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All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Abstract

Background. There is little evidence regarding the best way to treat adhesive capsulitis. Physical therapy can reduce pain and improve function and range of motion. However, we lack clear indications on the regimen, techniques or intensity of physical therapy to achieve better results. Intensive physical therapy seems to be confined to the later stages of adhesive capsulitis (chronic stage) given that rehabilitation-induced pain could worsen the outcomes. Here we describe a protocol for a study comparing the efficacy of a standardized program of intensive mobilization under analgesic gas to a similar program under placebo gas and questioning the impact of pain.

Method/Design. A randomized, double blind, multicenter study — the MEOPA Trial — was designed to include adults with strictly defined clinical adhesive capsulitis for a 14-day intensive physical rehabilitation program under an equimolar mixture of oxygen and nitrous oxide or sham gas administration. Efficacy will be assessed by the Constant-Murley Score.

Data for secondary criteria including pain, disability, quality of life and perceived efficacy by the patient or physiotherapist will be collected over 6 months.
Discussion. This randomized controlled trial has been designed to test the effectiveness of intensive physical therapy under a simple and safe analgesic method. This study will also address the effect of pain during rehabilitation in adhesive capsulitis. Furthermore, results from the 6-month multidimensional follow-up of painful mobilization for this condition could be extrapolated to other musculoskeletal conditions.

Trial registration: ClinicalTrials.gov no. NCT01087229.
Keywords: Adhesive capsulitis, Shoulder, Physical therapy, Rehabilitation, Analgesia

Background

Adhesive capsulitis (AC), also called frozen shoulder, is usually characterized by a painful limitation of active and passive range of motion (ROM) of the shoulder [1]. Patients describe pain, which can be severe, an inability to sleep on the affected side, loss of function and limited movements that can become chronic. Consequently, treatment goals are designed to reduce pain, recover mobility and regain optimal function. Although the natural evolution of shoulder capsulitis is usually good at 2 years regardless of treatment, impairments can continue, with persisting pain and stiffness, and is described as a limiting condition [2]. To date, only glucocorticoid injections provide effective pain relief in the short term [3,4] and effective gain in passive motion [5]. A meta-analysis suggested that glucorticoid injections combined with exercise and manual therapy may provide greater active gain for ROM [6]. Other therapeutics in this indication include arthroscopic capsular distension [7,8], manipulation under anesthesia [9] self-care or physical therapy [10-12], with conflicting results.

The effectiveness of physical treatment (physiotherapy, exercise, physical activity) for AC has not been clearly established [11]. Authors have previously reported the efficacy of a simple monitoring of patients informed about their disease versus intensive rehabilitation, which questions a quick management of the disease [13]. In contrast, intensive mobilization seems more effective than other methods but mostly for late stages of the disease (chronic) [14]. However, according to some authors, intensive treatments may foster the inflammation causing capsular retraction [13]. Therefore, the use of active treatments (e.g., to regain active motion) under the pain threshold is commonly considered a logical and ethical solution even

if the joint ROM improvements are slower. Logically, the use of additional interventions to increase the pain threshold would be relevant.

The premixed equimolar mixture of nitrous oxide and oxygen (EMNO) is a safe gas commonly used in painful procedures. Many papers describe its analgesic efficacy, safety, ease of use and quick reversibility [15]. Its usefulness was described during biopsy [16], venous access [17], colonoscopy [18] or local nursing care [19] in a pediatric population. It generally causes effective and transient analgesia without altering consciousness and cognition. Moreover, side effects are generally moderate, consisting of dysphoria, nausea, vertigo, or light-headedness [20]. Considering 1) the widely accepted notion that physical therapy improves pain, ROM and function [21]; 2) that to date, consensus is lacking on how to treat this condition [22]; and 3) the specific situation associating joint stiffness requiring aggressive mobilization and the potential increase in pain and/or inflammation, this additional safe analgesic method would be relevant in AC rehabilitation.

Objective/hypothesis

The main objective of this work was to demonstrate a significant difference between a rehabilitation protocol under analgesia with EMNO and the same protocol under analgesic placebo in terms of function and ROM.

Method/design

Ethical considerations and trial registration

This trial was approved by the regional ethics committee in accordance with the applicable regulations [2008.12.05 bis] and the French national agency for medicines and health products safety (ANSM [A90157-68]). The trial was registered at ClinicalTrials.gov (NCT01087229).

