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Review

Incidence of subsequent vertebral body fractures after vertebroplasty

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ABSTRACT

The causal relationship between vertebroplasty and new-onset vertebral fractures remains unproved. We undertook a systematic review and meta-analysis of randomized controlled trials to assess whether vertebroplasty increases the incidence of new vertebral fractures and adjacent vertebral fractures. A systematic literature search of PubMed, EMBASE and Cochrane Library databases up to April 2013 was conducted. Eligible studies were randomized controlled trials of osteoporotic vertebral fracture patients receiving vertebroplasty. Risk ratios (RR) and 95% confidence intervals (CI) were calculated and heterogeneity was assessed with both the chi-squared test and the I^2 test. Four studies with a total of 454 patients met the inclusion criteria. All four studies described the incidence of new vertebral fractures and three studies described adjacent vertebral fractures. The pooled results revealed that vertebroplasty was not associated with a significant increase in the incidence of new vertebral fractures (RR 1.12, 95% CI 0.75–1.67; $p = 0.59$) or adjacent vertebral fractures (RR 2.31, 95% CI 0.36–15.06; $p = 0.38$). Based on available evidence, it cannot be concluded that vertebroplasty can significantly increase the postoperative rate of new vertebral fractures and adjacent vertebral fractures. However, due to some limitations, the results of this meta-analysis should be cautiously accepted, but further studies are needed.

1. Introduction

Vertebroplasty, a minimally invasive technique, is widely used as an effective treatment for painful osteoporotic vertebral fractures [1]. After this surgery, most patients return to their normal daily activities. Although it is a safe and efficient procedure for controlling pain, there are still some risks after surgery, including the development of new fractures at non-treated vertebrae [2–4].

Investigators have frequently reported rates of new fracture after vertebroplasty, but the causal relationship between the procedure and new-onset vertebral fractures remains unproved. There is still controversy about whether new vertebral fractures are a consequence of vertebroplasty or simply a result of the natural progression of osteoporosis. Some authors believe that vertebroplasty is associated with a higher incidence of new vertebral fractures as a result of the augmented stiffness of the treated vertebrae or cement leakage in the adjacent vertebral disk space [5,6]. Others dispute this assumption and consider the incidence of new fractures to be dependent on the presence and severity of the osteoporosis [7,8].

Defining the relationship between vertebroplasty and new vertebral fractures is important for several reasons. First, if it can be established that vertebroplasty increases the rate of new fractures in patients with osteoporosis, prophylactic vertebroplasty of at-risk vertebrae might be necessary. Second, if a significant association is proven, it will prompt exploration and advancement of procedures, techniques, and cement design to minimize this risk.

Both retrospective and prospective studies have made efforts to clarify the role of vertebroplasty on new fractures [5–9]. However, definitively demonstrating or excluding the causative relationship will require well-designed, randomized controlled trials (RCT). At the time of writing the literature included several published RCT regarding the incidence of new fractures, but most of these studies have a modest sample size and convey inconclusive results. In order to clarify this debate, we searched available medical databases for published trials and performed a meta-analysis to evaluate if there is a relationship between vertebroplasty and new vertebral fractures.

2. Materials and methods

2.1. Literature search and inclusion criteria

We searched the PubMed, EMBASE and Cochrane Library databases from inception to April 2013. The search strategies used the following format of search terms: (vertebroplasty OR vertebral augmentation) AND (osteoporosis OR fracture). The search was limited to human subjects and RCT. No language restriction was

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imposed. In addition, reference lists of all the selected articles were hand-searched to identify other potentially eligible trials. This process was performed iteratively until no additional articles could be identified.

The following inclusion criteria were applied: (1) study must be a RCT, (2) study population must be patients with painful osteoporotic vertebral fractures, (3) vertebroplasty intervention, (4) conservative treatment or sham procedure comparison group, (5) measured outcomes of the incidence of new vertebral fractures and adjacent vertebral fractures, and (6) follow-up of between 6 to 12 months.

Trials were excluded if they (1) were abstracts, letters, reviews, or case reports; (2) had repeated data; or (3) did not report outcomes of interest.

2.2. Data extraction and outcome measures

Extracted data included the general characteristics of each study and the outcomes measured. General characteristics collected included first author, year of publication, study design, sample size, duration of clinical pain, intervention (unilateral or bilateral transpedicular vertebroplasty), mean number of vertebrae treated by vertebroplasty, comparison groups (conservative treatment or sham procedure), length of follow-up, and funding bias. The outcomes measured included the incidence of new vertebral fractures and adjacent vertebral fractures. When the same population was reported in several publications, we retained only the most informative article or complete study to avoid duplication of information. Data were extracted independently by two authors (Y.Z.Z. and L.D.K.). Any disagreements concerning paper eligibility were resolved by discussion and consensus.

