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Effectiveness and cost-effectiveness of surgery versus casting for elderly patients with Displaced intra-Articular type C distal Radius fractures: protocol of a randomised controlled Trial with economic evaluation (the DART study)

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ABSTRACT

Introduction Current literature is inconclusive about the optimal treatment of elderly patients with displaced intra-articular distal radius fractures. Cast treatment is less invasive and less expensive than surgical treatment. Nevertheless, surgery is often the preferred treatment for this common type of distal radius fracture. Patients with a non-acceptable position after closed reduction are more likely to benefit from surgery than patients with an acceptable position after closed reduction. Therefore, this study aims to assess non-inferiority of functional outcomes after casting versus surgery in elderly patients with a non-acceptable position following a distal radius fracture.

Methods and analysis This study is a multicentre randomised controlled trial (RCT) with a non-inferiority design and an economic evaluation alongside. The population consists of patients aged 65 years and older with a displaced intra-articular distal radius fracture with non-acceptable radiological characteristics following either inadequate reduction or redisplacement after adequate reduction. Patients will be randomised between surgical treatment (open reduction and internal fixation) and non-operative treatment (closed reduction followed by cast treatment). We will use two age strata (65–75 and >75 years of age) and a web-based mixed block randomisation. A total of 154 patients will be enrolled and evaluated with the patient-rated wrist evaluation as the primary outcome at 1-year follow-up. Secondary outcomes include the Disabilities of the Arm, Shoulder and Hand questionnaire, quality of life (measured by the EQ-5D), wrist range of motion, grip strength and adverse events. In addition, we will perform a cost-effectiveness and cost-utility analysis from a societal and healthcare perspective. Incremental cost-effectiveness ratios, cost-effectiveness planes and cost-effectiveness acceptability curves will be presented.

Ethics and dissemination The Research and Ethics Committee approved this RCT (NL56858.100.16). The results of this study will be reported in a peer-reviewed journal. We will present the results of this study at (inter)national conferences and disseminate the results through guideline committees.

Trial registration number Clinicaltrials.gov (NCT03009890). Dutch Trial Registry (NTR6365).

Strengths and limitations of this study

Strengths:
- Specific patient group (elderly with displaced type C fracture with non-acceptable fracture characteristics after reduction).
- Extensive inclusion criteria.
- Pragmatic study approach.

Limitations:
- There are no radiological exclusion criteria that define a fracture as being too poorly positioned to allow participation in the study.
- If the treating surgeon deems there is no equipoise and randomisation is unethical a patient may be withheld from the study.

INTRODUCTION

Open reduction and internal fixation (ORIF) for displaced intra-articular distal radius fractures in elderly patients has not been proven to be superior to non-operative treatment.[1–3] However, in the last decade, the number of surgical procedures in this age category has shown a fivefold increase.[4] The aim of ORIF is to restore anatomy, thereby allowing early functional rehabilitation and potentially yielding better functional outcome. On the down side, this might also result in unnecessary adverse events[2] and increased healthcare expenses.[4] In addition, distal radius fractures are very common in

the elderly population,[5] and in the coming decades, the total number of distal radius fractures will increase as a result of an increasingly ageing population.[6] Therefore, we need high-quality evidence to either justify the financial burden and adverse events associated with surgical procedures[2 3] or to support non-operative treatment in the elderly population.

Non-operative treatment consists of closed reduction followed by cast treatment and is widely available, safe and inexpensive. However, a fracture cannot always be adequately reduced non-operatively, and even after a successful reduction, a cast can fail to maintain an adequate position of the fracture.[7] Both scenarios lead to a mal-union, which could subsequently cause osteoarthritis,[8] pain and a decreased range of motion (ROM). However, the long-term outcome does not seem to differ with that of surgical treatment in terms of patient-reported outcomes.[9 10] Moreover, several studies suggest that elderly patients who are treated non-operatively have satisfactory function of their wrist even despite mal-union and poor radiographic outcome.[2 11–13]

