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Nordic Innovative Trials to Evaluate osteoPorotic Fractures (NITEP) Collaboration: The Nordic DeltaCon Trial protocol—non-operative treatment versus reversed total shoulder arthroplasty in patients 65 years of age and older with a displaced proximal humerus fracture: a prospective, randomised controlled trial

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ABSTRACT

Introduction The proximal humerus fracture (PHF) is one of the most common fractures in the elderly. The majority of PHFs are treated non-operatively, while 15%–33% of patients undergo surgical treatment. Recent randomised controlled trial (RCT) and meta-analyses have shown that there is no difference in outcome between non-operative treatment and locking plate or hemi-arthroplasty. During the past decade, reverse total shoulder arthroplasty (RTSA) has gained popularity in the treatment of PHF, although there is a lack of RCTs comparing RTSA to non-operative treatment.

Methods This is a prospective, single-blinded, randomised, controlled, multicentre and multinational trial comparing RTSA with non-operative treatment in displaced proximal humeral fractures in patients 65–85 years. The primary outcome in this study is QuickDASH-score measured at 2 years. Secondary outcomes include visual analogue scale for pain, grip strength, Oxford shoulder score, Constant score and the number of reoperations and complications. The hypothesis of the trial is that operative treatment with RTSA produces better outcome after 2 and 5 years measured with QuickDASH.

Ethics and dissemination In this protocol, we describe the design, method and management of the Nordic DeltaCon trial. The ethical approval for the trial has been given by the Regional Committee for Medical and Health Research Ethics, Norway. There have been several examples in orthopaedics of innovations that result in failure after medium-term follow-ups . In order to prevent such failures and to increase our knowledge of RSTA, we feel a large-scale study of the effects of the surgery on the outcome that focuses on the complications and reoperations is warranted. After the trial 2-year follow-up, the results will be disseminated in a major orthopaedic publication.

Trial registration number NCT03531463; Pre-Results.

Strengths and limitations of this study

- The publication presents the efficacy randomised controlled trial (RCT) on proximal humerus fracture.
- The trial fills an urgently needed knowledge gap in a rapidly increasing method used in proximal humerus fracture comparing reversed prosthesis with non-operative treatment.
- In order to improve generalisability of results, the trial will be conducted in several trauma centres in Nordic countries with similar healthcare system.
- The strength of our study setting is the experience of the researchers and personnel gained from previous large RCTs.
- The limitation is the normal issue of external validity.

INTRODUCTION

In the ageing population, the proximal humerus fracture (PHF) is one of the most common fractures. In addition to the significant disability caused by PHF among older individuals, such fractures are also associated with a high economic impact.[1 2] In general, the operative interventions and rehabilitation after a shoulder fracture are resource consuming. Furthermore, it has been suggested that a significant proportion

of common medical interventions— including orthopaedics—are not based on solid high-quality scientific evidence.[3] Despite this, many of them are still widely used.[4 5] There have been alarming reports showing that operative treatment of some common fractures, such as distal radius and proximal humerus, is increasing without any evidence to support the operative treatment of these fractures.[4 5]

The sex-specific fracture incidence for proximal humeral fractures for women in Sweden was 135 per 100 000 person-years[6]; in total, almost 10 000 fractures were diagnosed in 2012.[6] The majority of PHFs are treated non-operatively and approximately 15%–33% of patients are treated surgically.[7] Recent randomised controlled trials (RCTs) and meta-analyses have shown that there is no difference in functional outcome between non-operative treatment and locking plate or hemi-arthroplasty (HA) in the treatment of PHF. However, operative treatment has a significantly higher risk of complications and reoperations of up to 30%.[8–11]

