RESEARCH PROTOCOL

Kinetic motor imagery training during immobilization to improve wrist functional outcome after a distal radius fracture in women of 45-75 years of age

PROTOCOL TITLE: Kinetic motor imagery training during immobilization to improve wrist functional outcome after a distal radius fracture in women of 45-75 years of age

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Laboratory sites	Not applicable.
Pharmacy	Not applicable.

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Distal radius fracture (DRF) is a common injury that may lead to prolonged function restrictions, decreased range of motion, reduced grip strength and pain. These symptoms may be caused by physical changes due to the injury and/or by the 4-6 weeks immobilization that is part of the conservative treatment. However, it might also be that neural changes during the immobilization play an important role. Such changes might be prevented by motor imagery training during the immobilization period. So, when neural changes are prevented, this may lead to a better functional outcome.

Objective: The objective is to improve the functional outcome in distal radius fracture patients, specified as an increase in function, dexterity, grip strength, range of motion, and decrease of pain.

Study design: Parallel group randomized controlled trial, with a post-test only control group design. Patients in the experimental group perform motor imagery training during the immobilization period, in addition to the regular treatment. Patients in the control group receive regular treatment.

Study population: Female DRF-patients who are conservatively treated by a cast, aged 45-75 years. The fracture must be a low energy trauma caused by a fall. Patients with a score higher than 72 on the internal scale of the Vividness of Motor Imagery Questionnaire (VMIQ) are excluded, as well as patients with co-morbidities that might influence the wrist function, or motor imagery-ability, and patients with no understanding of Dutch language.

The patients are randomly allocated to the experimental or control group by restricted randomization to ensure equal group sizes. The randomization is conducted with use of PASW Statistics 18.

Intervention: Motor imagery training; 4 times a day 7 minutes of motor imagery training for 3 weeks (depending on duration of immobilization period).

Main study parameters/endpoints: The main study parameter is function. Secondary study parameters are dexterity, range of motion, grip strength, and pain.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: During the immobilization period, the patients in the experimental group are asked to perform motor imagery 4 times a day, whereby each session takes 7 minutes, so the time expenditure is 28 minutes a day. The outcome measures are determined twice in each group;

directly after cast removal and two weeks after cast removal. The measurements take place at the moments that the patients visit the hospital for a protocolized outpatient visit. Thus, the measurements do not require extra hospital visits.

Although there is only one study that examined the effectiveness of motor imagery training in peripheral injuries, many studies are conducted that demonstrate the effectiveness of motor imagery training in stroke patients, athletes and healthy subjects. Based on these studies, it is expected that motor imagery training will benefit recovery after a distal radius fracture. To our knowledge, there are no studies that identified the risks of motor imagery training. Since motor imagery training does not contain motion, it is highly unlikely that the intervention is harmful to the patients.

1. INTRODUCTION AND RATIONALE

1.1 Relevance

Distal radius fracture (DRF) is a common injury (1-5). In adults, the incidence rates for women are 368 per 100.000 persons per year, and for men 90 per 100.000 persons per year. (6). Incidence rates are higher with increasing age, due to a higher tendency to falls. They are also higher in women compared to men, mainly due to osteoporosis (4).

A DRF can be treated either conservatively or surgically by different methods, immobilization by plaster cast is one of it. Most DRF's are treated conservatively, especially when the fracture is not impacted, is reducible, stable and the joint surface is not involved. Mostly, a plaster cast is applied for 4-6 weeks to avoid the loss of fracture reduction (7). This immobilization period causes physical changes like muscle atrophy (8-10) and contractures (11,12).

Usually, DRF-patients are advised to do exercises after the immobilization period to prevent further complications associated with the fracture or the treatment, optimize functional recovery, and to be able to achieve normal functioning in activities of daily living again (13,14). However, research has shown that many DRF-patients suffer from pain, disability, decreased range of motion and reduced grip strength, shortly, but also long after the injury (15-18). It is reported that even after a few years, ranging from 2 to 26 years after injury, DRF-patients still had function restrictions (18). Also when DRF-patients follow a physiotherapy course or a home exercise program, 45-95% still have some form of pain and reduced function (15-17), which are most profound on work related and recreational activities (15,16). The fact that physiotherapy does not seem to improve the functional outcome (19-24), can partly be explained by high energy traumas and osteoporotic fractures (25). Such traumas mostly involve anatomical deformations which are related to poor functional outcome (26). However, in other cases with low energy trauma, it is likely that other factors relate to the functional outcome too.

