

The effectiveness and safety of vertebroplasty for osteoporotic vertebral compression fractures.

A double blind, prospective, randomized, controlled study

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Summary

Background: Vertebral compression fractures (VCFs) constitute a major health care problem in western countries. Several treatment modalities are available to relieve pain and allow increased activities. Percutaneous vertebroplasty (the injection of bone cement into the fractured vertebral body) is a relatively new procedure to manage patients with these fractures. The aim of this study is to evaluate the efficacy and safety of percutaneous vertebroplasty compared with standard conservative care.

Methods/Designs: In this double blind, prospective, randomized, controlled study the short- (3 months), medium- (6 months) and long-term (24 months) efficacy and safety of vertebroplasty to alleviate pain and improve function for painful osteoporotic vertebral fractures will be compared to standard conservative therapy. Conservative care will consist of 3 weeks of bed rest, wearing a rigid hyperextension corset, followed by 2-3 months in a Cheneau brace. In each of the two groups, patients will also receive treatment for osteoporosis according to their metabolic profile. Two hundred patients with painful osteoporotic vertebral compression fractures will be recruited over a 3 year period according to inclusion and exclusion criteria. We will randomly assign participants to receive either vertebroplasty or conservative care. Subjects will complete a battery of validated, standardized measures of pain, functional disability, and health related quality of life questionnaires at baseline and at post-randomization time points (1, 3, 6, 12 and 24 months). Each patient will be evaluated for pre-operative MRI, and pre- and post-operative radiographs; all scans will be evaluated independently by 2 orthopaedic surgeons. Laboratory tests to assess their metabolic bone profile

will be also performed. Our primary outcome will be change from baseline to 1, 3, 6, 12 and 24 months in the VAS score between the 2 groups.

Discussion: To date, vertebroplasty has been not been compared with standard conservative care for the management of patients with painful osteoporotic vertebral fractures in a randomised controlled trial. Therefore, the results of this study will allow to draw firm conclusions on this controversial topic.

KEY WORDS: vertebroplasty, cementoplasty, osteoporosis, vertebral compression fractures, osteoporotic fractures.

Introduction

Vertebral compression fractures (VCFs) represent a major health care problem in western countries. Each year in North America about 750,000 people experience a vertebral fracture, of whom only one third receive treatment (1). Clinicians can utilise several treatments to relieve pain and allow increased activities, including bed rest, bracing, and pain medications (2, 3). Surgery is required in patients with concurrent spinal instability or neurological deficit (4, 5).

Vertebroplasty and kyphoplasty are two percutaneous minimally invasive vertebral augmentation methods for cement injection into the vertebral body to manage symptomatic compression fractures without neurological impairment (6, 7). During the past 6 years, the number of vertebroplasty procedures performed in the United States has doubled, from 4.3 to 8.9 per 1000 persons (2).

The exact mechanism of the analgesic effect of vertebral augmentation remains under debate. Pain reduction with the use of these percutaneous vertebral augmentation techniques has been attributed to the mechanical effects of the reconstruction and stabilization of the endplates and vertebral body segment by stiffening of the cement, and to the therapeutic effect of the exothermic reaction of the cement, assuming that the pain originates from intraosseous nerve endings (8). The cornerstone of the controversy between kyphoplasty and vertebroplasty are height restoration, whether or not this height restoration is clinically relevant, and the risks related to height restoration (9-12).

The first 2 blinded, randomized, placebo-controlled trials of vertebroplasty showed no beneficial effect of vertebroplasty when compared with a sham procedure in patients with painful osteoporotic vertebral fractures (13, 14).

However, the results of these studies have been questioned (15). One of the major concerns of all the studies on vertebroplasty is that the conservative management has not been standardized (16). The aim of this randomized placebo-controlled trial is to evaluate the short- (3 months), medium- (6 months) and long-term (24 months) efficacy and safety of vertebroplasty for alleviating pain and improving function for painful osteoporotic vertebral fractures when compared to standard conservative therapy.

Methods

The trial will be submitted for approval to the local ethic committee, and will be conducted in accordance with the Declara-

tion of Helsinki and according to local and regional ethical standards.

Informed consent form for trial subjects

In obtaining and documenting informed consent, the Investigator will comply with the applicable regulatory requirements and adhere to the ICH GCP, ISO 14155 Part 1 and Part 2 (medical devices) and the requirements in the Declaration of Helsinki.

Prior to any trial-related activity, the Investigator will give the subject oral and written information about the trial in a form that the subject can read and understand.

A voluntary, signed and personally dated, informed consent form will be obtained from the subject prior to any trial-related activity. The responsibility for obtaining informed consent will remain with a medically qualified person, and will not be delegated to a non-medically qualified person. The written informed consent will be signed and personally dated by the person who will obtain the informed consent.

Trial design

Double blind, prospective, randomized, controlled study.

