PROTOCOL NAME: Action Observation Training in patients with chronic low back pain

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Abbreviations glossary

LBP	Low Back Pain
AOT	Action Observation Training
ODI-I	Oswestry Disability Index
NRS	Numeric Rating Scale
SF36	Medical Outcomes Study Short Form 36
TSK	Tampa Scale of Kinesiophobia

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1 Synopsis

Title	Action Observation Training in patients with chronic low back pain
Study coordinator	**Roberto Gatti**
Protocol number	**CLF19/01**
Version and protocol date	30th January 2019
Introduction and rational	Low back pain (LBP) represents the pathology of the musculoskeletal system with greater prevalence in adults and it is one of the main causes of disability. Structural and functional brain modifications have been described in patients with chronical pain in the musculoskeletal system. In these patients, the central nervous system can therefore be considered one of the target structures of the treatment. The Action Observation Training (AOT) represents an effective rehabilitative approach to enhance the motor function in both central nervous system and musculoskeletal pathologies. So far no study has investigated the effects of AOT in patients with chronical LBP. The study aims to determine the efficacy of an AOT treatment in patients with chronic LBP.
Population and patients recruitment criteria	N. 50 aspecific chronical LBP diagnosed patients will be sorted (duration of the symptoms over 12 weeks). The inclusion criteria will be: understanding of Italian language and an age over 65 years. Patients with severe sight and/or hearing impairment and with cognitive deficit (Mini Mental State Examination $\leq$21) will be excluded. Subjects with specific etiology LBP or who have previously undergone AOT will be excluded too.
Design and study duration	The study is a single-blind controlled randomized clinic trial.
Outcomes	The primary outcome will be the evaluation of the disability through a Oswestry Disability Index questionnaire. The secondary outcomes will be the rating of the pain (Numeric Rating Scale), the quality of life (Short-Form 36) and the fear of movement (Tampa Scale of Kinesiophobia). The outcome measures will be taken before the treatment (T0), after three weeks (T1) and four months upon the end of the treatment (T2). At T0 the subjects' attention skill will be evaluated.

Statistical methods and data analysis	Upon data collection the normality and homogeneity of the demographic variables and of the outcome measures to the baseline will be evaluated. Possible differences after treatment, inter-group, intragroup will be investigated through ANOVA test for repeated measurements including any possible post hoc analysis.
Ethical considerations	The subject study is aimed to determine the efficacy of an AOT treatment in patients affected by chronic LBP, by treating the participants with an intervention and evaluation as it was described in literature. They showed no evidence of adverse events for the health. The materials used for the study will be provided by the Physiotherapy Dept. of Humanitas Clinical Institute. The treatments will last 30 minutes while the evaluation will last 15 minutes.
Timing of the study	Patients recruiting: May 2019 Data analysis: July 2020 Report submitted: September 2020

2 Background and introduction

The Low Back Pain (LBP) represents the pathology of the musculoskeletal system with greater prevalence in adults (with a 18.6% to 57.4% variable index) [1]. It is one of the main causes of disability with a high rate of chronicity and absenteeism from work [1] [2] [3]. The clinical course of the LBP is highly variable and from 3 to 10% of the affected patients develops a chronic pain (more than 3 months lasting).

Different kinds of interventions have been proposed to handle this pathology (including different types of pharmacological and chirurgical approaches); they have achieved contrasting and sometimes not satisfactory results [4]. The treatment of the LBP traditionally focuses on what is defined as "end organ dysfunction", criteria according to which the symptom experienced by the patient derives from structural or functional anomalies of the musculoskeletal system. Hence the intervention aims to normalize the peripheral deficit through techniques such as stretching, anesthesia or denervation but with scarcely important results [5].

Parallelly, many studies have described structural and functional cerebral modifications in patients with musculoskeletal system chronic pain; these modifications would have a key role in the development and in the continuation of a state of pain which persists over time [5] [6]. The central nervous system can therefore be considered one of the target structures of the treatment of patients affected by chronical LBP, thus developing approaches such as the Action Observation Training (AOT) [7]. It consists in asking the patient to meet some tasks in order to recruit the same neural substrates involved while carrying out those tasks [8] The efficacy of this approach has been proven by the improvement of the motor function and the functional and structural brain plasticity [9] [10].