Limb disuse and immobilization can cause neural changes, such as reorganization in the sensorimotor cortex and cerebellum, and changes in excitability of the motor cortex (27-29). When this happens during immobilization after DRF, it will partly be responsible for complaints as clumsiness and functional restrictions that DRF-patients report (30-33). Motor imagery during the immobilization period might prevent (part of) these neural changes. Motor imagery is the mental process by which a subject performs an action mentally, and it has been found that during motor imagery, overlapping cortical areas are activated as during real execution of the same movement (34-37). So, motor imagery training of wrist movements during the

immobilization period following a DRF might prevent neural changes caused by limb disuse, which might underlie part of the remaining problems of these patients. Therefore, the aim of this study is to determine whether motor imagery training during the immobilization period following a DRF might prevent functional decay as result of limb disuse on short term. This might lead faster to a better functional outcome.

This study contributes to the existing knowledge of the effectiveness of motor imagery training, and it provides new knowledge about the effect of motor imagery during immobilization after peripheral injury. Furthermore, when it is found that motor imagery during immobilization following a DRF is beneficial, a simple and cheap rehabilitation method is found that can be used in addition to existing rehabilitation methods in treating DRF. When DRF-patients recover more quickly, health costs will decrease, and patients will be able to return to work and to normal daily activities earlier. This is an important aspect, because it is found that work related activities and recreational activities are affected most and the most prolonged (15,16).

1.2 Theoretical framework

They say 'Use it or lose it' when it comes to the health of the brain. This is demonstrated by the finding that limb disuse and immobilization cause cortical changes (38,39). This might be caused by diminished afferent input. Many studies have shown that the absence of afferent input, caused by injuries, diseases, or anesthesia, leads to cortical reorganizations (40-44). Areas in the sensory and motor cortex that do not receive input, will be taken over by adjacent areas (42,44,45). This process reflects the plasticity of the brain, changes in peripheral structures can cause large cortical reorganizations (46). It is therefore suggested that absence of efferent output causes such cortical reorganizations too.

The fact that conservative treatment of DRF involves a longer period of immobilization, suggests that the immobilization itself is partly responsible for complaints as clumsiness and functional restrictions following DRF (30-32), which would mean that immobilization causes undesirable effects. The immobilization itself cannot be avoided, but the corresponding neural changes might be, by using motor imagery. Motor imagery is the mental state in which an individual performs an activity mentally and explicitly feels himself performing it, without actually performing the activity physically (47). This mentally rehearsing of activities and movements is used as treatment method of many diseases of the central nervous system, like Parkinson's Disease (48) and stroke (49-53). Although motor imagery training is found to be effective in

enhancing complex motor skills (54-56), strength (55,57), and reaction time (55) in athletes, little research has been published to determine the effect of motor imagery on recovery after peripheral injuries, such as a hand injury. One study provides evidence that motor imagery is beneficial in rehabilitation following immobilization after hand injury (31).

