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ORIGINAL STUDY

Higher incidence of new vertebral fractures following percutaneous vertebroplasty and kyphoplasty – fact or fiction ?

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New vertebral fractures after percutaneous vertebroplasty or kyphoplasty are said to result from biomechanical changes induced by cementation. Fact or fiction ? The reported incidences for new vertebral fractures after cementation or after conservative therapy vary widely. This is mainly due to differences in their design, more specifically as to the duration of follow-up. Therefore a systematic review of the literature was performed, searching for *comparable* publications to assess the potential risk of new vertebral fractures following vertebroplasty and kyphoplasty versus conservative treatment. Studies were only included if they granted a standardized one-year radiological follow-up, so improving comparability. However, a high degree of heterogeneity was still seen among the results, which made it impossible to state that cement augmentation is as safe as conservative treatment with respect to new fractures. In other words, it was impossible to separate facts from fiction with the studies available to-day. The combined odds ratio of vertebroplasty and kyphoplasty versus conservative treatment, namely 0.96, gave a hint that there might be little difference. Large scale randomized studies will be necessary.

Keywords : vertebroplasty ; balloon kyphoplasty ; conservative treatment ; new vertebral fracture.

INTRODUCTION

A rise in the incidence of osteoporotic vertebral fractures is a major concern in an aging society. Due to an ongoing demographic change an even stronger increase seems to be inevitable (*19,57*). In Europe, the incidence of osteoporotic vertebral fractures is estimated to be 5.7/1000 for men and 10.7/1000 for women (*1*). At the age of fifty about 20 to 25% of all women suffer from at least one vertebral fracture (*35*).

Despite the frequency of osteoporotic vertebral fractures, only 30% of all fractures are detected in patients suffering from backache (*7*). Surgical intervention is recommended for patients whose fractures are resistant to conservative treatment consisting of immobilization and analgesic therapy. Vertebroplasty and (balloon) kyphoplasty are internationally

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known as minimally invasive surgical procedures for the treatment of osteoporotic vertebral fractures (*31,34,36,51,54,59,60*). However, the appearance of new vertebral fractures is a presumed complication following percutaneous vertebroplasty and kyphoplasty. This would be due to altered biomechanics after cementation. The reported incidences for new vertebral fractures following both procedures vary widely (*13,17,18,20,22,24,25,29,41,42,50*). This is due to differences in the study designs, such as inconsistent follow-up periods, lack of adequate radiological control, and mixed fracture pathology (osteoporosis, malignant tumour, haemangioma). The aforementioned items make it hard to compare the reported fractures related to both surgical procedures. On the other hand, new vertebral fractures have also been observed after conservative therapy (*30*).

Therefore, the purpose of the current study was to compare publications reporting new osteoporotic vertebral fractures, compared to baseline radiographs, after vertebroplasty, kyphoplasty and conservative therapy, at a standardized radiological one-year follow-up.

MATERIALS AND METHODS

The authors analyzed international data bases (e.g. PubMed, Medline, Cochrane Library) dealing with the keywords "vertebroplasty" or "kyphoplasty", as part of a computerized online literature search. Initially, no restrictions were placed on the language, the publication date or the publication type. The search resulted in 2015 entries covering the period up to July 2011 (Fig. 1). Subsequently the search was narrowed down by specifying the following inclusion criteria : clinical peer reviewed studies reporting vertebroplasty or kyphoplasty ; papers written in English or German ; only osteoporotic fractures ; studies in which a standardized radiological follow-up examination of the spine was conducted 12 months after vertebroplasty or kyphoplasty. This led (Fig. 1) to 13 + 3 = 16 studies about vertebroplasty, and 6 + 3 = 9 studies about kyphoplasty.

In addition the literature was searched for publications about new fractures following conservative treatment. The same inclusion criteria as above were used.

Statistical analysis was performed using the R program for statistical computing (R 2.12.1 ; packages : "meta"). Vertebroplasty (16 studies) (Fig. 2) and kyphoplasty (9 studies) (Fig. 3) : the proportion of patients with new fractures was calculated according to a random effects model (DerSimonian and Laird method), due to the heterogeneity between studies, as indicated by an I^2 of 74.5% for vertebroplasty and of 74% for kyphoplasty. For the 6 studies which compared cement augmentation with conservative treatment (Fig. 4), the odds-ratio (OR) of suffering from new fractures was calculated. Again, due to the heterogeneity between the studies (as indicated by $I^2 = 63.7\%$) a random effects model (DerSimonian and Laird method) was used to obtain combined odds ratio estimates and a 95% confidence interval (CI).

