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ORIGINAL
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The Association between the Duration of Preoperative Pain and Pain Improvement in Vertebral Augmentation: A Meta-Analysis

BACKGROUND AND PURPOSE: Most physicians consider length of preoperative pain as an important factor to include patients for SA. Our aim was to synthesize the available evidence regarding the influence of preprocedural pain duration on the outcome of vertebral augmentation procedures.

MATERIALS AND METHODS: The MEDLINE data base was reviewed up to March 2010. Meta-regression and mixed-effect subgroup analyses were performed to evaluate the association between the outcome of interest, which was pain improvement assessed by a VAS (0–10) and the duration of preoperative pain (independent variable).

RESULTS: We included 17 articles. The mean VAS improvements for subgroups of ≤ 6 weeks ($n = 12$), 6–24 weeks ($n = 5$), and > 24 weeks ($n = 3$) were 5.18, 4.90, and 5.04, respectively ($P = .86$). The regression coefficient was -0.024 , suggesting trivial association of the duration of preoperative pain and pain improvement.

CONCLUSIONS: Pain relief following spine augmentation was similar among groups of patients with varying lengths of preoperative pain duration.

ABBREVIATIONS: KP = kyphoplasty; NA = not applicable; SA = spine augmentation; VAS = visual analog scale; VP = vertebroplasty

Vertebral augmentation is widely applied for the treatment of painful vertebral compression fractures, both benign and malignant.^{1–10} Specific clinical and imaging selection criteria include duration and pattern of subjective pain; imaging characteristics on plain film, MR imaging, and CT; and findings on physical examination. Among these selection criteria, duration of pain has garnered substantial interest. When initially applied, vertebral augmentation was reserved for patients who had failed at least 4–6 weeks of conservative therapy. This waiting period was recommended, given the knowledge that in most patients, spontaneous osteoporotic compression fractures will heal without intervention during several weeks.

With increasing clinical experience, the indications for vertebral augmentation have expanded to include patients with relatively acute fractures. Indeed, some practitioners suggest that these early fractures represent the ideal candidates for augmentation and that more chronic fractures are poor candidates for intervention.^{11–14}

Several studies evaluated the impact of pain duration on the observed outcome following vertebral augmentation.^{15–17} Improved understanding of the impact of pain duration would help guide practitioners in selecting patients for augmentation. We conducted a systematic review and meta-analysis of the vertebral augmentation literature to synthesize the available evidence regarding the influence of preprocedural pain duration on the outcome of vertebral augmentation procedures.

Materials and Methods

A comprehensive review of the literature up to March 2010 was performed by 2 independent reviewers. “Vertebroplasty pain” and “kyphoplasty pain” were used as both controlled vocabulary and keywords to search MEDLINE by using the Ovid interface. The 2 reviewers discussed disagreements and reconciled their differences. The results were limited to case series, case-controlled studies, major clinical studies, clinical trials, and cohort studies. Inclusion criteria were the following: English language, > 50 patients, numeric VAS assessment for pre- and postoperative pain, and availability of the mean age of fracture or preoperative pain duration. The exclusion criteria were the following: case reports, in vitro or cadaveric studies, guidelines and general discussions, and technical notes.

The electronic search was supplemented by asking experts in the field and reviewing the bibliographies of included studies for relevant publications. Abstracts, methods, results, figures, and tables of full text were searched for pain questions, pre- and postoperative numeric pain scales and preoperative pain duration, and/or vertebral fracture age at the time of vertebral augmentation. Preoperative pain duration and age of fracture were considered interchangeable, because few studies distinguished these. Pain improvement was calculated on the basis of the pre- and postprocedural VAS (0–10) at 24 hours. Unfortunately, additional follow-up time points were incompletely reported among the identified studies.

To explore the impact of the mean duration of pain before intervention among studies, we grouped studies according to the mean preoperative pain duration (≤ 6 weeks, 6–24 weeks, and > 24 weeks) and compared pain improvement among these. We also evaluated the correlation between the age of fracture and pain improvement by using a VAS.