1.3 Hypothesis

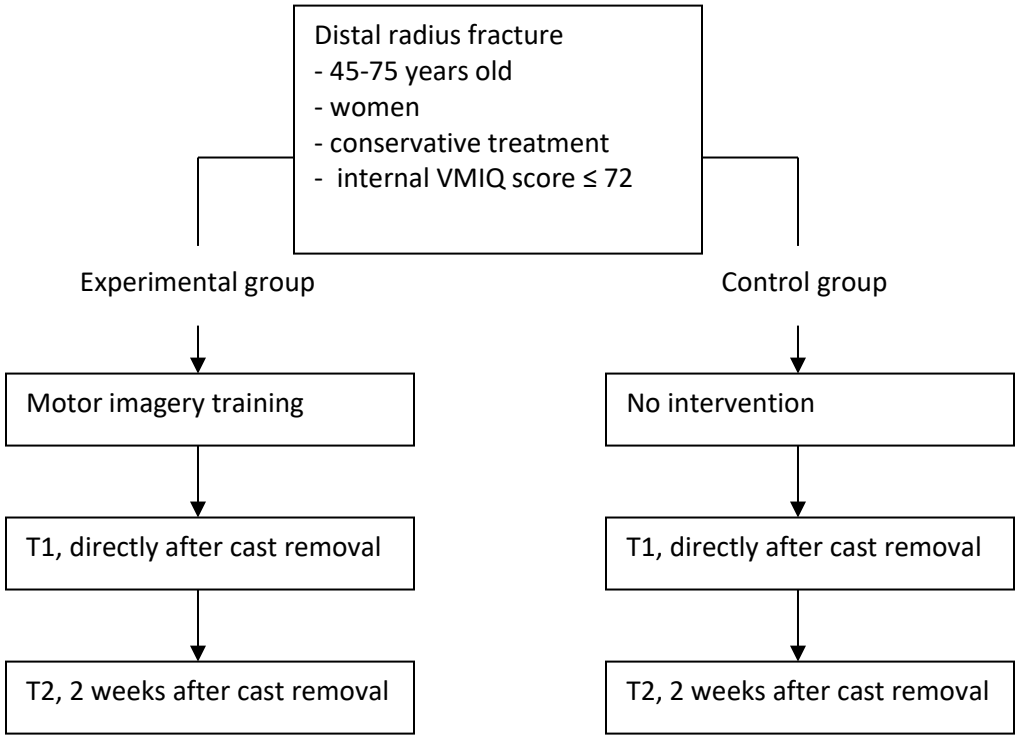
We hypothesize that motor imagery training during the immobilization period improves functional outcome, specified as an increase in function, dexterity, grip strength and range of motion, and a decrease in pain.

2. OBJECTIVE

The objective is to determine whether motor imagery training during the immobilization period in DRF patients, leads to an improved functional outcome, specified as increasing function, dexterity, grip strength, range of motion, and decreasing pain.

3. STUDY DESIGN

The above hypothesis can be tested by conducting a parallel-group randomized controlled trial. The duration of this study is 5 weeks, depending on the length of the immobilization period. The patients will be measured during their visits to the hospital. The first measurement is conducted directly after removal of the cast. The second measurement is two weeks later, when the patients visit the hospital for their check-up appointment. A schematic view of the study is given below:



4. STUDY POPULATION

4.1 Population

Participants are selected among distal radius fracture patients who are conservatively treated by plaster cast, or by closed reduction followed by plaster cast, from the University Medical Center Groningen. Female patients aged between 45-75 years will be included, because DRF is most common in women of 45-75 years of age (58). Patients are excluded when the internal (first perspective) VMIQ-score is higher than or equal to 72 points. This indicates that they are unable to perform motor imagery adequately.

4.2 Inclusion criteria

- Distal radius fracture patients diagnosed after radiological assessment
- Female patients
- Aged between 45-75 years
- Conservative treatment by plaster cast, or closed reduction followed by plaster cast
- Low energy trauma caused by fall

4.3 Exclusion criteria

- Internal Visual Motor Imagery Questionnaire-score ≥ 72
- Intra-articular, communitive fractures of the distal radius
- Complications likely resulting in worse functional outcome (e.g. dislocation)
- High energy trauma (such as car accidents or by falls from height)
- Pre-existent upper-extremity disorders
- No understanding of Dutch language

4.4 Sample size

This is the first study that investigates the functional outcome effect of motor imagery training during the immobilization period in DRF-patients. Therefore, the sample size calculation cannot be based on data of an imagery intervention during immobilization on function after a DRF. In this study, function is the primary outcome variable, and it is measured using the Patient Rated Wrist/Hand Evaluation (PRWHE). This instrument is derived from the Patient Rated Wrist Evaluation (PRWE). The only difference between the PRWE and PRWHE is that the PRWHE contains extra questions about aesthetics. It still contains the originally validated questions,

format and scoring system. The added questions about aesthetics are not part of the scoring. Therefore, it can be treated as the PRWE (59). The PRWE is proven to be the most responsive instrument to measure outcome in DRF-patients (60), as it measures disability during usual and specific activities and also documents pain. Subjects can score from 0 to 100 on the PRWHE; 0 indicates no problems at all and 100 indicates large functional difficulties and severe pain. The sample size calculation will be based on the expected outcomes of motor imagery training on the PRWHE.