Trial design

A randomized, multicenter, double-blind, controlled trial involving 3 French outpatient rehabilitation centers will be carried out. All centers are specialized in treating musculoskeletal disorders with structured shoulder rehabilitation programs supervised by trained physiotherapists. Participants and assessors in each center will be blinded for the total duration of the trial.

All patients included in this study will be involved in a standardized protocol of rehabilitation with 2 physiotherapy sessions per day (one under gas) for 10 days. Only the intervention group will receive EMNO. To our knowledge, this is the first time EMNO has been tested in this indication and more generally during a rehabilitation program as an additional analgesic treatment.

In each of the centers, randomization will be performed by dedicated investigators via a secure Internet access. Data collected will include patients' initial, year of birth and allocated group (intervention or control), which will be kept by the pharmacist of each center. The list of all patients included in the study will be centralized at the promotor center. The physiotherapist and physician involved in the care protocol will not be informed of the allocated group.

Sample size calculation

No data are available with both the Constant-Murley score (CMS) for evaluation and EMNO for a part or for the entire treatment procedure. However, the CMS was previously used in a study comparing 4 groups, including 2 groups receiving intra-articular injections (triamsinolone – sodium hyaluronate) and rehabilitation as well as a control group [23]. The physical therapy session was similar to that proposed in the present study. The mean CMS at 2 weeks was 57.9 (SD 11.5) and 66.5 (SD 11.6) for the control and intervention groups. With a bilateral alpha risk set at 0.05 and power 90%, as well as a 10-point difference between groups at day 15 for the main criterion considered clinically significant [24], the number of participants needed is 76 (38 per arm). This number is rounded up to 80 to account for any unusable data. To avoid selection bias, a minimum of 8 patients per center will to be recruited. Although we could not ensure that the CMS in the triamsinolone group would be the same as for patients receiving nitrous oxide, the required number of participants included will be greater than the number observed in studies in this field.

Participants' eligibility (Table 1)

Inclusion criteria are both sexes older than age 18 with AC > 3 months. AC is often defined as ROM loss greater than 50% amplitude limitation in at least 2 directions. More recently, AC was defined as ROM > 25% in at least 2 movement planes, together with at least 50% loss of passive external rotation [25]. However, and to simplify the inclusion procedures, most randomized controlled trials (RCTs) retain only the 50% loss in one or more directions with duration of pain > 3 months. Therefore, we defined restrictive criteria to treat at least severe

AC. Initially, the ROM of the shoulder limitation was set at 50% in 3 directions. Considering difficulties in collecting objective measures for shoulder ROM, we expected that most of the AC patients recruited in this trial would be defined by at least 50% loss of motion in one direction. Exclusion criteria are in Table 1 (right column).

Outcomes (Schedule in Table 2)

Baseline assessment

After inclusion, data on medical history including main medical history with compulsory recording of diabetes, respiratory condition, hypertension, neurological disorders and surgical history will be collected. Specific AC history with main events, time of occurrence and previous treatments received (medications, injections etc.) will be also recorded. After checking that the patient is not under steroids or strong opioids (morphine, oxycodone, fentanyl, hydromorphone or buprenorphine), medications will be quantified (nature and daily dose) and recorded.

Primary outcome

To compare the efficacy of EMNO versus placebo in a standardized rehabilitation protocol for AC of the shoulder, a validated evaluation method is required. Among available shoulder function scores, the CMS is widely used and has acceptable psychometric properties [26]. Notably, the CMS demonstrated good responsiveness to changes after interventions (with large effect sizes in various conditions). Testing of a French version confirmed its excellent reliability [27].

Secondary outcomes

For joint ROM gain, kinetics of passive glenohumeral and global active motions will be considered during each visit. For pain, the visual analog scale (VAS) will be used for perceived spontaneous pain (48 hr) and induced pain (therapist-induced during mobilization sessions). Drug intake will be standardized (same type of analgesics for all patients included) and catches recorded in the protocol specification. Function and quality of life will be assessed by the self-administered validated Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire [28] and the Medical Outcomes Study Short Form 36 (SF36) [29]. Adverse events will be recorded only during the active intervention (day [D] 1 to D14) because no effect could reasonably be expected after that time (see EMNO description above).

Procedures

Assessment

For articular changes, we followed Struyf's recommendations so as to avoid compensatory movements [30] for glenohumeral passive gains in flexion (sagittal plane), abduction (frontal plane) and external rotation, with the arm at the side and global ROM active gains in elevation (scapular plane), flexion (sagittal plane), external rotation with shoulder abducted at 90°, and internal rotation with thumb-C7 distance. Specific guidelines to use pictures and written explanations will be handed out in each center (supplement files). Moreover, 2 training sessions specifically designed for conducting standardized evaluations will be scheduled for each investigator.