Studies that were not adjustable to any of the above categorizations were excluded. From comparative studies between vertebral augmentation and conservative therapy or placebo control, only augmentation arms were included. All original preoperative pain lengths

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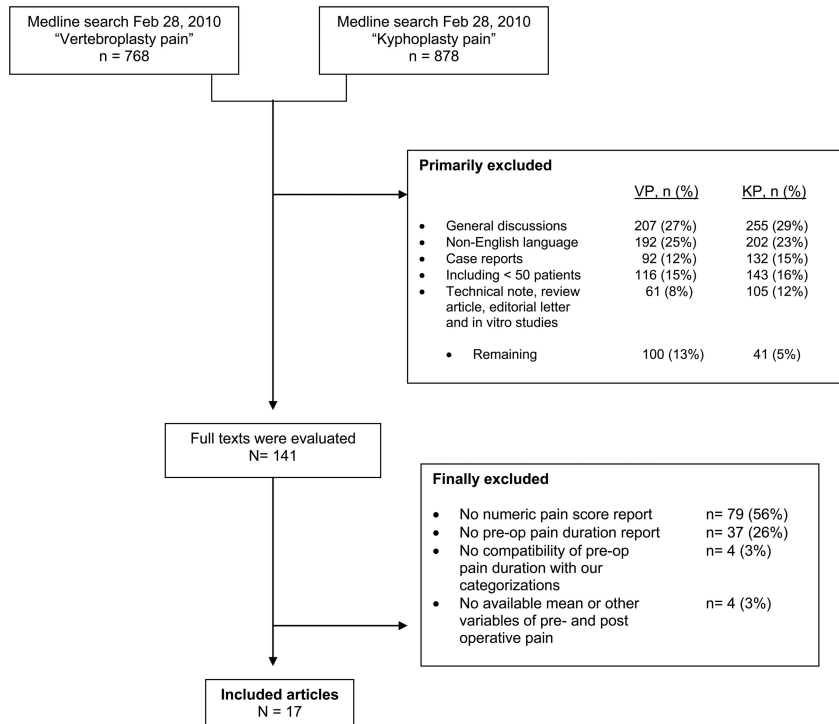


Fig 1. Inclusion of the final 17 articles.

Table 1: Characteristics of included studies

Authors	Study Design	SA Type	Patients (levels)	Preoperative Pain		Postoperative VAS ^a	Level of Evidence
				Age of Fracture	VAS		
Alvarez et al ¹	Prospective, double cohort	VP	101 (152)	5 Months	8.9	4.0	2
		Conservative	27 (28)	5.8 Months	7.3	7.3	
Chen et al ¹⁹	Retrospective	VP	70 (87)	8 Months	80 (0–100)	38 (0–100)	4
Diamond et al ²⁰	Prospective, non-randomized	VP	88 (133)	1–6 Weeks	20 (0–25)	8 (0–25)	2
		Conservative	38 (NA)	1–6 Weeks	20 (0–25)	19 (0–25)	
Garfin et al ²¹	Prospective single-arm interventional cohort	KP	155 (214)	128.5 Days	15 (0–20)	5 (0–20)	4
Kallmes et al ²⁸	Randomized double-blinded controlled trial	Placebo	63 (93)	20 Weeks	7.2	3.9	1
		VP	68 (95)	16 Weeks	6.9	4.2	
Kobayashi et al ²⁹	Prospective	VP	175 (250)	19 Days	7.2	2.1	4
Lee et al ³⁰	Retrospective	KP	105 (132)	4.5 Weeks	8.7	2.3	4
Liu et al ³¹	Randomized clinical trial	KP	50 (50)	15.8 Days	8.0	2.6	2
		VP	50 (50)	17 Days	7.9	2.3	
Prather et al ³²	Prospective	VP	50 (103)	14 Months	7.8	3.1	4
Rapan et al ³³	NA	VP	55 (85)	44 Days	8.36	2.23	4
Rhyne et al ²⁵	Retrospective	KP	52 (82)	31 Weeks	9.16	2.9	4
Rolloinghoff et al ³⁴	Prospective	KP	45 (53)	3 Weeks	8.6	3.4	2
		VP	45 (51)	3 Weeks	8.8	4.8	
Rousing et al ³⁵	Randomized clinical trial	Conservative	24 (32)	6.7 Days	8.8	NA	2
		VP	25 (31)	8.4 Days	7.5	2.0	
Schofer et al ³⁶	Prospective	KP	30 (30)	9.5 Days	8.2	3.2	2
		VP	30 (30)	10.5 Days	8.3	3.0	
Vogl et al ²⁶	Retrospective	VP	61 (NA)	19 Days	8.8	2.6	4
Voormolen et al ⁹	Prospective	VP	112 (168)	4 Months	8.8	3.3	4
Wardlaw et al ³¹	Randomized clinical trial	Conservative	151 (195)	6.4 Weeks	7.0	5.9	2
		KP	149 (214)	5.6 Weeks	6.9	3.6	