Originally, reverse total shoulder arthroplasty (RTSA) was used in osteoarthrosis in patients without cuff function to gain better functional outcomes. During the past decade, however, RTSA has gained popularity in the treatment of PHF. In a recent Medicare population analysis carried out between 2005 and 2012, the proportion of surgical procedures for PHF that were total shoulder arthroplasties (TSA) (of which RTSAs constituted 89% in 2011) increased from 3% to 17%, while the proportion of HA decreased from 42% to 24% during the same time period.[7 12] There have been some systematic reviews based on case series and patient cohorts including one RCT that compared HA and RTSA. The results are equivocal, RTSA resulted in better functional outcomes compared with HA in some studies,[13 14] with no difference seen in others.[15] In the RCT, the complication rate in the HA group was significantly higher than in the RTSA group (24% vs 10%, respectively).[16] However, an arthroplasty registry analysis including 10 844 operations (6658 TSA and 4186 RTSA) showed the RTSA postoperative complication rate to be 22% at 2 years.[17] The results from a cost analysis concluded that RTSA treatment is significantly more expensive than HA treatment ($57 000 vs $33 480, respectively).[18]

Currently, there are no RCTs comparing RTSA to locking plate or non-operative treatment after PHF. The current literature seems to discourage the operative treatment of PHF with locking plate or HA, and there is no evidence that favours surgery over non-operative treatment.[9 11] In spite of the substantial costs and lack of evidence supporting the effectiveness of RTSA for PHF, it has become the accepted standard of care in the USA.[19] Therefore, there is an urgent need for high-quality RCTs that compare RTSA with non-operative treatment.

The Nordic Innovative Trials to Evaluate osteoporotic fractures—NITEP collaboration began with a trial of proximal humerus fractures (R10127, NCT01246167). The aim of the present trial is to compare RTSA and non-operative treatment in the treatment of proximal humerus fracture in the elderly. When conducting a randomised controlled multicentre trial, the critical points are the patient recruitment rate and the stability of key personnel. Therefore, a multicentre Nordic collaboration is warranted. In our previous RCT, our collaboration was found to be both reliable and effective in the recruitment of patients. Furthermore, we are confident that the planned Nordic DeltaCon trial is feasible and that it will have an impact on the daily management of these difficult and controversial fractures.

METHODS AND ANALYSIS

This is a prospective, superiority, single-blinded, randomised, controlled, multicentre and multinational trial that will compare RTSA and non-operative treatment in proximal humerus fractures in patients aged 65–85 years with displaced three-part and four-part fractures (B and C types) according to the recent AO/OTA 2018 revision.[20] The trial setting has been drafted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statements.

The hypothesis of the trial is that RTSA produces a better functional outcome and less pain compared with non-operative treatment at 2 years.

The primary outcome in this study will be the QuickDASH (the short form of Disabilities of the arm, shoulder and hand) score measured at 2 years. Secondary outcomes will be the QuickDASH score after 1, 2 (short term) and 5 years (medium term), general visual analogue scale (VAS) for pain, grip strength, the Oxford shoulder score (OSS), the Constant score (CS) and the number of reoperations and complications. Quality of life will be assessed with 15-D. Cost-effectiveness analysis will be performed after completion of the trial. The questionnaires used in the trial will be repeated after 10 years with those patients who are still reachable. During all time points, the complications and reoperations will be recorded.

Patient selection

The eligible study population will comprise all consecutive patients aged 65–85 years with a proximal humerus fracture diagnosed within 7 days and operated within 14 days of the trauma. The upper age limit was chosen to limit loss to follow-up due to unrelated cause mortality and to exclude those patients with a very high surgical risk. The lower age limit was chosen according to a recent publication by Sebastian-Forcada *et al*.[16] They found that RTSA had better outcomes in patients >70 years of age compared with HA. Additionally, the complication rate with RTSA was found to be lower than for HA, and thus we decide that it would be safe to set the lower age limit at 65 years. In another RTSA trial that included patients aged 65 years or over,[21] the number of adverse events (AEs) after interim analysis was less than reported in the literature, which also supports the lower age limit.

