Title: "Cost-Effectiveness of Rotator Cuff Repair Surgery by Open and Arthroscopic Techniques. Randomized Clinical Trial"

Responsable Researcher: Prof., M.D, Ph.D Mário Lenza
Av. Albert Einstein, 627 – building A1 – 3º floor – Locomotive Program, Morumbi, São Paulo – ZIP code: 05652-900; Phone: (11) 2151.1444; e-mail: mario.lenza@einstein.br

Project Contributors:

Rafael Pierami[1,2]

Isadora Orlando de Oliveira[1]

Mario Ferretti[1]

[1]Hospital Israelita Albert Einstein, São Paulo, Brasil.

[2]Hospital Alvorada,Moema, São Paulo, Brasil.

Project submitted to FAPESP for research grant request
January 2019

Abstract

Background: Shoulder pain is one of the most common musculoskeletal complaints in orthopedic practice. Rotator cuff injuries account for up to 70% of pain in the shoulder girdle. There is no clinical study carried out in Brazil comparing cost effectiveness between the open and arthroscopic methods of rotator cuff repair surgery. **Purpose**: to determine which method of repair of the rotator cuff, open or arthroscopic, has the best cost effectiveness ratio. **Methods**: a randomized clinical trial will be carried out in which patients with symptomatic rotator cuff lesion will be submitted to repair surgery by either open or arthroscopic technique and will be subsequently evaluated. Inclusion criteria: a) patients with complete or incomplete high-grade rotator cuff lesion whose previous treatment failed or who did not tolerate non-surgical treatment; b) patients in good clinical condition to undergo surgery; c) clear understanding of the Portuguese language and accepting to participate in the study by signing the informed consent form. Exclusion Criteria: patients with previous shoulder surgery; b) limited range of motion of the shoulder (joint stiffness); c) previous fractures in the affected shoulder; d) signs of glenohumeral osteoarthritis; e) neurological injury; f) patients who opt not to participate and / or are not willing to sign the informed consent form; g) patients unable to complete the follow-up evaluation (inability to read or complete the forms). The sample size was calculated with safety margin and is 50 patients per group. All randomized patients will be monitored preoperatively and at 6, 24 and 48 weeks postoperatively for clinical outcomes (Constant-Murley and EuroQol-5D-3L) along with pain assessment (VAS). The Pearson's chi-square test or Fisher exact tests will be used to analyze the results of the two groups in relation to the categorical variables and for the inferential analysis of the numerical clinical outcomes, mixed models will be used and, if the normal distribution is not adequate, generalized mixed models will be used. The significance level of 5% (*alpha* = 0.05) will be used for all statistical tests, such that tests have a value of less than 0.05 will be considered statistically significant. Cost effectiveness analysis will also be performed, with Utilities calculations, quality adjusted life years (QALY), and incremental cost effectiveness ratio (ICSI).

Keywords: rotator cuff; surgery; arthroscopy; open repair; cost-effectiveness; QALY

Introduction

Musculoskeletal injuries are a major cost to the healthcare system. In 2004, 30% of the North American population had some kind of musculoskeletal disorder that required medical treatment; between 2002 and 2004, the estimated cost of treating these changes was $ 510 billion. Shoulder diseases represent the third most common cause of these changes, behind only spinal and knee disorders. (referências)

An evaluation of the primary health care system in Cambridge, United Kingdom, showed that the average frequency of shoulder pain was 9.5 per 1,000 individuals. Of these, 86% had rotator cuff tendinopathy. North American data estimate that approximately 4.5 million patients annually seek medical attention due to shoulder pain; of these, two million have some symptoms related to the rotator cuff. About 250,000 rotator cuff repair surgeries are performed annually in the United States of America (US), and with the continued increase in life expectancy and aging, there is a tendency to increase this number. (ref)

The rotator cuff is composed of the tendons of the subscapularis, supraspinatus, infraspinatus and teres minor muscles. The long portion of the biceps tendon also contributes to cuff function, which is to stabilize the humeral head in the glenoid cavity, preventing superior migration of the humeral head. (ref)

The possible lesions range from tendon degeneration (tendinosis / tendinopathy), through partial lesions (articular, interstitial or bursal), to complete lesions. Diagnosis is made by associating history and physical examination along with imaging methods, and magnetic resonance imaging (MRI) is considered the method of choice. (ref)

Currently the indication for surgical treatment is based on the persistence of symptoms and / or the degree of muscle weakness and / or size of the lesion, after a time of conservative treatment. In general, when opting for surgery, imaging can assist in the planning of surgical treatment, since it allows measuring the extent of the lesion (partial or total) and discriminating which tendons are involved (supraspinatus, infraspinatus, etc.).

