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Editorial

Plea for continuing but rational use of vertebroplasty for osteoporotic vertebral fractures

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Nearly 10 years have elapsed since we were asked to write an editorial for Joint Bone Spine on a similar topic [1]. Two randomized controlled trials published in the New England Journal of Medicine a few months earlier seemed to indicate that vertebroplasty was not more effective than a sham procedure in relieving pain due to one or more vertebral fractures [2,3]. Despite the good methodological quality of both trials, the flaws identified in our earlier editorial remain relevant and deserve to be pointed out here [1]. The sample sizes were limited, with 78 [2] and 131 [3] patients, respectively. In the trial by Kallmes et al. [3], patients with only very moderate pain intensities could be included, as the cutoff was ≥ 3 on a 0-10 visual analog scale (VAS). Both trials included patients with pain durations of up to 12 months, although vertebroplasty cannot provide benefits in patients with longstanding pain, except in a few specific situations (see below). In the trial by Buchbinder et al. [2], a visible fracture line was sufficient for inclusion, even in the absence of magnetic resonance imaging (MRI) evidence of bone marrow edema. Finally, Kallmes et al. [3] did not consistently perform MRI to select patients for study inclusion, although MRI findings are crucial for determining whether vertebroplasty is indicated.

Subsequent studies produced conflicting results about the efficacy of vertebroplasty in relieving pain due to osteoporotic vertebral fractures [4–7]. A task force convened by the American Society for Bone and Mineral Research recently published a position paper stating that vertebroplasty had no role in the management of patients with pain due to osteoporotic vertebral fractures [8]. Neither our clinical experience of more than 25 years with vertebroplasty in this indication nor the data in the literature support this position. In France, vertebroplasty is performed far more often than kyphoplasty and other vertebral augmentation procedures, and the most recent studies focused on vertebroplasty, which we therefore chose as the subject of this editorial. The conclusions of the above-mentioned position paper should be viewed with considerable circumspection, and each study should be interpreted in the light of its specific details [8].

Since the publication of our first editorial on vertebroplasty [1], a well-designed study demonstrated that vertebroplasty was superior over conventional treatment in relieving pain due to vertebral fractures [4]. The patients had one to three vertebral fractures, severe pain with a score ≥ 5 on a 0-10 VAS, and high vertebral body signal on T2-weighted MRI sequences. Follow-up was 1 year. Vertebroplasty was clearly more effective than conventional treatment, and the difference was apparent as early as 1 day after the procedure. Furthermore, the pain relief was sustained over time until the end of the follow-up period. Improvements were noted in both quality of life (QUALEFFO score) and function (Roland-Morris disability questionnaire). One of the investigators involved in the two randomized trials published in 2009 [2,3], whose limitations are mentioned above, conducted a further trial versus a sham procedure, using eligibility criteria designed to select those patients most likely to benefit from vertebroplasty [6]. The inclusion criteria were severe pain (numerical rating scale [NRS] ≥ 7), pain onset within the last 6 weeks, and high vertebral body signal on T2-weighted MRI sequences. The trial included 120 patients. The primary outcome measure was the proportion of patients whose pain score on the NRS was ≤ 4 on day 14 after the procedure. This proportion was 44% in the vertebroplasty group and 21% in the sham group, a highly significant difference ($P = 0.011$). The between-group difference remained significant at the end of the 6-month follow-up ($P = 0.027$). Vertebroplasty was particularly effective when the vertebral fracture was located at the thoracolumbar junction. Furthermore, the magnitude of the NRS score decrease was significantly greater in the vertebroplasty group at all the study time points until the end of the 6-month follow-up. Improvements in the QUALEFFO score were less pronounced, but the difference with the sham group was statistically significant on day 14, declined to a nonsignificant value by month 1, then increased again to become significant by month 6. The fully validated generic quality-of-life scale EQ-5D was assessed also. The results showed improvements over time, which were usually more marked in the vertebroplasty group, with significant differences versus the sham group after 1 and 6 months. Finally, analgesic consumption diminished in both groups, to a greater extent in the vertebroplasty group 1 and 6 months after the procedure with statistically significant differences at both time points.