3 Study rational

So far there have not been studies which investigated the effects of AOT in patients with chronic LBP. The AOT enables to activate specific areas of the cerebral cortex, strengthening some networks and facilitating the activation of the ones which have been damaged due to a neurological damage, pain or immobilization [7]. Functional and structural plastic modifications of the central neurological system are subtended to the use of AOT. This approach could therefore give positive results in patients with chronic LBP, pathology in which the functional and structural cerebral alterations have been described.

4 Study outcomes

4.1 General outcomes

The outcome of the study is to determine the efficacy of the Action Observation Training in the treatment of chronical LBP affected patients.

4.2 End-points

4.2.1 Primary Endpoint

The primary outcome will be to evaluate the disability through the Oswestry Disability Index (ODI-I). This is a specific pathology questionnaire, it is self-administered and validated in Italian [11]. It is made of ten items about everyday activities. The scores will be interpreted as described by

Fairbank [12]: 0-20% is considered minimum disability, 21-40% modest disability, 41-60% severe disability, 61-80% serious disability and 81-100% total disability [13].

4.2.2 Secondary Endpoint

The secondary endpoints will consist in the evaluation of the pain, of the quality of life and of the fear of movement. The pain will be examined through the Numeric Rating Scale (NRS); it consists in a 10 cm segment numbered from 0 to 10, through which the subject will have to rate his/her perception of the pain (0 corresponds to "no pain", while 10 to "maximum pain"). The quality of life will be evaluated through the Medical Outcomes Study Short Form 36 (SF36), while the fear of movement through the Tampa Scale of Kinesiophobia (TSK).

5 Criteria for the recruitment of the patients

5.1 Inclusion criteria

- Patients with chronic aspecific LBP (documented story of more than 12 week-long symptomatology)
- Good understanding of Italian language
- Aged over 65

5.2 Exclusion criteria

- Severe sight or hearing impairement
- Cognitive deficit (objectified by a Mini Mental State Examination score $\leq$21 [14]).
- Specific LBP (previous spine surgery, deformation, infection, fracture, malignant tumor, general disorders or neuromuscular pathologies)
- Patients who previously underwent AOT

As confirmation of the eligibility of the subjects in the study the following will be used: their clinical history, x-rays of the lumbar spine and in particularly uncertain cases, the computed tomography or the nuclear magnetic resonance. Common degenerative modifications such as the degeneration of the disc or the spondyloarthrosis will not be considered as exclusion criteria [15].

6 Study design

The study is a single-blind controlled randomized clinic trial. See Enclosure A

6.1 General design

The patients will be recruited and then randomly assigned by an external collaborator (allocation concealment) to the experimental group or to a control group. The patients belonging to the experimental group will be asked to watch a video showing a person carrying out some exercises (12 exercises: 3 stretching exercises, 3 core stability exercises, 3 mobilization exercises and 3 functional exercises) and later on they will be asked to repeat them. The observation of the exercise and its performance will last 8 minutes (4 minutes for observation and 4 minutes to repeat them). On the other hand, the patients belonging to the control group will be given a brochure with the same exercises the patients of the experimental group received through the video. They will be asked to read the exercise 3 times and to carry it out for 4 minutes. Both groups will have to watch the video or read the brochure and repeat the exercises 5 times per week for 3 weeks. They will be

provided with a diary to write daily notes about the performance of the exercises (day and time of the performance, possible problems, etc).
The patients will be evaluated before the treatment (T0), three weeks upon its beginning (T1) and 4 months upon the end of it (T2). The evaluation will consist in the administration of the Oswestry Disability Index, of the Tampa Scale of Kinesiophobia, of the Numerical Rating Scale and of the Medical Outcomes Study Short Form 36. At T0 the subjects' attention skill will be evaluated through the Brief Cognitive Assessment Tool [16]
A physiotherapist will instruct the patients about the exercises to repeat while a second blinded physiotherapist about the group the patients belong to, will administer the evaluation scales.