RESULTS

Vertebroplasty and kyphoplasty

The literature search initially resulted in 2015 publications (Fig. 1), of which 634 fulfilled the criteria of being clinical studies published in either English or German. All other publications were case reports, reviews, biomechanical studies, publications in foreign languages etc., and therefore were excluded from the analysis.

Twenty-two out of the 634 trials fulfilled all the required inclusion criteria : 13 publications were on vertebroplasty, 6 on kyphoplasty, and 3 on both techniques.

Fifteen of these 22 publications were prospective clinical trials (*2,3,8,14,16,21,23,26,37,38,40, 42,46,54,56*). Four studies were retrospective case series (*9-11, 33*). In the 3 remaining trials the study design was not reported (*6,44,47*).

All 16 (13 + 3) publications reporting new vertebral fractures following *vertebroplasty* are listed in figure 2 and in table I. These publications reported heterogeneous (I = 74.5%) rates of new vertebral fractures ranging from 0% to 48.3% at the end of the first year. By pooling the data from these 16 publications the mean proportion of patients suffering new vertebral fractures one year after vertebroplasty, obtained via a random effects model, was 0.20 (95% CI : 0.15-0.27).

The 9 (6 + 3) publications (Fig. 3) (Table II) reporting new vertebral fractures one year after *kyphoplasty* showed that 79 out of 458 treated patients sustained new fractures within the first year. Pooling these data resulted in a mean proportion of

