Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial

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Lancet 2009; 373: 1016–24

Published Online February 25, 2009 DOI:10.1016/S0140-6736(09)60010-6

See Comment page 982

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Summary

Background Balloon kyphoplasty is a minimally invasive procedure for the treatment of painful vertebral fractures, which is intended to reduce pain and improve quality of life. We assessed the efficacy and safety of the procedure.

Methods Adults with one to three acute vertebral fractures were eligible for enrolment in this randomised controlled trial at 21 sites in eight countries. We randomly assigned 300 patients by a computer-generated sequence to receive kyphoplasty treatment (n=149) or non-surgical care (n=151). The primary outcome was the difference in change from baseline to 1 month in the short-form (SF)-36 physical component summary (PCS) score (scale 0–100) between the kyphoplasty and control groups. Quality of life and other efficacy measurements and safety were assessed up to 12 months. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00211211.

Findings 138 participants in the kyphoplasty group and 128 controls completed follow-up at 1 month. By use of repeated measures mixed effects modelling, all 300 randomised participants were included in the analysis. Mean SF-36 PCS score improved by 7·2 points (95% CI 5·7–8·8), from 26·0 at baseline to 33·4 at 1 month, in the kyphoplasty group, and by 2·0 points (0·4–3·6), from 25·5 to 27·4, in the non-surgical group (difference between groups 5·2 points, 2·9–7·4; p<0·0001). The frequency of adverse events did not differ between groups. There were two serious adverse events related to kyphoplasty (haematoma and urinary tract infection); other serious adverse events (such as myocardial infarction and pulmonary embolism) did not occur perioperatively and were not related to procedure.

Interpretation Our findings suggest that balloon kyphoplasty is an effective and safe procedure for patients with acute vertebral fractures and will help to inform decisions regarding its use as an early treatment option.

Funding Medtronic Spine LLC.

Introduction

Every year an estimated 1·4 million vertebral compression fractures that cause pain and disability and diminish quality of life[1,2] come to clinical attention worldwide.[3] Despite non-surgical management, including analgesia, bed rest, physiotherapy, and back bracing, pain sometimes resolves slowly, and can persist.[4] The resulting vertebral deformity can cause height loss, kyphosis, reduced pulmonary function, and mobility and balance impairment.[4–6] Vertebral fracture is associated with an increased risk of future fractures.[7]

Since conventional open surgery for vertebral fractures is associated with risks resulting from open reduction and internal fixation, it is usually reserved for fractures that cause neurological impairment. Balloon kyphoplasty is a minimally invasive procedure that is intended to reduce pain, disability, and vertebral deformity by use of catheters with inflatable bone tamps placed inside the affected vertebral body. Balloon inflation compacts the cancellous bone and pushes the endplates apart, which might partly restore height and correct angular deformity.[8] Once the balloons have been removed, the resulting void is filled with viscous bone cement to stabilise the vertebral body. The procedure can be done under general anaesthesia or conscious sedation, either as a day case, or with an overnight stay, dependent on medical need. Although investigators have reported reduced pain and improved function after kyphoplasty treatment,[9–11] there are no data from randomised trials assessing its efficacy and safety. We compared the efficacy and safety of kyphoplasty with non-surgical management for the treatment of acute vertebral compression fractures, to test the hypothesis that kyphoplasty would result in increased improvement in quality of life.

Methods

Participants

We undertook a randomised controlled trial (Fracture Reduction Evaluation [FREE] trial) at 21 sites in eight countries between February, 2003, and December, 2005. Patients were eligible for enrolment if they had one to three vertebral fractures from T5 through L5. At least one fracture needed to have oedema assessed by MRI and at least one had to show a 15% loss of height or more; single fractures were to meet both these criteria. Patients with fractures due to osteopenia arising from

primary or secondary osteoporosis, multiple myeloma, or osteolytic metastatic tumours were included. Painful fractures were diagnosed by investigators; patients with up to three contiguous or non-contiguous fractures at any level could be included in the study if these additional fractures also had MRI signal changes, progressive height loss, or pseudoarthrosis. Participants also had to have a back pain score of 4 points or more on a 0–10 scale.

Patients were excluded if they were younger than 21 years of age; had chronic fractures (estimated fracture age more than 3 months), pedicle fracture, previous vertebroplasty, neurological deficit, radicular pain, spinal cord compression, or canal narrowing; were taking uninterruptible anticoagulation therapy; had allergies to kyphoplasty materials or contraindications to MRI; had dementia or were unable to walk before fracture (walking aids were allowed); or if their vertebral fractures were from primary bone tumours, osteoblastic metastases, or high energy trauma.

Participants gave written informed consent before enrolment. The protocol and consent form were approved by local ethics committees.

Procedures

We randomly assigned study participants to receive kyphoplasty treatment or non-surgical care. Computer-generated randomisation was stratified by sex, aetiology, current treatment with corticosteroids, and any bisphosphonate treatment within 12 months before enrolment. A permuted block randomisation (stratified as indicated) was generated before the study start by Advanced Research Associates, (Mountain View, CA, USA), the statistical contract research organisation, by use of SAS PROC PLAN.

Kyphoplasty was done with introducer instruments, inflatable bone tamps, and polymethylmethacrylate bone cement and delivery devices (manufactured by Medtronic Spine LLC, Sunnyvale, CA, USA), by a percutaneous, bilateral, transpedicular, or extrapedicular approach.[12] Most procedures were done under general anaesthesia. Six patients had conscious or deep sedation with local anaesthesia.

All participants received analgesics, bed rest, back braces, physiotherapy, rehabilitation programmes, and walking aids according to standard practices of participating hospitals. Investigators referred participants for treatment with calcium and vitamin D supplements and antiresorptive or anabolic agents. Subsequent clinical fractures were to be treated according to original assignment.

