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Randomized Clinical Trial of Early Percutaneous Vertebroplasty versus Usual Care for Multiple Myeloma Patients with Vertebral Compression Fracture.

1. Background

Multiple myeloma is a plasma cell cancer in the bone marrow associated with activated osteoclastic bone degradation, lack of bone formation, and pathological fractures that does not heal 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 multiple myeloma 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 years. Osteolytic 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].
Vertebral augmentation, including percutaneous vertebroplasty (PVP) and kyphoplasty (KP), has been used as a minimally invasive treatment option for vertebral compression fractures (VCFs)[4,7-8]. The procedure is considered to be well suited for treatment of patients with malignant spine disease because it can be done under local anaesthesia, provides rapid pain relief[9-10], and prevents prolonged immobilization. PVP and KP provide stability within the fractured vertebral body by preventing microscopic movement and macroscopic collapse. It has also been suggested that polymethylmethacrylate (PMMA) bone cement induces exothermic reactions that are toxic to nerve endings and therefore provide pain relief.

A recent published Danish National clinical guideline[11] on painful vertebral compression fractures, caused by cancer including multiple myeloma, recommends percutaneous vertebroplasty as pain management. The evidence is mainly based on two randomized studies: The CAFE study by Berenson et al.[12] including 49 patients suffering from multiple myeloma randomized between kyphoplasty and conservative treatment and the study by Audat et al.[13] randomizing 27 patients to either conventional therapy or conventional therapy adding vertebroplasty and kyphoplasty. Thus, the evidence base is very weak and requires more robust investigations regarding the indications, timing, and the role of vertebroplasty in the treatment algorithm of multiple myeloma with spinal involvement.

2. Objectives

To determine the clinical effectiveness of early PVP compared to usual care for the treatment of vertebral compression fractures in patients with multiple myeloma.

2.1 Study 1: To determine if there are differences in improvement in Patient Reported Outcomes (PROs) in patients treated with early PVP compared to usual care at four weeks after initiation of treatment

2.2 Study 2: To determine if there are improvements in Patient Reported Outcome (PROs) in patients treated with early PVP compared to usual care at six months after initiation of treatment

2.3 Study 3: To determine if there are differences in costs of treatment of patients treated with early PVP compared with usual care at six months after initiation of treatment – Costs will be estimated from a societal perspective and will include costs related to surgery, the municipal rehabilitation, costs of primary and secondary health care services and lost wages for both the patient and the care giver within the first year after initiation of treatment

3. Outcomes

3.1 Primary outcomes

Primary improvement in back-specific disability using Oswestry Disability Index v2.1 (ODI) 4-weeks post-initiation of treatment.

3.2 Secondary outcomes

- Oswestry Disability Index v2.1 (ODI) at 8-weeks, and 6- and 12-months post-initiation of treatment
- Pain intensity (VAS) during the preceding 24 hours at initiation of treatment, and weekly for 12 weeks after initiation of treatment. The rating scale from 0-100, with higher scores indicating more severe pain
- Quality of life using t questionnaires
- ECOG performance status
- Long-term stability of the treated vertebra (e.g., fracture, vertebral body height, or malalignment) as measured by MRI and long-standing radiographs
- Patients in Region of Southern Denmark will have performed FDG-PET-MRI preoperative
- During PVP, biopsies from the fractures vertebral body will be saved in a biobank for further research
- Patients will be given a questionnaire about use of general health services, including questions about sick leave, home care etc.
- Patients will be given a questionnaire about use of analgesics

Besides the primary outcome, we will have several secondary outcomes. In addition, we will have Back-specific Functional Status using ODI at 8-weeks post-randomization, and 6- and 12-moths post-randomization.
Patient's rating of 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.
Prospectively assesses quality of life using FACT-G and EQ-5D questionnaires and in addition EORTC QLQ-C30 and MY20 multiple myeloma specific supplement questionnaires.

