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ABSTRACT

Introduction An increasing number of patients with displaced proximal humerus fractures (PHF) are being offered non-surgical treatment, including short immobilisation and structured rehabilitation. There are no randomised controlled trials (RCTs) comparing structured rehabilitation with non-structured rehabilitation to investigate the benefits of structured rehabilitation.

Methods and analysis In this RCT, patients with a displaced PHF will be assessed for eligibility at a Danish university outpatient clinic. Patients with competing injuries or patients offered surgery will be excluded, and randomisation will be 1:1. All patients will receive standard orthopaedic follow-up, including 14-day postinjury immobilisation, and advice about returning to activities of daily living before being allocated to structured rehabilitation in the municipalities or non-structured rehabilitation. The primary outcome is the between-group difference in the Oxford Shoulder Score (0–48 points, 48=best, minimal clinically important difference=10) at 6 months. A sample size of 60 patients will allow us to show a 10-point difference with 80% power.

Ethics and dissemination Funded by Department of Orthopaedics, Zealand University Hospital (grant number N/A) and Region Zealand Health Science Research Foundation (R32-A1108-B14), 14 January 2022; The Ethics committee in Region Zealand approved (EMN-2022-02449), 8 April 2022. The site opened on 5 May 2022, and the final results will be updated on trial registries, submitted to a peer-reviewed journal, and inform rehabilitation strategies after displaced PHFs. Protocol version 1, 21 April 2022.

Trial registration number NCT05302089.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study has a solid patient recruitment base.
⇒ Non-structured rehabilitation may potentially be effective and suitable for future treatment.
⇒ Outcomes are patient administrated.
⇒ The interventions cannot be blinded.
⇒ The structured rehabilitation may vary slightly between the municipalities.

INTRODUCTION

Proximal humerus fractures (PHFs) are the third most common non-vertebral fractures in the elderly and are closely related to osteoporosis. The lifetime risk of suffering a PHF in females aged 50 or above is 13%.[1] About half of the fractures are minimally displaced.[2] The remaining half of the patients suffer from displaced fractures, traditionally managed surgically by open reduction and internal fixation or shoulder replacement. Over the last decades, several high-quality randomised controlled trials (RCTs) and meta-analyses have failed to document the superiority of surgical management in displaced PHFs.[3] Therefore, an increasing number of patients are offered non-surgical treatment, including a variety of different regimes of immobilisation and rehabilitation.

Most elderly experience loss of function following a PHF regardless of treatment.[4] Therefore, recovery of function is paramount to prevent a substantial impact on the patient's independent living and morbidity. A Cochrane review from 2022[3] concluded evidence of no effect of surgical management and that the optimal non-surgical management after PHF is unknown.[3] Studies related to non-surgical management included immobilisation and rehabilitation interventions after minimally displaced fractures. Rehabilitation after displaced fractures is sparsely studied. A systematic review by Bruder *et al*[5] concluded that currently prescribed rehabilitation regimens were not clearly shown to be effective in reducing impairments and improving activity following upper limb fractures in general. Similarly, Østergaard *et al*[6] called for high-quality RCTs to study the effect of supervised rehabilitation interventions

after PHF. However, none of these included displaced PHF.

Rehabilitation delivered as structured training is commonly assumed to add value to patients with PHFs, but this is not supported by current evidence. We may even harm patients with intensive training programmes compared with non-structured rehabilitation (patient education about returning to activities of daily living (ADL) without prescribing individualised exercise intervention supervised by a health professional). Most RCTs with a non-surgically treated group use the same rehabilitation intervention in the two groups to best identify the difference between surgery and non-surgical treatment. Therefore, the effect of structured training cannot be justified by these studies. The aim of the study is to investigate the effect of structured rehabilitation versus non-structured rehabilitation in terms of patient reported shoulder function and quality of life in patients with displaced PHF following end of rehabilitation usually after 6 months.

Research question

What is the effect of structured rehabilitation (current standard care in Denmark) compared with non-structured rehabilitation for improving self-reported shoulder function at 6 months in patients with displaced PHF managed non-surgically?

Primary objective

To investigate the group difference with Oxford Shoulder Score (OSS) at 6 months between structured rehabilitation and non-structured rehabilitation in patients with displaced PHF managed non-surgically.

Primary research hypothesis

A treatment is considered superior if the mean between-group difference is above the minimal clinically important difference (MCID) for the primary outcome. Our hypothesis is that structured rehabilitation is superior to non-structured rehabilitation on self-reported function 6 months postinjury.

