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Protocol

Comparison of the effects of two concentrations of adrenaline (0.33 mg/l versus 1 mg/l) in the irrigation serum for arthroscopic shoulder surgery: protocol of a randomized controlled trial

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ABSTRACT

Background: Controlling bleeding during arthroscopic shoulder surgery helps improve the clarity of the arthroscopic visual field. Adrenaline is considered an effective and safe method to reduce bleeding. Two doses of adrenaline (0.33 mg/l and 1 mg/l) have been evaluated in the literature, but never against each other.
Methods: This prospective, double-blind, randomized controlled trial will study the clarity of the visual field using a numerical scale (NS) during rotator cuff surgery on 180 patients across 5 centres. The secondary objectives include: the duration of the operation, volume of saline used, increase in baseline pressure, number of arthropump hyperpressures, mean systolic blood pressure and heart rate, as well as sudden variability.
Results: Among the 154 patients in the Clinical Trial Group, 70/154 (45%) continued to have proteinuria, while 84/154 (55%) had no proteinuria (remission) compared to 41 (28%) in remission and 104 (72%) with continued proteinuria in the Usual Care group ($p<0.001$).
Conclusions: This study aims to determine which of the two dosages previously studied in the literature (0.33 mg/l versus 1 mg/l) provides better clarity.
Trial Registration Number: 2021-A02773-38.

Keywords: Adrenaline, Clinical trial, Shoulder arthroscopy

INTRODUCTION

Shoulder arthroscopy has progressed significantly, particularly for the treatment of rotator cuff pathologies (rotator cuff repair, tenotomy or tenodesis of the long biceps, and acromioplasty) reducing the risk of infection and increasing precision.[1,2]

Perioperative bleeding, by disturbing the visual field, is a factor limiting these interventions. Methods that help reduce this risk include tourniquets (impractical for use on the shoulders), and lowering blood pressure (but which increases the risk of stroke).[3] The use of electrocoagulation probes helps stop bleeding, but increases the risk of tissue burn.[4] Adrenaline is considered an effective and safe method to reduce bleeding.[5] Vascular circulation has been

shown[6], although serious adverse events are rare in the literature.[7-14]

Two doses of adrenaline (0.33 mg/l and 1 mg/l) have been evaluated in the literature against placebo but have never been compared with each other.[5,6,15-17]

Objectives

The primary objective of the study is to compare the visual clarity of the operating field between adrenaline 1 mg/l versus 0.33 mg/l in the irrigation fluid.

The secondary objectives include: mean arterial pressure; mean heart rate during the intervention, as well as sudden variations in these measures; the change in arthropump pressure during the procedure; the nature and quantities of haemodynamic medications used during the procedure; the total volume of irrigation fluid used; and adverse events.

METHODS

Study design

Prospective, double-blind, randomized controlled multicentre clinical trial comparing two doses of adrenaline (0.33 mg/l versus 1 mg/l) during arthroscopic surgery of the shoulder rotator cuff. Patients were included by 5 surgeons at 5 different sites. The clarity of the arthroscopic operating field will be evaluated, as in most similar studies in the literature, using a numerical scale (NS) from 0 to 10, which has good inter- and intra-observer reliability.[6,15,17,18]

Moreover, the NS is more relevant than a centralized evaluation because it directly reflects the surgeon's perception at the end of the intervention of the arthroscopic image obtained in the context of the technical procedure performed.

Participants and population size

Inclusion criteria

Patients over 18 years of age having read and signed the consent form after a reflection period, and presenting with rotator cuff pathologies (subacromial impingement, long biceps tendinopathy, or cuff tendinopathy) indicated for arthroscopy.

Exclusion criteria

Allergy to epinephrine; history of Takotsubo cardiomyopathy; coagulation disorders; patients under legal protection, guardianship or curatorship; breastfeeding, pregnant or women of childbearing age not using any means of contraception; patients not covered by the French social security system; patients participating in another therapeutic protocol; patients unable to understand information and/or give informed consent.

Duration of treatment and follow-up

The maximum duration of patient participation will be one day, the duration of the inclusion period is set at 6 months. The total expected study duration is 6 months and one day.

Number of subjects required

The objective of the study is to compare two scores on a numerical scale from 0 to 10 evaluating the clarity of the arthroscopic surgical field.