For pain assessment, we wanted to differentiate 2 dimensions: first, the capacity of both interventions to modify the natural course of daily pain usually observed in this condition and second, the safety of the intervention (e.g., the pain induced by the physical intervention). Both dimensions will be evaluated on a VAS (0-100). Furthermore, the physiotherapist will be asked to measure the effect of the patient's pain on the mobilization session and to score the perceived pain-related limitations on a 6-point Likert scale (0, no limitation, to 5, extreme limitation).

Intervention

Before the protocol, the gas bottles A or B with the patient number will be covered with a Jersey sock. The bottles will be fitted with a flow-regulator, which will be hidden because the gas outlet could be identified. Therefore, bottles will be rendered identical by the sock mask making it impossible to distinguish one from the other except by the identification number assigned by the pharmacist in charge of the study. All rehabilitation centers involved in this RCT will have an adapted room suitable for storing nitrous oxide gas.

The physiotherapy sessions (Appendix) are scheduled to last about 30 to 40 min maximum per patient. The duration of the session will be recorded. The protocol includes 2 sessions per day over a 10-day period. Each day, only the first session will be conducted under gas. Patients have their own mask and balloon. The patient is supported by the physiotherapist providing care and a third party (other physiotherapist, physician, nurse). Both will be unaware of the gas administered to the patient (EMNO or placebo). The patient will be placed comfortably on the table, and the height will be adjusted at the discretion of the physiotherapist. The mask will be applied to the patient's face and the instructions will be for

the patient to breath normally. The induction rate is based on the expansion of the balloon (not too tight or too empty). The induction time is set at 3 min as recommended by the EMNO instructions and will be enforced similarly for the placebo group. Each flow change will be recorded for dose calculation. The therapist will begin the session while the third person controls the position of the mask (leakage), the patient's vigilance (eyes remained open throughout the session), and the proper gas flow suitable for the session according to the patient's respiratory rhythm. At the end of the session, the mask will be removed; the patient will resume breathing normally and wait 15 min before leaving the room. The bottle will then be closed and verified before the third person leaves the room.

All rooms designed for this study will properly ventilated and at least one window will be opened during the session with gas. For each session, a new filter (between the balloon and the mask) will be used. Each balloon can be used for a maximum of 10 times, corresponding to the number of sessions included in the protocol. After each session, a line can be drawn on the balloon to control the number of sessions conducted with each mask.

Data analysis

Descriptive analysis

Socio-demographic quantitative characteristics will be described with median (and 5th and 95th percentiles). Qualitative sociodemographic characteristics will be described by frequencies (%). All variables will be compared at the time of inclusion by Student *t* test or Kruskal-Wallis test for continuous variables and chi-square test or Fisher exact test for qualitative variables to control the comparability of both groups.

Main analysis

CMS gain from D1 to D14 will be compared between the 2 arms by Student *t* test after checking for normality assumptions.

Secondary analysis

The motion gain on glenohumeral abduction, flexion and external rotation between D1 and D14 will be compared between the 2 arms by Student *t* test after checking for normality assumptions; the glenohumeral gains (measured on days 1, 7, 14, 45 and 180) in each of the 3 directions will be analyzed by ANOVA for repeated measures with the group as a fixed factor and after checking the assumption of sphericity. Kinetics of the recovery function (DASH) and quality of life (SF-36) will be assessed and graphically presented. A repeated measure modelling will be proposed. The use of analgesics in each arm will be descriptively studied.

The proportion of patients who will interrupt at least one of their training sessions between D1 and D14 due to pain or the proportion of sessions that are limited due to the pain will be assessed in both groups and compared by chi-square test.

Patient satisfaction assessed by the VAS and physiotherapist evaluation assessed by the Likert scale will be compared (mean) by Student *t* test if conditions of normality and equal variance are satisfied at each time.

The adverse events and the security of the RCT will be presented and described in each arm.

To provide an unbiased assessment of the intervention efficacy, all effectiveness data will be analyzed according to the intent-to-treat principle. The analyst will be blinded to patient data during the analysis.

Discussion

AC is a painful condition with a barely unknown etiology characterized by both active and passive ROM restriction of the shoulder [31]. Although most cases resolve spontaneously, some patients have to wait 1 or 2 years, and 10% will experience persisting residual disability many years later [2]. Consequently, we need to find new strategies to quickly treat this non-lethal, yet disabling condition. Despite numerous studies, we have little evidence of an optimal non-surgical way to treat AC.