Treatment of rotator cuff diseases depends on the type of injury, the patient's degree of activity, age, and the presence of symptoms. In general, tendon degeneration and partial lesions are treated non-surgically, with physiotherapy, infiltrations and analgesic medications. Complete and incomplete lesions that did not respond well to

conservative treatment, however, should be treated surgically. (ref) Among the surgical options, the open method is still considered the gold standard, with good or excellent results in over 90% of cases (ref). With the advent of arthroscopy and the evolution of arthroscopic instruments and implants in the last decade, the arthroscopic repair technique has gained space and is widely used in our country. Several studies abroad (REF) did not demonstrate superiority of one technique over another in terms of clinical outcomes. As the cost of arthroscopic surgery is higher, due to the equipment needed to perform it, it is important to establish which option has the best cost-effectiveness.

Some studies abroad (REF) even suggest the superiority of the open method over the arthroscopic method. However, there are no studies comparing cost-effectiveness between open and arthroscopic methods in Brazil. Therefore, the aim of the present study is to compare the open and arthroscopic methods for rotator cuff repair and determine which presents the best cost-effectiveness ratio.

This project will be submitted to FAPESP for research grant request in order to register it in TRIALS.GOV, as well for its publication and the acquisition of part of the surgical material (fixation anchors).

Hypothesis

The hypothesis of this study is that the open method of rotator cuff repair will be more cost-effective compared to the arthroscopic method.

Justification

In a systematic literature search, it was observed that there are no studies in the Brazilian literature comparing the cost-effectiveness of open and arthroscopic rotator cuff repair methods. Data from the international literature (REF) suggest that the open repair method is more cost-effective than the arthroscopic method (same clinical outcome and lower cost).

Thus, despite the high incidence of rotator cuff injury, there is insufficient evidence from the Brazilian experience to determine the best method for treating these injuries. So, this project proposes to conduct a study to answer the clinical question of which method, open or

arthroscopic, has the best cost-effectiveness in the surgical treatment of rotator cuff injury. According to the levels of scientific evidence, the most appropriate study design to answer this clinical question is a randomized clinical trial (Figure 1).

Study Goal

The aim of the present study is to compare the open and arthroscopic methods for rotator cuff repair and determine which presents the best cost-effectiveness ratio.

Methodology

Study Design

This project will be a multicenter randomized clinical trial and has a 33 month schedule, where 1 month will be the period for organizing the structure in which patients will be seen, followed by 18 months of recruitment, 12 months for follow-up of outcomes, and 02 months for analysis of the results. The study will be conducted at Hospital Alvorada Moema (Shoulder and Elbow Surgery Center of Excellence), Sao Paulo, Brazil, in conjunction with the Israeli Institute of Teaching and Research at Albert Einstein Hospital, Sao Paulo, Brazil, and D Municipal Hospital Dr. Moysés Deutsch (M'Boi Mirim) between August / 2019 and December / 2021. This project will be submitted to FAPESP for research grant request in order to register it in TRIALS.GOV, as well for its publication and the acquisition of part of the surgical material (fixation anchors).

This study will be submitted to the research ethics committee of Albert Einstein Hospital, Alvorada Moema Hospital and Dr. Moysés Deutsch Municipal Hospital (M'Boi Mirim).

In order to ensure methodological quality in this project, we will follow the guidelines and flowchart (Figure 2) recommended by the Consolidated Standards of Reporting Trials (CONSORT Statement), which are: adequate randomization, sample calculation, description and justification for losses, use of the intention-to-treat principle and appropriate follow-up time (REF).

Participants

Patients participating in the study will be recruited and evaluated at the Shoulder and Elbow Surgery Center of Excellence at Alvorada Moema Hospital, a referral center for the treatment of shoulder and elbow injuries, and at Dr. Moysés Deutsch Municipal Hospital (M'Boi Mirim). Both hospitals will be co-participants in the project in question. Patients will undergo clinical evaluation, plain radiography and magnetic resonance imaging to confirm the diagnosis of rotator cuff injury. At this moment, the type of lesion will be evaluated, as well as its size, retraction (REF) and the degree of fatty infiltration of the muscular belly, according to the Goutallier classification (REF). The lesions will be classified as small (<1cm); moderate (1-3cm); large (3-5cm) or very large (> 5cm) (30). All patients will undergo examinations and preoperative clinical evaluation.

