5)	0 (0/6)	0 (0/4)
With activity	Improved or resolved	89 (8/9)	100 (8/8)	80 (4/5)	100 (6/6)	100 (4/4)
	Resolved	11 (1/9)	25 (2/8)	20 (1/5)	50 (3/6)	25 (1/4)
	Improved	78 (7/9)	75 (6/8)	60 (3/5)	50 (3/6)	75 (3/4)
	No change	11 (1/9)	0 (0/8)	0 (0/5)	0 (0/6)	0 (0/4)
	Worse	0 (0/9)	0 (0/8)	20 (1/5)	0 (0/6)	0 (0/4)

Note:—Post-op indicates postoperative.

Table 2: Mobility and pain medication usage at all follow-up time points					
	Result	1 Week (%)	1-Month Follow-Up (%)	6 Months (%)	1 Year (%)
Mobility	Improved	100 (7/7)	80 (4/5)	100 (6/6)	100 (5/5)
	No change	0 (0/7)	0 (0/5)	0 (0/6)	0 (0/5)
	Worse	0 (0/7)	20 (1/5)	0 (0/6)	0 (0/5)
Pain medication use	Decreased or none	67 (4/6)	60 (3/5)	100 (6/6)	100 (3/3)
	None	17 (1/6)	0 (0/5)	17 (1/6)	33 (1/3)
	Decreased	50 (3/6)	60 (3/5)	83 (5/6)	67 (2/3)
	No change	33 (2/6)	20 (1/5)	0 (0/6)	0 (0/3)
	Increased	0 (0/6)	20 (1/5)	0 (0/6)	0 (0/3)

broplasty. We found high rates (80%–100%) of partial or complete pain relief up to 1 year following vertebroplasty. Furthermore, a high percentage of treated patients demonstrated improved mobility and decreased use of pain medications following vertebroplasty. Because patients with dementia are thought to have decreased expectation-related placebo response compared with other patient subgroups, our data offer evidence that the improvement in pain severity and functional outcome following vertebroplasty may be a true effect. To our knowledge, this is the first study directly addressing the potential impact of patient-expectation-related placebo response to vertebroplasty.

Other investigators have studied the impact of the expectation-related placebo effect among patients with dementia. Benedetti et al<sup>7</sup> applied either an overt or hidden local anesthetic to patients with Alzheimer disease undergoing painful venipuncture and reported that these patients had a reduced placebo response compared with control subjects.<sup>7</sup> This group concluded that the loss of expectation for improvement due to the cognitive impairment of dementia can decrease the placebo effect and, by extension, the perceived efficacy of analgesics. These findings support the notion that patients with dementia exhibit a decreased expectation-related placebo response.

Patient expectations and the placebo effect have been studied widely among patients undergoing procedures for pain relief. Patient expectations clearly have been shown to influence the outcome of treatment.<sup>6,18,19</sup> For example, a recent study demonstrated that acupuncture resulted in significantly greater pain reduction for the treatment of chronic low-back pain, headaches, and knee osteoarthritis in patients with high preprocedural expectations for treatment compared with those with lower expectations.<sup>19</sup> This was reported in both authentic and sham treatments. High patient expectations may facilitate improvement by changing patient focus to positive experiences, decreasing time to resumed physical activity,

reducing anxiety, and reinforcing the perception of patient control of pain.<sup>6</sup>

The placebo effect is a function of many factors in addition to patient expectations, such as treatment reputation, cost, and perceived “impressiveness.”<sup>6</sup> For example, cognitively intact individuals would likely perceive a relatively new minimally invasive procedure such as vertebroplasty as an “impressive” therapy. These individuals would also recognize the initial expense of vertebroplasty. One could postulate that the quick dramatic response to vertebroplasty reported in the literature can be explained by these factors, in addition to expectation for improvement. Although patients with dementia might also have a decreased placebo response due to the lack of recognition of these factors, this hypothesis has not been studied independently in patients with dementia, to our knowledge. We could not control for these factors in this study.

Although vertebroplasty has been subjected to study in several controlled trials, none of these previous studies have allowed determination of the placebo effect. Diamond et al<sup>2</sup> reported short-term decreased pain and increased rehabilitation in 55 patients who had undergone vertebroplasty compared with 24 patients who refused it and instead underwent conservative therapy. Alvarez et al<sup>3</sup> demonstrated early pain reduction and improved quality of life in 101 patients who underwent vertebroplasty compared with 27 who refused it; and Voormolen et al<sup>1</sup> reported short-term pain relief and increased mobility in 18 patients treated with vertebroplasty compared with 16 patients treated only with optimal pain medication in a randomized study.<sup>1</sup> Not only do these methods fail to account for a possible placebo effect but also the lack of randomization in the studies by Diamond et al and Alvarez et al may have selected patients who had higher-than-average expectations for improvement with vertebroplasty for the treatment group. The randomization process used by Voormolen et al was not fully disclosed, impairing assessment of potential selection bias in this study.<sup>20</sup> Moreover, this study

did not include an intention-to-treat analysis of the patients who refused the assigned treatment, which could also be a source of selection bias.<sup>20</sup>

This study offers evidence against the placebo effect as the sole source of clinical improvement following vertebroplasty. The true effect of vertebroplasty will remain unknown until large placebo-controlled trials have been completed, however. At least 2 such controlled trials are currently underway, though these trials are comparing vertebroplasty to injection of an anesthetic rather than to a true “placebo” (personal communication, R. Buchbinder, MD, October 2007).<sup>21</sup> These trials are near completion of recruitment, but results of long-term follow-up may not be available for some time.

There are several limitations to our study. It can be difficult to assess pain in cognitively impaired individuals.<sup>12–15,22</sup> For example, they may express pain with atypical nonverbal cues and might demonstrate a reduced ability to recall and describe pain.<sup>13,14</sup> We could not blind caregivers or the nursing staff to the treatment, and their expectations are not eliminated in this study. The pain experience in individuals with dementia may be different from that of cognitively intact individuals.<sup>12,22</sup> Nonetheless, each patient was compared with himself/herself at different time points, which served as an internal control. To control for expectation, we have necessarily sacrificed pristine generalizability to patients of all cognitive abilities.

## Conclusion

Treatment of painful compression fractures in patients with dementia with vertebroplasty demonstrates a high rate of success regarding pain relief and mobility. Because patients with dementia likely are less susceptible than other patients to expectation-related placebo effects, this study offers additional evidence that the benefits of vertebroplasty cannot be accounted for solely by expectation-related placebo effect.

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