ECOG performance status.
To determine the long-term stability of the treated vertebral bone (e.g., fracture, vertebral body height, or malalignment) as measures by MRI and long-standing radiographs.
In addition, patients in Region of Southern Denmark will have performed FDG-PET-MRI pre-operative.
During PVP, patients usually will have taken biopsies from the fractured corpora. These biopsies will be saved in a biobank for further research.
Additionally, all patients will be given a questionnaire about general health services, including questions about ex. sick leave, home care etc.

4. Methods

Design
The study design is a randomized, prospective, clinical trial where patients are randomized to either usual care or vertebroplasty with a possibility of crossover 4 weeks after randomization. The study design has been developed in collaboration with the patient organization "Dansk Myelomatose Forening" and designed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines[14] including involvement of patients appointed from the Danish Cancer Society.

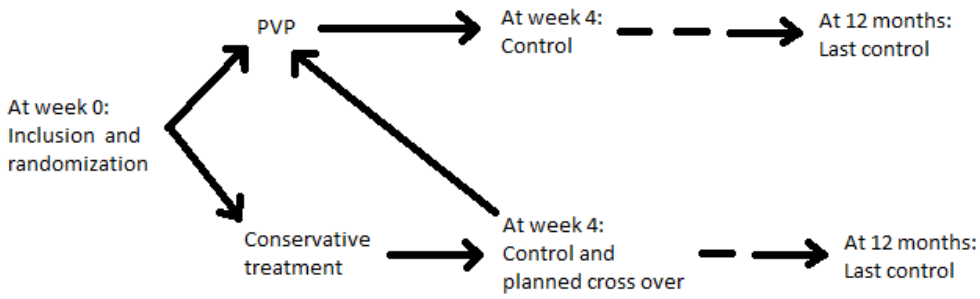
Population
Study subjects will be recruited from patients diagnosed with multiple myeloma assessed and found eligible for vertebroplasty due to vertebral compression fractures.

Inclusion criteria
- Patients diagnosed with symptomatic multiple myeloma and spinal compression fractures
- Fractures verified on MRI- and CT-scan between Th6 and L5
- Fracture involves to 4 or less levels
- PVP can be done in one procedure
- Possible indication for vertebroplasty (KNAK 43)
- Back pain score measured on a visual analogue scale (VAS) ≥ 50
- Age ≥ 18 years
- Able to understand and read Danish
- Written informed consent
- Relevant pain started ≤ 3 months prior to inclusion

Exclusion criteria
- Contra-indications for spine surgery
    - Platelets < 30 mia/l
- Bedridden
- Presence of neurologic deficit
- Psychological or psychiatric disorder that is expected to interfere with compliance

5. Patient course

Patients identified by the attending consultant as eligible are invited to participate. Patients who express an interest in participating will be given written and oral information on the purpose, nature and implications of study-participation. Information and inclusion of participants will be conducted in accordance with the guidelines of The Health Research Ethics Committee System in Denmark, from which approval will be sought.
Possible candidates will be identified at the departments of Hematology where the patients are treated for their disease. All Danish departments of Hematology will be invited to participate.
The hematologist will inform the patient of the protocol and decide if they fulfil the inclusion and exclusion criteria. If the patient wishes to participate the hematologist will fill out screening forms regarding disease stage, lines of treatment, current disease status, bisphosphonate status, and pain relief treatment. The hematologist will refer the patient to their collaborating surgical department. The surgical department will decide if the patient has contraindications for surgery and inform the patient of the risk of the procedure.
If the patient decides to participate, he or she will fill out forms regarding ODI, VAS pain score, QoL.
Before randomization, the patients will be divided into two groups, stratifying between patients with known multiple myeloma with new diagnosed spine fracture and relevant pain ≤ 3 months prior to inclusion and patients with newly diagnosed multiple myeloma with new spine fracture. Furthermore, to ensure balanced control and intervention groups the included patients at randomization will be stratified according to 1) panned PVP of 1 vs 2-4 levels, and 2) former vertebral fractures that are not planned treated with PVP.
The patients will be randomized to either PVP treatment or conservative treatment by drawing. It is therefore not possible for patients to choose between the treatments.
Patients randomized to vertebroplasty will be referred to a facility performing vertebroplasty.
Patients randomized to non-vertebroplasty will receive the departments' usual care with the option to change treatment arm after 4 weeks.
The randomization will be performed by the diagnosing clinician, but orchestrated by one individual central to the clinics. The clinics will receive sealed envelopes containing the choice of randomization equally divided between PVP and conservative treatment. When all sealed envelopes have been used for randomization, the clinics will receive new envelopes.
It will not be possible to randomize more than one patient at a time.
All patients will be contacted by a research nurse on a weekly basis the first 12 weeks after enrolment and after 3 and 12 months.
All patients randomized to vertebroplasty will undergo standard operative treatment involving a standard scheduled outpatient clinical control with the surgeon 12-weeks post-operative including long-standing radiographs of the spine.