2.3. Assessment of methodological quality

The methodological quality of the trials was evaluated independently by two authors (L.D.K. and J.M.C.) without masking the trial names. The reviewers followed the instructions provided in the Cochrane Handbook for Systematic Reviews of Interventions [30]. The following domains were assessed: sequence generation, allocation concealment, blinding, incomplete data outcomes, revealing of selective outcomes, and any remaining biases. When the information in the study was inadequate, attempts were made to contact the authors in order to ensure that the study was evaluated correctly.

2.4. Statistical analysis

Only dichotomous outcomes were mentioned in our study, so risk ratios (RR) and 95% confidence intervals (CI) were calculated for outcomes. All analyses were carried out on an intention-to-treat basis. Heterogeneity was analyzed with both the chi-squared test and the I^2 test. A p value of <0.10 for the chi-squared test was interpreted as evidence of heterogeneity, and I^2 was used to estimate total variation across the studies. A fixed-effect model was adopted if there was no statistical evidence of heterogeneity, and a random-effect model was adopted if statistically significant heterogeneity was present. Studies with an I^2 statistic of 25–50% were considered to have low heterogeneity, those with an I^2 statistic of 50–75% had moderate heterogeneity, and those with an I^2 statistic of >75% had high heterogeneity.

Because patient characteristics, study designs, interventions, and other confounding factors were not consistent between studies, we further conducted several sensitivity analyses to identify potential confounding sources. We also investigated the influence of a single study on the overall pooled estimate by omitting each study in turn. Sensitivity analyses were only performed for new vertebral fractures due to rather small numbers of studies for adjacent vertebral fractures.

The presence of publication bias was assessed using the Begg and Egger tests. A p value <0.05 was judged as statistically significant, except where otherwise specified. All statistical analyses were performed using Review Manager version 5.1 (The Cochrane Collaboration, Oxford, UK).

3. Results

3.1. Study identification and selection

A total of 217 records were identified by the initial database search. Ninety-six records were excluded as they were duplicate studies and 111 were excluded for various reasons (reviews, non-randomized studies, or not relevant to our analysis) on the basis of the titles and abstracts. The remaining 10 were retrieved for full text review, and six of them were excluded; three did not report outcomes of interest [10–12], one reported duplicated data [13], and two were currently ongoing [14,15]. Finally, four RCT that met our inclusion criteria were included in the present meta-analysis [16–19]. The selection process for RCT included in this meta-analysis is shown in Figure 1.

3.2. Study characteristics

The main characteristics of the four RCT included in the meta-analysis are presented in Table 1. These studies were published between 2009 and 2012. The sizes of the RCT ranged from 49 to 202 patients (total of 454). A total of 228 patients underwent vertebroplasty, and the remaining 226 patients received other treatments. In the study of Buchbinder et al., vertebroplasty was compared with sham injection, while in the other trials, pain medication, brace treatment and physiotherapy were used in the control groups [17]. Two of the four trials included patients with a duration of clinical pain <12 months [16,17]. The other two trials included patients with back pain <6 weeks [18] or <8 weeks [19]. Patients in three of the included studies were followed up for 12 months [16,18,19].

3.3. Assessment of risk of bias

The risk of bias is demonstrated graphically in Figure 2 and summarized in Figure 3. The randomization technique was mentioned in all four trials. However, only two trials stated the method of allocation concealment [17,19]. Blinding is rarely used in orthopedic surgery trials and only one study was blinded to the participants and personnel [17]. Patients were lost to follow-up in all studies, resulting in a high attrition bias risk, with the exception of one trial which had balanced missing outcome data across intervention groups [19].

3.4. New vertebral fractures

All four RCT reported new vertebral fractures in study patients. The test for heterogeneity was not significant, and the studies had low heterogeneity (p for heterogeneity = 0.16; I^2 = 42%). Using the fixed-effect model, the aggregated results of these four studies suggested that vertebroplasty was not associated with a significant increase in the incidence of new vertebral fractures (RR 1.12, 95% CI 0.75–1.67; p = 0.59) (Fig. 4). Subsequently, we performed sensitivity analyses to explore potential sources of heterogeneity. Exclusion of the trial conducted by Blasco et al. [16] resolved the heterogeneity but did not change the result (RR 0.86, 95% CI 0.53–1.40; p = 0.55; p for heterogeneity = 0.40; I^2 = 0%). Further