Surgical treatment is more invasive by nature and consequently involves more risk for the patient. On top of that, it is also more expensive. If surgery is performed, the most commonly used surgical treatment in the Netherlands is ORIF. ORIF allows early mobilisation, which is believed to prevent both stiffness and loss of strength. Early mobilisation is thought to accelerate the independence of elderly patients. Consequently, even though surgery is initially more expensive, these costs might eventually be offset by reductions in healthcare, informal care and/or unpaid productivity costs.[14]

We plan to compare the functional outcome and the cost-effectiveness over the course of 1 year after trauma between non-operatively and surgically treated elderly patients with displaced intra-articular distal radius fractures. We hypothesise that both treatment groups have similar patient-reported wrist function, despite radiological mal-union in the non-operatively treated group. We also hypothesise that non-operative treatment is more cost-effective compared with surgical treatment over the course of 1 year due to substantially lower direct healthcare costs.

METHODS AND ANALYSIS

Study design

This study is a multicentre randomised controlled trial (RCT) with an economic evaluation alongside. Our trial was registered at clinicaltrials.gov and the Dutch Trial Registry. The protocol is written according to the Standard Protocol Items: Recommendations for Interventional Trials guidelines. The article describing the results will be written according to Consolidated Standards of Reporting Trials guidelines. In the process of study design and startup, both the patient council of the initiating centre and the Netherlands Patients Federation (Nederlandse Patiëntenvereniging - NPV) were consulted.

Setting

The study is conducted in the Netherlands and coordinated by OLVG, a large teaching hospital and level-2 trauma centre in Amsterdam. The first patient was included and randomised on 23 January 2017. Patients are recruited in 19 participating hospitals.

Participants

Inclusion criteria

- ≥ 65 years at time of trauma.
  - Six of the participating hospitals only include patients aged 75 years or older.
- Displaced intra-articular distal radius fracture (Arbeitsgemeinschaft für Osteosynthesefragen (AO) type C). Classifications will be made based on posterior–anterior (PA) and lateral radiographs. CT images may be acquired in case of doubt about articular involvement or when additional imaging is required to fully appreciate the fracture or to facilitate surgery planning.
- A non-acceptable fracture directly after reduction or within 3 weeks post-trauma due to redisplacement. A non-acceptable fracture is defined by having one or more of the following fracture characteristics according to the Dutch guideline for the treatment of distal radius fractures[15]:
  - ≤15° radial inclination.
  - ≤5 mm radial length, also known as radial height. This is measured as the distance between the distal ulnar surface (not the ulnar styloid process) and the tip of the radial styloid process.
  - >15° dorsal tilt.
  - >20° volar tilt.
  - >2 mm intra-articular gap and/or step-off. This can be measured on either a radiograph or CT.
- < 3 weeks post trauma.
- Independent living.
- Fit for surgery.
- Dutch fluency and literacy.
- Informed consent.

Exclusion criteria

- Open fracture.
- Neurovascular damage.
- Multiple-trauma patient with an Injury Severity Score of >16.
- Other fractures in the injured extremity other than ulnar styloid process fractures.
- Simultaneous fracture of the contralateral forearm.
- Previous fracture of the ipsilateral radius resulting in a malunion or an impaired function.
- Patients with dementia or patients who are unable to understand the consequences of the treatment options and who are unable to give informed consent.

Participant recruitment

A radiograph is made for every patient who visits the emergency department (ER) with a suspected wrist fracture. After diagnosis, the surgeon on call or the emergency

physician reduces the fracture after which all patients receive a temporary below-elbow forearm cast. This is standard care in the Netherlands. Participating hospitals and physicians may use their own preferred technique for casting and follow their local protocol for anaesthetics. After reduction, a second radiograph will be acquired.

Eligible patients will receive information about the study at the ER. The study team will also screen the ER lists for eligible patients who were initially missed and will contact them by telephone to provide information about the study. If patients are willing to participate, their informed consent will be acquired at the next follow-up visit. After providing informed consent, patients will be randomised using a web-based computerised randomisation programme.