Participants

Participants will be recruited from general practitioners, specialists who manage acute osteoporotic vertebral fractures, and hospital inpatient and emergency departments.

All potential participants will be screened to determine eligibility according to the following inclusion and exclusion criteria. Inclusion criteria will be:

- 1) ≥ 50 years of age;
- 2) back pain (back pain score ≥ 4 points on a 0–10 scale);
- 3) one to three recent painful osteoporotic vertebral fractures (VF) from T5 through L5. VF has been defined as vertebral collapse (minimal 15% loss of height) and oedema or fracture line within the vertebral body. Fractures will be confirmed by thoracic and lumbar spine radiograph. If not already obtained, all participants (unless contraindicated) will have an MRI examination of the thoracic and lumbar spine to determine the position, extent, and stability of the vertebral fracture and to ensure no exclusion criteria exist. When a MRI will be unable to be performed, a CT scan, to determine the position and extent of the vertebral fracture/s will be performed;
- 4) decreased bone density T-scores ≤ -1 .

Exclusion criteria will be:

- 1) the presence of > 3 recent spinal fractures, pedicle fracture, previous vertebroplasty or kyphoplasty procedure, neurological deficit, radicular pain, radicular and/or myelum compression syndrome, or canal narrowing;
- 2) osteoporotic vertebral collapse of $> 90\%$; fracture through or destruction of posterior wall; retropulsed bony fragment or bony fragments impinging on the spinal cord;
- 3) systemic or local infection of the spine (osteomyelitis, spondylodiscitis);
- 4) vertebral fractures from primary bone tumors or osteoblastic metastases; current malignancy;
- 5) severe cardio-pulmonary condition;
- 6) dementia;
- 7) untreatable coagulopathy or uninteruptible anticoagulation therapy;
- 8) allergies to vertebroplasty or kyphoplasty materials or contraindications to MRI;
- 9) inability to give informed consent.

Endpoints

The primary endpoint will be the difference in change from baseline to 1, 3, 6, 12 and 24 months in the VAS score between the 2 groups. The secondary endpoint will be: Roland–Morris disability questionnaire, Oswestry disability index (ODI) (version 2.0), Asses-

sment of Quality of Life (AQoL) utility score (Health-related Quality of Life), incidence of new fractures.

To determine the incidence of new vertebral fractures radiologically, all participants will undergo plain film examination of the thoracic and lumbosacral spine at 1, 3, 6, 12 and 24 months. Regular serial follow-up films are recommended standard care following vertebroplasty to evaluate the treated vertebrae and to look for fractures in untreated vertebrae. Two independent blinded radiologists will interpret the radiographs using the validated and reliable Genant semi-quantitative method to identify and gauge the severity of the fracture. A new vertebral fracture will be defined as an increase in deformity grade (equivalent to a decrease of $>15\%$ in any vertebral height) from the baseline radiograph to the end of the study; or a new fracture in an existing prevalent fracture if there is progression to a higher grade of deformity (equivalent to a further vertebral height reduction of $>15\%$).

All adverse events and serious adverse events will be reported. Investigators will inform the local ethical committees/institutional review board of any serious adverse events or serious adverse effects.

Adverse event (AE)

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Serious adverse event (SAE):

A Serious AE is an experience that at any dose results in any of the following:

- Death
- A life-threatening experience
- In-subject hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Non-serious adverse event

A non-serious AE is any AE which does not fulfill the definition of a serious AE.

Severity assessment definitions

- **Mild** – No or transient symptoms, no interference with the subject's daily activities.
- **Moderate** – Marked symptoms, moderate interference with the subject's daily activities.
- **Severe** – Considerable interference with the subject's daily activities, unacceptable.

Relationship to trial product assessment definitions

- **Probable**: good reasons and sufficient documentation to assume a causal relationship.
- **Possible**: a causal relationship is conceivable and cannot be dismissed.
- **Unlikely**: the event is most likely related to an aetiology other than the trial product.

Randomisation

We will use a random-numbers table to allocate subjects. Star-

ting with an arbitrary point in the table, we will select 200 sequential random numbers. The first 100 numbers will be assigned to the vertebroplasty group, and the next 100 will be assigned to the conservative group. These assignments will be then arranged in an ascending order. This procedure produces a random sequence of consecutive treatment allocations. Sealed, opaque numbered envelopes containing the treatment assignments will be prepared, with care being taken to make sure that the order of the envelopes exactly matched the allocation schedule.