The primary endpoint was the difference in change from baseline to 1 month in the short-form (SF)-36 physical component summary (PCS) scale between the kyphoplasty and control groups. The SF-36 PCS is a validated global quality-of-life measure weighted on physical abilities. Although scaled from 0 to 100, the expected range is between 8 and 59 points for participants aged over 65 years.[13] Prespecified secondary outcome measures at 1, 3, 6, and 12 months after randomisation were SF-36 subscales (scaled 0–100); the 0–1-point EuroQol-5D (EQ-5D) quality-of-life questionnaire;[14] self-rated back pain (average pain in past week) on a 0 (no pain) to 10 (worst pain imaginable) visual-analogue scale;[15] back function by the 0–24-point Roland–Morris scale;[16] and restricted activity days and bed rest because of back pain during the previous 14 days.[17] Back pain and analgesic use were also assessed 5–10 days after randomisation (control group) or after surgery. All adverse events and serious adverse events, defined per ISO14155, were reported; investigators assessed whether they were related to device or procedure. Investigators informed both the study sponsor and local ethical committees/institutional review boards of any serious adverse events or serious adverse device effects. Dan Jolivette (Medtronic Spine LLC, Sunnyvale, CA, USA) reviewed (in conjunction with the late Olof Johnell) all safety issues related to the trial; data were reviewed on a 6-month basis throughout the trial. All adverse events were categorised by body system according to MedDRA.[18]

Standing lateral spinal radiographs were taken at baseline, 3 months, and 12 months. Two radiologists independently made semiquantitative[19] and quantitative morphometric[20] assessments at a central laboratory (Bio-Imaging Technologies Inc, Newtown, PA, USA). A new or worsening fracture was defined by consensus that deformity increased by 1 Genant grade or more.[19] Genant is a semiquantitative assessment that describes normal vertebrae (grade 0) or mild (grade 1, 20–25%), moderate (grade 2, 25–40%), or severe (grade 3, more than 40%) deformity in any vertebral vertical dimension. The readings from the two radiologists were highly concordant (κ=0·80). If semiquantitative readings differed, a decrease of 20% and 4 mm in any vertical dimension[2] or a third expert resolved disagreements.[21] Because bone cement is radio-opaque, we could not blind treatment assignment. Bone cement extravasation was assessed by investigators with intraoperative fluoroscopy and postoperative radiographs and included vertebrae with any noticeable cement outside the vertebral borders.

Statistical analysis

From a pilot study of 42 patients randomised to kyphoplasty or non-surgical treatments, 75 patients per group provided 80% power with a two-sided α of 5% to detect a 0·5 SD for the 1-month difference in change for the SF-36 PCS score. To compensate for possible loss, 300 patients were enrolled. At least 200 patients with fractures caused by osteoporosis were needed to focus the study on osteoporosis-related fractures without excluding other causes such as fractures related to cancer.

Endpoints were analysed by intention to treat, including all data available from all (300) randomised patients. We

