Motor performance modulation after total knee replacement

PROTOCOL NAME: Motor performance modulation after total knee replacement.

PROTOCOL IDENTIFYING NUMBER: CLF18/06

PROTOCOL VERSION DATE: 07-11-2018

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Glossary of abbreviations

TKR: Total Knee Replacement

AMI: Arthrogenic Muscle Inibition

STS: Sit To Stand

10MWT: 10 Metres Walking Test

MdF: Torque

RoM: Range of Motion

OS: Overshoot

FRE: Force Reproduction Error

ICH: Istituto Clinico Humanitas

KOOS: Knee Injury and Osteoarthritis outcome score

IPAQ: International Physical Activity Questionnaire

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1 Synopsis

Title	Motor performance modulation after total knee replacement
Study Coordinator	Roberto Gatti
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Background	Functional recovery after total knee replacement (TKR) is characterized by incomplete recovery of muscular strength due to arthrogenic muscle inhibition (AMI) and difficulty in functional level self-estimation. Moreover, the widely described alteration of sensory feedback can influence the ability to modulate motor performance in these patients. To date, no studies have investigated the ability to modulate the motor performance in patients with TKR with respect to healthy subjects.
Population and selection criteria	In this study, 20 patients who undergo TKR and 20 healthy subjects will be enrolled. Inclusion criteria are: age between 40 and 80 years, TKR for primary knee osteoarthritis, knee flexion ≥ 90° and complete knee extension. Patients must be able to perform a sit to stand on a 46 cm chair and to walk for 50m without aids. Exclusion criteria are: TKR following traumas, previous tibial or femoral osteotomy, partial or complete revision, cognitive impairments, other disorders able to influence motor or functional recovery.
Study design	This is a prospective observational study. Patients will be enrolled from June 2019 to October 2019. After the completion of the trials, we will proceed with data analysis.

Objectives	Primary endpoint is to investigate motor performance modulation during a leg extension, sit-to-stand and walking (10 Meters Walking Test) tasks. Secondary endpoint is to investigate pain, rate of perceived exertion and load symmetry during all tasks. TKR group will be evaluated the day before surgery (T0) and at 5 days (T1), whereas healthy subjects will perform two evaluation sessions at a distance of 5 days.
Statistical Methods and Data analysis.	Normality and homogeneity of demographic variables will be evaluated at the end of data collection. Differences within-group from T0 to T1 and between TKR group and healthy subjects will be investigated with t Student test or Wilcoxon-Mann-Whitney test.
Ethical considerations	This is and observational study involving healthy subjects and TKR patients. The assessment procedures will be performed according to previous studies described in literature and without adverse effects. The assessments will be conducted in the Motion Analysis Lab of Humanitas Research Hospital.
Timeline	Patients enrolment: July 2019 - October 2019 Data analysis: November 2019 - December 2019 Report Presentation: January 2020

2 Background and introduction

Knee osteoarthritis is a common disease in patients over 60 years old **(Heidari, 2011)**. Total knee replacement (TKR) is a definitive treatment able to relief pain and improve function and quality of life. **(Callahan, 1994; da Silva et al., 2014).** In spite of rapid functional recovery, some deficits, such as the incomplete restoration of muscular strength, can persist for several months after this type of surgery. The decreased muscular strength seems to depend on the reduced efficiency in neuromuscular activity (arthrogenic muscular inhibition - AMI) rather than muscle atrophy **(Kauppila et al., 2010; Roos et al., 2011; Smith et al., 2014) (Pietrosimone et al., 2011).** In fact, AMI cam be explained through a spinal and supraspinal excitability modification due to the alteration of the sensory feedback from the damaged joint **(Rice et al., 2010).** It affects not only muscles of the operated limb, but also muscles of the non-operated side **(Urbach D et al., 2002).** Moreover, a lack of awareness of functional level represents another feature of patients after TKR. To date, only a single study have investigated this aspect in patients with musculoskeletal disorders, highlighting the trend to underestimate their functional level **(Fisher et al., 2003)**. However, these deficits can also affect the ability to modulate and generate muscle force during the execution of motor and functional tasks.

