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BMJ Open Vertebroplasty in patients with multiple myeloma with vertebral compression fractures: protocol for a single-blind randomised controlled trial

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ABSTRACT

Introduction Multiple myeloma (MM) is a plasma cell cancer where about 1/3 of the patients present with pathological fractures at the time of diagnosis. Despite treatment, the majority of the patients will develop additional fractures. Because survival and prognosis has improved significantly over the last two decades for patients with MM, there is an increased need to focus on optimal fracture treatment. Traditionally, fracture pain is treated conservatively with opioids, bisphosphonates, bracing and radiation therapy. Vertebral augmentation has been used for the last three decades as a minimally invasive treatment option for vertebral compression fractures, but the evidence base for the efficacy is weak. We describe a trial assessing the impact of vertebroplasty on clinical outcome in the treatment of patients with MM with painful vertebral fractures.

Methods 100 patients with MM with painful vertebral fractures will be randomised in a prospective, single-blinded, multicentre, clinical trial where patients are randomised to either usual care or usual care supplemented with vertebroplasty with a possibility of crossover 4 weeks after randomisation. The primary outcome will be change in Oswestry Disability Index at 4 weeks.

Analysis Primary and secondary outcomes are assessed at baseline and at 4, 8, 26 and 52 weeks. Categorical data will be presented by means of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics.

Ethics and dissemination The study has been evaluated by the Regional Committees on Health Research for Southern Denmark (S-20200075) and notified and approved by the Region of Southern Denmark and listed in the internal record, journal no. 20/22355. All participants provide consent. The protocol will follow the SPIRIT (Standard Protocol Items for Randomized Trials) statement. The Danish Myeloma Patient Organization supports the study. Findings will be disseminated in peer-reviewed publications and presented at national and international conferences.

Trial registration number NCT04533217.

INTRODUCTION

Multiple myeloma (MM) is a plasma cell cancer in the bone marrow associated with

Strengths and limitations of this study

- Randomised controlled trial.
- Nationwide study (participation of all haematological departments in Denmark).
- Single-blinded randomisation.

activated osteoclastic bone degradation, lack of bone formation and pathological fractures with protracted healing due to inhibited osteoblast function.^{1 2} These biological changes are induced by the expansion of proliferating malignant plasma cells in the bone marrow.²

The incidence is about 7 per 100.000 in Denmark, equivalent to approximately about 400 new cases a year.³ At the time of diagnosis, pathological fractures are present in about 1/3 of the patients and a greater proportion develop fractures during the course of the disease.^{3 4} The annual risk of spontaneous spinal fractures is 15%–24% despite bisphosphonate prophylaxis.³

Although MM is incurable, survival and prognosis has improved significantly over the last two decades.⁵ This justifies and necessitates increased focus on optimal fracture treatment to ensure good physical function and quality of life for the patients' remaining lifetime. Vertebral fractures are very painful and affect patients' daily function.^{2 4 6} Traditionally, the fracture pain is treated conservatively with opioids, bisphosphonates, bracing and radiation therapy.³

Vertebroplasty was first reported in the late 1980s for the treatment of vertebral haemangiomas and osteolytic vertebral tumours.⁷ Under fluoroscopy, a Jamshidi needle is inserted through the pedicles⁸ into the vertebral body. Polymethylmethacrylate (PMMA) is injected into the vertebral body, still under



imaging guidance, to minimise extravasation into the spinal canal. Vertebral augmentation, including percutaneous vertebroplasty (PVP) and kyphoplasty (KP), has been used as a minimally invasive treatment option for vertebral compression fractures (VCFs).^{4 9 10}

The procedure is considered to be well suited for treatment of patients with malignant spine disease as it can be done under local anaesthesia, provides rapid pain relief^{11 12} and prevents prolonged immobilisation. PVP and KP provide stability within the fractured vertebral body by preventing microscopic movement and macroscopic collapse. It has also been suggested that PMMA bone cement induces exothermic reactions that are toxic to nerve endings and therefore provide pain relief.¹³

Two randomised trials and a later review was published in 2009^{14 15} and 2018,¹⁶ respectively, regarding vertebral augmentation. The two trials were done in different patient populations, namely patients with benign osteoporosis. The disappointing outcome of these two trials has unfortunately led to uncertainties regarding the effect in other indications, such as metastatic disease.

In 2019, a systematic review on vertebral augmentation of cancer-related painful vertebral lesions was published.¹² This review included randomised studies and other publications involving vertebral augmentation techniques. In all, 87 studies were included in the study and meta-analysis was performed. The review demonstrated clinically relevant improvement in pain and health-related quality of life (HRQL).

A recent Danish national clinical guideline^{17 18} on painful VCFs, caused by cancer including MM, recommends PVP as pain management. The evidence is mainly based on two randomised studies: the Cancer Patient Fracture Evaluation (CAFE) study by Berenson *et al*¹⁹ including 49 patients suffering from MM randomised between KP and conservative treatment and the study by Audat *et al*²⁰ randomising 27 patients to either conventional therapy or conventional therapy adding vertebroplasty or KP. The recommendations in the Danish guideline are weak due to risk of bias, including lack of blinding in randomised studies. In addition, the CAFE study was further downgraded for indirectness as the study contains a population consisting predominantly of patients with primary cancer other than MM.