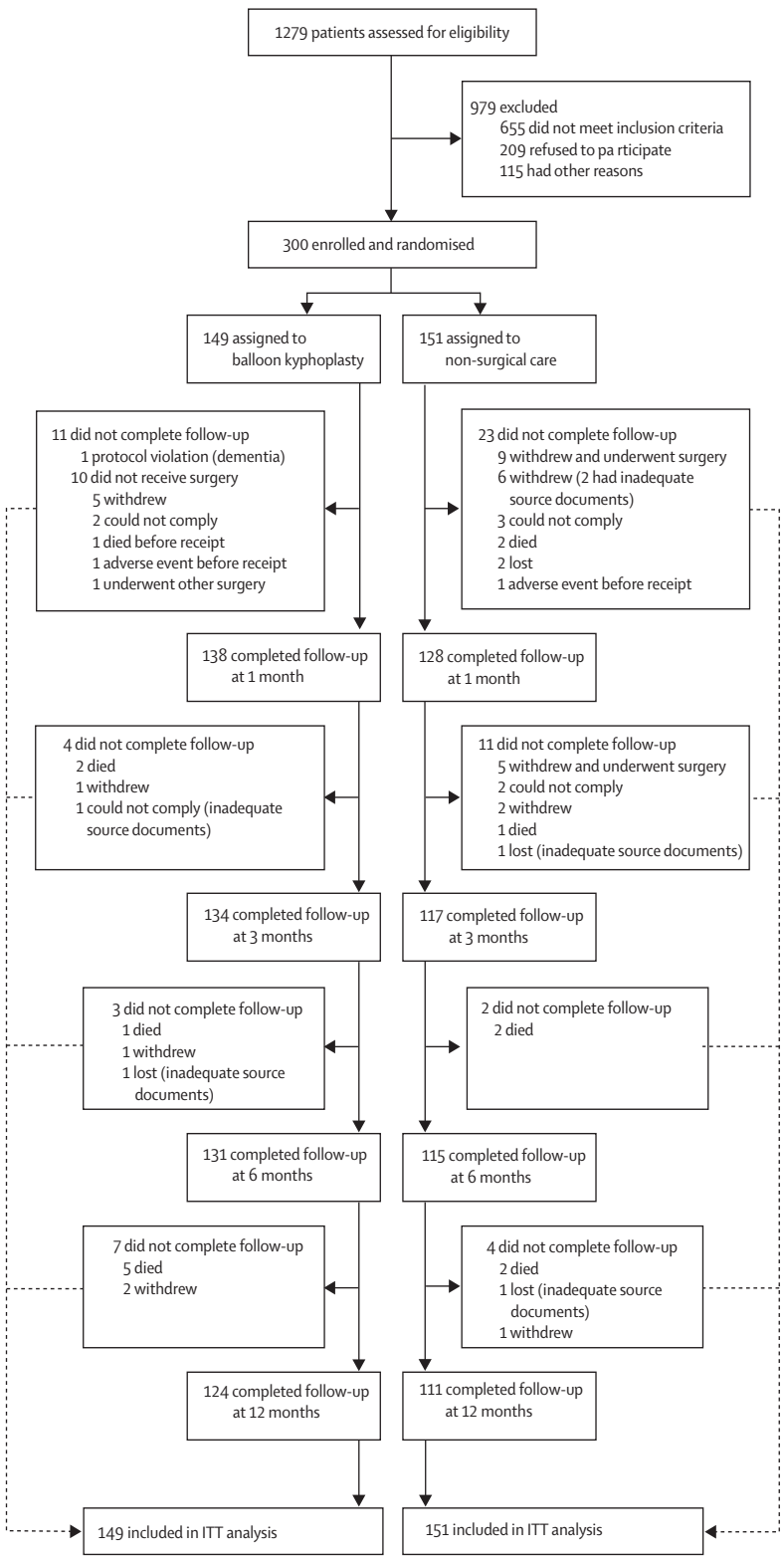

Figure 1: **Trial profile**
Notes in parentheses are patients considered protocol violations.

used repeated measures analysis of variance with mixed models that assumed a compound symmetry covariance structure to undertake an analysis of the primary and secondary endpoints of the full analysis set, which contained unbalanced data (ie, some patients had missing data at some timepoints).[22] Treatment, visit (ie, hospital appointment), and treatment by visit interaction were included in the model. Analyses of difference (between groups) in change from baseline scores included baseline as a covariate. We used the *t*-test to compare the calculated means at every timepoint. Patient proportions (adverse events, drugs, baseline fractures) were compared by the stratified Cochran-Mantel-Haenszel χ^2 test. All analyses included randomisation stratification factors as covariates; no adjustments were made for multiple tests.[23]

Because not all vertebrae were readable by radiologists, the frequency of new or worsening fractures, including worsening index fractures, was analysed in participants with data available for at least seven vertebrae (T5 to L5) at baseline and 12 months; the proportion of patients with subsequent fractures was tested with Fisher's Exact test. SAS version 8.0 was used for all statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT00211211.

Role of the funding source

Medtronic Spine LLC (JBT, KT, Dan Jolivette) contributed to study design, data monitoring, and reporting of results, and paid for statistical analysis (Advanced Research Associates Inc, Mountain View, CA, USA). All authors had complete access to data and provided all analyses requested. An independent statistician (JR) received the entire data set and verified the statistical analyses and the primary endpoint data by comparing a 10% random sample with case report forms. The publication committee (DW, SRC, JVM, LB, RE, JR, and SB), which did not include the sponsor, reviewed and approved the final version and had final responsibility for the decision to submit for publication.

Results

300 patients were screened and randomly assigned to balloon kyphoplasty (n=149) or non-surgical care (n=151; figure 1). Table 1 shows the baseline characteristics of the enrolled participants. Of the ten patients assigned to kyphoplasty treatment who did not have the procedure, one underwent vertebroplasty because the investigator judged that kyphoplasty was no longer feasible (figure 1). 14 patients assigned to the control group withdrew and underwent surgery; five of these patients had 1-month assessments. There were no differences in baseline SF-36 PCS, EQ-5D, Roland–Morris, or back pain scores, or in the number of baseline fractures between those who completed 12-month follow-up and those who discontinued (data not shown). There were also no differences in these

measures between the 15 patients who underwent surgery different from that assigned and the participants who received assigned treatment (data not shown).

For the primary outcome measure, eight patients had missing baseline data, 39 had missing 1-month data (34 terminated and five did not complete SF-36), and 75 had missing 12-month data (65 terminated and ten did not complete SF-36). Two participants in each group had all data missing. Eleven patients included in the dataset violated the protocol (three kyphoplasty and six control patients with inadequate source documents, one kyphoplasty patient had dementia, and one had an unfractured vertebral body treated). All 300 randomised participants were included in the intention-to-treat analysis by use of mixed effects modelling that includes patients with incomplete follow-up data.

Fractures were a mean of 5·6 weeks (SD 4·4) old at randomisation in the kyphoplasty group and 6·4 weeks (5·2) old in the non-surgical group. At baseline, of 338 index vertebrae that were available for Genant assessment, 236 (70%; kyphoplasty n=113, control n=123) were grade 2 or more (more than 25% deformity) and 99 (29%; kyphoplasty n=49, control n=50) were grade 3 (more than 40% deformity). The mean time between randomisation and kyphoplasty procedure was 6·8 days (4·5) and 1-month assessments were made 28·8 days (8·9) after surgery. 1-month assessments were made a mean of 35·6 days (8·9) and 32·5 days (7·4) after randomisation for the kyphoplasty and control groups, respectively.

More patients in the control group received walking aids, back braces, physical therapy, and analgesics during follow-up than did patients in the kyphoplasty group. Similar proportions of patients in each group received treatments for osteoporosis (table 2).

The improvement in mean SF-36 PCS score from baseline to 1 month was 5·2 points (95% CI 2·9–7·4) more in the kyphoplasty group than in the non-surgical group (p<0·0001; figure 2). The mean differences in improvement between the groups were 4·0 points (1·6–6·3; p=0·0008), 3·2 points (0·9–5·6; p=0·0064), and 1·5 points (–0·8 to 3·9; p=0·208) at 3, 6, and 12 months, respectively. The SF-36 PCS score improved during the year by a mean of 3·5 points (1·6–5·4; p=0·0004 *vs* control) more in the kyphoplasty group than in controls. There was a significant interaction between treatment and follow-up time (p=0·0104); this interaction suggests that the treatment effect over the year was not uniform across follow-up because of an early improvement in the kyphoplasty group.