Inclusion Criteria

• Patients over 18 years old
• Patients with complete rotator cuff injury, symptomatic, where there was failure or the patient could not support the non-surgical treatment;
• Patients with high-grade partial rotator cuff injury where therapy failed or the patient did not support non-surgical treatment;
• Patients without medical contraindications for surgery
• Patients with good understanding of Portuguese language and who agree to participate and sign the Informed Consent Form.

Exclusion Criteria

• Patients under 18 years old
• Patients with previous shoulder surgery,
• Passive range of motion limitation (joint stiffness),
• Previous fractures
• Signs of glenohumeral osteoarthritis
• neurological injury
• Patients who choose not to participate and / or who do not accept to sign the consent form.

Allocation and Randomization

After eligibility assessment, all patients will be informed about the nature and purpose of the study and will only be included in the randomized distribution after signing the informed consent form. Patients will be consecutively allocated to one of two proposed treatment methods: open rotator cuff repair or arthroscopic rotator cuff repair. Allocation will be made according to instructions contained in opaque and sealed envelopes that will be numbered according to the computer generated randomization list (http://www.randomizer.org). The sealed, opaque envelope containing the method to be applied will be attached to the patient record. A person not associated with the study will open the envelope before the intervention and after the anesthetic technique is applied.

Blinding of outcome evaluators

Outcome evaluators will be masked (blinded) and not involved with the study. The statisticians who will conduct the analyzes will also be masked to the treatment status until the analyzes are completed. Due to the types of interventions, it will not be possible to mask the participants and providers of the intervention.

Intervention

Patients included in the study will undergo one of two possible interventions: open rotator cuff repair (1) or arthroscopic rotator cuff repair (2).

Team

Five surgeons with at least 03 years of surgical technique experience will participate of this study: Dr. Eduardo da Frota Carrera, group leader and specialist in shoulder and elbow surgery since 1983; Dr. Maria Thereza Calil Angelini, medical doctor graduated from UNICAMP/Sao Paulo (State University os Campinas) in 1999, with a residency in Orthopedics and Traumatology from UNIFESP (Federal University of Sao Paulo) in 2003 and specialist in shoulder and elbow surgery from Santa Casa de São Paulo in 2005; Dr. Rafael Pierami, medical

doctor graduated from UNIFESP (Federal University of Sao Paulo) in 2008, residency in Orthopedics and Traumatology from UNIFESP between 2009 and 2012, specialist in shoulder and elbow surgery from UNIFESP in 2013; Dr. Bruno Akio Matsumura, medical doctor from USP (State University of Sao Paulo) between 2008 and 2013, residency in Orthopedics and Traumatology from USP between 2010 and 2013, specialized in shoulder and elbow surgery from USP in 2014; Dr. Vitor Rodrigues, medical doctor graduated from USP in 2011, residency in Orthopedics and Traumatology from USP between 2012 and 2015, specialist in shoulder and elbow surgery from USP in 2016. Also, may be part of the project and participate in surgeries the residents of shoulder and elbow surgery from Hospital Alvorada Moema, as well as the residents of Orthopedics and Traumatology at this hospital. In addition, residents in shoulder and elbow surgery at Albert Einstein Hospital will participate in the study.

As with patient randomization, surgeons will be randomized; it will be done by computer software (http://www.randomizer.org), where each surgeon will be assigned a number from 1 to 5. This will be attached to the patient's envelope and the responsible surgeon will be revealed prior to the intervention, immediately after application of anesthetic technique.

Anesthetic Technique

All patients will undergo balanced general anesthesia (inhalatory and intravenous) without brachial plexus block. At the end of the procedure, 20 milliliters of local anesthetic will be administered in the subacromial space.

Open rotator cuff repair

Patients will be positioned in a beach chair position with the affected limb pending off the table, allowing manipulation and full range of motion range. After asepsis, antisepsis and placement of sterile surgical fields, anterolateral incision will be made in the shoulder in question; the deltoid muscle belly will be gently divided along its fibers until exposure of the subdeltoid / subacromial bursa, which will be partially excised for exposure of the subacromial space and rotator cuff tendons. After mobilization and release of the ruptured tendons and debridement of the rotator cuff footprint, the tendon repair to the bone will be performed using 5.5m metal anchors, according to the preference and technique

chosen by the surgeon. In all cases, the release of the coracoacromial ligament and acromioplasty will be performed.