Displaced fractures have a tendency to redisplace, even after adequate initial reduction. Therefore, patients with acceptable fracture characteristics after reduction will be monitored and are approached for participation in case of redislocation within 3 weeks after trauma.

Randomisation and blinding

Patients will be randomly allocated to either the surgery group (ORIF) or the non-operative treatment group (closed reduction and cast immobilisation). In order to avoid age imbalance between treatment groups, patients will be randomised in two strata using mixed block randomisation with block sizes of 4, 6 and 8 patients. The two strata consist of age groups: 65–74 and 75 years or older. Randomisation will be performed with a web-based computerised randomisation programme to ensure concealment of treatment allocation. The interventions do not allow for blinding of patients and physicians. Data analysis will be blinded.

Interventions

Surgical treatment

Patients will undergo surgical ORIF with a volar locking plate. A dorsal plate may be used in combination with a volar plate. The location, size and type of plate are left up to the discretion of the surgeon. An additional cast may be applied for a maximum of 2 weeks postsurgery for wound protection and pain reduction.

Cast treatment

The non-operative group receives a permanent circular cast between 1 and 2 weeks after trauma. The total duration of cast treatment may vary between 4 and 6 weeks.

There are no radiological fracture characteristics that mandate crossover to the surgical treatment arm. Patients can crossover to the surgical treatment arm on their own request or at the discretion of the surgeon.

Other interventions

Patients are referred to physical therapy according to local protocol, at their own request or at the discretion of their treating physician or general practitioner.

Outcomes

The study focuses on the following patient-reported outcome measures (PROMs). Table 1 gives an overview of all the measurements at different time points.

Primary outcome

The primary outcome is wrist function as reported by the patient over the course of 1 year after trauma measured with the patient-rated wrist evaluation (PRWE) score (Dutch version).[16 17] The PRWE and Disabilities of the Arm, Shoulder and Hand (DASH) are both valid and reliable instruments for patients with a distal radius fracture.[18] The PRWE, however, is a more wrist-specific instrument for evaluating the outcome of distal radius fracture patients.[19] However, the DASH is still commonly used for research involving patients with a distal radius fracture.[1] To be able to compare study results and to pool individual patient data in an individual patient data meta-analysis, also DASH scores are collected. In the study team's opinion, these benefits of collecting both scores outweigh the burden for the patient of filling out an extra questionnaire.

Table 1 Follow-up moments and tests

	PRWE	DASH	VAS pain	Frailty	PCS	EQ-5D-3L	Economic questionnaire	X-ray of wrist	ROM	Grip strength
Baseline (situation before fracture) (t0)	X	X	X	X		X				
0 weeks (t1)			X					X		
3 weeks (t2)			X					X		
6 weeks (t3)	X	X	X		X	X	X	X	X	X
3 months (t4)	X	X	X			X	X	X	X	X
6 months (t5)	X	X	X			X	X		X	X
9 months (t6)	X	X	X			X	X			
12 months (t7)	X	X	X			X	X		X	X

EQ-5D-3L = euroqol 5 dimensions questionnaire 3 levels
DASH, Disabilities of the Arm, Shoulder and Hand; PCS, Pain Catastrophizing Scale; PRWE, patient-rated wrist evaluation; ROM, range of motion; VAS, visual analogue scale.

The PRWE is a 15-item questionnaire designed to measure wrist pain and disability in activities of daily living. The minimal clinical important difference (MCID) of the PRWE is deemed at 14.[20] This MCID value was used as the non-inferiority threshold in the sample size calculation. Smaller differences are not considered clinically relevant.