One reason to explain this dearth of evidence is probably the diagnostic uncertainty. Indeed, most authors reported difficulties defining and accurately measuring AC [22,26,30]. Glenohumeral loss of motion is probably the main symptom reported by patients, so an accurate and objective measure in different directions is necessary to assess treatment efficacy. In this trial, each passive and active measure will be carefully described, and all investigators participating in the study will be properly trained. Since other disorders such as rotator cuff tears or shoulder impingement can affect active movements, passive ROM may be less affected if the examination requirements are clearly described (position, direction, scapula fixation, rotation of the thorax) [30]. However, to objectively assess intervention effectiveness in AC, the functional dimension would probably provide more objective results if validated scores are used. Our use of CMS guarantees accuracy.

Another reason for lack of evidence is the lack of recommendations for physical therapy. A recent systematic literature review reported that most studies promoted the role of physical therapy for improving pain, function, and ROM [21]. However, there were no clear indications for regimen, technique or intensity that would provide better results. Most authors recommend the use of manual mobilizations and stretching (supervised and home exercises)

for all stages of AC and high-grade mobilizations in the last stages [13-15]. Some argue that intensive therapy, considered “aggressive”, could lead to worse results as compared with no treatment [13]; however, one single negative study is not sufficient to avoid intensive physical therapy definitely. The present study is not able to demonstrate the superiority of intensive physical therapy because no control group is included. However, if such intervention under analgesia is effective, then induced pain could represent a potential negative factor contributing to a poor long-term evolution of the AC pathology.

Furthermore, and as suggested by previous reviews [5,6] effective mobilization and stretching programs may extend and complete the well-recognized effect of intra-articular injections of glucocorticoids.

Finally, this study will help answer whether intensive physical therapy of the shoulder is better tolerated when induced pain level is lower or whether pain level during rehabilitation affects medium-term outcomes. Moreover, time-related changes in parameters will help us evaluate how reduced pain during rehabilitation of shoulder AC can improve outcomes. These results can give clinicians additional ideas to combine painful physiotherapy with a simple and safe analgesic method to facilitate intensive rehabilitation when needed.

Conclusion

This RCT will provide clinicians with multidimensional results about the relevance of analgesia during intensive physical therapy for AC of the shoulder.

Legend

Figure 1. Flow chart illustrating the process of the study. EMNO, Equimolar mixture of oxygen and nitrous oxide; ITT, intent-to-treat principle