Secondary objective

To investigate the group difference in European Quality of life-5 Dimensions-Three-Level (EQ-5D-3L) and conversion to surgery (failure for both groups) at 6 months between structured rehabilitation and non-structured rehabilitation in patients with displaced PHF managed non-surgically. Further, to investigate the group difference in OSS, EQ-5D-3L and conversion to surgery at 12 months.

METHODS AND ANALYSIS

Study design

This study is a pragmatic, randomised, clinical superiority trial with a two-group parallel design, comparing structured and non-structured rehabilitation following a displaced PHF managed non-surgically at a Danish university outpatient clinic. Primary surgically managed patients are not eligible for inclusion. Participants will be randomised with a 1:1 allocation ratio, without an option to cross over between groups. Routine X-rays will be taken according to usual care at least at baseline, at day 10–14, at week 6 and after 6 months. Secondary surgical treatment is offered to patients with persistent pain more than 3–4 weeks after the injury who wish to undergo surgery. The primary endpoint will be the OSS score at the 6-month follow-up. The trial was registered at www.clinicaltrial.gov (NCT05302089, 31 March 2022). The recruitment period is expected to be 18 months, from May 2022 to October 2023, and the follow-up period is 12 months. This study protocol is based on the PREPARE Trial guide[7] and the SPIRIT checklist.[8] The study report will adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting parallel-group randomised trials. Protocol modifications will be reported to the ethics committee, and changes will be added to the trial's registration.

Participants

Patients aged 60 years or above with a displaced PHF (Neer's definition[9] planned for non-surgical management (two-part, three-part or four-part fractures) after a low energy trauma will be considered for eligibility. Prior to the first visit to the outpatient clinic, all patients with PHFs will be screened for eligibility based on initial radiographs and medical records by an experienced orthopaedic surgeon (SB) at Zealand University Hospital, Køge, Denmark. SB classifies all fractures according to Neer. Patients should be cognitively capable of complying with structured training and answering the two questionnaires.

The following exclusion criteria will apply:

- Dependent on daily personal care for basic ADL.
- Diagnosed with dementia or institutionalised.
- Do not understand written and spoken Danish.
- Pathological fracture or previous fracture in the same proximal humerus.
- Concomitant injury or fracture.
- Polytrauma, high-energy trauma or multiple fractures.
- Fracture dislocation or articular surface fracture.
- Isolated tuberosity fracture.
- Fractures not expected to heal by non-surgical treatment.
- SB considers the patient unsuitable to attend the study for medical reasons (substance abuse, affective or psychotic disorders, apoplexy, chronic pain, malignant disease).
- Symptomatic glenohumeral osteoarthritis, rheumatoid arthritis or rotator cuff-arthropathy.

All eligible participants will be provided with verbal and written information about the study. If eligible and willing to join the study, a consent form (online supplemental file 1) will be signed following a face-to-face inclusion session.

Interventions

Patients receive standard pain management according to the local guidelines and a sling and swathe on the day of injury. After 10 to 14 days, all patients are seen in the outpatient clinic and will receive an optional sling for comfort for 1–2 weeks. Patients will receive one-time oral and written instruction by BL about returning to ADL during the first 3 months (online supplemental file 2). At week 6, all patients are seen for clinical and radiological follow-up by SB (current usual care). If required, an extra consultation can be provided at week 12 (current usual care).

Intervention

The intervention group will receive usual follow-ups in the outpatient clinic and the one-time oral and written instruction by BL. No referral to structured rehabilitation in the municipalities (which is the current usual care) is provided to the intervention group.

Comparator

The comparator group will receive usual structured rehabilitation (standard care) in the municipalities. SB refers at the visit 10–14 days after the injury. The journal note is attached. It is sent within 24 hours to the municipality, which searches for a physiotherapist near the patient's home. Within a week after receiving the referral, the municipality will refer the patient to the physiotherapist. The physiotherapist then schedules the start date, typically 3 weeks after the injury. The rehabilitation content and duration are planned according to the choice of the local treating physiotherapist but will typically last for 6–12 weeks. After the RCT, we will collect information about the training content to maintain the pragmatic design.

Criteria for discontinuing or modifying allocated interventions

Patients converting to surgery after inclusion will be excluded from the trial. However, they will be included in a sensitivity analysis described in the Statistical methods section.

Strategies to improve adherence to interventions

Patients in the intervention group will not receive other strategies besides the 1-page leaflet with advice about pain management and returning to ADL. The comparator group will receive individualised strategies (not controlled by the research group) to improve adherence to the rehabilitation care by the municipal physiotherapists.