Arthroscopic Rotator Cuff Repair

The patients will be positioned in lateral decubitus position, with the limb to be operated attached to a skin traction device, which trough a traction post and 07 kilograms (kg), will maintain the shoulder in the following position: abduction of 30 to 60 degrees and flexion of 20 to 30 degrees. After asepsis, antisepsis and placement of impermeable sterile surgical fields, a posterolateral incision will be made in the shoulder for optic introduction, with a 50 mmHg pressure pump and a 0.90 flow, and inspection of the glenohumeral joint. If necessary, anterior accessory portal will be performed for intraarticular instrumentation. After joint inspection, the optic will be introduced into the subacromial space with detachment of the subacromial and subdeltoid bursa with the trocar. After visualizing the lesion, an accessory lateral portal will be performed. With the use of shaver blades, partial bursectomy will be performed and any adherence to the tendon stumps will be released, as well as debridement of the rotator cuff footprint. The tendon will then be reinserted to the bone using metallic 5.5mm anchors, according to the preference of each surgeon. The technique used, as well as the suture configuration and type of knot used will be defined by the surgeon, according to his preference. After tendon repair, the coracoacromomial ligament will be released, as well as acromioplasty.

Postoperative rehabilitation

All patients will undergo the same postoperative rehabilitation regimen: use of Velpeau sling for 6 weeks; pendulum exercises from the second week; active movement and recovery of the range of motion from the sixth week and strengthening from the twelfth week.

Primary outcomes

The Constant-Murley Score (CM) validated for the Portuguese language (33) will be measured preoperatively at 6, 24 and 48 weeks after the intervention. The evaluators will ask the patients to fill in the validated

CM form for the Portuguese language and measure the range of motion with a goniometer. The CM scale covers different domains of shoulder function (pain, activities of daily living, range of motion and power), punctuating each of them; it ranges from 0 to 100, with higher scores indicating better function.

EuroQol-5D-3L (European Quality of Life), a generic score developed to describe health-related quality of life (34) will also be assessed preoperatively, at 6, 24 and 48 weeks postoperatively. This score includes five health domains: mobility, self-care, usual activities, pain / discomfort and anxiety / depression; each domain has 3 levels: no problem; some problems and extreme problems. In addition, the EuroQol-5D-3L has a visual analog scale where the participant assigns a value between zero and one hundred to his or her own health condition (35). At the end of its application, EuroQol-5D-3L will provide a unique numerical value that can be used for longitudinal comparison between two time periods (pre and postoperative, for example).

Secondary Outcomes

Clinical outcome will also be assessed by the Simple Shoulder Test (SST), validated for Portuguese (36), preoperatively and at 6, 24 and 48 weeks after the procedure. SST is a simple, quick and widely used questionnaire for shoulder function measurement; consists of 12 dichotomous questions answered by the patient himself. Each positive answer (yes) is given a score; at the end of the questionnaire the percentage of positive answers (score) is made, and the higher the percentage, the better the shoulder function. Other outcomes measured will be VAS (visual analogue pain scale) at hospital discharge, 1, 2, 6, 24 and 48 weeks after the intervention. This scale allows pain intensity to be measured with maximum interobserver reproducibility; it consists of a 10 cm straight line with the ends determining the limits of pain sensation (no pain; worst pain ever experienced); the distance between zero (no pain) and the patient's demarcation defines the intensity of pain. Complications and failures of the proposed methods wills also be assessed.

Failures will be characterized as need for additional surgical procedure and / or change of the initially proposed procedure.

After the 48th week all patients will be submitted to Magnetic Nuclear Resonance (MRI)of the operated shoulder to evaluate the integrity and healing of the repair performed.

Statistical Planning

Descriptive analyzes of variables will be based on absolute frequencies and percentages for categorical variables and summary measures as means and standard deviations or medians and quartiles, as well as minimum and maximum values for numerical variables (37). Clinical scores will be represented by individual profile graphs separately by surgical technique group.

The groups will be compared for the presence of categorical clinical outcomes (failures, complications and healing integrity) by Chi-square or Fisher's exact tests, depending on the distribution observed after data collection.

For inferential analysis of numerical clinical outcomes, mixed models will be used and, if the normal distribution is not adequate, generalized mixed models will be used (38). The models will have time effects (preoperative, 6, 24 and 48 weeks after intervention), surgical technique group (open repair or arthroscopic repair) and the interaction effect between time and group. The size of the lesion (smaller than three cm or larger than three cm) will also be included in the models as a control variable, seeking to avoid possible biases.

The analyzes will be performed with the aid of the SPSS program (39), considering a significance level of 5%.

Sample Size Estimate

The sample size estimate was obtained to detect differences between the open and arthroscopic repair groups in relation to the primary outcome of the study, Constant-Murley Score (CM) instrument after the intervention.