Compared with controls, the kyphoplasty group had greater improvements in quality of life as assessed by the EQ-5D questionnaire from baseline to 1 month (difference between groups 0·18 points, 0·08–0·28; p=0·0003) and from baseline to 12 months (0·12 points, 0·01–0·22; p=0·0252; figure 2). The Roland–Morris score improved by 4·0 points (2·6–5·5; p<0·0001) and 2·6 points (1·0–4·1; p=0·0012) more in the kyphoplasty group than in the non-surgical group at 1 month and 12 months, respectively. Patients in the kyphoplasty group reported 2·9 fewer days of restricted activity per 2 weeks (1·3–4·6; p=0·0004) because of back pain at 1 month than did controls, although the difference in improvement was no longer significant at 12 months (1·6 days, –0·1 to 3·3; p=0·0678). A mean of 2·5 fewer days of restricted activity per 2 weeks (1·2–3·8; p<0·0001) was reported during the year for patients in the kyphoplasty group than in controls.

Back pain score decreased by 2·2 points (1·6–2·8; p<0·0001) more in the kyphoplasty group than in controls at 1 week and by 0·9 points (0·3–1·5; p=0·0034) after 12 months (figure 2). The kyphoplasty group also had a greater reduction than had controls in the percentage of patients needing narcotic analgesics between 1 month and 6 months (figure 2).

Several SF-36 subscale scores improved more in the kyphoplasty group than in the non-surgical group. Averaged across 12 months, patients assigned to kyphoplasty had greater improvements than controls for body pain (difference between groups 9·2 points, 3·9–14·6; p=0·0008), role physical (12·5, 4·8–20·2; p=0·0016), vitality (5·2, 0·2–10·1; p=0·0399), and social function

	Kyphoplasty (N=149)	Control (N=151)
Age (years)	72·2 (9·3)	74·1 (9·4)
Female	115 (77%)	117 (77%)
Underlying cause		
Primary osteoporosis	145 (97%)	143 (95%)
Secondary osteoporosis	2 (1%)	6 (4%)
Multiple myeloma/metastatic	2 (1%)	2 (1%)
Bisphosphonate use for stratification	49 (33%)	49 (32%)
Glucocorticoid use	26 (17%)	26 (17%)
Baseline fractures		
One	100 (67%)	115 (76%)
Two	34 (23%)	28 (19%)
Three	15 (10%)*	8 (5%)
Baseline fracture location†		
Thoracic (T5–T9)	49 (23%)	41 (21%)
Thoracolumbar junction (T10–L2)	127 (59%)	130 (67%)
Lumbar (L3–L5)	38 (18%)	24 (12%)
Treated fractures per patient		
None‡	10 (7%)	N/A
One	100 (67%)	N/A
Two	29 (19%)	N/A
Three	10 (7%)	N/A

Data are n (%) or mean (SD). N/A=not applicable. Groups were similar at baseline with the exception of multiple fractures. *One patient had a fourth index fracture identified between screening and planned surgery. †Kyphoplasty N=214, control N=195 (ie, number of index fractures identified at baseline). ‡Ten kyphoplasty patients did not receive surgery.

Table 1: **Patient characteristics**

	Kyphoplasty			Control		
	Baseline	1 month	12 months	Baseline	1 month	12 months
Non-pharmacological medical therapies	105/148 (71%)	45/136 (33%)	32/121 (26%)	109/151 (72%)	79/129 (61%)	44/107 (41%)
Walking aids	49/148 (33%)	33/136 (24%)	30/121 (25%)	55/151 (36%)	54/129 (42%)	38/107 (36%)
Back braces	21/148 (14%)	9/136 (7%)	3/121 (2%)	23/151 (15%)	26/129 (20%)	8/107 (7%)
Miscellaneous aids*	19/148 (13%)	9/136 (7%)	4/121 (3%)	16/151 (11%)	16/129 (12%)	6/107 (6%)
Bed rest (≥1 day per 14 days)	85/146 (58%)	30/133 (23%)	5/120 (4%)	92/144 (64%)	51/121 (42%)	8/106 (8%)
Physical therapy	17/148 (11%)	13/136 (10%)	4/121 (3%)	19/151 (13%)	23/129 (18%)	5/107 (5%)
Analgesics	132/140 (94%)	81/114 (71%)	61/117 (52%)	135/146 (92%)	105/115 (91%)	69/101 (68%)
None	8/140 (6%)	33/114 (29%)	56/117 (48%)	11/146 (8%)	10/115 (9%)	32/101 (32%)
Non-opioid	29/140 (21%)	28/114 (25%)	28/117 (24%)	36/146 (25%)	31/115 (27%)	35/101 (35%)
Combination (non-opioid and opioid)	81/140 (58%)	47/114 (41%)	28/117 (24%)	82/146 (56%)	65/115 (57%)	29/101 (29%)
Strong opioid	22/140 (16%)	6/114 (5%)	5/117 (4%)	17/146 (12%)	9/115 (8%)	5/101 (5%)
Osteoporosis therapies						
Bisphosphonates	63/149 (42%)	103/141 (73%)	98/124 (79%)	70/151 (46%)	97/135 (72%)	85/112 (76%)
≥3-month bisphosphonate use	21/149 (14%)	20/141 (14%)	95/124 (77%)	23/151 (15%)	24/135 (18%)	83/112 (74%)
≥12-month bisphosphonate use	13/149 (9%)	12/141 (9%)	77/124 (62%)	16/151 (11%)	14/135 (10%)	63/112 (56%)
Vitamin D	60/149 (40%)	104/141 (74%)	103/124 (83%)	77/151 (51%)	96/135 (71%)	90/112 (80%)
Calcium	69/149 (46%)	111/141 (79%)	106/124 (85%)	83/151 (55%)	101/135 (75%)	98/112 (88%)
Oestrogen-receptor modulators	2/149 (1%)	3/141 (2%)	2/124 (2%)	6/151 (4%)	5/135 (4%)	3/112 (3%)
Calcitonin	2/149 (1%)	0/141 (0)	0/124 (0)	6/151 (4%)	4/135 (3%)	1/112 (1%)
Parathyroid hormone	0/149 (0)	0/141 (0)	1/124 (1%)	1/151 (1%)	1/135 (1%)	5/112 (4%)