Secondary outcomes

Response variables

- Wrist function as reported by the patient, using the DASH questionnaire (Dutch version).[21]
- Quality of life as reported by the patient (EQ-5D-3L). The EQ-5D-3L shows acceptable to good responsiveness in patients with distal radius fractures.[22]
- Wrist pain on a visual analogue scale (VAS).
- Cosmetic discomfort as reported by the patient (as part of thepatient-rated wrist/hand evaluation (PRWHE).
- Wrist ROM measured with a goniometer on both the injured and uninjured wrist:
  - Dorsal flexion/palmar flexion.
  - Radial deviation/ulnar deviation.
  - Pronation/supination.
- Grip strength measured with a hydraulic hand dynamometer as the mean of three measurements.
- Adverse events occurring within the 1-year follow-up period, for example:
  - Hardware removal.
  - Hardware failure.
  - Complex regional pain syndrome.
  - Tendon rupture.
  - Nerve damage/lesion.
  - Tendinitis.
  - Superficial wound infection.
  - Deep wound infection.
  - Carpal tunnel syndrome.
  - Mortality.
  - Other relevant injuries or hospitalisation.

Explanatory variables

- Patient characteristics including:
  - Sex.
  - Gender.
  - Diabetes patient.
  - Previous corticosteroid use.
  - Smoking.
  - Dominant side.
- Radiographic parameters:
  - Radial inclination.
  - Radial length.
  - Volar angulation.
  - Dorsal angulation.
  - Gap or step off.
- Frailty questionnaire: Groningen frailty indicator.[23]
- Grip strength as a biomarker for frailty.[24]
- Patient-reported pain catastrophising (Pain Catastrophizing Scale).[25]
- Pain medication including opioid use.

Acquisition of questionnaires

Data will be obtained either through the online database software or by hardcopy. Patients will receive the questionnaires at the predefined follow-up moments (table 1) through mail or through e-mail based on their preference. If patients are unable to either mail or e-mail, a researcher can support the patients by visiting or calling them by phone. Patients are invited by (e-)mail at each follow-up moment and are contacted by telephone if they do not reply to the initial invite. Treating physicians are not involved in the acquisition of questionnaires to minimise interview bias. Also patients did only receive support from a researcher if necessary for the acquisition of data.[26]

Acquisition of VAS scores

At each follow-up visit, a VAS for wrist pain will be filled out by the patient. By hardcopy, this is done by putting a mark on a visual 0 to 10 scale. On a computer this can be done by dragging an arrow across a 0 to 10 scale. By phone, patients are asked to visualise a 0 to 10 scale.

Acquisition of physical measurements

These measurements can be carried out in the hospital if the patient is able to visit the hospital. If the patient is unable or not willing to visit the hospital the researcher can also visit the patient at home.

ROM will be tested in both the injured and the non-injured side. An analogue Jamar goniometer will be used to measure the degree of motion in three planes as described above (secondary outcomes).

Grip strength will be measured three times on each side. The average of the three measurements on each side will be used as a response variable for the treatment effect. Grip strength will also be used as an explanatory variable because it is considered a diagnostic biomarker for frailty.[24] For this, the measured grip strength on the non-injured side at 6 weeks will be used.

Adverse Events

The researcher will ask the patients if he or she has experienced any adverse events. At each follow-up moment, the researcher will also check the patient's records for adverse events. These are noted in the online database at each follow-up moment.

For each complication, it is considered whether a serious adverse event has occurred (see ethics and dissemination).

Acquisition of radiographic parameters

Radiographs will be obtained in both the PA and lateral view. Radiographic parameters will be measured at each follow-up visit by the coordinating researcher in the picture archiving and communication system of each participating hospital. Due to the pragmatic nature of this trial, radiographs will be made within standard care processes. The follow-up moments listed in table 1 correspond to the Dutch guidelines, but some deviation by local hospitals is anticipated.

Sample size

Prior to the start of this trial, the required sample size was calculated. The sample size calculation was based on a non-inferiority design, six participating centres, a power of 90%, an alpha of 0.025, an SD of 23 points and a minimal important clinical difference of 14 points based on the PRWE[10 20] as primary outcome measure after 1 year. We calculated that with 20% loss to follow-up after 12 months, 77 patients are needed per group in this non-inferiority trial. This means 154 patients need to be included.

