Ototoxicity in patients with Metal-on-Metal hip Arthroplasties

PROTOCOL TITLE: Ototoxicity in patients with Metal-on-Metal hip Arthroplasties

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PROTOCOL SIGNATURE SHEET

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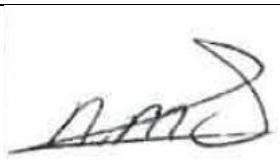
Principal Investigator ***Dr. N.M.C. Mathijssen***		**11-07-2022**
Coordinating Investigator ***M.C. Koper***		**11-07-2022**

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
AR	**Adverse Reaction**
ARMD	**Adverse Reaction to Metal Debris**
Co	**Cobalt**
Cr	**Chromium**
ENT	**Ear, Nose, Throat**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MoM	**Metal-on-Metal**
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.**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Patients with a Metal-on-Metal (MoM) hip prosthesis have an increased risk of elevated serum metal ions. High plasma levels of cobalt (Co) and chromium (Cr) are associated with local and systemic adverse reactions. Ototoxicity, such as hearing loss, tinnitus and dizziness, could be related to high plasma levels of these ions.

Objective: To evaluate the prevalence of ocular-vestibular symptoms in patients with a (revised) MoM hip prosthesis. Our hypothesis is that patients with high plasma metal ion levels have a higher prevalence of damage to the auditory system.

Study design: Multi-centre cohort study.

Study population: All patients with MoM hip arthroplasties implanted in the participating clinics (both revised arthroplasties as well as patients with an arthroplasty in situ).

Intervention (if applicable): A once only non-invasive auditory test, blood samples at the outpatient clinic and a questionnaire.

Main study parameters/endpoints: Auditory test results, levels of Co and Cr in patients with MoM hip arthroplasties, subjective hearing loss and general

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden is primarily time, a questionnaires and one visit to the outpatient department. During that visit we will also obtain a blood sample.

1. INTRODUCTION AND RATIONALE

Many young patients with end stage hip osteoarthritis received hip arthroplasty with a Metal-on-Metal (MoM) bearing in the mid-2000s. These MoM bearings offered lower wear-rates and early return to work and sport activities [1, 2]. However, due to the high revision rates, elevated serum cobalt (Co) and chromium (Cr) levels and Adverse Reaction to Metal Debris (ARMD) there is a significant decline in use of MoM bearings and in some countries even a prohibition [3-5].

Guidelines in most countries recommend a yearly outpatient control with physical examination and determination of plasma metal ion levels. The fact that increased serum metal ions are related to local adverse reactions (ARMD) is already proven, however the relationship with systemic effects is still unclear. Increased levels of plasma metal ions have been associated with different systemic diseases such as peripheral neuropathy, vision loss and hearing loss [6-10]. However, no clear relation has been established yet.

With this study, we aim to investigate the prevalence of ototoxicity (and related hearing loss) in patients with a (revised) MoM hip prostheses.

2. OBJECTIVES

HYPOTHESIS

It is hypothesized that patients with an episode or continuous high plasma cobalt or chromium levels (parts per billion) have a greater risk of damage to the auditory system, therefore, prevalence of ototoxicity (and hearing loss) will be higher in these patients compared to the prevalence of ototoxicity (and hearing loss) in patients with low plasma cobalt or chromium levels.

Primary objective:

To assess the prevalence of damage to the auditory system in patients with a Metal-on-Metal or revised Metal-on-Metal bearing, especially regarding mid frequency hearing loss. A distinction will be made between prevalence in patients with high plasma cobalt or chromium levels and patients with low plasma cobalt and chromium levels. A non-invasive, objective audiometry test will be obtained and serum metal ion levels will be determined.

Secondary objective(s):

To assess which factors are associated with damage to the auditory system (We will only perform this if possible, if we have enough cases with hearing loss).

- Factors of interest: highest known cobalt plasma concentration, highest known chromium plasma concentration, type of prosthesis, age, work in a noisy environment, presence of ARDM, revision
- Patients will be asked to complete the hearing questionnaire as well as the Metal-on-Metal Prosthesis Questionnaire for Assessing General Health in order determine the general health of these patients and subjective hearing loss.