Data are n/N (%). Patients might have received more than one treatment. *For example, wheelchairs, hospital beds, transcutaneous electrical nerve stimulation, or crutches.

Table 2: **Non-surgical treatments received in kyphoplasty and non-surgical care groups**

(11·4, 4·0–18·9; p=0·0026). There was no significant treatment–time interaction for these outcomes. For physical function, the interaction was significant (p=0·0381); the kyphoplasty treatment effect for physical function was 9·3 points (2·4–16·2; p=0·0081) at 1 month and 1·9 points (–5·2 to 9·0; p=0·603) at 12 months.

During follow-up, 21 (14%) participants in the kyphoplasty group had new clinical vertebral fractures; nine (6%) underwent additional kyphoplasty (six within 3 months and three more within 6 months of initial treatment).

Plain radiographs were available for 143 (96%) and 140 (93%) participants at baseline, 130 (87%) and 107 (71%) at 3 months, and 120 (81%) and 103 (68%) at 12 months in the kyphoplasty and non-surgical groups, respectively. Of these, 115 who underwent kyphoplasty and 95 controls had data available for at least seven vertebrae at baseline and 12 months. At 12 months, 38 of 115 (33%) patients in the kyphoplasty group and 24 of 95 (25%) in the non-surgical group had new or worsening radiographic vertebral fractures (7·7% difference, 95% CI –4·5 to 20·0; p=0·220).

The overall frequencies of adverse events (table 3) did not differ between the kyphoplasty and control groups. About a third of patients in each group had a serious adverse event, none of which occurred perioperatively; five kyphoplasty patients had myocardial infarction and three had pulmonary embolism (earliest occurrence 46 days postoperative). Thus, there were no procedure-related or device-related myocardial infarctions, pulmonary embolisms, neurological injuries, or deaths. Two serious adverse events were attributed to kyphoplasty; a soft tissue haematoma at the surgical site and a postoperative urinary tract infection that needed intervention. Cement extravasation occurred in 51 (27%) of 188 vertebrae treated in 48 patients; all cases were asymptomatic. Most were endplate or discal leakages; there was one foraminal leakage and none to the spinal canal and no cement embolisms.

Discussion

This randomised controlled trial showed that in patients with acute, painful, vertebral fractures, balloon kyphoplasty improved quality of life, function, mobility, and pain more rapidly than did non-surgical management, with significant differences in improvement between the groups at 1 month. For most outcome measures, the differences between kyphoplasty treatment and control were diminished at 12 months because the non-surgical group improved over time, probably as a result of fracture healing. There were two serious adverse events related to kyphoplasty treatment (haematoma and urinary tract infection); other serious adverse events (such as myocardial infarction and pulmonary embolism) did not occur perioperatively and were not related to procedure. Kyphoplasty treatment did not result in a significant increase in new radiographic vertebral fractures at 1 year compared with controls.

