PROTOCOL NAME: Changes in quadriceps muscular activity in patients after total knee arthroplasty compared to healthy subjects

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Glossary of abbreviations:

TKA	Total Knee Arthroplasty
AMI	Arthrogenic Muscle Inhibition
QAB	Quadriceps Activation Battery
TUG	Timed Up and Go Test
NRS	Numeric Rating Scale
sEMG	Surface Electromyography

INDICE

1 Abstract

Title	Changes in quadriceps muscular activity in patients after total knee arthroplasty compared to healthy subjects
Coordinator of the study	**Roberto Gatti**
Protocol number	CLF19/03
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Introduction and rationale	During Total Knee Arthroplasty (TKA), the joint is subjected to considerable stress, which has been shown to be related to a recruitment and activation deficit of the quadriceps femoris muscle. The explanation for this correlation lies in a complex mechanism called Arthrogenic Muscle Inhibition (AMI). So far, AMI has been directly studied only in sub-acute and chronic phase after TKA because of the invasive procedures employed in order to evaluate it; However, clinical observation and some experimental studies also suggest the presence of this phenomenon in the initial postoperative days. The aim of the study is to investigate possible differences in quadriceps muscular activity, which could be associated with AMI and which may be investigated in the acute phase; data acquisition will be made on the first and third days after surgery.
Population and selection criteria	15 healthy subjects and 15 patients on hold for TKA will be recruited between July and September 2019. The inclusion criteria will be: age greater than 18 years old and a recent TKA or revision of TKA. Those patients with arthrogenic muscle inhibition before TKA with QAB<6 and the subjects with conditions (other than those which led to the TKA) that could interfere with quadriceps muscle activation or with motor performance will be excluded from the study.
Design and duration	Prospective observational study. It will start in July 2019 and the recruitment period should last until September 2019.
Aims	The primary aim of this study is the evaluation of possible differences in quadriceps muscular activation after TKA. Subjects will be asked to perform different tasks in isometric contraction, keeping the biomechanical context constant. Secondly, the correlation between the primary aim and the pain referred by the patient, registered using the NRS scale, will be investigated along with the patient's functional ability, assessed by means of the Timed Up and Go Test (TUG). There will be three assessment sessions: the day prior to the TKA procedure and at one and three days postoperatively.

Statistical methods and data analysis	At the end of data acquisition, the normality and homogeneity of the demographic variables will be assessed, as will the outcome measures at baseline. Differences in the outcome measures will be investigated with the t student test (or with the related non-parametric tests) and by means of the mixed models repeated measures ANOVA test. Linear regression will be applied so as to evaluate the correlation between outcomes.
Ethical considerations	The study population will comprise subjects who have undergone TKA; they will be assessed in isometric contractions of quadriceps femoris in the acute phase after surgery. It is assumed that this type of evaluation does not lead to adverse events, since in terms of demands made on muscle and joints, it is comparable with the physiotherapeutic treatment administered to all patients twice a day after TKA. The aim of this study is to understand how the quadriceps activates in acute phase after TKA in order to identify the best physiotherapeutic approach for the initial postoperative days. Data acquisitions will be made so as to allow the patients to participate in both physiotherapy sessions. For the study, the materials supplied to the Movement Analysis Laboratory of the Humanitas Clinic will be used. Each assessment session will last about 20 minutes.
Timing of the study	Recruitment of subjects: July– September 2019 Data analysis: September - October 2019 Report presentation: November 2019

2 Background and introduction

Total Knee Arthroplasty is currently considered an effective treatment in reducing pain, improving functional abilities and quality of life in patients with advanced-stage knee osteoarthritis and in other diseases affecting the knee joint [1] [2]. However, considering that TKA is recognised as major surgery, the knee joint is subjected to considerable stress. This has been shown to be related to a recruitment and activation deficit of the quadriceps femoris muscle, both in sub-acute phase (starting from two weeks after surgery) and chronic phase (up to one year if compared with the contralateral limb) [3] [4] [5] [6]. This complex mechanism is termed arthrogenic muscle inhibition (AMI), properly defined as the long-lasting inability to fully activate the quadriceps muscle in the absence of nerve damage, following surgery and/or traumatic injury of the knee joint [7]. Although AMI has to date been described only in sub-acute and chronic phase after TKA because of the invasive procedures employed in order to evaluate it, some researchers have investigated this phenomenon by inducing in healthy subjects the same symptoms which are characteristic of the immediate postoperative period following knee surgery. These studies report a positive correlation; in particular they have shown how, inducing inflammation, pain and increasing intra-articular pressure, a recruitment deficit of the quadriceps muscle arises [8] [9] [10]. Clinical practice and published scientific research indicate the presence of AMI also in the acute phase after TKA.