More recently, the Dutch group led by Paul Lohle reported a well-designed sham controlled trial [7], whose results contradict those obtained by Clark et al. [6]. The inclusion criteria were similar

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to those used by the same group in a 2010 study, namely, back pain (VAS $\geq$ 5) with onset within the last 6 weeks and signs of vertebral body edema on T2-weighted MRI images. The primary outcome was an at least 3-point decrease in the VAS pain score. Recruitment was slow initially, prompting the investigators to include patients with pain durations of up to 9 weeks. The patients were evaluated on days 1 and 7 then after 3 and 12 months. In addition to pain intensity, the Roland-Moriss disabilityquestionnaire, generic EQ-5D quality-of-life index, and specific QUALEFFO quality-of-life score were measured. The number of patients was 90 in the vertebroplasty group and 86 in the sham group. The patients had severe pain at baseline, with mean VAS scores of 7.72 and 7.92 in the vertebroplasty and sham groups, respectively. No significant between-group difference in the primary outcome was found, as pain intensity decreased gradually and similarly in the two groups. After 12 months the mean VAS pain score was 2.72 after vertebroplasty and 3.17 after the sham procedure. However, after 12 months a significantly higher proportion of patients in the sham group had a VAS pain score $\geq$ 5 (44% vs. 24% in the vertebroplasty group). This evaluation criterion may seem arbitrary but was chosen because a VAS pain score $\geq$ 5 was required for study inclusion. The same group has conducted another trial (VERTOS V, ClinicalTrials.gov #NCT01963039) focused on patients with vertebral fractures, a VAS pain score $\geq$ 5 after 12 weeks, and persistent vertebral body edema by MRI [9]. The findings will be available next year.

Another angle from which this issue can be tackled consists in factoring in the severity of vertebral fractures, which are among the fractures associated with excess mortality. Using a 20% random sample from a Medicare database, McCullough et al. evaluated the risk of death after a vertebral fracture managed with versus without vertebroplasty, applying multiple adjustments for potential selection bias [10]. The risk of death was 17% lower in the vertebroplasty group than in the conventional treatment group, and this difference was statistically significant. After propensity score matching - the most reliable method in the absence of randomization - the difference decreased by 8% and was no longer statistically significant [10]. Ong et al. [11] performed a more recent Medicare database study using the entire population instead of a random sample, as well as a longer time period (2005–2014). As with the earlier study, one of the objectives was to assess associations between vertebroplasty and mortality. Overall, for the entire study period, the effect was statistically significant even after matching on a propensity score. The difference in mortality was most noticeable during the first few years after the diagnosis of vertebral fracture. Differences in favor of vertebroplasty were 30% after 1 year, 20% after 2 years, 12% after 5 years, 9% after 8 years, and 8% after 10 years. These studies are interesting and complement those discussed at the beginning of this editorial. Nevertheless, their retrospective design mandates circumspection when seeking to draw conclusions, although propensity score matching is the best available method in the absence of randomization. In addition to efficacy, safety deserves careful attention. Cement leakage outside the vertebral body is the most commonly reported adverse event. Leakage is common but fortunately asymptomatic in the vast majority of cases. In the trial by Firanescu et al. [7], nearly 65% of patients had cement leakage visible on the postoperative CT at any site. The most common sites are the intervertebral disk and soft tissues, as expected given that vertebral fractures produce multiple endplate fragments. Another controversial issue that remains incompletely resolved is the frequency of fractures at the levels adjacent to the augmented vertebra. Both biomechanical reasons and indirect arguments suggest an increase in the risk of adjacent vertebral fracture [12]. Nevertheless, despite the availability of numerous studies conducted under stringent conditions, no convincing evidence of an increased fracture risk in adjacent vertebras has been obtained [13,14]. Another consideration is the potential effect of vertebral fractures on spinal alignment, which is crucial in the medium term. Spinal alignment was not assessed in the above-mentioned randomized trials. A single wedge fracture of the thoracolumbar or thoracic spine can generate up to 15° or 20° of kyphosis. Kyphosis induces sagittal spinal misalignment and increases the risk of falls and therefore of further fractures. Kyphosis is associated with morbidity, functional impairments, declines in respiratory function, and a higher risk of death [15]. Furthermore, the vertebral compression fracture may worsen gradually [14], notably when the thoracolumbar junction is involved. In this situation, vertebroplasty prevents further vertebral collapse from resulting in increased kyphosis.

Our conclusion based on the data discussed here is that vertebroplasty deserves to be used but only in carefully selected patients. The conflicting data in the literature may seem confusing. We believe the confusion is only apparent. Thus, in the study by Clark et al. showing benefits from vertebroplasty [6], mean patient age was older than in the other studies and most of the patients were hospitalized. Therefore, in elderly patients admitted for a recent vertebral fracture responsible for severe pain, particularly if it is located at the thoracolumbar junction and/or if the patient has comorbidities, rapid vertebroplasty is an appropriate treatment whose benefits have been demonstrated. The second indication of vertebroplasty is marked pain in ambulatory patients that persists despite optimal pharmacological therapy and is accompanied with vertebral body edema on T2-weighted images. At present, this second indication is based on expert opinion. The results of the VERTOS V trial that will be presented next year will say whether it is justified.

Vertebroplasty should always be performed as part of a multidisciplinary treatment program involving the operator and a rheumatologist in charge of the pharmacological and nonpharmacological management of the bone fragility.

Disclosure of interest

The authors declare that they have no competing interest.

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