Description of calculation process

A previous study has described the change of the PRWE-score over time as a result of the process of natural recovery after a DRF (61). Based on the results of this study, a mathematical model was created using Matlab R2010a that estimates the PRWHE-scores between data collection moments. This way, a model was build to estimate the natural recovery process with respect to the outcome of the PRWHE. Using this model, it could be determined what the decrease of the PRWHE-score is, two weeks after cast removal. The results of this model showed that a decrease of 10 points can be expected between the first (T1) and second measurements (T2). This decrease is due to natural recovery, and therefore, we expect it to be present in both groups.

Based on expert's knowledge, we find a 1 week lead in the functional recovery of the motor experimental group on the control group a clinically significant difference. With use of the mathematical model, the change in the PRWHE-score after 1 week after cast removal could be estimated. Next, the mean standard deviation of the PRWHE-scores over time was calculated. By dividing the change in the PRWHE-score by the mean standard deviation, the effect size was calculated. Now, the sample size could be calculated using the statistical power analysis software G*Power 3 (62).

Effect size calculation

The model describing the change in the PRWHE-score as result of natural recovery following a DRF, showed that 1 week after cast removal a decrease of 5.3 points on the PRWHE can be expected, which indicates improved function. This would mean that the experimental group would show an extra decrease of 5 points on the PRWHE, two weeks after cast removal.

The mean standard deviation was calculated using the following formula:

$$\sigma = \sqrt{\frac{n_x^2 s_x^2 + n_y^2 s_y^2 - n_y s_x^2 - n_y s_y^2 - n_x s_x^2 - n_x s_y^2 + n_y n_x s_x^2 + n_y n_x s_y^2 + n_x n_y (\overline{X} - \overline{Y})^2}{(n_x + n_y - 1)(n_x + n_y)}}$$

This provided a mean standard deviation of 26.13… points.

The effect size was calculated using the following formula:

$$ES = \frac{\mu_1 - \mu_2}{\sigma}$$

This provided an effect size of 0.20…

Settings for sample size calculation

Test Family: F-tests

Statistical test: Repeated Measures ANOVA, within-between interaction

Effect size: 0.20

Significance level α = 5%

Preferred power = 80%

Number of groups: 2

Number of measurements: 2

Other settings were kept as the default setting.

Sample size calculation

The effect size, preferred power, significance level and two-tailed testing were entered in G*Power 3. Running the program resulted in a calculated sample size of 52 patients.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

The treatment that the experimental group receives is motor imagery training, in addition to the regular treatment. The control group receives regular treatment only. Motor imagery is the mental state in which an individual performs an activity mentally and explicitly feels himself performing it, without actually performing the activity physically (47). This mentally rehearsing of a task can be done with two different strategies, by visual or kinetic motor imagery. When a person imagines the movement from a third person perspective, it is called visual motor imagery. When a person imagines the movement from a first person perspective, as if they are performing the movement themselves, it is called kinetic motor imagery (63). Research has shown that the neural structures activated during kinetic motor imagery are more similar to the neural structures activated during movement execution, than when visual motor imagery is performed (64,65). For that reason, the imagery training of DRF-patients in the present study will consist of kinetic imagery.

Potential participants are informed about this study by sending them an information letter, directly after their initial hospital visit. Patients who want to participate, return an informed consent by mail. When the patients who are willing to participate visit the hospital for a medical check one week after initial treatment, they are asked to fill in the VMIQ, because the VMIQ-score is an important inclusion criterion. When the patients reach the inclusion criteria, they are included in this study. After that, they receive information about the measurements and patients in the experimental group receive also instructions about the motor imagery training. The patients in the experimental group do the motor imagery training at home, unsupervised. The training starts with 1 minute of relaxation, where the patients are seated comfortably in a quiet environment, with their eyes closed. Such relaxation has proven to be promote the concentration, and as a consequence, the vividness of motor imagery (66). After that, the motor imagery training starts for about 6 minutes. This is well within the recommended maximal duration of 20 minutes, and long enough to be effective, as research has shown that the longer the imagery training session takes, the smaller the beneficial effect is (67). The patients imagine flexion, extension, abduction, adduction, pronation and supination of their injured wrist, following the procedure as explained during the instruction. Each set of movements (i.e. flexion-extension, adduction-abduction, pronation-supination) is executed in blocks of 10 repetitions.

The series of movements (10 times flexion-extension, 10 times adduction-abduction, 10 times pronation-supination) is repeated three times. The patients are asked to follow this procedure 4 times a day, which will take about 28 minutes a day.