The mean score observed in the literature with a dose of 1 mg of adrenaline per litre of irrigation is estimated to be 8±2 points.[5] A difference of one point between groups is considered clinically significant. To highlight this difference, 170 patients (85 per group) must be analysed. These patients will be included in 5 five centres (34 per centre). The calculation was performed using the assumption of a common standard deviation of 2, a type 1 risk of 0.05 and a power of 90%.

This number was increased to 180 subjects (i.e. 90 per group) in order to take into account the delay between inclusion and surgery. During this time, patients may cancel their surgery or postpone it to a date incompatible with the study. It was considered that 5% of patients could be in this situation.

Randomization and blinding

Randomisation

A randomization list per centre will be established. After obtaining informed consent, the investigating doctor will request that the patient be randomized into the study. The centre's pharmacist will allocate the treatment in accordance with the order in the randomization list.

Blinding

The centre's pharmacist will allocate the treatment in accordance with the order in the randomization list. The pharmacist will send a sealed envelope containing the dosage with only the patient's name on it to the operating room. It will be transmitted to the nurse responsible for preparing the bags in a different room to the operating room, where the surgeon does not have access. The 3-litre bags of irrigation fluid with one of the two dosages of adrenaline will then be used in the operating room without any distinctive elements compared to a “normal” bag. No person present in the operating room will be aware of the dosage of adrenaline during the surgery.

Intervention

The interventions will be performed arthroscopically with irrigation bags containing 0.33 mg/l or 1 mg/l of adrenaline. The placement of the patient in a dorsal supine or semi-sitting position, the number and type of anchor, as

well as the surgical technique will be left to the discretion of the surgeon. At the end of the procedure, the surgeon will establish a score between 0 and 10 for the clarity of the operating field for the performed surgery.

Data collection

The investigating doctor will receive a login ID and a password, which will allow him or her to connect to online electronic case report forms (eCRFs*)* to enter the data of each patient included in the study. The eCRFs will be developed by ENNOV clinical and will be hosted on ENNOV company servers. These servers will be located in France and will be subject to physical and logical security measures. CRFs may also be provided in printed format. All data must be recorded there and will then be entered into the online database. Only surgeons will collect their data. The investigator must verify that all data entered is accurate and correct. All entries, corrections and modifications to the CRFs must be made by the investigator or other authorized personnel. Correct data must be entered, dated, and approved by the investigator or an authorized study staff member. The duly completed CRFs will be monitored by the study sponsor to determine their acceptability. If necessary, data correction forms will be generated and transmitted to the centre. They must be completed, signed and dated by the investigator or an authorized member of staff at the centre and returned to VIVACTIS M2 research.

Population analysed

Three populations will be considered

Intention to treat: all randomized patients will be analysed in the adrenaline dose group they were initially randomized to and all their data will be used.

Per protocol: patients will be analysed in the adrenaline dosage group they received and only patients without major deviations from the protocol will be considered in the analysis.

Tolerance: all patients who received the study treatment.

Data integrity and analytics

The investigating centre will retain all CRFs and source documents for each subject, as well as all study documents essential for the conduct of the clinical trial and all study documents specified for regulatory requirements. These documents will be stored for a period of 15 years after the end of the study or its early closure.

Statistical analysis

Description of populations

The inclusion populations will be described according to all the initial characteristics of the patients included. The variables described will be: demographic data (age, weight, height), pathology that necessitated the intervention. Data from the preoperative examination (heart rate and blood pressure). The quantitative variables will be described by their number, mean, standard deviation, median, extreme values and missing data. Qualitative variables will be described by their number, percentage and missing data. The population will be described overall and by group.

Statistical methodology

Analysis of the main endpoints

Comparisons between the two groups will be made using student's t-test. This comparison will be made relative to 1, as a difference of at least 1 point is considered clinically significant.

Analysis of secondary endpoints

For mean blood pressure, mean heart rate, duration of intervention and quantity of serum used, the mean value of each variable will be compared between the two groups using student's t-test. Significant variations in blood pressure and heart rate, depending on the distribution of the number of significant variations within each group will be analysed using Student's t-test if the distribution is normal, or by the Mann-Whitney test if the distribution is not normal. The number of patients with at least one variation will be compared using a Chi-square test.

Change in arthropump pressures: the mean pressure set at the start of the intervention, the mean maximum pressure reached during the intervention and the delta between the two pressures will be compared using student's t-test. The number of transient hyperpressures during the intervention will be analysed in the same way as the number of significant variations, depending on the distribution of the data.