3 Rationale of the study

The ability to modulate the performance during motor and functional tasks represents a measure of neuromuscular control **(Dover G et al 2003)**. To our knowledge, no studies have evaluated this ability in patients after TKR with respect to healthy age-matched subjects. Our clinical observations and the neurophysiological rationale underlying the deficits of these patients lead us to hypothesize the reduction of this ability after TKR.

4 Study objectives

4.1 General objectives

The aim of the study is to investigate the ability to modulate the motor performance during motor and functional tasks in subjects undergoing TKR.

4.2 End-points

4.2.1 Primary endpoint

The primary endpoint is to investigate the ability to modulate the motor performance in subjects after TKR during a knee extension, sit-to-stand (STS) and walking (10 Meters Walking Test – 10MWT) tasks. Knee extension will be performed using an isokinetic dynamometer (Ω = 60 °/s) and the peak torque (PT) will be measured. The difference between the PT-target and the PT-observed will be computed in order to quantify the Force Reproduction Error (FRE). The STS will be evaluated using two force platforms (BTS P-6000, BTS, Italy) in order to detect the Ground Reaction Force (GRF) and to calculate the difference between the GRF-peak and body weight

(Overshoot-OS). The error between OS-target and OS-observed will be calculated. Finally the 10MWT will be used to measure the walking speed. The difference between the "target speed" and the "observed speed" will be calculated.

4.2.2 Secondary endpoint

The self-perceived pain (Visual Analogue scale - VAS), the rate of perceived exertion (modified Borg scale) and the perceived symmetry of load during these tasks will be assessed. Any correlation among these variables and the ability to modulate the motor performance will be investigated.

5 Selection criteria

5.1 Inclusion criteria

Inclusion criteria:

- Age between 40 and 80 years old
- TKR due to primary knee osteoarthritis
- Flexion ≥ 90° and complete knee extension
- Ability to perform STS from a 46 cm chair without the use of the upper limbs
- Ability to walk for 50 meters without aids

5.2 Exclusion criteria

Exclusion criteria:

- TKR for traumatic events
- Tibial or femoral osteotomy
- Partial or total TKR revision
- Cognitive and psychiatric disorders
- Neurological or musculoskeletal disorders able to affect functional or motor recovery.

Healthy subjects will have to match all the eligibility criteria except "intervention of TKR for primary knee osteoarthritis".

6 Study design

This is a prospective observational study and it will take place at the Motion Analysis Lab of Humanitas Reasearch Hospital.

6.1 General design

Twenty subjects undergoing TKR and twenty age-matched healthy subjects will be enrolled in the study. Patients will be evaluated the day before (T0) and five days after (T1), whereas healthy subjects will undergo two evaluation sessions at 5 days distance. The evaluation will start with the STS, performed using a 46 cm chair without armrests. The chair will be placed adjacent to the two force platforms and a physiotherapist will standardise the subjects' position. In particular, the trunk will be placed in vertical position and the hips and knees will be set at 90° flexion (using a goniometer), whereas the feet will be placed equidistant (inter-malleolar distance of 20 cm). Twenty-one retro-reflective markers will be placed on lateral malleolus, between the heads of the second-third metatarsus, heel, lateral surface of the tibia, lateral condyle and lateral surface of the femur, apex of the iliac crest and acromial angle of both sides. Other five markers will be placed on sacrum (S2), seventh cervical vertebrae (C7), eighth thoracic vertebrae (T8), incisura jugularis and xiphoid process. This marker-set will allows us to monitor the kinematics of the trunk, hip and knee during the task, as well as to standardise the starting position of the subjects. All participants will be asked to perform three STS with their hands crossed over the chest. In particular, they will be asked to perform the first task at maximum speed, the second one at 50% of maximum speed and the third one at 25% of maximum speed. All tasks will be repeated twice without giving any feedback on participants' performance. Subsequently, the knee extension task will be performed with both lower limbs using an isokinetic dynamometer. The subjects' position will be standardized (hips and knees at 90° flexion) and they will be asked to perform three knee extensions for each limb at 60 °/s speed starting from 90° flexion. In particular, they will be asked to perform the first task at maximum force, the second one at 50% of maximum force and the third one at 25% of maximum force. The same procedure will be repeated with the contralateral lower limb.