^a Visual Analog Scale.

Table 2: Demographics of categories with various preoperative pain durations^a

	≤6 Weeks ^{20,26,29-31,34-37}	6–24 Weeks ^{1,9,21,28,33}	>24 Weeks ^{19,25,32}
No. of included studies	12	5	3
No. of patients (mean) (SD, range)	71 (49, 25–175)	98 (39, 55–155)	57 (11, 50–70)
No. of levels (mean) (SD, range)	93 (78, 30–250)	143 (53, 85–214)	91 (11, 82–103)
Preoperative pain duration by week (mean) (SD, range)	2.7 (1.3, 1.2–5.6)	15.9 (5.7, 6.3–21.5)	42 (16, 31–60)

^a The studies^{11,13,15} that did not present a single number for preoperative pain or age of fracture were excluded from this calculation.

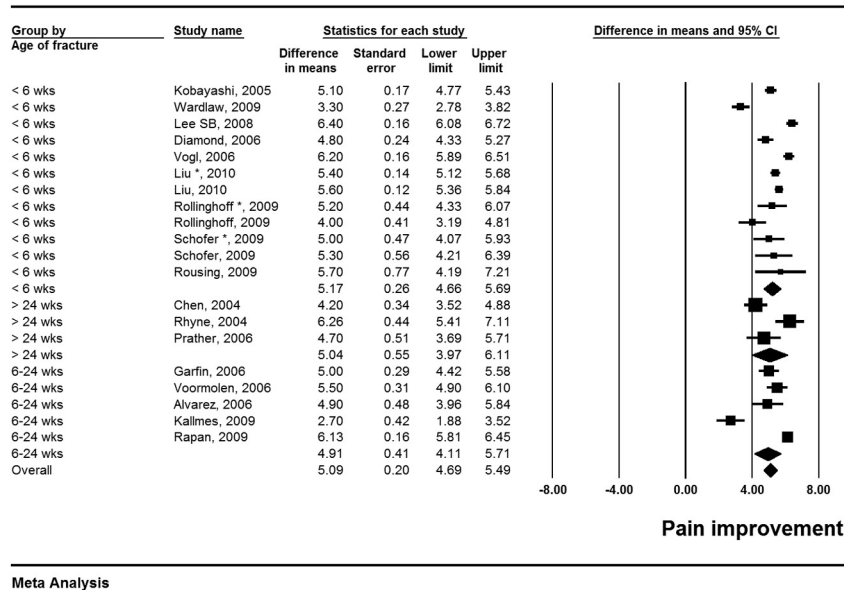


Fig 2. The forest plot shows subgroup analysis.

were converted to weeks, and numeric pain scores other than 0–10¹⁸⁻²² were converted to 0–10 scores.

Statistical Analysis

Statistical analysis was performed by using Comprehensive Meta-Analysis, Version 2 software (Biostat, Englewood, New Jersey). Continuous data, including mean pain improvement on the VAS, were pooled to calculate weighted mean differences with 95% confidence intervals. A random-effects model was used²³; subgroups were compared by using the Z-test. The null hypothesis was that the effect size was the same for all subgroups. I² was used to assess heterogeneity across studies.²⁴ The influence of sample size was assessed by funnel plots and the trim-and-fill method, and the presence of publication bias was assessed by the Egger regression test. A random-effects meta-regression was used to assess the preoperative pain duration covariate with pain improvement as a dependent variable. Publication bias was assessed by using the trim-and-fill model. We excluded 1 study²⁰ because preoperative pain was reported only as a range (<6 weeks) without a mean. SDs for 3 studies^{9,25,26} were calculated through other formulas.²⁷ Sensitivity analysis was performed by excluding every single study from the analysis to assess the robustness of final assumptions and by conducting a cumulative meta-analysis to explore how pre- and postoperative mean pain differences varied with increasing preoperative pain duration.