Relevant concomitant care permitted or prohibited during the trial

Patients in the intervention group will not receive a referral to rehabilitation care in their municipality. Some patients may be offered concomitant treatment through their private health insurance.

Provisions for post-trial care

No post-trial care will be provided to the patients. However, participants are not restricted from getting other treatments during and after the trial.

Outcomes

Outcome measures will be collected 6 months and 12 months postinjury. Due to the acute nature of the PHF injury, no baseline measures will be obtained (table 1).

The primary outcome will be the OSS, a validated patient-administrated questionnaire used to assess shoulder function.[10] It consists of 12 questionnaire items with five ordinal response options each, and the combined total gives a score between 0 and 48, with a higher score implying a greater degree of disability. The Danish version of OSS has shown good validity in the assessment of patients with post-traumatic shoulder diseases including PHF.[10]

Secondary outcomes will include the EQ-5D-3L and conversion to surgery after inclusion. Patients discontinuing for other reasons than surgery will be registered. The general conversion to surgery criteria is based on an overall clinical evaluation by SB in close collaboration with the patient, with the main reason being persistent pain.

Safety will be assessed based on observed and patient-reported fracture-related adverse events/complications[11] and their relation to the interventions. A limited number of changes to late surgical intervention is expected to occur in both groups as part of the natural history of the injury. Intervention-related hospitalisation or death, although unexpected, will be reported to The National Committee of Health Research Ethics within 7 days from the event.

Statistical methods

Sample size and power considerations

The SD value of 12 for the primary outcome (OSS) was derived from Handoll 2009.[12] The MCID for the OSS is in the range of 5–6.9.[13] In the absence of a patient-derived MCID for PHF, an MCID of 10 (corresponding to approx. 20% larger improvement on 0–48 scale in the intervention group than in the control group) was taken to represent the presumptive MCID. The calculation was expected to power the study for the primary outcome measure of the OSS score. Power was set at 80%, alpha 5% and the estimated required sample size was 24 per group. A recruitment target of 60 participants (30 per group) was selected to allow a 20% lost to follow-up (three patients in each group) and conversion to surgery (three patients in each group).

Statistical analysis

Recruitment will be depicted in a CONSORT flow diagram. We will use descriptive statistics to report baseline participant characteristics (age, sex, fracture type) using mean (SD), median (IQR) or number and proportion (%). Continuous data will be checked for normality using the Shapiro-Wilk test and visual inspection of histogram and quantile-quantile plot.

The primary analysis will be performed at 6 months (primary endpoint). The intention-to-treat analysis will include all patients as randomised excluding those

Table 1 Time schedule of enrolment, interventions, assessments and visits for participants

	Study period			
	Preallocation		Allocation	Postallocation
	Enrolment	Baseline	Days 10–14	Months 6 and 12
Timepoint	-*t*	t_0	0	t_1 and t_2
Enrolment				
Eligibility screening	x			
Informed consent	x			
Allocation			x	
Intervention				
Intervention (advice)			⟷	
Comparator (advice +rehabilitation care)				
Assessments				
Age, sex, fracture type		x		
Primary outcome measure				
Oxford shoulder score, 0–48				x
Secondary self-reported outcomes				
EQ-5D-3L <0–1				x
Fracture-related adverse events/complications				x
Conversion to surgery (failure in both groups)				x

EQ-5D-3L, European Quality of life-5 Dimensions-Three-Level

who converted to surgery. A linear regression model will assess the between-group difference at the 6-month follow-up. The assumptions underlying the regression models will be assessed, and appropriate measures will be taken if violated. The model will include the primary outcome (OSS) at 6 months as the dependent variable and the treatment group (intervention or comparator) as the main effect. A sensitivity analysis with all patients randomised will be performed, and a second sensitivity analysis including those who answered the follow-up questionnaires (per protocol). Additional sensitivity analyses will repeat the previous regression models adjusted for age, sex and fracture type. If the number of dropouts excluding conversion to surgery surpasses 5%, then multiple data imputation will be utilised. A similar approach will be used for the secondary outcome (EQ-5D-3L). The same statistical methods will be used for data at 12 months.

Type of fracture-related adverse events/complications and conversion to surgery will be reported descriptively with number and proportion (%), and Fisher's exact test will be used to asses difference between groups. Number of adverse events/complications will be presented with descriptive statistics.