3 Rationale

For ethical reasons, there are no studies currently published that directly investigate the presence and the size of AMI in the initial postoperative days following TKA. Clinical practice, and the study of AMI in sub-acute patients and in experimental clinical conditions, indicate an activation deficit of the quadriceps from the first day following surgery. This study aims to evaluate the role that AMI could play in the postoperative acute phase after TKA, examining possible differences in the activation patterns of the quadriceps muscle between patients and healthy subjects.

The results could be useful to better manage the treatment of patients affected by a recruitment deficit of quadriceps muscle, by reducing motor impairment and by improving the quality and precision of the physiotherapy in the acute phase after TKA.

4 Aims

4.1 General aims

The objective of the study is to evaluate possible differences in quadriceps muscular activation after TKA during the acute phase, with a comparison with healthy subjects. Moreover, it will be investigated whether any correlation exists between the outcomes obtained, the pain reported by the patient and his or her functional ability.

4.2 Endpoints

4.2.1 Primary endpoint

The primary aim is to observe possible activation alterations of the quadriceps femoris, more specifically of the vastus medialis, lateralis and rectus femoris muscles, by means of electromyographic signal acquisition. The subject will be asked to perform different tasks in isometric contractions, without changing the biomechanical context. The subjects will be asked to perform a homolateral knee extension, a homolateral hip flexion, a contralateral hip extension with

a contemporary homolateral hip flexion. The activation of the three muscles will be recorded through surface electromyography (sEMG) with four channels (FREEEEMG 1000, BTS SpA). The electromyographic surface sensors will be positioned following the European SENIAM guidelines regarding vastus medialis, lateralis and rectus femoris of quadriceps femoris homolateral in terms of surgery access, in order to evaluate the activation intensity during the different tasks [11].

4.2.2 Secondary endpoint

The secondary aim is to understand whether there is a correlation between the acquired surface EMG data and the pain referred by the patient and the patient's functional ability. The secondary outcomes will be the pain referred by the patient and the patient's functional ability. The referred pain will be assessed through the Numeric Rating Scale (NRS) at the beginning of every session. The functional ability will be assessed with the Timed Up and Go Test (TUG) on the third day post-surgery and via a descriptive analysis on the patient's deambulation autonomy, considering the following characteristics: ambulatory aids, need for supervision or assistance, and maximum distance covered.

5.1 Inclusion criteria

- age: over 18 years.
- subjects eligible for TKA.

5.2 Exclusion criteria

- QAB (quadriceps activation battery) < 6 the day before the operation [12].
- neurological or musculoskeletal diseases (different from the causes that which led the patient to the TKA), which may interfere with the quadriceps muscle activation or with motor performance of the subject.
- Uncooperative subjects.

6 Design

Prospective observational study. See *Attachment A*.

6.1 General design

The patients scheduled for TKA will be recruited through the criteria mentioned above; moreover, healthy subjects will be recruited as control group. The patients will be assessed through a motor ability test (TUG), a referred pain scale, and a quadriceps isometric contractions session recorded with surface electromyography. The assessment sessions will be conducted the day before the operation and on the first and third postoperative day. The control group will be exposed once to the same assessments, with the EMG applied on the quadriceps muscle of the dominant limb.

The sEMG data will be acquired by asking the subjects to perform the following tasks: "homolateral knee extension", "homolateral hip flexion" and "contralateral hip extension with a contemporary homolateral hip flexion". Each task will be repeated twice and the execution order will be randomized. The subject will be placed in the supine position and three bands will be positioned respectively at the level of the malleolus and the inferior margin of the patella in order to immobilise the inferior limb and ensure an isometric contraction of the quadriceps, while keeping

the biomechanical context unchanged. For each subject belonging to the two study groups, the same setting will be used. During the data acquisitions, every subject will be encouraged to perform each contraction with the maximum strength. The performance of tasks will be video recorded in order to monitor the correct execution.
The NRS scale will be administered to the patients after each quadriceps evaluation session, while the TUG test will be conducted the day before the operation and on the third day after surgery.
In the first and third day after surgery, the session will take place after 3pm in order to allow the patients to participate in both of the physiotherapeutic treatments provided by the Humanitas Clinic Institute.
The TUG test consists in asking the patient to stand up from a chair, walk at spontaneous speed, turn back at a cone placed at a distance of 3 metres and sit back down on the chair. The patient will be timed starting from the operator mark and stopping when the patient has resumed the seated position on the chair. The test will be performed once in a session, with a mock test before.
The NRS scale consists of one 10cm segment, numbered from 0 to 10 on which the subject has to quantify their pain perception where 0 equals “no pain” and 10 equals “the worse pain ever perceived”.
Every assessment session will be conducted by one expert operator.