Results

Between July 1985 and March, 2010, 768 articles were retrieved by using the term “vertebroplasty pain” and 878 arti-

cles were found by using the term “kyphoplasty pain.” Fig 1 details the study-selection processes and the reasons for exclusion. The final cohort included 17 studies^{1,9,19-21,25,26,28-37} described in Table 1. Among these included studies, 6 (35%) reported age of fracture,^{21,28,29,32,35,37} 13 (76%) described preoperative pain duration,^{1,9,19,20,25,26,28,30,31,33,34,36,37} and 2 (12%) stated both.^{28,37}

There were 3 (18%) articles that compared vertebroplasty with kyphoplasty,^{31,34,36} 4 (24%) compared vertebroplasty with conservative therapy,^{1,20,28,35} and 1 (6%) compared kyphoplasty with conservative therapy.³⁷ Six (35%)^{9,19,26,29,32,33} of 17 articles included exclusively vertebroplasty procedures, while 3 (18%) studies reported kyphoplasty procedures exclusively.^{21,25,30} We included 1516 patients and 2010 treated levels through 20 treatment arms of 17 studies. The mean (±SD) number of patients and levels was 76 (43.8) and 106 (67.6), respectively, per study. The median follow-up was 12 months (range, 3–24 months).^{21,33,35} The characteristics of each subgroup are shown in Table 2.

For the meta-analysis, the Q-statistic was 0.311 with *df* = 2 and *P* = .86 (Fig 2). Thus, we cannot reject the null hypothesis that the effect size is the same for all 3 groups (Table 3).

With the random-effects model, the raw mean difference (pain improvement) for 19 studies was 5.10 VAS with a confidence interval of 4.70–5.50, which yields a Z value of 24.860 (2-tailed *P* < .001). Because of the weak correlation, the null hypothesis of no linear relation between the length of pain and pain improvement was rejected.

Within-group heterogeneity expressed by using the I² statistic was quite high: 92.61%, 93.81%, and 95.74% for studies

Table 3: Details of meta-analysis under the random-effects model

	Point Estimate	Standard Error	Variance	Lower Limit	Upper Limit	Z value	P value
≤6 Weeks	5.18	0.263	0.069	4.66	5.70	19.683	<.001
6–24 Weeks	4.90	0.406	0.165	4.11	5.70	12.081	<.001
>24 Weeks	5.04	0.547	0.299	3.97	6.11	6.110	<.001

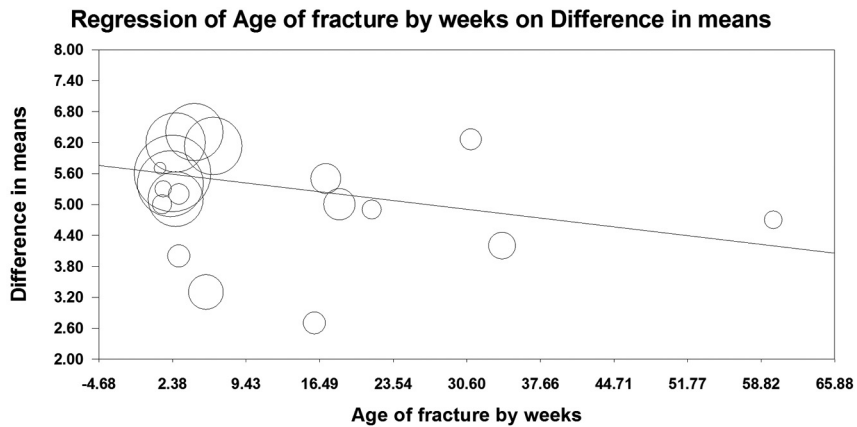


Fig 3. The linear correlation between preoperative pain duration and pain improvement is shown.