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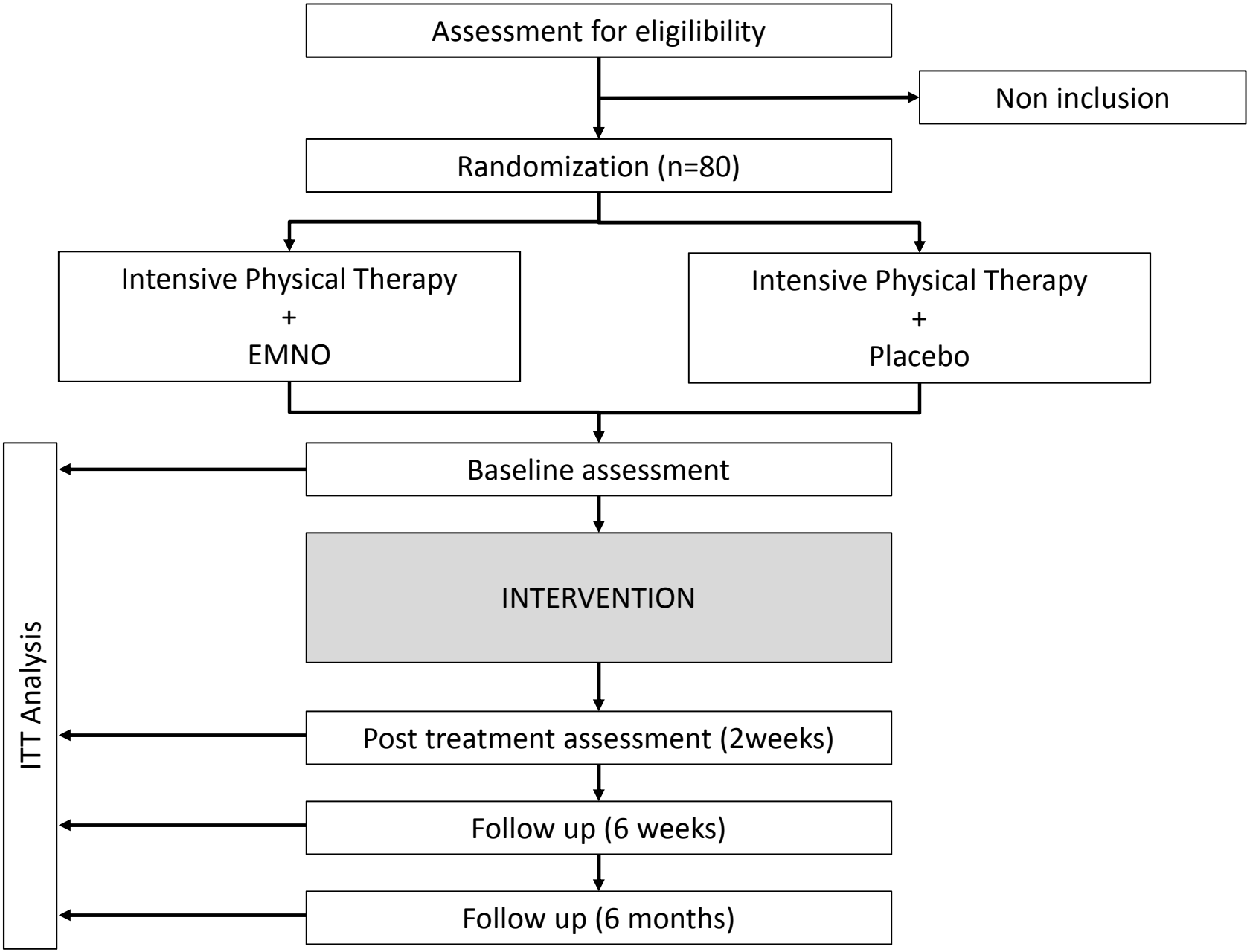
Assessment for eligibility
Non inclusion
Randomization (n=80)
Intensive Physical Therapy
+
EMNO
Intensive Physical Therapy
+
Placebo
Baseline assessment
INTERVENTION
Post treatment assessment (2weeks)
Follow up (6 weeks)
Follow up (6 months)
ITT Analysis

Table 1. Inclusion and exclusion criteria.

Inclusion	Exclusion
Age > 18 years Social insurance Signed informed consent Shoulder: adhesive capsulitis defined as a ROM loss of > 25% in 3 movement planes, together with at least 50% loss of passive external rotation. Frozen shoulder stage 2. Cartilage integrity respected on plane radiography	Concomitant illness: cancer, severe infection, non-controlled cardiovascular disease Treatment: steroids, painkillers, morphine, chemotherapy Shoulder: history of local infection, arthritis or neurological conditions that may be causing shoulder pain, lack of cervical radiculopathy origin, rotator cuff or shoulder tendinopathy. EMNO Head injury with disturbance of consciousness, intracranial hypertension, spontaneous pneumothorax, emphysema, abdominal gas distension, bowel obstruction, sinusitis, otitis, fractures of facial bones, maxillofacial trauma, mask phobia. General: pregnant or nursing, mental state whereby the subject is unable to understand the nature, objectives and possible consequences of the study. Patient unable to comply with the requirements of the protocol. Patient under judicial protection under guardianship. Patient exclusion period determined by a previous study.

ROM, range of motion; EMNO, equimolar mixture of nitrous oxide and oxygen

Table 2. Schedule for data recording.

	D1 Assessment	D1-D6 Protocol (5 sessions)	D7 Assessment	D7-D13 Protocol (5 sessions)	D14 Assessment	D45 Assessment	D180 Assessment
Motion GH Global	 X X	 X*	 X X	 X*	 X X	 X X	 X X
Disability (CMS)	X		X		X	X	X
DASH	X		X		X	X	X
Pain (VAS)	X	X*	X	X*	X	X	X
Safety (VAS)		X		X			
Physiotherapist feed-back (Likert)		X		X			
SF-36	X				X	X	X
Drug intake	X		X		X	X	X
Side effects	X	X	X	X	X	X	X

D, day; GH, gleno-humeral; CMS, Constant-Murley score; DASH, Disability of the Arm, Shoulder and Hand; VAS, visual analog scale; SF-36, Medical Outcomes Study Short Form 36
* evaluations will be made twice, right before and after the rehabilitation session under gas.