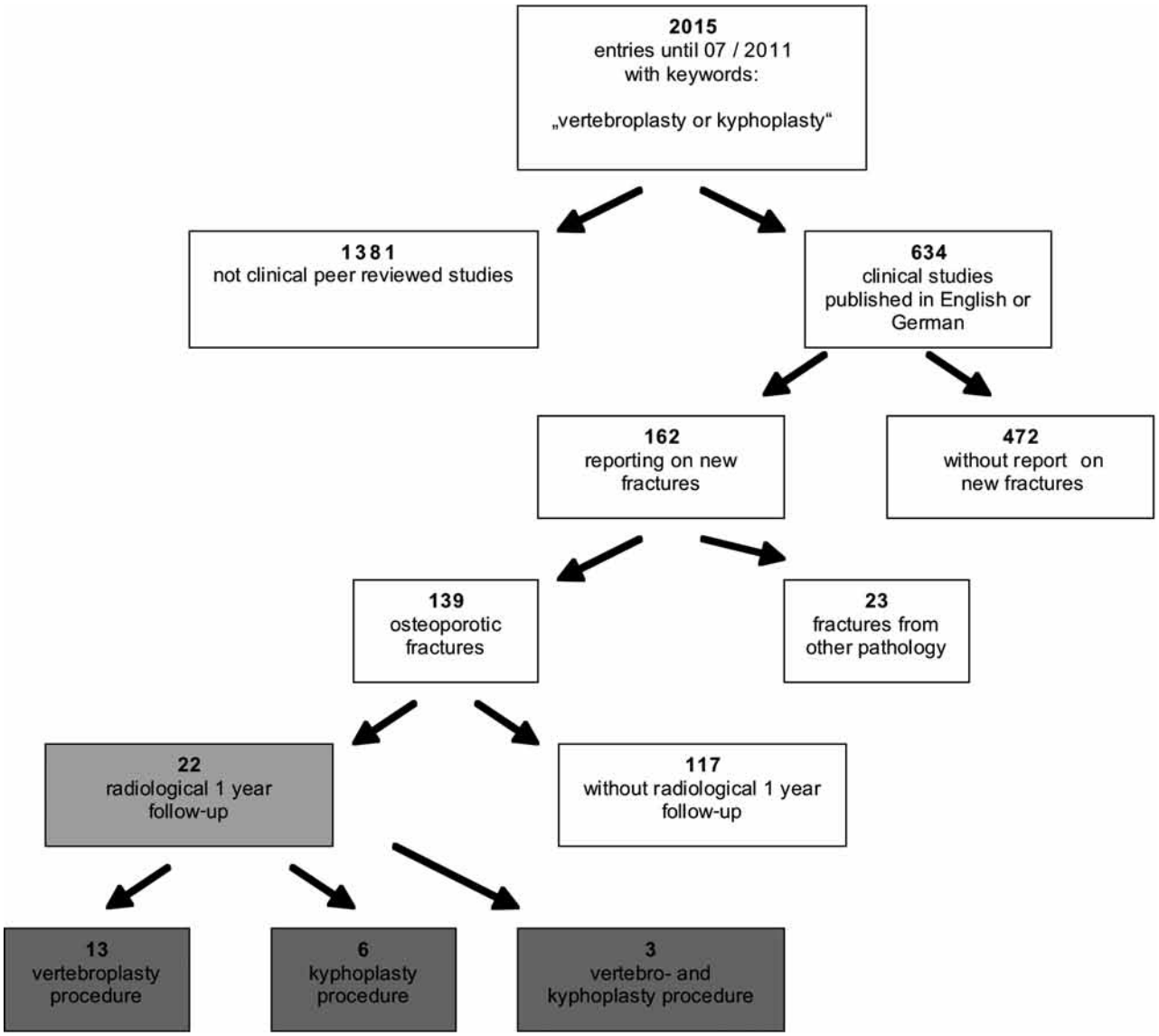

Fig. 1. — Systemic analysis of the literature

0.14 (95% CI : 0.08-0.22) (Fig. 3). Again, these 9 publications were quite heterogeneous (I = 74%) as to the rate of new vertebral fractures at the end of the first year : from 4.2% to 33%.

In the analyzed publications (Table I and II) the thoracolumbar junction was most often affected by fractures. The injected amount of cement varied strongly (1-13 ml), even within the same series (Table I and II). Refractures of already augmented vertebrae have been reported in 5.9%-16.1% of the cases following vertebroplasty and kyphoplasty (*8,15*).

Cementation versus conservative treatment

The literature search for studies which compared cementation with conservative treatment resulted in 6 publications with radiological follow-up after one year (Fig. 4). Three of these publications were randomized trials, 3 were not.