5.2 Use of co-intervention

Patients in the experimental group will do the motor imagery training in addition to the usual medical treatment and a usual session of advice by a physiotherapist, which patients receive after cast removal. The patients in the control group will receive usual medical treatment and session of advice by a physiotherapist, but no motor imagery training. This single session of advice by a physiotherapist, is part of the standard treatment protocol for DRF's. The DRF-patients receive tips how to handle their casted hand. DRF-patients do not receive physiotherapy during the immobilization period. Thereby, only DRF-patients with complications or with severe affected hand function long term (> 2 weeks) after the immobilization period, will be advised to visit a physiotherapist. So, the patients who will be included in the current study, will not receive physiotherapy during the study.

After the last measurements, all patients will be asked whether they followed other interventions or received other treatments during the study period. If this is the case, the results of that patient will not be included in the statistical analysis, to control for confounding effects.

6. INVESTIGATIONAL MEDICINAL PRODUCT

Not applicable.

6.1 Name and description of investigational medicinal product(s)

6.2 Summary of findings from non-clinical studies

6.3 Summary of findings from clinical studies

6.4 Summary of known and potential risks and benefits

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labeling of Investigational Medicinal Product

6.8 Drug accountability

7. METHODS

7.1 Study parameters

Based on literature about the outcome following a DRF (19-24), and experts' opinions, we decided to use 5 outcome measures. The main outcome measure is function. Other outcome measures used are the range of motion, grip strength, dexterity, and pain.

7.1.1 Main study parameter/endpoint

Research has shown that DRF-patients suffer more on long term from function restrictions than pain (15,16). Therefore, function is the main outcome measure. Function is measured using the Patient Rated Wrist/Hand Evaluation (PRWHE). This instrument is developed to measure disability during usual and specific activities, and it also documents pain and aesthetics. The PRWHE is derived from the PRWE and contains some extra questions about aesthetics. Because the PRWHE retains the originally validated questions, format and scoring system of the PRWE, it can be treated as the PRWE (59). A study that critically reviewed the available outcome assessment tools, showed that the PRWE is the most responsive instrument to measure outcome in DRF-patients (60). The PRWE is a self-rated questionnaire, and its mean completion time is 4 minutes (61). It consists of 15 questions, divided in 3 domains; pain, functional activities, and usual activities. The patients have to rate the severity of their pain or disability in different situations. The final score of the PRWE and PRWHE lies between 0-100, where 0 represents the best and 100 represents the worst outcome. The PRWE is found to be reliable and valid, and therefore provides a simple and quick method to measure patient-rated pain and disability (61).

7.1.2 Secondary study parameters/endpoints

Secondary outcome measures are dexterity, active range of motion, grip strength, and pain. The Sequential Occupational Dexterity Assessment (SODA) is used to determine dexterity. The SODA is a valid and reliable instrument that measures bimanual dexterity during activities of daily living (68). The SODA consists of 12 tasks, and it takes 20 minutes to complete it. The performance on the tasks is scored by the experimenter. The score for each task is build up by two different components. One component concerns how the task is performed, and the other component concerns the difficulty the patient experiences during the execution of the task. For some tasks, only one hand is scored, while for other tasks both hands are scored. The final score

ranges from 0-108, where 0 means that the patient is unable to perform any of the tasks, and 108 means that all tasks were performed as requested without any difficulty (68).
Range of motion (ROM) is determined using a digital goniometer. Because unrestricted movement is essential for normal function, wrist movement in all directions is measured; flexion, extension, radial deviation, ulnar deviation, pronation and supination. The literature available concerning the amount of measurements needed to provide reliable outcomes, is contradicting (69). Some researchers have found that only one measurement is sufficient (70), whilst others have found that the average of several measurements is more reliable than one measurement (71). It is recommended to use the average of multiple measurements in the ROM that shows large variation or a systematic increase (69). We repeatedly measured the different ranges of motion, and this provided consistent results. Based on this we decided to use a single measurement of each aspect of ROM (i.e. flexion, extension, abduction, adduction, supination, and pronation). To control for within-group variability, ROM is measured on both hands.
Grip strength is important for the execution of many occupational activities (72). It is measured using a hydraulic dynamometer, which is found to be reliable and valid (73). Research has shown that the position of the wrist can influence the maximal grip strength that can be applied. This is especially the case when the wrist is in ulnar or radial deviation, which is one of the deformities that is common after a DRF malunion (74). Therefore, it is useful to determine different grip strengths; grasp, tip pinch, key pinch, and three-jaw chuck pinch (72,73). The measurements will be conducted using a standardized protocol (73), to counter the effects of confounders. The mean of three trials has the highest test-retest reliability (73), and therefore, it is decided to measure the strength of each grip three times. To control for within-group variability, grip strength is measured on both hands.
Two dimensions of pain are measured using a Visual Analog Scale (VAS) (75); pain intensity and pain relief (76). This results in a score between 0 and 100, where 0 represents severe pain and low pain relief, and 100 represents no pain and large pain relief.