The 10MWT will be performed only three times because in order to reduce any risk of fall. Subjects will be asked to walk for 10 meters without aids at maximum speed, at 50% and 25% of maximum speed. Each trials will be spaced with 1 minute of rest.

Standardized instructions will be provided by the same physiotherapist before each test and at the end of each task, pain (VAS Scale) and perceived exertion (modified BORG Scale) will be evaluated. Finally, only for STS the self-perceived load symmetry will be evaluated using a specific scale. It consists of a 20 cm line with two ends respectively defined as "maximum load on the left" and "maximum load on the right". Subjects will have to put a tick along the line according to their perception of load distribution. A numerical score will be obtained by measuring the distance (in centimeters) between the tick and the ends of the line.

Finally, subjects will fill in KOOS and IPAQ scales in order to monitor the knee function during the activities of daily living, its impact on quality of life and their level of physical activity.

7 Statistical considerations

7.1 Sample size

This is a pilot study and no normative data are available. There are no studies in literature aimed at assessing the ability to modulate the motor performance in patients after TKR. However, the few studies assessing the ability to reproduce different force levels at the level of the upper limb, have enrolled a small sample size **(Mugge W et al., 2015)**. Therefore, a sample of 40 subjects (20 per group) will be considered in order to estimate any change in outcome measures.

7.2 Analysis

Statistical analysis will be performed at the end of data collection using SPSS 20.0 software for Windows. Categorical variables will be described in terms of proportion, whereas continuous variables in terms of mean and standard or median deviation and interquartile range. The assumption of normality will be checked using the Kolmogorov-Smirnov test. Paired t-test for or the Wilcoxon test will be used to investigate any within-group difference over time. Student's t-test for independent samples or the Mann-Whitney test will be used to assess any difference between TKR patients and healthy subjects at T0 and T1. The level of significance will be set at α=0.05.

8 Drop-out

Individuals who will decide to withdrawn the study will be immediately excluded.

9 Modules and procedures for data collection and management

Demographic variables and outcome measures will be entered anonymously in an Excel sheet (Annex B). Data will be collected by two investigators in order to minimize any errors and will be mantained in electronic format, protected by password.

10 Ethical considerations

10.1 Patient protection

The study coordinator ensures that this work will be conducted following the principles outlined in the Helsinki Declaration (Annex C) and according to the laws of the country in order to guarantee the maximum protection of the study participants. The study will be conducted according to the Guidelines (ICH) for Good Clinical Practice.

10.2 Subjects identification – Personal data protection

Participants' privacy will be protected and no information will be disclosed to the public. Subjects will be identified with an ID code and only researcher who are actively involved in the study can have access to the database. Each person will be informed through an appropriate form about the protection of personal data. Moreover, each participants will be asked to sign in a written informed consent.

11 Conflict of interest

All study members declare to have no conflict of interest.

12 Data ownership

In accordance with the Guidelines (ICH) for Good Clinical Practice and considering that this is a single-center study. Therefore, the data owner is the Istituto Clinico Humanitas.

13 Publication policy

At the end of the study, the coordinator will prepare a manuscript containing the results of the study. This manuscript, after revision, will be sent to an appropriate scientific journal. All publications, abstracts, presentations, manuscripts and slides, including the data of this study will be submitted and reviewed.

14 Timeline

1. Subject enrolment: July 2019 - October 2019
2. Data Analysis: November 2019 - December 2019
3. Report presentation: January 2020

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