The research nurse will be notified of any patients screened for the trial who decline to take part or are excluded from the randomisation. The nurse will then complete a patient information form in order to collect the total number of patients screened.[16] Patients who decline from taking part in the trial will be asked to join the follow-up cohort allowing us to evaluate external validity.

The following criteria will be used throughout the study for patient selection.

Inclusion criteria:

- Low-energy AO/OTA group 11-B1.1, 11-B1.2 and 11-C1.1, 11-C3.1. Both B and C type includes the subgroups: displaced,[2] impacted[3] or non-impacted[4] from the universal modifiers list.

Exclusion criteria:

Radiographic

- Mal-inclination less than varus 30°or valgus 45°.
- Less than 50% contact between head fragment and metaphysis/diaphysis.
- Head split fractures (group 11-C3.2 and 11-C3.3) with >10% of the articular surface in the main head fragment.
- Dislocation or fracture dislocation of the gleno-humeral joint.
- Pathological fracture.
- Glenoid abnormality (retroversion, >15°; glenoid fracture; cuff arthropathy).

General

- Refuses to participate in the study.
- Aged <65 years or >85 years.
- Serious poly-trauma or additional surgery.
- Non-independent, drug/alcohol abuse or institutionalised (low co-operation).
- Contraindications for surgery (severe cardiovascular, pulmonal or neurological comorbidity).
- Does not understand written and spoken guidance in local languages.
- Previous fracture with symptomatic sequelae in either shoulder.
- Patients living outside the hospital's catchment area.

Randomisation

Patients will be randomised using a random number matrix in block allocation fashion. The blocks will be stratified by age (65–75 years and >75 years) since age has been shown to associate with the main outcome measure. The treatment allocations from the matrix will be acquired from an online randomisation system (website http://randomize.net), where the researcher logs in after written consent and receives the correct intervention. The physician responsible for the intervention or treatment will not participate in any part of the collection of patient outcomes during the follow-ups. The research coordinator will monitor the study flow. An independent monitoring committee has been established with our previous RCT.

Surgical treatment

Operative treatment will be performed as a daytime procedure by trained and experienced upper extremity surgeons. The surgeons' skills and number of procedures from each centre will be reported according to the criteria given by the Consort Group.[22]

The aim of surgical treatment is to restore proper biomechanics, to achieve an optimal range of motion and to minimise patient discomfort. The standardised approach will be the delto-pectoral to minimise any damage to the deltoid muscle. Supraspinatus excision and biceps tenotomy will be performed. A cemented monoblock humeral stem will then be implanted, in a neutral version. An important point that will be addressed is to ensure proper tension and stability of the prosthesis. Fixation of the greater and lesser tubercles is important in optimising the ability and strength of internal and external rotation.[23] When necessary, braided polyester suture–cerclages engaging the insertion of the subscapular and infraspinatus tendons enforced by a bone graft or a 'horseshoe-graft'[24] from the humeral head will be used. If the surgical neck fracture extends further distal than the humerus metaphysis, a diaphyseal cerclage will be applied to prevent further diaphyseal fracturing. Finally, to reduce the risk of the radiographic 'scapular notching', the largest glenosphere will be used to secure an inferior prosthetic overhang with reference to the scapular neck and to reduce the risk of any instability of the prosthesis.[25]

Non-operative treatment

Patients in the non-operative group will be immobilised in a sling for 2 weeks before starting self-exercises and instructed physiotherapy. Postoperative treatment differs with respect to timeline between the surgical treatment group and the non-operative group due to the different degree of stability for a reversed prosthesis and a non-operatively treated displaced fracture (table 1). The elements of physiotherapy will, however, be the same.[21 26]

Rehabilitation

In order to achieve as good functional outcomes as possible, the rehabilitation protocols will be standardised in both treatment groups and the patients will be given a written protocol. Patients in both groups will be guided by in-ward physiotherapists and will be given written physiotherapy guidelines for both instructed physiotherapy and self-exercises. After discharge from the hospital, patients will be referred to physiotherapy for further guidance. Patients in the operative group will start exercises from the first postoperative day to reduce haematoma in the 'dead space' created by resection of the supraspinatus tendon and the design of the reverse prosthesis. For a detailed rehabilitation programme, please see table 1.