3. STUDY DESIGN

All MoM patients from participating centers will be asked to participate in this study.

After informed consent, we will include the patient and allocate a research number. We will send them the questionnaires (online) and make an appointment for the hearing test in the participating center. If necessary, the questionnaires can also be completed during the clinic visit. During this clinic visit, blood will be obtained to determine the plasma Co and Cr levels.

4. STUDY POPULATION

4.1 Population

A total of 462 patients with a MoM hip prosthesis will be contacted.

- Reinier de Graaf Gasthuis: 153 patients received a large head MoM total hip prosthesis (160 prostheses).
- Erasmus Medical Centre: A total of 63 patients who received a resurfacing MoM hip prosthesis.
- HAGA Hospital: a total of 46 patients from received a large head MoM total hip prosthesis.
- Zuyderland Hospital: A total of 200 patients of which 143 received a resurfacing MoM hip prosthesis (39 bilateral) and 57 patients a large head MoM total hip prosthesis (16 bilateral).

Note: Patients of Reinier de Graaf Gasthuis and Haga Hospital are operated in that hospital. However, follow up might have been performed in Reinier Haga Orthopedic Center (RHOC). Therefore, RHOC will also participate in the current study.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all the following criteria:

- All MoM patients from the different clinics
- Revision MoM
- Willing to participate
- Speak/write the Dutch language.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Not willing to participate
- Previous ENT surgery or ENT pathology

4.4 Sample size calculation

We did not calculate a sample size since we will ask all MoM patients from the different centres to participate in the study.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

Prevalence of damage to the auditory system in patients with a Metal-on-Metal or revised Metal-on-Metal bearing, especially regarding mid frequency hearing loss. A distinction will be made between prevalence in patients with high plasma cobalt or chromium levels and patients with low plasma cobalt and chromium levels.

5.1.2 Secondary study parameters/endpoints

- If possible (if we have enough cases to perform the analysis); factors associated with damage to the auditory system in these patients will be determined:

  Factors of interest: highest known cobalt plasma concentration, highest known chromium plasma concentration, type of prosthesis, age, work in a noisy environment, subjective hearing loss (measured with the hearing questionnaire), presence of ARDM, revision

  - Work in a noisy environment will be determined through a question on (prior) work in a noisy environment.
- Subjective hearing loss and general health. Patients will be asked to complete the Amsterdamse questionnaire on hearingloss as well as the Metal-on-Metal Prosthesis Questionnaire for Assessing General Health in order determine subjective hearing loss and general health of these patients.

5.2 Study procedures

The physician will contact all patients who are known/operated in the various clinics and have a MoM hip prosthesis or revised MoM prosthesis by letter. Patients will receive written information on the study and the informed consent. After one week, these patients will be contacted by telephone by a member of the research team. These patients will be informed about the study and will be invited to participate.

If the patient agrees to participate, an outpatient clinic appointment will be booked. Patients of Haga, RHOC and RdG hospitals will be invited to visit RdG hospital in Delft. Patients of EMC or Zuyderland Hospital will visit the outpatient clinic of these hospitals. During the outpatient visit, the informed consent will be signed, a hearing test will be conducted to every patient by a trained student, nurse or physician. This test includes a non-invasive audiological test for about 30 minutes. Furthermore, a blood sample will be taken and the patients will be asked to complete a questionnaire, which can be done on paper (at the clinic) or online (at home).

If the hearing test result deviates from 'normal', assessed by the software, and related to age category, the test results will be reviewed by one of the researchers (DK) in Reinier de Graaf Hospital. Results of the hearing tests in the different hospitals are comparable regarding standards for 'normal' outcomes.
If the hearing results need further assessment or treatment the patient will be reviewed by the ENT specialist in their hospital.
If the results from the blood samples defers from the accepted values given by the Dutch Orthopedic Association, we will contact the patient and schedule an outpatient control appointment with their Orthopedic Surgeon.

In addition, we will also review the patients' medical history regarding surgery, previously measured cobalt/chrome values and whether there has been a previous ENT visit or hearing problems.
The patient data, plasma metal ion levels and hearing test results are collected in a Castor database.
The following data will be collected of each participant:
Age, gender, cobalt and chromium plasma concentration, highest known cobalt plasma concentration, highest known chromium plasma concentration, type of prosthesis, date of arthroplasty, work in a noisy environment, subjective hearing loss (measured with the hearing questionnaire), presence of ARDM, revision, hearing loss, previous ENT visit or hearing problems, general health.