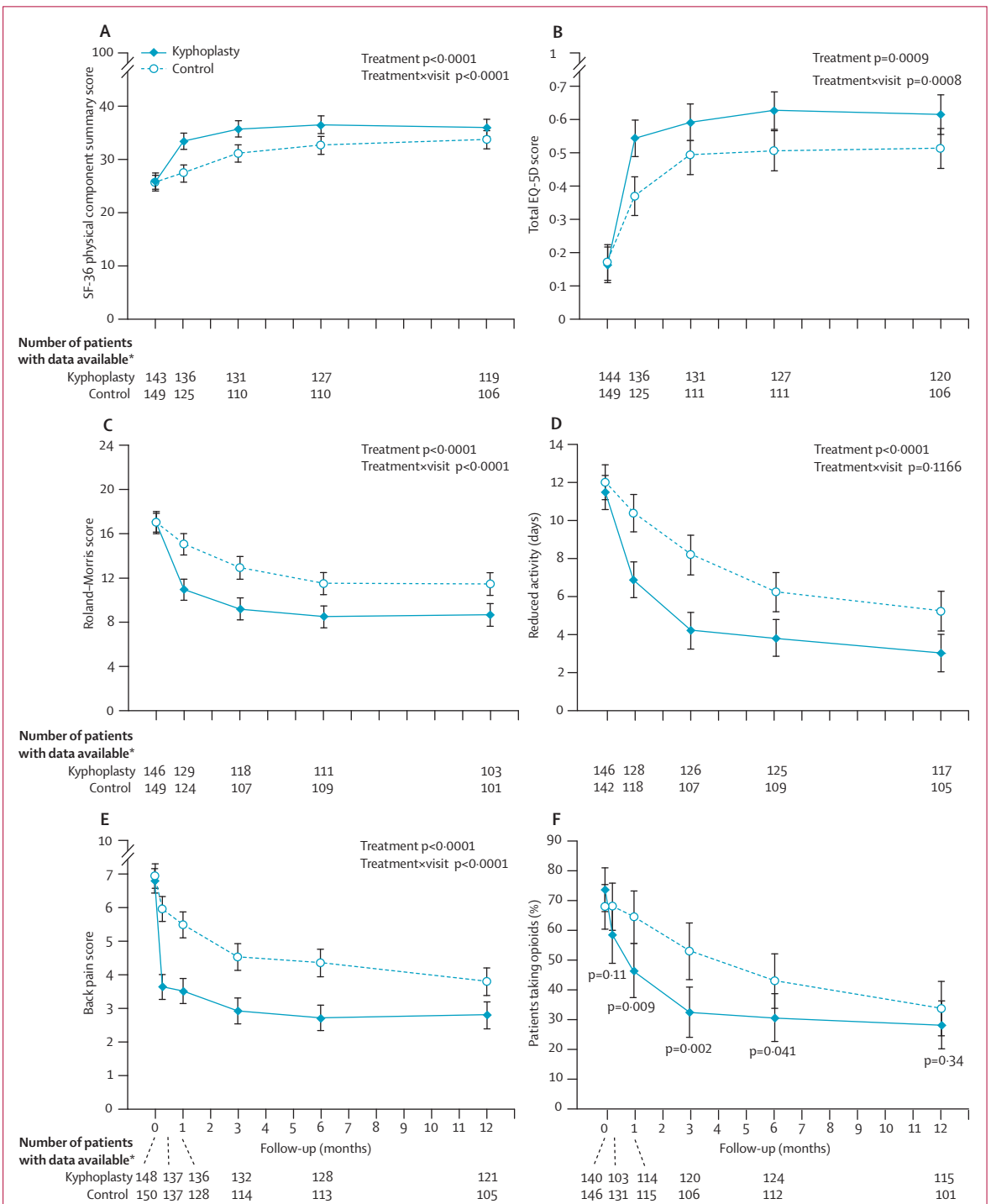

***Figure 2*: Quality of life, disability, and back pain at baseline and after kyphoplasty treatment or non-surgical care**
Group calculated means and 95% CIs are shown for balloon kyphoplasty (n=149) and non-surgical control (n=151) groups for (A) the short-form (SF)-36 physical component summary scores (scale 0–100); (B) total EuroQol-5D (EQ-5D) scores (scale 0–1·0); (C) Roland–Morris scores (scale 0–24); (D) the number of days (within past 2 weeks) patients reported spending greater than half the day in bed because of back pain; and (E) back pain (0–10 scale; 0=no pain). The proportions and 95% CIs of patients are shown for (F) patients taking opioid drugs to control back pain. In panels A and B, higher scores indicate improvement. For all other panels, lower values indicate improvement. In panels A–E, the treatment p value refers to the average treatment effect difference during follow-up. The treatment by visit p value relates to a time-related change of this difference. A significant treatment by visit interaction indicates that the treatment effect difference is not constant throughout the year. p values for each timepoint comparison are shown in panel F. *Numbers of patients with data available are shown to provide information about the amount of missing data that exists for each measure.

	Kyphoplasty (N=149)	Control (N=151)
Adverse events within 12 months	130	122
Withdrew because of adverse event	1	1
Serious adverse events* within 12 months	58†	54†
Anaemia	3	1
Back pain	10	10
Cardiovascular and vascular disorders		
Coronary heart disease	7	4
Arrhythmia	2	2
Pulmonary embolism	3	0
Stroke	1	1
Haematoma	1‡	0
Other	6	5
Infections		
Clostridium infection	1	1
Sepsis	1	2
Urinary tract infection	1‡	2
Neoplasms/cancer	6	6
Nervous system disorders	3	2
Psychiatric disorders	3	0
Respiratory disorders		
Pneumonia	6	5
Other	5	1
Serious adverse events that resulted in death		
Cardiovascular	5	3
Pneumonia	0	1
Cancer	2	1
Other	2	2

*An adverse event was serious if it resulted in death, life-threatening injury, or permanent impairment, or if it required extended hospital stay or intervention to prevent impairment. †Patients might have had multiple serious adverse events (SAEs). MedDRA catergories listed are those where there was a procedure or device-related SAE, any SAE occuring in 2% or more patients treated, or any SAE where there was a difference between groups with a p value less than 0·2. ‡Event was judged to be related to kyphoplasty procedure.

Table 3: **Patients with adverse events in the kyphoplasty and non-surgical care groups**

Patients in this study had substantially reduced baseline quality of life compared with other patients with chronic diseases.[13] At 1 month, kyphoplasty treatment resulted in mean SF-36 PCS scores (33 points) that were close to Swedish age-matched normative values (scores of 39 points for women 70–74 years and 37 points for women more than 74 years); the score in the control group at 1 month was 27 points.[24] Similar normative values are reported for the US population.[13]

Minimally clinically important differences are often used to assess the clinical significance for outcome measures since they could be different from statistical differences. These differences have been estimated for several of the outcome measures used in this study. Although they were developed for degenerative spinal conditions other than acute vertebral fractures and the effects of kyphoplasty, and they might vary because of different methods used for estimation,[25] estimated minimally clinically important differences have ranged between 3·5 and 4·3 points for the SF-36 PCS,[25] 1·0 and 2·5 points for back pain,[15,25] and between 2 and 3 points for the Roland–Morris scale.[16] The SF-36 physical function and EQ-5D estimates are 15 and 0·08 points, respectively.[26,27] At 1 month, the kyphoplasty treatment effect exceeded the smallest estimate for all measures apart from SF-36 physical function, and exceeded the largest estimate for EQ-5D, Roland–Morris, and SF-36 PCS. The effect of kyphoplasty treatment was higher than the smallest estimate for EQ-5D and Roland–Morris scales throughout the 12 months of follow-up. For SF-36 PCS, the kyphoplasty treatment effect met the smallest estimate for 3 months and when averaged over 12 months. The effect of kyphoplasty on back pain exceeded the smallest estimate up to 6 months. From reports of restricted activity days, we estimate that patients in the kyphoplasty group had about 60 fewer days of restricted activity during the year than had controls.