After the start of the trial, we noticed that recruitment rates were lower than expected; therefore, more hospitals were invited to participate. Moreover, the dropout rate was lower than anticipated. A recently updated power analysis indicated that if there is truly no difference between surgery and cast treatment, then 114 patients are required to be 90% sure that the lower limit of a one-sided 97.5% CI (or equivalently a 95% two-sided CI) will be above the non-inferiority limit of −14.[27] To minimise the risk of being underpowered, we still aim for 154 participants.

Data analysis

Effectiveness analysis

To assess the non-inferiority of non-operative treatment, we will use a linear mixed model and an intention-to-treat approach. In the primary mixed model, wrist function quantified by the PRWE will be analysed with treatment group as key independent variable and age and baseline PRWE score as covariates. To evaluate whether the two groups differed in change over time, the interaction of group and time will be assessed. Non-inferiority is demonstrated when the 97.5% CI of the between-group effect over 1 year after trauma does not include the non-inferiority margin of 14 points. To explore robustness of this primary analysis, we will also use an 'as-treated' approach and perform sensitivity analyses using similar mixed models, expanded with several patient and fracture characteristics (eg, frailty, grip strength, pain catastrophising, centre of inclusion, redisplacement and post-treatment physiotherapy) as covariates. Additionally, we will evaluate potential confounding and effect modification by these characteristics. DASH and EQ-5D-3L outcomes will be analysed using similar mixed models.

As it is not plausible to measure baseline ROM and grip strength of the fractured wrist, we will compare the difference between the fractured and the contralateral wrist at 1-year follow-up between groups, using unpaired t tests. Adverse events will be reported descriptively, and the incidence will be compared between groups using a χ^2 or Fisher exact test. The level of statistical significance is set at α=0.025 for the primary non-inferiority analysis, and at α=0.05 for the secondary analyses.

Economic evaluation

The economic evaluation will be performed from a societal and a healthcare perspective[28] and in accordance with the intention-to-treat principle. When the societal perspective is applied, all relevant costs accrued by the participants will be taken into account irrespective of who pays or benefits, whereas solely those accruing to the formal Dutch healthcare sector will be taken into account when the healthcare perspective is applied.[29] Intervention costs will be estimated using a microcosting approach.[30] Cost questionnaires will be administered on a 3 monthly basis to collect data on healthcare utilisation (primary care, secondary care and medication), the use of informal care and unpaid productivity losses during follow-up. Resource use will be valued in accordance with the Dutch Manual of Costing.[30]

Both a cost-effectiveness analysis in terms of the primary outcome (ie, PRWE) and a cost-utility analysis in terms of quality-adjusted life years (QALYs) will be performed. For the cost-utility analysis, the patients' EQ-5D-3L health states will be converted into utilities using the Dutch tariff.[31] The number of QALYs gained during follow-up will subsequently be calculated using linear interpolation between time points, with higher QALY values indicating a higher quantity and/or quality of life.

Missing data will be handled using multiple imputation.[32] Incremental cost effectiveness ratios and incremental cost utility ratios will be calculated by dividing the differences in costs by those in effects/utilities. Analyses will be performed using linear multilevel analyses in order to account for the possible clustering of data.[33] Bootstrapping techniques will be used to estimate uncertainty surrounding the cost-effectiveness estimates. Uncertainty will be shown in cost-effectiveness planes and cost-effectiveness acceptability curves. A secondary analysis will be performed according to the recommendations of Bosmans *et al*[34] to assess whether conservative treatment is non-inferior to surgery. Sensitivity analyses will be performed to test the robustness of the results (eg, per-protocol analysis, likely EQ-5D-3L values).[35–37]

Monitoring

This study will be monitored on a yearly basis. A dedicated trial monitor will conduct an onsite monitor visit. The trial monitor is employed by the initiating centre.

Every year, three of the participating centres are selected for remote monitoring.

Ethics and dissemination

This study will be conducted in accordance with the Declaration of Helsinki and the Medical Research Involving Human Subjects Act (WMO - Wet medisch-wetenschappelijk onderzoek met mensen). Also, all institutional review boards have approved the start of the study. All substantial amendments to the protocol will be notified to the ethics committee. Non-substantial amendments will not be notified to the accredited Medical Ethical Committee but will be recorded and filed by the sponsor. Written informed consent will be obtained from all participating patients. The research coordinator will report all Serious Adverse Events (SAE) within 7 days of

noticing, using the online submission system of the ethics committee. The ethical committee judges will decide whether the safety of the patients is jeopardised and whether the trial can be continued or not. We will submit our study results for publication in peer-reviewed journals and present at international conferences.