Rationale for this study

Evidence-based guidelines for supplementing chemotherapy with vertebral augmentation when treating patients with MM with pathological fractures are lacking. The overall evidence from the two randomised controlled trials comparing supplementary vertebral augmentation to usual care is of low quality^{17 18} and requires more robust investigations regarding the role of vertebroplasty in the treatment algorithm of MM with spinal involvement.

For that reason, we decided to perform a single-blinded, randomised, controlled trial comparing usual care versus usual care supplemented with vertebroplasty in treating patients with MM with pathological fractures.

METHODS AND ANALYSIS

Purpose

To examine the efficacy of PVP in patients with MM with VCF, based on improvement in patient-reported outcome.

Patient and public involvement

The initial idea behind this project was created by a patient appointed by the Danish Cancer Society to participate in the working group behind the National Clinical Guideline on PVP for the palliative treatment of malignant VCFs caused by MM.^{17 18} She urged the group members to set up a study to provide high-quality evidence needed to recommend the treatment.

The study design has been developed in collaboration with the Danish Myeloma Patients' Association 'Dansk Myelomatos Forening'.

Study design

The study design is a randomised, prospective, single-blinded, multicentre, clinical trial where patients are randomised to either usual care or usual care supplemented with vertebroplasty with a possibility of crossover 4 weeks after randomisation. It is designed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.²¹

Trial sites

The trial is a multicentre trial with the participation of all Danish haematological departments. The departments are as follows:

- ▶ Department of Haematology, Aalborg University Hospital.
- ▶ Department of Haematology, Aarhus University Hospital.
- ▶ Department of Haematology, Holstebro Regional Hospital.
- ▶ Department of Haematology, University Hospital of Southern Denmark, Esbjerg.
- ▶ Department of Haematology, University Hospital of Southern Denmark, Vejle.
- ▶ Department of Haematology, Zealand University Hospital, Roskilde.
- ▶ Department of Haematology, Herlev Hospital.
- ▶ Department of Haematology, Rigshospitalet, Copenhagen.
- ▶ Department of Haematology, Odense University Hospital.

Participating spine surgical units are as follows:

- ▶ Department of Orthopaedic Surgery, Rigshospitalet.
- ▶ Spine Center of Southern Denmark, Lillebaelt Hospital, Middelfart.
- ▶ Department of Orthopaedic Surgery, Aarhus University Hospital.

Study population

Study subjects will be recruited from patients diagnosed with MM assessed and found eligible for vertebroplasty due to painful VCFs. Possible candidates will be identified at the

departments of haematology where the patients are treated for their disease.

Inclusion criteria

- ▶ Patients diagnosed with symptomatic MM and spinal compression fractures.
- ▶ Fractures verified on MRI- or CT-scan (OF-type 1–4) between and including Th6 and L5.
- ▶ Fracture involves four vertebral body levels or less.
- ▶ PVP can be done in one session.
- ▶ Possible indication for vertebroplasty.
- ▶ Back pain score measured on a visual analogue scale (VAS) ≥ 5 .
- ▶ Age ≥ 18 years.
- ▶ Able to understand and read Danish.
- ▶ Written informed consent.
- ▶ Relevant pain started ≤ 3 months prior to inclusion.

Exclusion criteria

- ▶ Contraindications for spine surgery:
 - Platelets < 30 mia/L.
 - OF-type 5 and Pincer-type.
- ▶ Bedridden.
- ▶ Presence of neurological deficit.
- ▶ Psychological or psychiatric disorder that is expected to interfere with compliance.

Randomisation

Prior to randomisation, the patients will be divided into two groups, stratifying between patients with known MM with a newly diagnosed spinal fracture and relevant pain ≤ 3 months prior to inclusion and patients with newly diagnosed MM with relevant pain associated to a spine fracture initiating ≤ 3 months prior to the diagnosis.

Furthermore, to ensure balanced control and intervention groups, the included patients at randomisation will be stratified according to (1) planned PVP of 1 vs 2–4 levels and (2) former vertebral fractures that are not planned treated with PVP.

The patients in each subgroup will be randomised to one of two parallel treatment arms allocated in a 1:1 ratio. Sealed numbered envelopes containing electronically randomised group allocations will be prepared prior to trial commencement. Following informed consent, a sealed prerandomised envelope will be allocated by the study nurse and the patient label affixed to the envelope.

Control treatment

The patients will receive the treating departments' standard care, following the Danish National Guidelines.²²

Investigational treatment

The investigational treatment arm will be the group receiving supplementary vertebroplasty of the VCFs.

Outcomes

Primary outcome

- ▶ Back-specific Functional Status using Oswestry Disability Index (ODI) at time of randomisation and 4 weeks postrandomisation. The ODI assesses

pain-related physical functioning in spinal disorders.²³ The ODI contains 10 questions about how back pain affects the ability to manage everyday life. These are summarised in a score ranging from 0 to 100. Higher scores reflect worse pain and disability.