7.1.3 Other study parameters

Confounding factors that might influence the dependent variables are age, motor imagery ability, type of fracture, occupation, sport activities and involvement of their casted hand in activities. The patients will be asked for their occupation, sport activities and involvement of the

casted hand in activities. The confounding factors will be included in the statistical analysis as covariates to control for their influence.

7.2 Randomization, blinding and treatment allocation

Potential participants are randomly allocated to the experimental or control group before the start of the study, i.e. before inclusion. In this way, the potential participants allocated to the control group can receive other information about this study than potential participants allocated to the experimental group. This is done to prevent occurrence of the bias that might be present when the patients in the control group are aware of the working mechanism of motor imagery, and its potential benefits. When the patients in the control group know that they participate in a study that is conducted to determine whether motor imagery can promote the recovery after DRF, it is possible that they perform motor imagery during the immobilization, or pay more attention to their injured hand as normal. Such bias cannot be detected and may severely confound the results of this study. Therefore, we decided to keep the patients in the control group ignorant.

Because randomization is performed before inclusion, it is likely that some patients will decide not to participate, reducing the number of participants in that group. The experience of 2.5 years inclusion teaches us that the response rate to participate is different for each group (experimental group 35%, control group 62%). Therefore, the number of patients who will be asked to participate is controlled for this difference. This means that more patients are allocated to the experimental group, than to the control group. The random allocation is performed with remaining equal group sizes, and equal distribution of the different fracture types (intra-articular vs. extra-articular distal radius fractures).

The randomization process is done using PASW Statistics 18. Subject numbers are randomly allocated to the experimental or the control group. The order in which the patients receive their initial treatment determines their subject number. There is no blinding of the patients, nor the researcher is blinded.

Based on national statistics concerning the diseases and injuries diagnosed on a yearly basis, it is expected that 6-7 DRF-patients will be treated in the UMCG every week, and 2-3 of them will be women of 45-75 years of age (58).

7.3 Study procedures

The study coordinator checks the diagnose lists of the department of Traumatology and Orthopedics, and indentifies the female DRF-patients in the age of 45-75 years of age, who are conservatively treated. These patients will be randomly allocated to the experimental or control group. They receive an information letter and are asked to participate. When they decide to participate, they return an informed consent. When the patients visit the hospital for a medical check one week after initial treatment, the patients who are willing to participate are asked to fill out the Vividness of Motor Imagery Questionnaire. A score of 72 point or less on the internal scale (first person perspective) of the VMIQ, is one of the inclusion criteria. Therefore, this questionnaire is filled out before inclusion. The score on the VMIQ determines whether the patient can participate in the study or not. The patients who are allocated to the experimental group will receive information and instructions about the motor imagery training. To promote the imagery, the instructions are task-related:

- Flexion and extension: Patients are asked to imagine making a fist and imagine that they are slowly knocking on the table with their knuckles, making an exaggerated large movement.
- Adduction and abduction: Patients are asked to imagine that there are two dots drawn horizontally on the table in front of them. The hand lies between those dots, but there is still space between the hand and the dots. They are asked to imagine that they are trying to touch the right and the left dot with their little finger and thumb repeatedly, by only moving the palm of their hand.
- Pronation and supination: Patients are asked to imagine that they turn a key back and forth, by only using their hand and forearm.

In addition to these task-related instructions, the movements that have to be imagined are demonstrated by the study coordinator. Next, the patients are asked to repeat that movement once with their uninjured hand. The patients receive a letter that contains the instructions and are asked to repeat this protocol unsupervised at home. To promote their adherence to the motor imagery training, the patients in the experimental group will be contacted by phone on a weekly basis. To control for bias as a consequence of this extra attention, also the patients in the control group will be contacted by phone weekly.