Kukkonen's et. al study (40) estimated the clinically important minimal difference in CM score in 10.4 points in patients with rotator cuff rupture after three months of surgical treatment by the arthroscopic method.

The estimated sample size of 45 patients per group, 90 patients in total, would reach 90% power to detect a 10.4 point difference between groups in the CM instrument postoperative score with standard deviation of up to 15 points with significance level of 5% using a t-Student test. Predicting a loss of around 10% at 12 months of follow-up, we aimed to recruit 50 patients in each group.

The sample size estimate calculations were performed with the aid of the PASS software (41).

Intention to Treat Principle

Patients who for any reason demonstrate treatment failure or require additional interventions will be followed and their results included in the group in which they were initially randomized according to the intention-to-treat principle.

Economic analysis

Analytical Decision Model: Decision Tree

Evaluated Strategy: To analyze the cost-effectiveness between open and arthroscopic repair techniques for patients with symptomatic rotator cuff injury.

Intervention period: From preoperative questionnaires to patient follow-up 48 weeks after surgery.

For the cost effectiveness model, a sensitivity analysis will be performed in order to highlight possible variations in the model and the impact of variations in the final decision of the best treatment strategy, by calculating Utilities (EQ-5D-3L together with EVA), quality-adjusted life years (QALY) and incremental cost-effectiveness ratio (ICER).

The analysis will be conducted taking into account open versus arthroscopic treatment considering direct and indirect costs related to the surgical event and the patient's treatment time, with all costs generated during the intervention period. According to the recommendations of the Ministry of Health Methodological Guidelines, health outcomes and costs will not be discounted at a 5% discount rate. The costs analyzed will refer to the treatment in the study and may also simulate other scenarios according to the need for evidence of effectiveness in other health system scenarios.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest in the project entitled “Cost-Effectiveness of Rotator Cuff Repair Surgery by Open and Arthroscopic Techniques. Randomized Clinical Trial”.

Expected results

Patients from both groups will have clinically better outcomes after the surgical procedure, but considering international experience, it is expected that the open rotator cuff repair method will be more cost-effective when compared to the arthroscopic method.

Schedule

The research project follows the following steps described in the table below:

Research Steps (Included -Time Analysis)	*Period to be realized (month / year)*
Research grant request from FAPESP	01 to 03/2019
Submission for ClinicalTrials registration: http://clinicaltrials.gov/	09/02/2019 to 09/30/2019
Trials submission for protocol publication: http://www.trialsjournal.com/	08/12/2019 to 09/30/2019
Organization of patient recruitment and treatment structure	08/01/2019 to 08/31/2019
Patient recruitment	09/2019 to 09/2021
Outcome analysis and follow-up (override recruitment)	09/2019 to 09/2022
Data Analysis - Description of Results	10/01/2022 à 11/01/2022
Submitted for publication: JOURNAL OF BONE AND JOINT SURGERY-AMERICAN VOLUME	12/01/2022 à 12/31/2022

Dissemination and Evaluation

This research project, within the IIEPAE (Israeli Institute of Research and Teaching Albert Einstein) postgraduation program, will cover participants from scientific initiation to master's and doctoral degrees; Orthopedics residents at Alvorada Moema Hospital and Albert Einstein Hospital will be able to participate in surgical procedures as part of the internship. The protocol will be submitted for publication in an international journal and the results will be published in presentations at national and international orthopedic congresses and will be submitted for publication in an indexed international journal.

Details of the physical and technological infrastructure to be used

To carry out this project will be used the physical and technological structure of the Locomotive Program of Hospital Israelita Albert Einstein, Hospital Alvorada Moema and Municipal Hospital Dr. Moysés Deutsch (M'Boi Mirim). Expenses foreseen in the initial budget of this project were calculated, for which we are requesting funding for FAPESP:

ITEM	Quantity	Unit Value (R$)	Total Value (R$)
Metal Anchors 5.5mm	140	968,00	135.520
Protocol Publication Rate in TRIALS Journal	01	1.000	1.000,00
Total			136.520,00

Technical Justification for the use of anchors

Rotator cuff repair surgeries were initially performed openly using transosseous points for tendon repair to the bone. With the evolution of this type of surgery, the anchors were developed to provide the same quality and strength of repair, without the need for extensive surgical exposure. Thus, they become indispensable for performing rotator cuff repair surgery, either by the open technique with mini incisions, or by the arthroscopic technique, as it provides the same strength and quality of repair as the transosseous point and allows the surgical procedure to be performed with smaller incisions and lower risk of injury associated with surgical exposure.