The age, sex and fracture type will be presented descriptively between those patients attending the 6-month follow-up and those dropping out, converting to surgery or missing at follow-up.

No interim analyses or formal stopping guides are planned. All statistical analyses will be performed using Stata (StataCorp. 2019. Stata Statistical Software: Release 17.0., StataCorp). The level of significance is set to 5% for all analyses. A blinded biostatistician will conduct the data analysis.

Randomisation

The allocation sequence will be computer-generated with permuted block randomisation without stratification, set up by a data manager outside the project. Participants will be randomly assigned with a balanced allocation ratio. Randomisation is performed automatically in Research Electronic Data Capture (REDCap)[14] by BL. To ensure allocation concealment, everyone is blinded to block sizes (4–6) and unaware of the next assignment in the allocation sequence. All eligible patients who consent for participation and who fulfil the inclusion criteria will receive the one-time face to face advice about returning to ADL. Immediately following the advice session, BL will complete the randomisation and reveal the unique group allocation to the patient. Emergency unblinding is considered not relevant, since all patients are under the responsibility of the orthopaedic consultant (SB) (current usual care).

Blinding

Due to the study's pragmatic nature, the investigators (BL and SB) cannot be meaningfully blinded to group

allocation. However, the investigators have no conflict of interest related to the interventions. All patients will receive the same information about pain management and return to ADL based on a standardised one-page leaflet (online supplemental file 2). Furthermore, BL will provide advice before performing the randomisation to reduce potential provider bias. We will also inform patients that it is currently unknown whether structured rehabilitation is better than non-structured rehabilitation, and they will not be told the direction of the study hypothesis. Personel blinded to group allocation will deliver and collect the two patient-reported questionnaires without involvement of the investigators. An independent biostatistician blinded to group allocation will perform the primary RCT analysis. To reduce the risk of interpretation bias, blinded results from the analyses (group A compared with group B) will be written, including two alternative interpretations before the external data manager unblinds the randomisation code.

Data management

REDCap will be the data collecting and storage system to accomplish the legislative requirements about management and safekeeping of data. All personal information about potential and enrolled patients will be collected and saved in REDCap, which complies with international recommendations for confidential data protection. The two questionnaires are answered in writing and added to REDCap using double data entry and range checks for data values. Patients who deviate from intervention protocols (eg, convert to surgery) will be asked to complete the two follow-up questionnaires. Medical information about participants in the study will be confidential, and disclosure to third parties other than the research group will be prohibited. Data will be de-identified when exported from REDCap. When publishing data from this study, the presentation format will not include names, recognisable photos, personal information or other data which may disclose the identity of participants. The severity of adverse events is expected to be noncritical, and the intervention is not considered a high-risk intervention; therefore, a data-monitoring committee will not be established.

End of trial

The trial will end when all participants have completed their 12-month follow-up.

Patient and public involvement

Not applicable.

ETHICS AND DISSEMINATION

The project protocol, the informed consent form, written patient information and relevant supporting information was approved by The Ethics committee in Region Zealand prior to study initiation. The ethics committee are annually selecting some studies for auditing. The audit process is independent of investigators and sponsors. The study will be conducted according to the Danish legislation on ethics, the local data protection agency and the local ethical committee's requirements. The trial will follow the principles of the Declaration of Helsinki. BL will obtain oral and written consent after the first visit (week 2) and ensure that patients have been offered at least 24 hours to consider their participation. All patients will receive usual treatment and be seen in the outpatient clinic during routine visits (after 10–14 days, after 6 weeks and 6 months, with an optional visit at week 12).

All results from the study—both positive, negative and inconclusive—will be submitted to relevant international scientific peer-reviewed journals. We will follow 'The CONSORT 2010 statement' to report our results. Patient data will be anonymised on dissemination of results. The principal investigator will ensure publication, with authorship following the International Committee of Medical Journal Editors guidelines. Results will be presented at relevant national and international conferences and patient associations, for example, the Danish Orthopaedic Society. Prior to publication, a statistical analysis plan will be published online at Open Science Framework to ensure transparency and high-quality dissemination. The results will be communicated to patients and the public through the media and workshops. The patients can ask about our findings after study completion.

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Contributors BL and SB conceived the study idea and initiated the study design. BL drafted the study protocol, and both authors contributed to protocol refinement and approved the final version. BL and SB will ensure the execution and completion of the project. BL is the grant holder and principal investigator and takes overall responsibility for participant inclusion and data collection. BL will draft the manuscripts for publication with contributions and approval of final versions from SB.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

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