The results of this randomised trial are similar to those of two small controlled but non-randomised studies that show that kyphoplasty treatment was associated with greater improvement in back pain and physical functioning than non-surgical management for at least 6 months[11] and 12 months.[10]

Vertebroplasty, an alternative treatment for vertebral fractures, consists of percutaneous needle placement into fractured vertebrae with infusion of bone cement. One small randomised trial showed that vertebroplasty reduced disability and improved quality of life at 2 weeks compared with non-surgical treatment,[28] but crossovers precluded long-term comparisons.

Vertebral fractures change the biomechanics of the spine,[29] which might increase the risk of additional vertebral fractures.[7] The effect of kyphoplasty treatment on this risk has been unclear. Two non-randomised studies reported fewer subsequent fractures after kyphoplasty than non-surgical care,[10,11] whereas other uncontrolled studies have suggested that kyphoplasty might heighten the risk.[30] In our study, the rate of subsequent fracture was numerically higher in the kyphoplasty group but was not significantly different from that of controls, although it is worth noting that this study was not powered to detect differences in fractures between the two groups. Although most patients used bisphosphonates or other osteoporosis treatments, the rate of new radiographic fracture during the following year was high (about 30%), as has been seen in other patients with painful vertebral fractures.[10,11] A probable explanation for this high rate is that patients included in this study had symptomatic vertebral fractures, whereas in other reports, incident fractures were identified morphometrically at baseline.[7] The high subsequent fracture rate underscores the importance of treatments specifically intended to reduce risk of future fractures in osteoporotic patients who qualify for kyphoplasty.

This study has several limitations. Because the intervention was not blinded, we cannot rule out the possibility that knowledge of the treatment assignment might have determined patient responses to questions or radiologist assessments of new vertebral fractures, which could have contributed to the greater improvements seen in the kyphoplasty group. However, other potential biases—eg, the high frequency of new vertebral fractures (similar in both groups)—might have decreased the apparent improvements in pain and disability after kyphoplasty. Out of 300 patients randomised, 235 (78%) completed the study with more patients in the control group discontinuing than in the kyphoplasty group; however, baseline pain, function, and quality of life were similar between those who completed 12-month follow-up and those who discontinued. Non-surgical treatment was not standardised; for generalisability, every study centre was asked to provide non-surgical care consistent with local practices. We present 12-month data of a study with a planned minimum of 24 months follow-up.

Thus, compared with non-surgical management, balloon kyphoplasty resulted in improvements in quality of life and disability measures and reduction of back pain in patients with acute painful vertebral fractures; however, differences in improvement between kyphoplasty and non-surgical control groups diminished by 1 year. These findings will help to inform decisions about the use of balloon kyphoplasty as an early treatment option for this patient population.

Contributors

DW, JVM, and LB contributed to data collection and interpretation. SRC, JBT, JR, SB, RE, and PS contributed to data interpretation and analysis. SRC and KT contributed to the study design. DW, SRC, JBT, JR, SB, and KT contributed to manuscript development. JVM, LB, RE, and PS contributed to manuscript revisions. KT contributed to the study interpretation. DW, SRC, JVM, LB, JR, SB, and RE made the decision to submit the manuscript for publication. All authors approved the final manuscript for submission.

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Conflict of interest statement

DW has received honoraria for consulting from Medtronic Spine LLC and Cryolife, and has received research funding from Medtronic Spine LLC, Zimmer, Apatec, and Cryolife. SRC has received consulting and honoraria from Medtronic Spine LLC, and research support, consultation, or honoraria from Lilly, Pfizer, Novartis, Amgen, Merck, Procter and Gamble, Zelos, Roche, GlaxoSmithKline, and Organon. JVM and LB have received honoraria for consulting from Medtronic Spine LLC. JBT was employed by and owned stock and stock options in Kyphon Inc (now Medtronic Spine LLC) and is currently employed by Medtronic Spine LLC and owns stock options in Medtronic Inc. JR is employed by the Swedish National Competence Centre for musculoskeletal disorders at Lund University Hospital, Sweden, an organisation that has received compensation for work by Medtronic Spine LLC. RE has received honoraria for consulting from Medtronic Spine LLC and has received research funding or consultation honoraria from Lilly, Pfizer, Novartis, Amgen, Procter and Gamble, and Organon. PS is employed by and is an owner of Advanced Research Associates Inc, an organisation compensated for work by Medtronic Spine LLC. KT was employed by and owned stock and stock options in Kyphon Inc and is currently employed by Medtronic Spine LLC. SB received honoraria for consulting from Kyphon and Medtronic Spine LLC, received research funding or grant support from Amgen, Eli Lilly, Kyphon, Medtronic Spine LLC, Merck, Novartis, Procter and Gamble, Sanofi-Aventis, Servier, and Roche–GlaxoSmithKline.

Acknowledgments

This study was sponsored and funded by Medtronic Spine LLC. We thank the patients who consented to participate in the FREE trial and all participating staff at the investigational centres. We wish to acknowledge and dedicate this manuscript to the late Olof Johnell, whose contributions as the original principal investigator were invaluable. We thank M Nevitt and P Lips for initial review of the data and manuscript and G Jiang for providing third readings of radiographic images. SB is senior clinical investigator of the Fund for Scientific Research (FWO-Vlaanderen). DW and SRC are co-primary authors. JR, biostatistician at the Swedish National Competence Centre for musculoskeletal disorders at Lund University Hospital, Sweden, did the independent statistical review.