Follow-up

Patients will visit the orthopaedic outpatient clinic at the hospital for a follow-up visit with the orthopaedic

Table 1 The rehabilitation guidelines

Elements of physical therapy	Group 1 Reversed prosthesis	Group 2 Non-operative treatment
Antioedema elbow, hand and fingers.	Day 1	Day 1
Positioning of the scapula.	Day 1	Day 1
Pendulum exercises. Passive and active assisted exercises in flexion, abduction and rotation.	Day 1*	2 weeks
Active exercises. Functional exercises. Isometric resistance with the shoulder in neutral position.	6 weeks	6 weeks
Active dynamic strengthening exercises.	8 weeks	8 weeks
Stretching exercises to progressively increase ROM in all positions.	No	10 weeks
Progress strengthening exercises, weightbearing exercises through the upper extremity to improve shoulder proprioception.	12 weeks	12 weeks

All weeks mean after treatment start in weeks.
*Gradually increasing mobility, external rotation to neutral position in the first six weeks after surgery.
ASA, American society of Anesthesiologists - Physical status classification system; ROM, range of motion.

surgeons at 3 months. We recommend a 2 weeks follow-up for the non-operative group to confirm the rehabilitation program can start: An additional radiographic examination to exclude secondary facture displacement, and instruction by a physiotherapist after removal of the sling. Research visits will take place at 1, 2, 5 and 10 years. During these visits, the QuickDASH, OSS, CS, 15D and plain X-rays examinations will be performed. At the research visit, the patients will be asked to wear a shirt and instructed not to provide information about their treatment group to ensure the researcher or physiotherapist are blind to the initial treatment.

Should any AE occur at any point during the follow-up, an AE report will be sent to the Tampere research nurse. Patients initially allocated to the non-operative group but later operated on during the trial will be analysed based on the intention-to-treat principle.

At 1-year control in selected sites, patients will be asked for their consent to take part in an additional study. Should patients agree to take part they will have accelerometer censors attached by plasters to both upper arms for a week. The sensors will measure 24/7 activity and degree of movement. With these data, we will be able to compare the activity levels of both treatment groups

Table 2 Assessments and procedures of the trial

Assessment	Preoperative	2. Visit 3 months	3. Visit 1 year	4. Visit 2 year	5. Visit 5 years	6. Visit 10 years
X-ray	X	X	X	X	X	X
CT	X			X		
Exclusion/inclusion	X					
Medical history	X					
Consent	X					
Questionnaire	X	X	X	X	X	X
Self-assessment	X		X	X		
VAS pain	X	X	X	X	X	X
QuickDASH	X		X	X	X	X
15D	X		X	X	X	X
OSS	X		X	X	X	X
CS score			X	X	X	X
Physician visit	X	X	X	X	X	X
Research visit			X	X	X	X
Grip strength	X	X	X	X	X	X

CS, Constant score; OSS, Oxford shoulder score; VAS, visual analogue scale.

at 1 year after the fracture treatment and to compare the acquired data with the patients' healthy side. A full list of trial assessments and procedures is presented in table 2.

Patients who decline to attend the intervention trial will be asked to join the external follow-up group. This group will be used as external validation; the group content and outcomes will be compared with the allocated intervention and control groups. The treatment will be carried out in line with normal clinical practice, but the patients will have the same follow-up and be asked to fill out the same questionnaires as the allocated patients.

Complications

Complications will be categorised as follows:

- Infection.