Vertebroplasty

For percutaneous vertebroplasty, the left pedicle of the fracture site will be identified with the use of a metallic marker. A 25-gauge needle will be used to infiltrate the skin overlying the pedicle, and a 23-gauge needle will be used to infiltrate the periosteum of the posterior lamina. An incision will be made in the skin, and a 13-gauge needle will be placed posterolaterally relative to the eye of the pedicle. Gentle tapping guided the needle through the pedicle into the anterior two thirds of the fractured vertebral body. Anterior-posterior and lateral images will be recorded with the needle in the correct position. Prepared PMMA (approximately 3 mL) will be slowly injected into the vertebral body, and satisfactory infiltration of the vertebral body will be confirmed radiographically. A bipedicular approach will be used only if there will be inadequate instillation of cement with the unipedicular approach. Injection will be stopped when substantial resistance will be met or when the cement reached the posterior quarter of the vertebral body; injection will be also stopped if cement will leak into extrasosseous structures or veins. All participants in the vertebroplasty group will receive cephalothin, administered intravenously immediately after PMMA injection. After the intervention, all participants will receive usual care.

Conservative care

Conservative care will consist of a 3 weeks period of bed rest, wearing a rigid hyperextension suspension brace, with positive three point suspension (sternal, suprapubic and thoracolumbar). The brace is an aluminum and white vinyl construct, fully adjustable for height, width and degree of hyperextension. A pelvic band produces lateral stability and eliminates bladder pressure by anchoring on the lateral halves of the ilium. After this period, patients will wear a Cheneau brace for 2-3 months. During this period, patients will be allowed to walk normally. The Cheneau brace is a thermoplastic brace modelled on a hyper-corrected positive plaster mould of the patient. This brace will be fabricated in polypropylene, and will have an anterior opening with velcro straps for fastening. In each of two group, patients will be also managed for osteoporosis on basis of the metabolic profile.

Clinical Evaluation

We will perform pre-operative evaluations the day before the procedure, and report the results of post-operative evaluation at 1, 3, 6, 12 and 24 months the procedure. Each patient will be evaluated for pre- and post-operative VAS, RMD, ODI and AQoL; pre-operative MRI, and pre- and post-operative radiographs (17). The Roland-Morris disability questionnaire (18) is a 24 yes/no items score related specifically to physical functions to specifically assess the disability from LBP. The physical functions considered include walking, bending over, sitting, lying down, dressing, sleeping, self-care and daily activities. Patients are asked whether the statements apply to them that day (i.e. the last 24 h). In the scale, one point is given for each item. The RDQ score can be obtained by adding up the number of items checked. The final score ranges from 0 (no disability) to 24 (severe disability). The questionnaire is self-administered by the patient, it can be completed in a maximum of 5 min, and an un-weighted score can be calculated in less than 1 min (19). The Oswestry disability index (ODI) (version 2.0) (20) includes 10

sections of questions that evaluate the activities of daily living, which can be drastically influenced by LBP. The ODI 2.0 domains are the following: pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life and travelling. Each section contains six statements that are scored from 0 (minimum degree of difficulty in that activity) to 5 (maximum degree of difficulty). If more than one statement is marked in each section, the highest score should be taken. The total score is obtained by summing up the scores of all sections, giving a maximum of 50 points. The final score is expressed as a percentage with the following formula: total score/(5 x number of questions answered) x 100%. The authors suggest rounding the percentage to a whole number for convenience. The higher the percentage, the greater the perceived level of disability by the patient. The total score ranges from 0 to 100%, with 0 representing no disability and 100 representing maximum disability. A total score between 0 and 20% means minimal disability; between 20 and 40%, moderate disability; between 40 and 60%, severe disability; between 60 and 80%, crippled; between 80 and 100%, bed bound or symptom magnifier (21). The questionnaire is self-administered by the patient, it is usually completed in less than 5 min, and scored in less than 1 min. The Assessment of Quality of Life (AQoL) is a 15 items health-related quality of life instrument derived from scores on five dimensions measuring: illness, independent living, Social relationships, Physical senses and Psychological well-being (22, 23). The AQoL is scored on a life-death scale ranging between 0.00, which represents death-equivalent states, and 1.00, which represents the best possible life state (perfect health). It responds to rapid changes in health status and it is sensitive to changes in the frail elderly. The AQoL incorporates utility weights that have been derived from an Australian population sample using time-trade off (TTO). The instrument has been well validated in a range of settings for delivery via self-administration, face-to-face or by proxy and takes approximately 5 minutes to complete (24). Moreover, we will perform the following laboratory tests: measurement of calcium, phosphorus, 1,25-dihydroxyvitamin D, PTH and alkaline phosphatase in the blood; measurement of calcium and phosphorus in the 24h urine; full blood count; blood protein level and blood protein electrophoresis. Bone mineral densitometry (BMD or DEXA) assessed on femoral neck and the lumbar spine will be also performed.

Statistical analysis

Statistical analyses will be blinded and performed according to the 'intention-to-treat' principle. The analyses will be performed by using SPSS version 16.0.1 (SPSS Inc, Chicago, Illinois). Confidence intervals will be calculated.