References

1 Borgstrom F, Zethraeus N, Johnell O, et al. Costs and quality of life associated with osteoporosis-related fractures in Sweden. *Osteoporos Int* 2006; **17:** 637–50.

2 Silverman SL, Minshall ME, Shen W, Harper KD, Xie S. The relationship of health-related quality of life to prevalent and incident vertebral fractures in postmenopausal women with osteoporosis: results from the Multiple Outcomes of Raloxifene Evaluation Study. *Arthritis Rheum* 2001; **44:** 2611–19.

3 Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int* 2006; **17:** 1726–33.

4 Lyritis GP, Mayasis B, Tsakalakos N, et al. The natural history of the osteoporotic vertebral fracture. *Clin Rheumatol* 1989; **8** (suppl 2)**:** 66–69.

5 Schlaich C, Minne HW, Bruckner T, et al. Reduced pulmonary function in patients with spinal osteoporotic fractures. *Osteoporos Int* 1998; **8:** 261–67.

6 Lyles KW, Gold DT, Shipp KM, Pieper CF, Martinez S, Mulhausen PL. Association of osteoporotic vertebral compression fractures with impaired functional status. *Am J Med* 1993; **94:** 595–601.

7 Lindsay R, Silverman SL, Cooper C, et al. Risk of new vertebral fracture in the year following a fracture. *JAMA* 2001; **285:** 320–23.

8 Voggenreiter G. Balloon kyphoplasty is effective in deformity correction of osteoporotic vertebral compression fractures. *Spine* 2005; **30:** 2806–12.

9 Garfin SR, Buckley RA, Ledlie J. Balloon kyphoplasty for symptomatic vertebral body compression fractures results in rapid, significant, and sustained improvements in back pain, function, and quality of life for elderly patients. *Spine* 2006; **31:** 2213–20.

10 Grafe IA, Da Fonseca K, Hillmeier J, et al. Reduction of pain and fracture incidence after kyphoplasty: 1-year outcomes of a prospective controlled trial of patients with primary osteoporosis. *Osteoporos Int* 2005; **16:** 2005–12.

11 Komp M, Ruetten S, Godolias G. Minimally invasive therapy for functionally unstable osteoporotic vertebral fracture by means of kyphoplasty: prospective comparative study of 19 surgically and 17 conservatively treated patients. *J Miner Stoffwechs* 2004; **11** (suppl 1)**:** 13–15 (in German).

12 Garfin SR, Yuan HA, Reiley MA. New technologies in spine: kyphoplasty and vertebroplasty for the treatment of painful osteoporotic compression fractures. *Spine* 2001; **26:** 1511–15.

13 Ware J, Kosinski M, Keller S. SF-36 physical and mental health summary scales: a user's manual. Boston, MA: Health Assessment Lab, New England Medical Center, 1994.

14 EuroQol Group. EQ-5D user guide. Rotterdam, Netherlands: EuroQol Group, 1996.

15 Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001; **94:** 149–58.

16 Roland M, Fairbank J. The Roland–Morris disability questionnaire and the Oswestry disability questionnaire. *Spine* 2000; **25:** 3115–24.

17 Nevitt MC, Ettinger B, Black DM, et al. The association of radiographically detected vertebral fractures with back pain and function: a prospective study. *Ann Intern Med* 1998; **128:** 793–800.

18 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. MedDRA data retrieval and presentation: points to consider. ICH-endorsed guide for MedDRA users on data output. http://www.ich.org/LOB/media/MEDIA2841.pdf (accessed Dec 17, 2008).

19 Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993; **8:** 1137–48.

20 Eastell R, Cedel SL, Wahner HW, Riggs BL, Melton LJ. Classification of vertebral fractures. *J Bone Miner Res* 1991; **6:** 207–15.

21 Jiang G, Eastell R, Barrington NA, Ferrar L. Comparison of methods for the visual identification of prevalent vertebral fracture in osteoporosis. *Osteoporos Int* 2004; **15:** 887–96.

22 Mallinckrodt CH, Clark WS, David SR. Accounting for dropout bias using mixed-effects models. *J Biopharm Stat* 2001; **11:** 9–21.

23 Rothman KJ. Statistics in nonrandomized studies. *Epidemiology* 1990; **1:** 417–18.

24 Sullivan M, Karlsson J, Taft C. SF-36 Halsoenkat. Svensk manual och tolkningsguide (Swedish manual and interpretation guide). Goteborg: Sahlgrenska University Hospital, 2002.

25 Copay AG, Glassman SD, Subach BR, Berven S, Schuler TC, Carreon LY. Minimum clinically important difference in lumbar spine surgery patients: a choice of methods using the Oswestry disability index, medical outcomes study questionnaire short form 36, and pain scales. *Spine J* 2008; **8:** 968–74.

26 Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005; **14:** 1523–32.

27 Davidson M, Keating JL, Eyres S. A low back-specific version of the SF-36 physical functioning scale. *Spine* 2004; **29:** 586–94.

28 Voormolen MH, Mali WP, Lohle PN, et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. *AJNR Am J Neuroradiol* 2007; **28:** 555–60.

29 Briggs AM, Wrigley TV, van Dieen JH, et al. The effect of osteoporotic vertebral fracture on predicted spinal loads in vivo. *Eur Spine J* 2006; **15:** 1785–95.

30 Fribourg D, Tang C, Sra P, Delamarter R, Bae H. Incidence of subsequent vertebral fracture after kyphoplasty. *Spine* 2004; **29:** 2270–76.