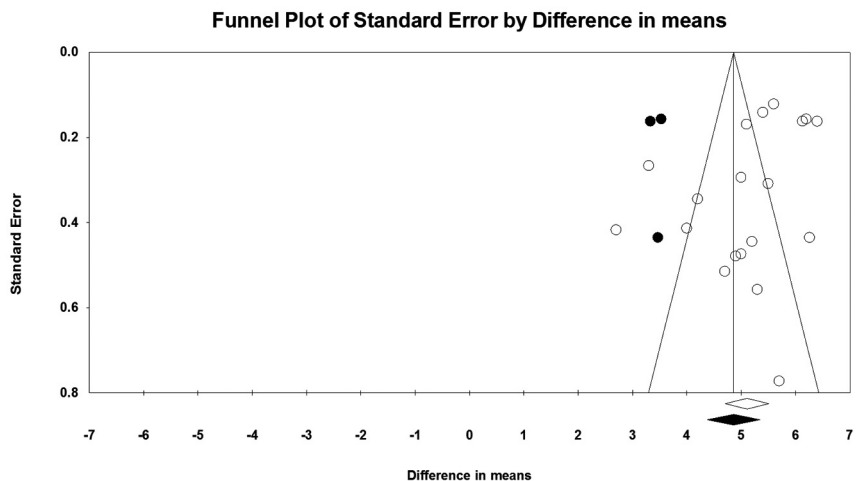


Fig 4. Publication bias among studies is shown.

with <6 weeks', 6–24 weeks', and >24 weeks' preoperative pain. The regression coefficient for preoperative pain duration was -0.024 , which indicates that for each 1-week increase in the length of preoperative pain, the VAS in pain improvement decreased by 0.024 (Fig 3). The model and residual Q were 16.43 and 208.23, respectively. The clinical significance of this trivial correlation is unclear. There were 3 missing studies on the left of the mean in the funnel plot (Fig 4). Adjusted mean pain improvement was 4.9 (4.4–5.3) and $Q = 510.9$. The cumulative meta-analysis shows how increase in the age of fracture from the shortest preoperative pain duration³⁵ to the longest one³² shifts pain improvement among studies (Fig 5).

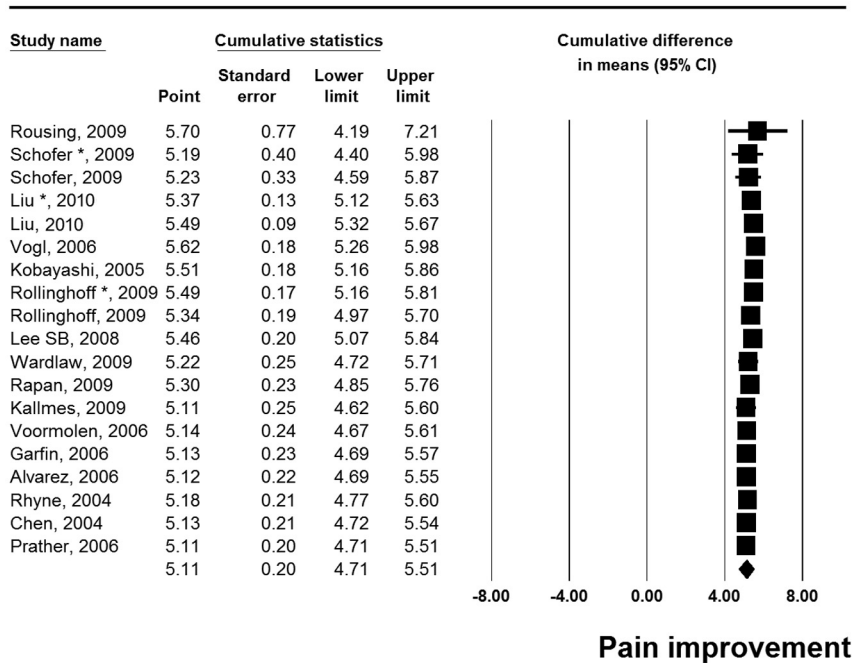
The impact of sample size is shown in cumulative meta-analysis from the biggest sample size study²⁹ to the smallest one (Fig 6).³⁵ The Egger regression test for publication bias was significant ($P = .03$), suggesting the presence of publication bias.