7 Statistical considerations

7.1 Sample Size

The primary outcome of this study is the EMG signal detected during different isometric contractions of the quadriceps muscle. In the published scientific literature, there is insufficient data to define the minimal statistically significant difference for this outcome. Therefore, it is not possible to calculate the sample size. Some studies exist which compare the muscular activation in the inferior limb between healthy subjects and patients who have undergone PTG, with 10 subjects for each group [13]. In this study, 15 healthy subjects and 15 patients will be recruited; it is estimated that this sample will be enough to obtain a preliminary valuation of the differences between groups.

7.2 Analysis

The statistical analysis will be carried out at the end of the data collection, using the SPSS 20.0 software. The categorical variables will be described via mean and standard deviation or median and interquartile range. The normality of the demographic variables and the outcome measures will be evaluated through the Kolmogorov-Smirnov test.
The t Student test (with normal variables) or the Mann-Whitney test (with non-normal variables) will be used to verify the pre-intervention homogeneity of the demographic variables. The mixed models ANOVA test for repeated measures will be used to analyse possible differences inter-groups and intra-groups. A post hoc analysis will be conducted in the eventuality of significant outcomes. Linear regression will be used to investigate the correlation between the EMG outcomes and the secondary outcomes (NRS and TUG).
The threshold value for the statistical significance will be fixed at 0.05.

8 Withdrawal from the study

Subjects who decide to leave the study for any reason will be immediately excluded from it. The subjects will be also informed about the possibility of withdrawal from the study at every session provided for by the protocol, including during the planned follow-up period, giving prior notification to any of the experimenters. Data acquired from those subjects who do not complete the study will be excluded from the analysis.

9 Forms and procedures for the data collection and management

The demographic and outcome data will be input into an anonymous form within an Excel sheet (*Attachment B*). This data will be collected by two experimenters in order to minimise any errors and will be saved in password-protected electronic format.

10 Ethical considerations

10.1 Patient protection

The coordinators of the study guarantee that this work will be conducted following the criteria laid out in the Helsinki Declaration (*Attachment C*) and in accordance with the law and the regulations of the country in order to ensure the utmost protection for each person included in the study. The study will be conducted in accordance with the ICH guidelines for Good Clinical Practice. The protocol and the documents attached will be inspected and approved by the authorised Independent Ethics Committee (IEC).

10.2 Subject identification – Data protection

All data related to data acquisition and analysis and all the information related to each individual subject shall be handled in the strictest confidence and to the fullest extent of the applicable law. Privacy shall thus be safeguarded, and no information shall be made public. Each subject will be identified with an ID (*Attachment B*). The name and surname of the subject will not be required. The data required will pertain to sex and age. Only those personnel actively involved in the study will have access to the database. Each subject will be informed about data protection by means of an appropriate form in this regard (*attachment D*) and will be asked to sign an informed consent form in order to participate in the study.

10.3 Informed consent

All subjects will receive information regarding the manner in which the study is to be carried out, and the study aims. They will also be informed about the rigorous manner in which their data will be handled and protected. It will be underlined that participation is voluntary and that the subject can withdraw from the study at any time. Each subject will complete the informed consent form, and only after it is collected will the data be inserted into the Excel sheet (*attachment E*).

11 Conflict of interest

Each member of this study declares that he or she has no conflict of interest.

12 Data ownership

In accordance with the ICH guidelines for Good Clinical Practice, and taking into consideration that this study is monocentric, the owner of all the data is ICH.

13 Publication policy

On completion of the study, the coordinator will prepare a draft manuscript containing the final results of the study based on the statistical analysis. This manuscript will be submitted to an

appropriate peer-reviewed scientific journal for publication. Any publications, abstracts, slides and data arising from this study will be subject to revision by the study coordinator.

14 Timing of the study

1. Subject recruitment: 2019, July - September
2. Data analysis: 2019, September - October
3. Report Presentation: 2019, November

15 Scheme of the study

See *Attachment A*.

16 References

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List of the attached documents

Attachment A_ Scheme of the study

Attachment B_ Data collection form

Attachment C_ Helsinki Declaration

Attachment D_ Informed consent form

Attachment E_ Privacy report

Attachment F_ Equipment CEE trademark

Attachment G_ Equipment technical report

Attachment H_ Curriculum vitae of Roberto Gatti