The definition of infections is the following:

a. Less serious infection: Superficial wound infection with sign of skin inflammation and/or a positive bacterial culture, without call for resurgery.[27]
b. Deep infection: Any postoperative wound infection or sign of deep infection that calls for resurgery with positive perioperative bacterial cultures or as defined after in consensus criteria for periprosthetic joint infection (musculoskeletal infection society).

- Non-union.
- Implant failure, including dislocation.
- Painful capsulitis after 6 months.
- Nerve damage.
- Complex regional pain syndrome.

Power analysis

Assuming the effect size of a 14-point difference in the QuickDASH score and an SD of 26.8 points (from previous Olerud and MacDermid trials), the estimated sample size will be 59 patients per group (delta=14, SD=26.8, alpha=0.05, power=0.8).[28–30] With this age group, the estimate of loss in follow-up rate will be set to 30% and results in a total of 154 patients in the trial.[31]

Statistical analysis

The differences between groups in main outcome variables will be analysed by t-test when variables are unskewed, and by the Mann-Whitney U test if continuous skewed. Results will be presented with 95% CIs. Two-way tables with the χ^2 test will be used for dichotomous variables. In subgroup analysis, the effect of age, sex, fracture group, smoking, ASA class and premorbidity will be evaluated against the scores and overall quality of life after fracture.

The effect of the treatment using the QuickDASH will be investigated in the multivariate manner. Multivariable analysis will be performed with linear regression analysis since the outcome variable QuickDASH is normally distributed due to adequately sized groups. The main variable of interest included will be the intervention, and age, sex, fracture group, smoking and premorbidity will be used as confounding variables.

Data management plan

Each patient will be assigned a unique trial identification number (TIN), which is matched with the patient's identification. The matching key will be stored in a locked partition on the hospital research server at Tampere University Hospital, Finland, and will only be available to two study nurses. The identification of each patient will only be possible after retrieving the matching key. Throughout the trial, the research data will only be handled with a TIN. The research data will be saved to a database with a NITEP tailored online patient management programme (Berta) located on a secure research server provided by Tampere University Hospital and approved by the Security Committee of Tampere University Hospital. Only users with a registered account will be able to log in to the system and registered accounts will be provided by the administrator. The research data saved to the server will contain only anonymous TINs with a set of numbers acquired from the questionnaires; that is, each question is answered with a number. This will ensure the anonymity of each individual patient, and that the identity of the patient will remain secret, even if the server data are revealed to third parties.

All primary and secondary data will be acquired and stored on the study trial server. Data will be entered either by the patient during the control visits (via tablets) or by a researcher or research nurse when the questionnaires are returned by post. The researchers from each hospital will have access to the secure study server where the trial research data are stored. Each researcher will gain access to the data at the end of the trial for further analyses. All variables in the data set will be described, and suitable metadata standards will be used, when available.

The copyright of the trial research data will be owned and created by the collaboration parties. The data will be shared freely among collaboration parties, and all participating researchers will receive access after the trial is completed. Due to confidentiality and legal agreements, public data sharing will be restricted because we only have permission to hold the data in the specific research server, not to transfer data. Under certain circumstances, for example, when a new member joins the collaboration, we will grant access to the data. All data will be saved for 15 years after the end of the trial.

Patient and public involvement in trial

In order to improve patient involvement in the trial, we will interview patients with proximal humerus fracture before the onset of the trial. The aim of the interviews will be to move towards patient-centred medicine by taking into account the goals, preferences and values of patients. We will further involve patients by asking questions at the beginning of the treatment (self-assessment) in order to identify the questions to ask and the outcomes to measure. The interviews will be repeated after 1 and 2 years, and the results (difference or indifference between the primary and follow-up responses) will be reported.

Interim analysis

The external trial board will execute the interim analysis after half of the patients have been recruited. The report will be focused on the number of AEs and will give a recommendation as to whether or not the trial should continue. AEs and serious adverse events (SAEs) will be reported according to the recommendations given by the Consort Group.