Three weeks later, which is 4 weeks after injury, the patients return to the hospital to remove the cast. At that moment, the first measurements will be performed. All tests will be performed by the study coordinator. Directly after cast removal, when they are still at the hospital, dexterity, the level of pain and pain relief, grip strength and range of motion will be determined. The PRWHE will be performed one day later by phone. Two weeks after cast removal, the second measurements will be conducted. Function, dexterity, the level of pain and pain relief, grip strength and range of motion will be measured.

The measurements will take place in the University Medical Center Groningen. The PRWHE and the VAS can be scored by the patients themselves, while the measurements with the SODA, goniometer and dynamometer will be conducted by the study coordinator. It is expected that the first measurements will take 30 minutes to complete, and the second measurements 35 minutes.

As explained in chapter 7.1, function is measured using the PRWHE. The PRWHE is a self-reporting instrument that determines the level of disability during specific and usual activities, and also contains some items to determine the level of pain and aesthetics (59). It takes on average 4 minutes to complete the questionnaire (61).

A digital goniometer is used to determine the active ROM. It is expected that the process of measuring ROM takes 6 minutes to complete.

Grip strength is measured using a hydraulic dynamometer (73). The strength of four different grips will be determined, according to the protocol as described by Mathiowetz et al. (1984). It is expected that the procedure to measure the grip strengths takes 4 minutes to measure both sides.

Dexterity is determined using the SODA. The SODA is a performance-based test, which measures the level of disability during activities of daily living (68). We expect that it takes 20 minutes to complete it. Instructions of the SODA will be given according to the protocol described by Van Lankveld et al. (1996).

The level of pain and the level of pain relief are determined using a VAS (75), a self-reporting scale. It is expected that it only will take a few seconds to complete it.

7.4 Withdrawal of individual subjects

The patients are free to withdraw from the study at any time, for any reason, and without consequences. Patients are withdrawn when the study coordinator thinks that participation by a

patient is unsafe, or when the medical condition changes in such way that participation is impossible or unadvised.

7.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

7.5 Replacement of individual subjects after redrawal

Individuals will be replaced after redrawal. The first eligible patient that presents at the first aid department will be allocated to the group of the redrawn patient, to remain equal group sizes.

7.6 Follow-up of subjects withdrawn from treatment

Patients who withdraw from the treatment will be followed-up. Because the patients are asked to enter the number of motor imagery sessions each day in a diary, it still provides information concerning the effectiveness of motor imagery training.

7.7 Premature termination of the study

When interim-analysis indicates that motor imagery causes deterioration of the hand function, causes severe pain, or causes other unwanted effects, this study will be terminated.

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / the experimental treatment]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions..

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Not applicable.

8.2.2 Annual safety report

Not applicable.

8.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

9. STATISTICAL ANALYSIS

9.1 Descriptive statistics

Patient characteristics are presented using descriptive statistics for the potential confounding variables.

Data of the main outcome measure are of interval level of measurement. The ROM and grip strength are of ratio level of measurement. Hence, the descriptive statistics of these outcome measures are presented by the mean and standard deviation. Dexterity is measured using the SODA, and the data of this instrument are of ordinal level of measurement. Therefore, the descriptive statistics are presented by the median and range. Pain is measured using the VAS, which provides data of interval level of measurement. So, the descriptive statistics are presented by the mean and standard deviation.

9.2 Univariate analysis

The effectiveness of motor imagery training will be determined with use of a multivariate analysis for the parametric data (as described later in chapter 9.3). The non-parametric data are analyzed using a Mann-Whitney U test for each variable, to determine whether the groups are different. This test is also used when the data is not normally distributed.

9.3 Multivariate analysis

With use of a MANOVA, the difference between the experimental and control group will be determined for each measurement time and for each variable. There are two factors included in the analysis; a between factor ‘group’ and a within factor ‘time’. The hypothesis is tested using two-tailed tests, with a significance level of 5%. The data of the patients in both groups will be analyzed using an intention to treat analysis.