Secondary outcomes

- ▶ Self-reported average pain intensity (VAS) during the preceding 24 hours at enrolment, and weekly in 12 weeks after enrolment. The rating scale from 0 to 10, with higher scores indicating more severe pain.
- ▶ HRQL on the EuroQol 5-dimension 3-level (EQ-5D-3L).²⁴ EQ-5D-3L is a widely used generic measure of HRQL. It evaluates five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three levels of severity. The resulting health is converted into a single summary index with a total score ranging from -0.6 to 1, where 1 corresponds to perfect health.
- ▶ HRQL according to the EORTC (European Organisation for Research and Treatment of Cancer) quality of life questionnaires EORTC QLQ C30 and EORTC MY20.
- ▶ Long-term stability of the treated vertebral bone (eg, fracture, including refracture, vertebral body height or malalignment) as measures by long-standing radiographs.
- ▶ Questionnaire about general health services, including questions about for example, sick leave and home care.

Data collection

After informed consent is obtained from the patient, the haematologist will fill out screening forms regarding disease stage, lines of treatment, current disease status, bisphosphonate status and pain relief treatment. The patient will complete surveys including the ODI, VAS pain score and QoL. Time points for data collection are presented in [table 1](#).

Sample size

The sample size calculations for this study is a challenge, as there are very few published papers reporting outcomes following vertebroplasty on vertebral fractures due to MM. The sample size calculations are thus based on results from treating osteoporotic vertebral fractures with vertebroplasty. To obtain a minimal clinically relevant improvement of at least 15 points on the ODI, we need to enrol 44 patients in each group. To account for approximately 10% dropout, we aim to enrol 100 patients.

$$N = (Z(\text{crit}) + Z(\text{pwr})) \times s^2 \times 2 / \text{MIREDF}^2$$

with a mean minimum difference between groups of 15, SD=25, two-tailed $p=0.05$, assuming a normal distribution with $Z(\text{crit})=1.96$, $Z(\text{pwr})=0.80$.

Table 1 Data collection – timeline

Clinical tools	At incl.	1	2	3	4	5	6	7	8	9	10	11	12	26	52	
		week post-incl.	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	weeks	
ODI	x				x				x					x		x
VAS leg and back	x	x			x		x		x		x			x		x
EQ-5D	x		x					x						x		x
EORTC QLQ-C30	x											x				x
EORTC QLQ-MY20	x												x			x
X-ray	x											x				x
MRI	x															
Biopsy	x															

EQ-5D, EuroQoL 5-dimension; ODI, Oswestry Disability Index; VAS, visual analogue scale.

Analyses

Baseline characteristics

The baseline characteristics of patients and operative details including complications will be recorded.

Statistical analysis

Data will be analysed according to their type using STATA, that is, categorical data will be presented by means of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics (mean, SD, number of observations, minimum, median, maximum).

The primary outcome measure will be improvement in ODI scores at 4 weeks after initiation of treatment. Repeated measures ANCOVA (Analysis of Covariance) with baseline ODI, VAS pain, EQ-5D-3L and number of levels involved will be performed.

Ethics and dissemination

The study will be performed according to the Declaration of Helsinki and the Danish Code of Conduct for Research Integrity.²⁵ The study has been evaluated by the Regional Committees on Health Research for Southern Denmark (S-20200075) and has been notified to and approved by the Region of Southern Denmark and listed in the internal record, journal no. 20/22355, and permission to extract data from hospital records will be obtained from the patients. Consent to use patient-reported information from the DaneSpine database is obtained electronically prior to patients completing the questionnaires. Patients who do not consent will not be included.

Findings will be disseminated in peer-reviewed publications and presented at national and international conferences following guidance from the SPIRIT guidelines.

DISCUSSION

This article presents a protocol for a single-blinded randomised controlled trial comparing usual care versus usual care supplemented with vertebroplasty in treating patients with MM with painful vertebral fractures. Further prospectively registered data on health, social variables and patient-reported outcomes are collected.

As the median survival is significantly better for patients with MM than for patients with spinal metastases associated with solid cancers, it justifies and necessitates increased focus on optimal fracture treatment in patients with MM specifically. An increasing number of patients with MM experience more than 5 years, even more than 10 years survival, which highlights the importance of ensuring good physical function and quality of life for the patients.

The outcome of the proposed project will impact future national and international guidelines on the treatment regimen for patients with MM and vertebral fractures.

The main strength of this study is the randomised treatment assignments, reducing the risk of selection bias.

Contributors LAW: PhD student, investigator; LC: cosupervisor; TL: consultant, mediation of contact to the Danish Myeloma Patients' Association 'DanSk

Myelomatose Forening'; NA: cosupervisor, mediation of contact to the Danish haematological departments; MDL: administration; MØA: principal supervisor. All authors have participated in the design and organisation of the study.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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