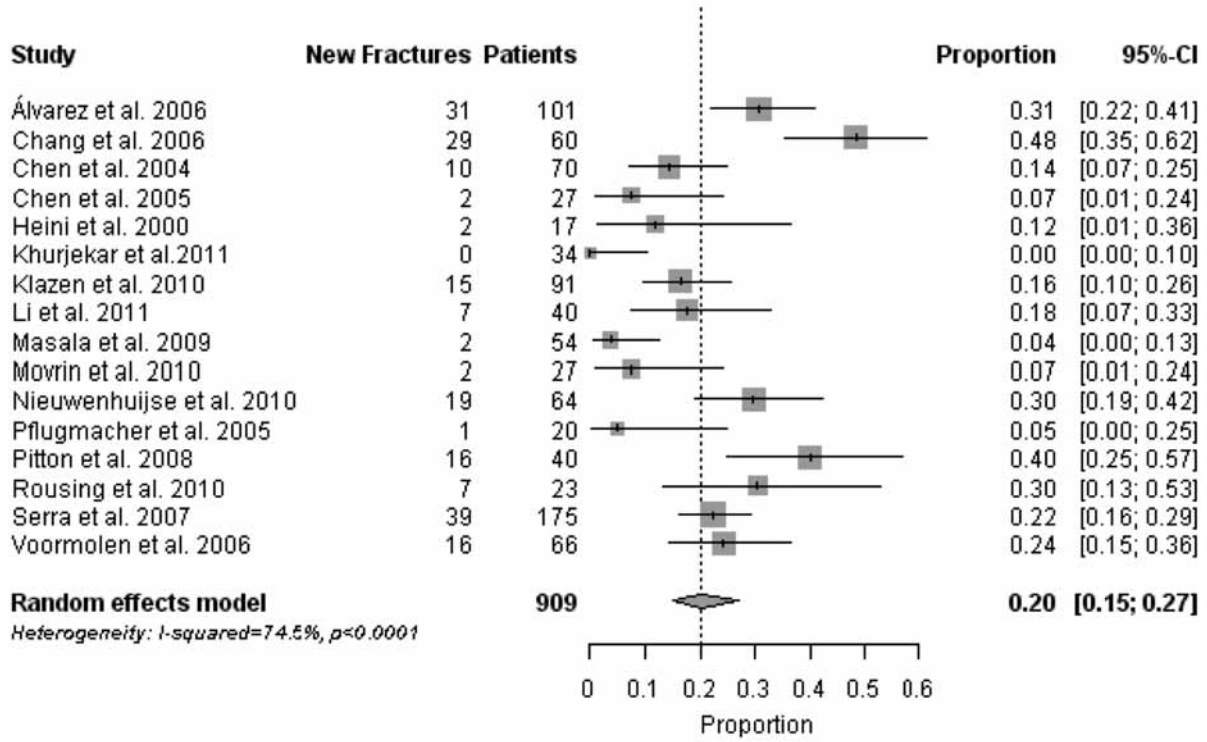

Fig. 2. — New vertebral fractures one year after vertebroplasty. Squares represent the proportion of new fractures. The size of the squares is proportional to the number of patients enrolled. Error bars represent the 95% confidence intervals (CIs). The diamond shape (bottom) represents the pooled estimate, with CI.

Vertebroplasty was compared to conservative treatment in 4 of these studies (Fig. 4, lower part). Analysis showed a large degree of heterogeneity, especially in terms of fracture age, number of treated vertebral fractures and osteoporosis prophylaxis (Table III). The numerical rate of new vertebral fractures was higher in the vertebroplasty group (55/269 or 20.44%) than in the conservative group (32/220 or 14.54%) (Fig. 4) (*2,23,33,46*). The odds ratio between vertebroplasty and conservative treatment in these 4 studies was 1.27 (95% CI : 0.51-3.14) (Fig. 4).

Kyphoplasty was compared to conservative treatment in 2 of these studies. Grafe *et al* (*14*) reported that kyphoplasty led to 7/40 or 17.5% new fractures after one year, versus 10/20 or 50% in the conservative group ($p = 0.0084$). Wardlaw *et al* (*56*) noted that kyphoplasty resulted in 38/124 or 30.64% new fractures after 1 year, versus 24/95 or 25.26% in the conservative group ; the 5.38% difference was not statistically significant (95% CI : -4.5 to 20.0 ; $p = 0.220$). A thorough investigation of both studies (*14,56*) revealed a high degree of heterogeneity between them, in terms of amount of cement, number of treated fractures and age of the treated fractures (Table III). As a whole, the numerical rate of new vertebral fractures was higher in the conservative group (34/115 or 29.56%) than in the kyphoplasty group (45/164 or 27.43%) (Fig. 4). The odds ratio was 0.57 (95% CI : 0.10-3.36) (Fig. 4).

The combined odds ratio of *vertebroplasty and kyphoplasty* versus conservative treatment (Fig. 4) was 0.96.

DISCUSSION

It is still controversial whether new vertebral compression fractures are a consequence of changes in spine statics after augmentation with bone cement, or simply the result of natural progression

Table I. — Studies on new vertebral fractures one year after vertebroplasty

Author	Language	Number of treated patients	Number of treated vertebral bodies	Mainly affected area in spine	Amount of injected cement	Number of patients suffering from vertebral fractures
Álvarez *et al*. 2006	English	101	151	thoracolumbar	- - - - -	31
Chang *et al*. 2006	English	60	95	thoracolumbar	- - - - -	29
Chen *et al*. 2004	English	70	87	thoracolumbar	2.5-13 ml	10
Chen *et al*. 2005	English	27	27	thoracolumbar	4-10 ml	2
Heini *et al*. 2000	English	17	45	thoracolumbar	4-8 ml	2
Khurjekar *et al*. 2011	English	34	34	thoracic + lumbar	2.5-5 ml	0
Klazen *et al*. 2010	English	91	134	- - - - -	1-9 ml	15
Li *et al*. 2011	English	40	52	thoracolumbar	- - - - -	7
Masala *et al*. 2008	English	54	54	thoracic + lumbar	- - - - -	2
Movrin *et al*. 2010	English	27	32	thoracolumbar	4-8 ml	2
Nieuwenhuijse *et al*. 2010	English	64	129	thoracic + lumbar	4.3-6 ml	19
Pflugmacher *et al*. 2005	English	20	32	- - - - -	2-8.5 ml	1
Pitton *et al*. 2008	English	40	102	thoracolumbar	4.7-5.5 ml	16
Rousing *et al*. 2010	English	23	23	thoracolumbar	- - - - -	7
Serra *et al*. 2007	English	175	242	thoracolumbar	- - - - -	39
Voormolen *et al*. 2006	English	66	102	thoracolumbar	1.9-3.7 ml	16

of osteoporosis. There are reviews summarizing clinical studies on fractures following vertebroplasty or kyphoplasty (*13,17,32,48*). These reviews share the problem that their selected clinical trials do not allow reliable conclusions concerning the incidence of vertebral fractures following vertebroplasty or kyphoplasty. The reasons for that are differences in study design with inconsistent follow-up periods as well as multiple fracture pathogenic mechanisms.