Tolerance analysis: patients having at least one adverse event, patients having at least one serious adverse event and patients having at least one adverse event leading to permanent discontinuation of treatment will be described for each treatment group. All adverse events will be described according to the preferred term (coded from the investigator's report) and by organ system according to the medical dictionary for regulatory activities (MedDRA). A table describing all adverse events will be provided per patient.

Taking missing data into account: given the duration of the study, the expected number of missing data is extremely low. A priori, missing data will not be replaced. However, if the number of missing data proves to be significant, a procedure will be decided upon during the data review and described in the statistical analysis plan. There will be no interim analysis.

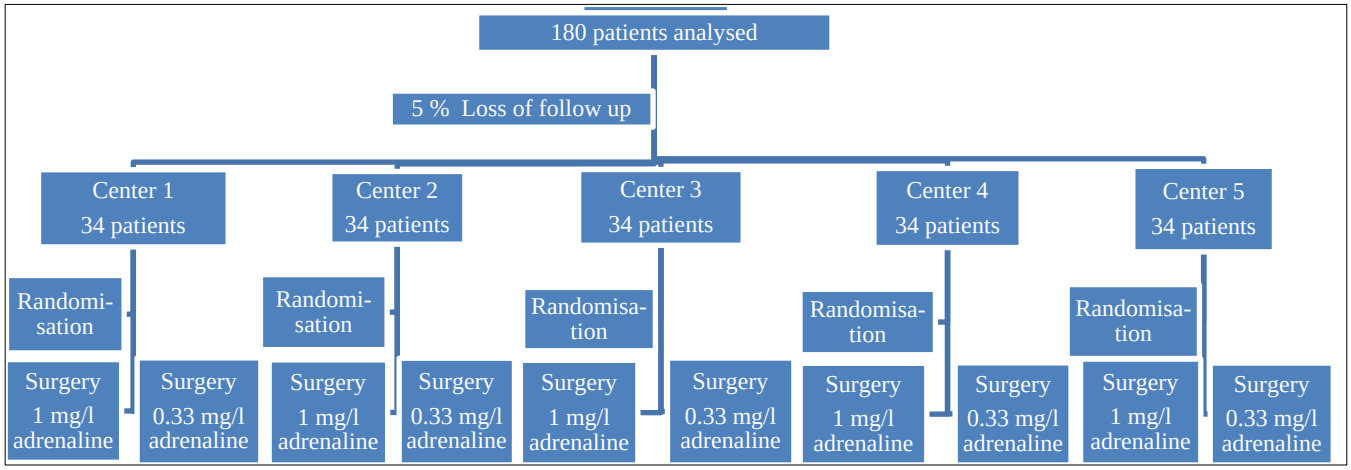

Figure 1: Flow chart.

DISCUSSION

Shoulder arthroscopy increased by +24.5% between 2012 and 2018 and an increase of between 13 and 300% is expected by 2050.[19] At present, the addition of adrenaline is not routine practice.

Arthroscopy is commonly used in rotator cuff surgery. It allows the treatment of subacromial impingements without complete rupture of the cuff by bursectomy, acromioplasty, tenotomy or tenodesis of the long biceps, repair of the rotator cuff tendons, and is also used in palliative cuff surgery (partial repair or muscle transfers).[20-26] Bleeding, by disturbing the image rendered on the arthroscope, is a known limiting factor in these interventions. It can even result in the surgeon resorting to so-called open surgery or to interrupt the surgery if the open route is not visible.

The systemic circulation of adrenaline and the perioperative variations in cardiovascular parameters justify the search for a minimum effective intra-articular adrenaline concentration.

Two doses of adrenaline, commonly used in practice, were evaluated separately in randomized controlled studies.

The dose of 1 mg/l, initially proposed based on empirical data was compared to placebo and demonstrated excellent results, both in terms of improving the arthroscopic visual field and in safety of use.[17,27]

The dose of 0.33 mg/l has also been shown to reduce bleeding and significantly improve visual clarity.[6,15,16,28] The two doses have never been compared with each other.

The main limitation of this study is the subjective and not objective scale of the principal objective. Indeed, the clarity of the visual field using a NS depend of each surgeon, but it's a valid scale.[18]

Another limitation is the lack of a standard procedure for all surgeons. Randomisation by centre is used to minimize bias.

CONCLUSION

Adrenaline in irrigation fluid is known to reduce perioperative bleeding and improve visual field clarity. It is not used routinely in arthroscopic shoulder surgery and the minimum effective dosage is unknown. This study will make it possible to determine which of the two dosages reported in the literature (0.33 mg/l versus 1 mg/l) which provides better clarity.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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