5.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6. SAFETY REPORTING

6.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the investigator will suspend the study if there is enough ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

6.2 AEs and SAEs

6.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to trial procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

6.2.2 Serious adverse events (SAEs)

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

- results in persistent or significant disability or incapacity or;
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

The investigator will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

6.3 Follow-up of adverse events

All AEs 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.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

7. STATISTICAL ANALYSIS

Descriptive analysis will be performed for all patient's data and questionnaires. Statistical software (SPSS (IBM SPSS Statistics for Windows)) will be used.

Primary outcome

Prevalence of damage to the auditory system in patients with a Metal-on-Metal or revised Metal-on-Metal bearing, especially regarding mid frequency hearing loss will be determined. A distinction will be made between prevalence in patients with high plasma cobalt or chromium levels and patients with low plasma cobalt and chromium levels.

Groups with and without high plasma serum levels will be compared with a Chi Squared test on the absence/presence of hearing loss, for both cobalt as well as chromium.

Secondary outcomes

A logistic regression model will be made to determine factors associated with ototoxicity (and related hearing loss).
Potential predictors are: highest known cobalt plasma concentration, highest known chromium plasma concentration, type of prosthesis, age, work in a noisy environment, subjective hearing loss (measured with the hearing questionnaire), presence of ARDM, revision
First, a univariable logistic regression model will be performed to identify variables significantly associated with the outcome. Variables with $p<0.20$ will be selected for the multivariable model. Then, with backward elimination the model will be made.
The ROC curve and AUC will used as performance parameters. Goodness-of-fit will be determined with the Howmer-Lemeshow test.

If we do not have enough cases of hearing loss, no logistic regression model will be made. Instead, descriptive statistics will be performed and both groups will be compared with a Mann Whitney U test or Chi Squared test.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 7, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

8.2 Recruitment and consent

Patients will be sent information on the study by mail. Afterwards, a member of the study team will contact the patient by telephone. If the patient is willing to participate, an appointment with a member of the study team will be made. At this consultation, details about the study will be provided. After the patient decides to participate the informed content will be signed. Patients will be given a minimum of 5 days and maximally 21 days to consider participation. If a patient wishes more information about this study before deciding to participate, the orthopedic surgeon can be consulted.

8.3 Benefits and risks assessment, group relatedness

There are no risks of benefits associated with participation

8.4 Compensation for injury

The sponsor/investigator applies for exemption from insurance, since participation in this study is without any risk for the patient. The administration of an auditory test is without possible injuries or risk.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

The data is coded and will be handled confidentially. All subjects participating in the cohort study will be linked to a subject identification code. This code is based on the order of participating patients and the hospital in which the patient visits the outpatient clinic for the trial. Each patient receives an individual number. The investigator safeguards the key to the code. All data will be stored for 15 years. The handling of personal data will comply with the Dutch Personal Data Protection Act.

All data will be documented in Castor and stored at the network of the Reinier de Graaf Hospital, which is safe and of which a backup will be made every day. Patient data will be registered in Castor with a subject identification code. The subject identification code will be stored locally, at the hospital in which the measurements take place.

The coordinating researcher of the current study, monitors and the IGJ will have access to the source documents. The local research team will have access to the source documents of that hospital. Blood samples of all participating centers will be analyzed by the Reinier Haga Medisch Diagnostisch Centrum (RHMDC).

9.2 Monitoring and Quality Assurance

Monitoring of the study will be performed by the RdG/RHOC using a risk-based approach. Monitoring, among others, includes checking informed consents, in- and exclusion criteria, reported serious adverse events and the case report form. The frequency of interim monitoring visits (besides one site initiation visit, and one close out visit per study site) will be determined by the study's risk based on a risk classification tool.

9.3 Amendments

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

9.4 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.

9.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor 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.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, 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.

9.6 Public disclosure and publication policy

This study will be prospectively (i.e. before the first patient is recruited) registered on www.clinicaltrials.gov.

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