Therefore the authors decided to search in the first place for *publications, dealing with vertebroplasty and kyphoplasty for osteoporotic vertebral fractures, with a standardized radiographic follow-up examination 12 months postoperatively*. This led to 22 publications (Fig. 1) reporting new vertebral fractures one year after vertebroplasty or kyphoplasty. From these studies, comparable as to follow-up period, data were pooled to increase the number of patients and the reliability of the results. It could be shown that, even if the follow-up period was limited to the first postoperative year, proportions of vertebral fractures varied widely in the vertebroplasty group (0%-48.3%) (Fig. 2) and in the kyphoplasty group (4.2%-33%) (Fig. 3). Summarizing the data, a proportion of 0.20 (Fig. 2) (Table I) in the vertebroplasty group suffered new vertebral fractures within the first year, and a proportion of 0.14 (Fig. 3) (Table II) in the kyphoplasty group.

In the second place the authors searched for *publications which compared cement augmentation with conservative therapy, with a radiological follow-up after one year.* Only 6 such studies were found (Fig. 4) : 2 about kyphoplasty, and 4 about vertebroplasty. The authors were not aware of the number of baseline fractures in these 6 studies. According to Lindsay *et al* (*30*) the number of baseline vertebral fractures has a strong impact on the risk for sustaining a new vertebral fracture. Once again, this meant that the 6 studies were probably heterogeneous, which limited their usefulness.

Vertebroplasty versus conservative treatment : 4 studies

In 4 of the studies included in the current review the occurrence of new vertebral fractures was com-

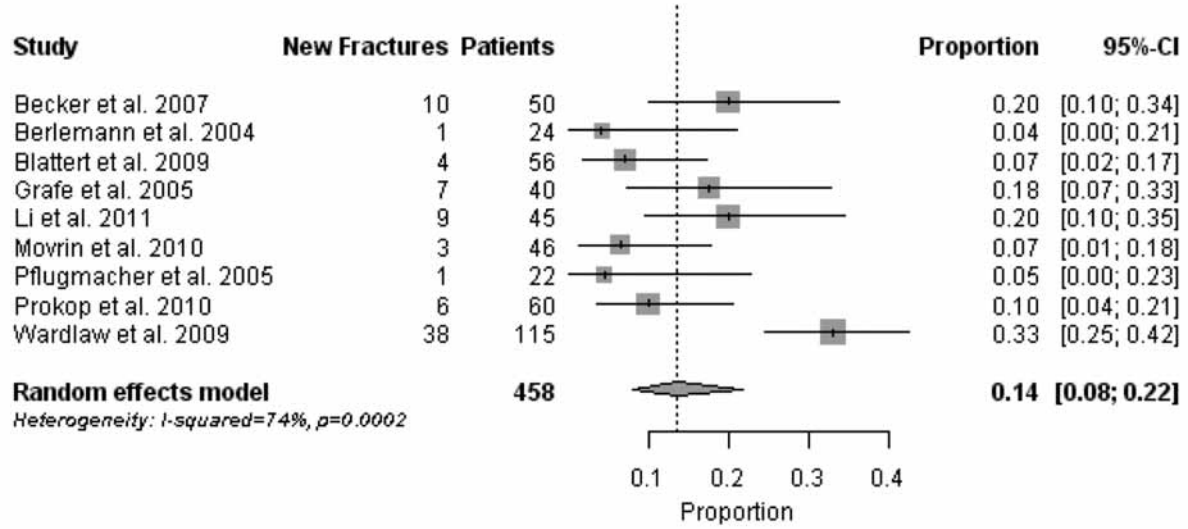

Fig. 3. — New vertebral fractures one year after kyphoplasty. Squares represent the proportion of new fractures. The size of the squares is proportional to the number of patients enrolled. Error bars represent the 95% confidence intervals (CIs). The diamond shape (bottom) represents the pooled estimate, with CI.