In sensitivity analysis, the final outcome did not depend on any single study result.

Discussion

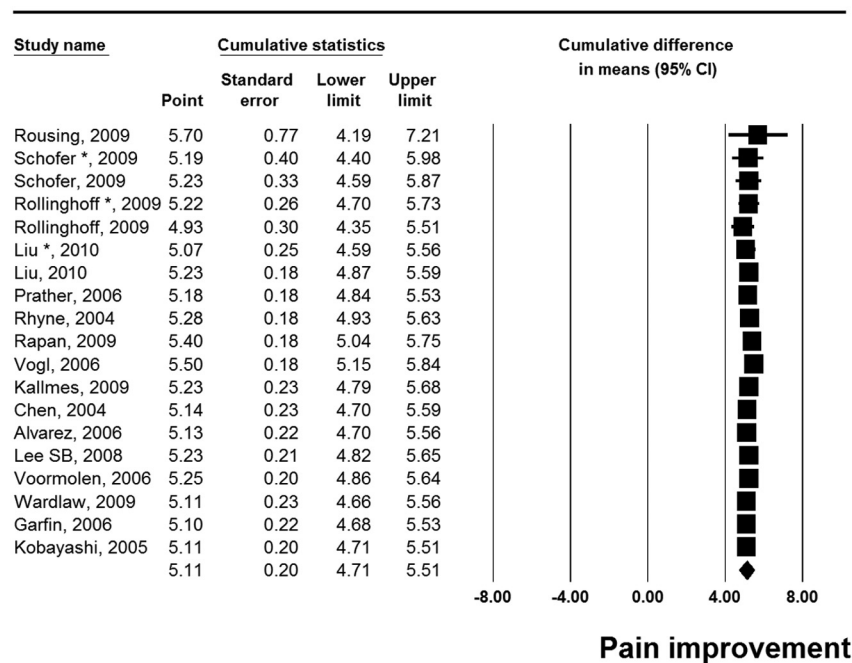
We conducted a meta-analysis that showed that vertebral augmentation is associated with significant reduction in back pain. However, we did not find any significant difference in pain improvement among subgroups with different preoperative pain durations. There was also a weak negative correlation between the age of fracture and immediate pain improvement after vertebral augmentation. The clinical significance of this slight correlation remains unclear. Thus, it seems that the age of fracture does not affect the outcome of vertebral augmentation; therefore, a wider range of patients could be referred for the procedure.

One prior study has shown that early treatment was correlated with greater patient satisfaction with the outcome. Un-



Meta Analysis

Fig 5. The cumulative meta-analysis shows the influence of increasing preoperative pain duration on the outcome of the study.



Meta Analysis

Fig 6. The cumulative meta-analysis shows the influence of increasing sample size on the outcome of the study.

fortunately, the metric of “satisfaction with care” is rarely reported in the spine-augmentation literature. Future studies should include this specific outcome.³⁸

Treatment of acute fractures might seem to be the ideal paradigm because pain in these fractures may be maximal. However, the few controlled studies currently available regarding acute fracture treatment have shown identical out-

comes between patients treated with augmentation versus those treated conservatively.^{20,35} The noted similar improvements between groups in those studies may relate to the natural history of vertebral fracture pain, which shows substantial improvement in the conservatively managed patient groups.

The limitations of this study mainly relate to ecologic bias (ie, comparisons are made across studies and not within stud-

ies), the presence of publication bias and statistical heterogeneity, and the methodologic limitations of the included studies (lack of random allocation, small sample size, and incomplete baseline and follow-up data). Another limitation relates to the inclusion of only English language literature. However, we attempted to minimize this limitation by asking experts in the field about relevant studies to complement our search strategy.

Conclusions

Pain relief following SA was similar among groups of patients with varying lengths of preoperative pain duration.

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