9.4 Interim analysis (if applicable)

An interim analysis will be conducted to determine the effect of motor imagery training on hand function, dexterity, ROM, grip strength and pain. When the results of this analysis shows serious unwanted effects of motor imagery training, this study will be terminated.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

We state that the study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

10.2 Recruitment and consent

The diagnose list of the Emergency department of the University Medical Center Groningen is checked daily for DRF. Within 48 hours after initial treatment, an information letter is sent to the patients who reach the inclusion criteria to inform them about this study and ask them for their participation. As explained in chapter 7.2, potential participants are already allocated to the experimental or control group, so the patients in the experimental group receive an information letter that is different from the information letter that the patients in the control group receive. In this letter, the patients are asked for their participation. When they are willing to participate, the patients return a signed informed consent. One week after initial treatment, the patients return to the hospital for a check-up appointment. At that moment, they have had 5-7 days to consider their participation. In the outpatient clinic, the patients who sent back a signed informed consent are asked to fill out the Vividness of Motor Imagery Questionnaire (VMIQ). The outcome of this test determines the final inclusion or exclusion of the patient. Patients who have an internal VMIQ-score > 72 are excluded, because this indicates that their ability to perform motor imagery is low. The patients with a VMIQ-score ≤ 72 are included . Patients allocated to the control group receive information about the measurements, the measurement times and the duration of the study. Patients allocated to the experimental group receive the same information about the measurements and duration, but also instructions to do motor imagery training. The patients in both groups will receive an information letter, but the patients in the experimental group also receive a letter that contains the instructions to do motor imagery training.

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

10.4 Benefits and risks assessment, group relatedness

Benefits

DRF is a very common injury, especially in elderly women (1-5). In most conservatively treated cases, the patients are immobilized by a plaster cast for 4 to 6 weeks (7). Immobilization can lead to muscle atrophy (8-10) and contractures (11). Research has shown that immobilization or limb disuse can cause cerebral reorganization and decreased excitability of the motor cortex (27-29,38), and therefore, can lead to deteriorated motor performance (77). During motor imagery, partly the same cortical areas are activated as during execution of movement (34-37). So, motor imagery might prevent such neural changes as cerebral reorganization and decreased excitability (31). Many studies to determine the effectiveness of motor imagery training are conducted in stroke patients, and these studies show that motor imagery is effective in regaining arm function (49,50,53,78). By making the patients do motor imagery training during the immobilization period, it is expected that these patients have a better outcome when their cast is removed. Hereby, these patients might recover more quickly, and possibly reach a better final outcome.

Risks

The risk of participation in this study is negligible. Measuring function and pain with use of respectively the PRWHE and VAS which are questionnaires, is not harmful to the patient. The measurement of ROM and grip strength is already part of the regular treatment protocol of DRF. Therefore, the measurements conducted in this study to determine ROM and grip strength will not provide a higher risk than the regular treatment protocol. The SODA is a test concerning the performance during activities of daily living. It is performed after cast removal when the medical treatment is completed. From that moment, the patients are advised to use their injured hand again, so it is improbable that the SODA will lead to a higher risk than the regular procedure. There are no studies found that determined the risks of motor imagery training. However, because the motor imagery training does not contain motion, it is highly unlikely that the intervention will be harmful.

The patients are measured twice, directly after cast removal and 2 weeks after cast removal. The measurements will take place during their regular visits to the hospital for a medical check, so this study does not require extra hospital visits.

Group relatedness

This study is group-related, as it is evident that this study can be conducted only with participation of DRF-patients.

10.5 Compensation for injury

Insurance

As the study has no risks, the Medical Ethical Committee of the UMCG decided to authorize dispensation from the statutory obligation to provide insurance (art. 4 paragraph 1 of 'Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen).

10.6 Incentives (if applicable)

The patients participating in this study do not receive any special incentives or financial compensation.

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

The research data are handled and stored confidentially and anonymously. The principal investigator and study coordinator will have access to the source data. Only anonymous and not-personally-identifiable results of interim-analyses will be showed to other physicians and researchers who are not involved in this study. For publication purposes, also anonymous and not-personally-identifiable data will be used.

Questionnaires are stored in a cupboard in the office of the principal investigator. The principal investigator and study coordinator are the only persons who have access to this cupboard. Data files are stored on the personal account of the principal investigator and on the account of the study coordinator. These accounts are protected by passwords. The data will be stored for 5 years.

11.2 Amendements

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

11.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/serious adverse reactions, other problems, and amendments.

11.4 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the

accredited METC.

11.5 Public disclosure and publication policy

The investigators have nothing to disclose. The results of this study will be published in a peer reviewed scientific magazine.

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