7 Statistical considerations

7.1 Sample size

The Oswestry Disability Index represents the primary outcome measure. The sample size has been calculated considering an MCID of 12.8 points among the general population with a 14 point standard deviation. Assuming a 80% power and a probability to refuse the null hypothesis when true (alpha error) of 5%, 25 patients per group will be recruited.

7.2 Analysis

The statistical analysis will be carried out upon the data collection through SPSS 20.0. software. The categorical variables will be described in terms of proportion, while the continuous variables in terms of average and standard deviation or median and interquartile range. The normal intake of the demographic variables and of the outcome measures will follow through the Kolmogorov-Smirnov. The possible post intervention inter-group and intra-group differences relative to the continuous outcome measures will be evaluated through the ANOVA test for repeated measurements and an eventual post hoc analysis will be carried out later. The threshold value of the level of significance will be set at 0.05.

8 Study abandonment

The patients who during or at the end of each scheduled evaluations set by the protocol will abandon the study will be immediately excluded from it. The patients will be informed about the possibility to quit the study also during the follow-up periods, after informing any experimenter. The acquisitions which have not been completed by the patients will be excluded from the analysis of the results.

9 Modules and procedures for data collection and management

All data relative to the demographical variables and the outcome measures will be entered anonymously in an Excel spreadsheet (*Enclosure B*). These data will be collected by just two experimenters in order to minimize eventual errors and will be filed, protected with a password.

10 Ethical considerations

10.1 Patients protection

The study coordinators ensure that the present work will be led following the principles complying with the Declaration of Helsinki (*Enclosure C*) and according to the laws and the rules of the country in order to grant the maximum protection of the subjects of the study. Upon the description of the protocol the study will be led according to the Guidelines (ICH) for the Good Clinical

Practice. The protocol and its enclosures will be subject to revision and approval by the relevant Independent Ethical Committee (ICE).

10.2 Subject identification – Personal data confidentiality

All data relative to the evaluations along with all the information about each subject will be subject to maximum privacy and in compliance with the standards of the current laws. The privacy will be therefore safeguarded and no information will be disclosed. Patients will not be asked their name and surname; they will be identified with an ID code as indicated in the *Enclosure B.* The patients will be asked about their date of birth, sex, weight and height. Only the people actively part of the study will be allowed to access the database. Every subject will be informed about the protection of their personal data by a suitable form (*Enclosure D)* and they will also be required to sign an informed consent without which he will not be able to be involved in the study.

10.3 Informed consent

All subjects will receive information regarding the study, the performance and the relevant outcome of the study. They will also be informed about the strict confidentiality their data will be treated. It is underlined that the participation is voluntary and that the subject will be allowed to quit the study at any time. The informed consent will be filled by each subject and only when it has been collected the relevant data will be entered in the collection sheet (*Enclosure E)*.

11 Conflict of interest

All the members of the study declare they have no conflict of interest.

12 Data ownership

In compliance with the Guidelines (ICH) for the Good clinical practice and considering that this is a single center study the owner of the data is Humanitas Clinical Institute.

13 Publication policy

Upon the study completion, the coordinator will issue a manuscript with the final results of the study according to the statistical analysis. This manuscript, upon revision, will be sent to a proper science journal. All the publications, the abstracts, the presentations, the manuscripts and slides, along with the data of the present study will be submitted to revision by the coordinator of the study.

14 Timing of the study

1. Patients recruitment: May 2019
2. Data analysis: July 2020
3. Report submission: September 2020

15 Study scheme

See *Enclosure A*.

16 References

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16- Rehabilitation Measures Database

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List of enclosed documents

Enclosure A_ Study Scheme

Enclosure B_ Data Collection sheet

Enclosure C_ Declaration of Helsinki

Enclosure D_ Informed consent

Enclosure E_ Privacy Informative

Enclosure F_ Devices EEC mark

Enclosure G_ Devices technical sheet

Enclosure H_ Roberto Gatti CV

Enclosure I_ Guido Grappiolo CV