6. Data handling and statistics

6.1 Datahandling

Collected data will be processed and stored by the research secretariat at Sector of Spine Surgery and Research, Middelfart, using DaneSpine database and in agreement with the requirements of the Danish Data Protection Agency.

6.2 Statistics

Data will be analyzed according to their type using STATA, i.e.; categorical data will be presented by means of frequencies and related percentages; continuous data will be displayed by means of descriptive statistics (mean, standard deviation, 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 with baseline ODI, VAS pain < ECOG status, and number of levels involved will be performed.

Sample size consideration:
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 multiple myeloma. 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 on the Oswestry disability index, we need to enroll 44 patients in each group.

$N = (Z(crit) + Z(pwr)) \times s^2 * 2 / MIREDIF^2)$,

with a mean minimum difference between groups of 15, SD=25, two tailed p=0.05, assuming a normal distribution with Z (crit)=1.96, Z (pwr)=0.80[14].

Quality control and quality assurance:
The study will be registered at the Ethical Committee of Southern Denmark and the Danish Data Protection Agency.
All patient data, including information on private matters or other confidential information, will be strictly confidential and stored according to the Danish Open Administration Act, the Danish Act on Processing of Personal Data and the Health Act.

The study will be performed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

7. Ethics

The study will be conducted according to Danish ethical principles, and notified at the Danish Data Protection Agency. Participation is voluntary and will only take place after subjects have received oral and written information about the purpose of the study.
The informed consent form will be stored at Center for Spine Surgery & Research, Middelfart. Participants can withdraw their consent at any time should they be inclined to do so. Furthermore, participants have the right to apply for access to data and documents concerning their own participation in the study according to the Danish Open Administration Act. The right is forfeited two years after completion of the study.
While planning the study, we considered making a blinded randomized trial, so that the patients would not know whether they had PVP or not. However, to expose immunosuppressed patients for tissue damage without conducting PVP was considered unethical. Thus, we landed on the actual design.

8. Finance

Expenses, including salary, tuition fees and miscellaneous for the PhD student will be applied for from the following:

- One-year scholarship from the Faculty of Health Sciences, University of Southern Denmark
- One-year scholarship from the research means, Region of Southern Denmark or from Hospital Lillebaelt Research Committee
- One-year scholarship + miscellaneous expenses from external funding

9. Publication and dissemination

It is the intension to publish the results of this thesis in relevant international peer-reviewed journals. Furthermore, to present the results at national and international conferences.

10. Organization

Principal Supervisor

- Mikkel Ø. Andersen, MD, Associate Professor, Senior Surgeon

Co-supervisors

- Niels Abildgaard, MD, Professor
- Leah Y. Carreon, MD, MSc, Professor

Appendix 1

Time line – table on data collection

Clinical tools	At incl.	1 week	2 w	3 w	4 w	5 w	6 w	7 w	8 w	9 w	10 w	11 w	12 w	6 months	12 m

		post-incl.													
ODI	x				x				x					x	x
SF-36	x				x				x					x	x
VAS leg and back	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
EQ-5D	x				x				x					x	X
X-ray	x												x		
MRI (rsyd: PET-MRI)	x (x)														
Biopsy	x														

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