Sample size

Calculation of sample size is based on a previous protocol (25). The primary outcome will be overall pain at 3 months. Very large effects (e.g. >7 on a 10 point scale) have been described for improvement in pain scores for individual patients. People who undergo standard conservative care will also tend to have some improvement as symptom's relief. To detect a large (i.e. at least a 2.5 unit) advantage of vertebroplasty over conservative care in pain score (SD = 3.0, $\alpha = 0.05$, $\beta = 0.80$, 2-tailed t-test) we would require only 24 participants per group. Because of natural history of the disease and increase risk of vertebral fracture in the vertebroplasty group, we expect smaller long-term (12-24 months) differences to exist between the groups. Using the same assumptions as above but considering a 15% advantage in the vertebroplasty group (mean vertebroplasty improvement = 4.0 units, mean conservative treatment improvement = 2.5 units) we would require 64 people in each group. The most relevant adverse event due to vertebroplasty consists of vertebral fractures. According to risedronate clinical trials (26) one year incidence of new fractures in women with at least one

fracture and not on preventive treatment is about 20%. A large part of participants in this trial will be probably in management for osteoporosis, which may theoretically reduce the risk of further vertebral fracture by 50% to around 10% (26-28). In the two controlled before-after studies there was between a zero and 3 fold increase in the 1 year new fracture risk (29, 30). With 82 people in each group we will have 80% power to detect a 3-fold excess in fractures in the vertebroplasty group ($\alpha = 0.05$, 2-tailed Log rank test). When medium or large excesses in adverse events are present, the study is adequately powered.

Health-related Quality of Life (AQoL utility score) is an important global secondary outcome at 2 years. This is a complex score which considers benefits such as vertebral-specific reduction in pain and decreased distress and adverse events such as vertebral fracture or hip fracture. The AQoL is a generic score which allows to detect health-related changes – both health declines and improvements. With a sample size of 82, there will be 80% power to detect a 0.13 change in Health-related Quality of Life (utility). For example, the improvement in the conservative care group may be 0.10 units compared with 0.23 in the vertebroplasty group ($sd = 0.3$, $\alpha = 0.05$, 2-tailed t-test). To allow for attrition, we will increase the sample by 20% to 100 patients per group.

Discussion and conclusions

Vertebral fractures complicating osteoporosis are the most common form of osteoporotic fracture. Osteoporotic vertebral fractures are frequent in women older than 60 years, and may result in debilitating pain and spinal deformity. Because of increasing of population's age and severe morbidity due to these fractures, painful vertebral fractures are a growing serious public health problem with important socio-economic effects. Intervention strategies which allow effective management of pain, short time of recovery, and which do not require an extended nursing and rehabilitation care are lacking. Effective treatments should improve personal care of affected people and also reduce the high management costs of disease. Vertebroplasty is a promising intervention that has only been evaluated in 2 blinded, randomized, placebo-controlled trials, in which authors showed no beneficial effect of vertebroplasty when compared with a sham procedure in patients with painful osteoporotic vertebral fractures (13, 14). However, the results of these studies have been questioned (15).

Although prolonged bed rest can lead to an increased bone loss due to inactivity with increase of vertebral fracture risk, fracture stabilization with percutaneous cement injection methods (vertebroplasty and kyphoplasty) is a potentially dangerous procedure. Safety and efficacy of vertebroplasty and kyphoplasty have been evaluated by Hulme et al. in a systematic review of 69 clinical studies (31). Authors showed that a large proportion of patients had some pain relief (87% with PV and 92% with KP). However, cement leakage was relatively frequent: leakage rates were higher for PV (41%) than KP (9%). Leakage of bone cement is one of the main potential complications following percutaneous cement injection, especially vertebroplasty (32). Polymethyl methacrylate may exit the vertebral body through deficiencies, fractures in the vertebral cortex, or by injection of cement into the vertebral venous system (32).

Eck et al. also performed a meta-analysis of the literature to evaluate safety and efficacy of vertebroplasty and kyphoplasty (33). Authors reported rates of complications of procedures, showing that two most common adverse events are cement leak (19.7% for PV and 7% for KP) and new compression fracture (17.9% for PV and 14.1% for KP). Other complications described in literature include pulmonary embolism, rib fracture, hematoma, arrhythmia, pneumonia, hypoxia, infection and myocardial infarction (6). Because vertebroplasty has been previously assessed and compared only with a placebo procedure, the aim of our proposed study

will be to establish efficacy and safety of vertebroplasty compared to standard conservative management for painful osteoporotic vertebral fractures. The findings of this research will be of major international importance and will be immediately translatable into clinical practice. If our results will show a benefit for vertebroplasty, we will have scientific evidence to support the currently application of this procedure. If, on the other hand, our results will indicate a benefit for conservative management, we will question the utility of a widespread used procedure such vertebroplasty.

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