AE is defined as follows:

1. For the RTSA intervention group, the primary focus will be postoperative deep infections[27] requiring revision surgery, instability, periprosthetic fracture, radiographic early signs of loosening (within 2 years of the surgery) of the humeral stem or notching of the scapula neck.
2. For the non-operative group, the primary focus will be on the rate of secondary surgery for any reason (eg, non-union, symptomatic avascular head necrosis, osteoarthrosis).

Both groups will be monitored for SAE during the first four weeks after discharge for embolism (cardiac or brain) or death. The research nurse will fill out AE and SAE forms at 3 months control, if needed.

At the halfway point of the trial (50% of patients recruited), an independent steering committee will evaluate the complication rates and correlate them to the expected rates published in the available literature.

An unexpected high rate of complications in either group will be reported to the project group, who will then decide whether to end the randomisation.

Contingency plan

All participating hospitals have a significant volume of trauma patients, and they provide continuous emergency care and trauma surgery. In addition, all collaboration sites are academic teaching hospitals that are familiar with good clinical research practices. Proximal humerus fractures are common in these hospitals, and thus the infrastructure of the hospitals is highly standardised. For example, all participating hospitals have upper-extremity treatment units. Moreover, all hospitals have the appropriate equipment available, such as an operating environment and facilities for postoperative hospitalisation. All participating institutes have agreed to provide all the equipment and facilities necessary to conduct the trial. Local science centres will provide support in maintaining Good Clinical Practice principles, in assisting in the administration and invoicing for the trials, and in executing trial monitoring.

Recruitment policy

The centres will be encouraged to recruit as many patients as possible. However, if one centre is unable to continuously recruit enough patients annually, it would be impracticable to include the centres findings in the statistical model, and therefore the centre would be excluded from the trail. The minimum number of patients recruited per year will be five.

TRIAL SCHEDULE

The initial piloting of the trial will begin in Norway in early October 2018 all-together with six sites. The other collaborators will join after the trial protocol has been shown to be working flawlessly. During 2019, all sites will begin recruiting, and we estimate that the inclusion process will be completed with full groups after 2 years (end of 2020). Analysis and results of the trial will be published (disseminated) during 2022.

ETHICS AND DISSEMINATION

The ethical approval for the trial has been given by the Regional Committee for Medical and Health Research Ethics, South-East Authority, Norway (2018/476 REK sør-øst D, https://helseforskning.etikkom.no/. All patients included in the trial and those who declined but were asked to take part in ordinary follow-up will be asked to give written informed consent. All patient data will be handled in an anonymous fashion and the results will be published at the group level only, and individual patients will not be identifiable.

In this protocol, we describe the set-up and management of the Nordic Deltacon trial. The efforts to develop new operative techniques during the past years seem to have resulted in no improvement for patients suffering from PHF. With all the excitement around the newest technique, RTSA, we feel there is an urgent need for a large-scale study of the effects of the technique on the outcome, with special attention on complications and reoperations. This will assure the safe and ethical usage of RTSA in the future.

The absolute strength of the study will be the experience of the study group in handling a large-scale RCT. In this kind of efficacy study, the paramount aspect is the uniformity of the patient handling, and it may be the limitation of the study if not taken care of properly. However, with our previous experiences, we have learnt to overcome these pitfalls by regular biannual meetings among the researchers, personnel education sessions and written aftercare and follow-up protocols. Third-party monitoring is essential for checking the trial management and for notifying of any missing parts in the data handling. External validity is always a matter of debate in RCTs. Good documentation, pre-trial workshops and continuous discussion among the team will clarify the patients recruited to the trial.

The previous data show moderate to good outcomes with non-operative treatment for patients with PHF in cases where the fracture parts are in continuity with the stem. And therefore, the usage of RTSA should be limited to only the most severe and displaced cases of PHF until the primary results of this trial are available.

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