Table II. — Studies on new vertebral fractures one year after kyphoplasty

Author	Language	Number of treated patients	Number of treated vertebral bodies	Mainly affected area in spine	Amount of cement injected	Number of patients with vertebral fractures
Becker *et al*. 2007	English	50	50	thoracolumbar	2-6 ml	10
Berlemann *et al*. 2004	English	24	24	thoracolumbar	- - - - -	1
Blattert *et al*. 2009	English	56	50	thoracic + lumbar	5.8-8.9 ml	4
Grafe *et al*. 2005	English	40	73	- - - - -	- - - - -	7
Li *et al*. 2011	English	45	66	thoracolumbar	- - - - -	9
Movrin *et al*. 2010	English	46	51	thoracolumbar	4-8 ml	3
Pflugmacher *et al*. 2005	German	22	35	- - - - -	2-8.5 ml	1
Prokop *et al*. 2010	German	60	76	- - - - -	7 ml	6
Wardlaw *et al*. 2009	English	115	188	- - - - -	- - - - -	38

pared between vertebroplasty and conservative treatment (Fig. 4, bottom) (*2,23,33,46*). Analysis of these studies showed a large amount of heterogeneity, within and between the treatment groups, in terms of fracture age : from 2 months (*46*) to 12 months (*2*). Also the number of treated vertebral fractures per patient differed between the single studies : while Masala *et al* (*33*) injected on average a single level, Klazen *et al* (*23*) injected a mean of 2.4 fractures per patient. As known from the literature (Lindsay *et al*) (*30,45*), such differences in pre-existing vertebral fractures might affect the rate of new adjacent vertebral fractures. Furthermore, as demonstrated in table III, there was a lack of homogeneity also in terms of conducted osteoporosis therapy. For instance, Klazen *et al* (*23*) and Masala *et al* (*33*) offered an osteoporosis therapy to all their patients, while Alvarez *et al* (*2*) and Rousing *et al* (*46*) did not. These differences in additional medication might have affected the development of

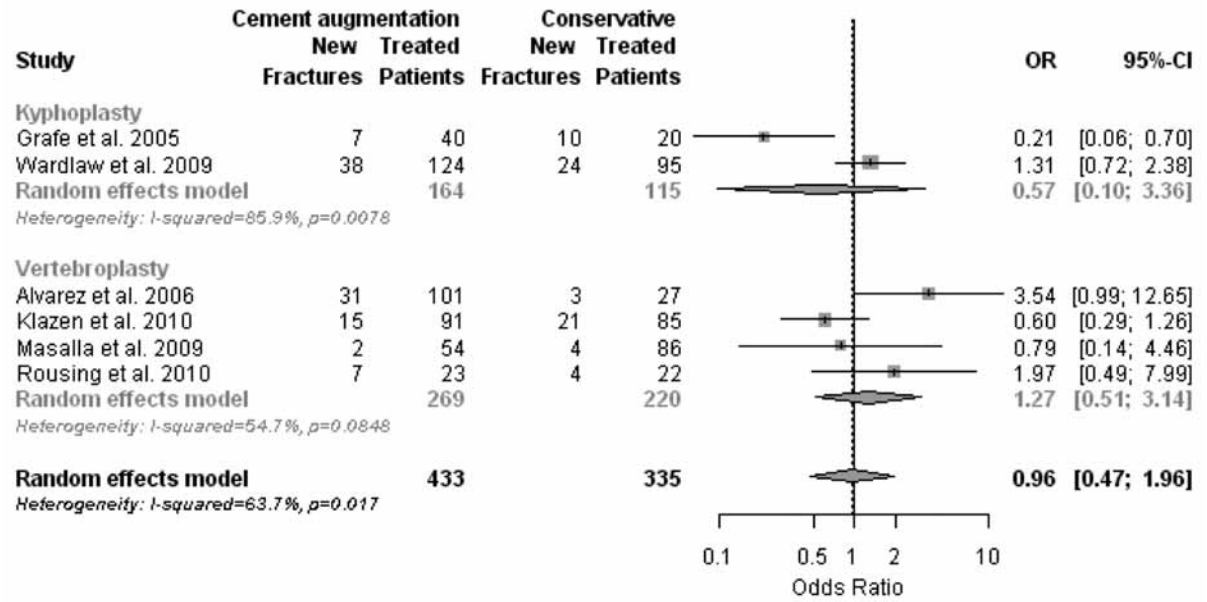

Fig. 4. — Cementation compared with conservative treatment. Squares represent the odds ratio (OR) for adjacent fractures between cement augmentation and conservative treatment. The error bars represent the 95% confidence intervals (CI). The size of the squares is proportional to the number of the patients enrolled. The random effects model gives a combined odds ratio (dotted line) and 95% CI (diamond shape). The dotted line is close to the solid line. The solid line indicates an odds ratio of 1, which would be the case if there would be no difference in the rates of new fractures between both groups. The diamond shape (bottom) represents the pooled estimate, with CI.