We aim to disseminate our results to guideline committees.

Anonymised data sets are available on reasonable request and/or in collaboration with other research project. Our aim is to combine study data for an individual patient data meta-analysis.

Patient and public involvement

As part of the grant acquisition progress, this study protocol was reviewed by the Netherlands Patients fFederation (Nederlandse Patiëntenvereniging - NPV).

The patient council of the coordinating centre (OLVG) reviewed patient information letter and the patient informed consent form.

Furthermore, our website will be updated on a regular basis to keep patients, media and participating centres well informed about study progress.

Data management

The study data will be collected by dedicated researchers employed by the initiating centre. Patient data will be stored in password-protected files and computers. Hard copy files will be stored in locked file cabinets. Outcome data are collected and are stored in a secure online database. The data in the online database are anonymised.

DISCUSSION

This is the protocol for an RCT in which we compare ORIF with cast treatment for elderly patients with a displaced intra-articular distal radius fracture with a non-acceptable position after reduction. Alongside this trial, we will perform a full economic evaluation.

The study has a non-inferiority design. If cast treatment proves to be non-inferior to surgical treatment in terms of patient-reported wrist function, the choice of treatment can be based on other factors such as patient preference or costs of treatment. In the economic evaluation, we will quantify the healthcare and societal costs of both treatments in relation to patient-reported wrist function and quality of life over 1 year.

Despite the effort we put in the protocol to avoid methodological weaknesses, this study is not without limitations. The major issue, as in many RCTs, is the external validity. According to the literature, there is currently no evidence that surgically treated elderly patients have a more favourable outcome than non-operatively treated patients. Nevertheless, surgeons may believe, based on own experience, that it would be unethical to withhold surgery from active and fit elderly patients. On the other hand, a surgeons also might refuse to perform surgery on a patient who, in their opinion, will be better off with a cast. Even though the subject at hand is controversial and opinions differ widely, we aimed to design the study in such a way that a majority of participating surgeons would agree with the therapeutic uncertainty, or equipoise, in this study population. By diligently choosing inclusion criteria such as 'living independently' and exclusion criteria such as 'suffering from dementia', we aim to exclude elderly who are very fragile and who are virtually never candidates for surgery. Also, we designed the study with two strata; one for patients from 65 to 75 years of age and one stratum for patient aged 75+. Each stratum had their own randomisation schedule. This allowed participating centres who did not want to include patients aged 65–75 to only randomise patients aged 75 or older.

Nevertheless, we cannot rule out the fact that patients will be withheld from the study by their treating physician because of a lack of equipoise. Therefore, we will also conduct a cross-sectional study on patient characteristics and clinical outcomes of patients who do not participate in the RCT. This is important to appraise the generalisability of the study findings. The patients in the cross-sectional study are treated at the coordinating hospital. These patients must meet the same inclusion criteria as the patients in the RCT. Clinical outcomes will be acquired once, at least 1 year after trauma. The results of this study will be published in a separate article.

This is a pragmatic study. This means participating centres may follow their local protocols and practices. As a result, there will be differences in, for example, reduction techniques, the duration of cast treatment, physiotherapy, surgical techniques and anaesthesia. These differences cause variety. However, by allowing this variety, the study will be more feasible and more importantly, the study will better reflect current practice. Therefore, the results of this study will be more generalisable.

Up to date, there has not been a definitive answer to the question whether elderly with a displaced distal radius fracture in general benefit from surgery but current literature suggests that there is no benefit from surgery.[3] With this study, we aim to produce the highest quality evidence for the treatment of displaced AO type C distal radius fractures in patients over 65 years old with a non-acceptable position after reduction.

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Competing interests None declared.

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