further vertebral fractures. Moreover, this heterogeneity made strict statistical computation impossible. The odds ratio between vertebroplasty and conservative treatment in these 4 studies was 1.27 (95% CI : 0.51-3.14) (Fig. 4).

Kyphoplasty versus conservative treatment : 2 studies

Grafe *et al* (*14*) and Wardlaw *et al* (*56*) were the only groups which compared kyphoplasty with conservative treatment, radiologically, after one year. Again, heterogeneity was a problem : Grafe *et al* used 50% PMMA cement and 50% calcium phosphate cement, while Wardlaw *et al* used PMMA cement (Table III). Biomechanical *in vitro* studies by Wilke *et al* (*58*) revealed that if cyclic loading is applied on vertebral bodies, PMMA seems to be more stable than calcium phosphate cement. In how far this increased rigidity results in an increased number of adjacent fractures is not clear yet. Again, this heterogeneity made strict statistical computation impossible. The odds ratio was 0.57 (95% CI : 0.10-3.36) (Fig. 4).

Vertebroplasty and kyphoplasty versus conservative treatment

The combined odds ratio of cement augmentation versus conservative treatment (Fig. 4) was 0.96 ; this might be interpreted as little difference between both groups.

Level of new fractures

According to the publications included in the present review, new vertebral fractures following vertebroplasty or kyphoplasty mainly occurred at the thoracolumbar junction (*2,3,6,9-11,15,21,26,37,38, 42,46,47,55*). Indeed, biomechanical analyses show that the thoracolumbar junction is more heavily burdened than other parts. This can lead to initial

Table III. — The 6 studies which compared cementation to conservative treatment

Study	Type of cementation	Randomized	Cement type	Fractures treated per patient, with cement	Fractures treated per patient, conservatively	Osteoporosis medication
Alvarez *et al*.	Vertebroplasty	no	PMMA	+/-1.5	+/-1.03	no
Klazen *et al*.	Vertebroplasty	yes	PMMA	+/-2.4	+/-2.1	yes
Masala *et al*.	Vertebroplasty	no	PMMA	+/-1	+/-1	yes
Rousing *et al*.	Vertebroplasty	yes	PMMA	+/-1.24	+/-1.33	no
Wardlaw *et al*.	Kyphoplasty	yes	PMMA	+/-1.43	+/-1.29	yes
Grafe *et al*.	Kyphoplasty	no	PMMA/calcium	+/-3.4*	+/-3.3*	yes

* rough estimate from available data.

vertebral fractures as well as to new fractures (*4,5,12, 16,27,39,43,49*). Strangely, this was not true in the conservatively treated control groups : no specific region of the spine was predisposed for the appearance of new vertebral fractures.

Amount of cement

In vertebroplasty the cement is injected with a needle. In kyphoplasty a balloon is first inflated in the fractured vertebral body generating a cavity which results in more space for the injected cement, after removal of the balloon. The amount of cement might have an effect on the occurrence of new vertebral fractures. However, in the 22 analyzed publications no significant differences in the cement volumes could be seen, due to the fact that the amount of injected cement was mainly reported in ranges.

Are new fractures simply caused by the natural evolution of osteoporosis ?

A biomechanical study by Villarraga *et al* (*53*) reported minimal stress and strain on spinal levels next to a cemented level. They suggested that new compression fractures are more likely the result of the progression of osteoporosis than of the intervention itself. The current study could not confirm this hypothesis, as the various publications were too heterogeneous to allow for strict statistical computation. But assuming that osteoporosis would be the main cause of those new vertebral fractures, an adequate anti-osteoporotic therapy and regular radiographic control is recommended (*9,28,56,61*). Therefore the diagnosis of osteoporosis should be confirmed with DEXA scanning (Dual Energy X-ray Absorptiometry).

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