RESEARCH PROJECT PROTOCOL

PROJECT TITLE:

Prospective, Randomised Comparative Trial of Surgical Treatment of Grade III-IV Haemorrhoids: Transanal Hemorrhoidal Dearterialization versus Milligan-Morgan Hemorrhoidectomy

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INDEX

A. PROJECT PROTOCOL

1. SUMMARY

Haemorrhoids are vasculoelastic structures located within the anal canal. When they enlarge and subsequently descend toward the anal margin, losing their original position, the patient develops a series of symptoms known as haemorrhoidal syndrome.

When haemorrhoidal syndrome is advanced (grade III-IV according to the Goligher classification), surgery is the only effective treatment.

There are two main types of surgeries: excisional surgeries and pexy surgeries.

All excisional techniques remove the prolapsed tissues, including the haemorrhoidal bundles, by sectioning at the vascular pedicles. Technical variants within this group pertain to the management of surgical wounds resulting from the procedure. Multiple studies have demonstrated their high efficacy in controlling haemorrhoidal symptoms. However, they are associated with significant and severe postoperative pain during the first two weeks. In addition, excessive scarring of the surgical wounds may occur, leading to anal stenosis.

To avoid these two complications, surgical techniques have been proposed that, instead of removing the haemorrhoidal bundles, aim to reposition them in their original place (pexy surgeries). Since there are no surgical wounds in the anoderm, postoperative pain is less and there is no possibility of anal stenosis. However, as they do not directly address the pathophysiological mechanisms that led to the descent, their long-term efficacy regarding recurrence is theoretically lower than that of excisional techniques.

Within the first group is the Milligan-Morgan hemorrhoidectomy (M-M), considered the "gold standard" technique. Within the pexy surgery group, transanal haemorrhoidal dearterialization (THD) is the most promising surgical technique.

Our primary objective is to compare the efficacy in terms of quality of life between transanal haemorrhoidal dearterialization (THD) and Milligan-Morgan excisional hemorrhoidectomy.

This is a prospective, randomised, controlled trial within the General and Digestive Surgery Department of Hospital Universitari Son Llàtzer, conducted by surgeons specialised in proctology and interested residents.

2. BACKGROUND AND JUSTIFICATION

INTRODUCTION

Haemorrhoids are vasculoelastic structures[1] located within the anal canal whose primary function is to facilitate passive continence. When, for unknown reasons, they

enlarge and consequently descend toward the anal margin, losing their original position, the patient develops a series of symptoms—rectal bleeding and the sensation of an anal mass being the most common—known as haemorrhoidal syndrome.

When haemorrhoidal syndrome is advanced (grade III-IV according to the Goligher classification[2]), surgery is the only effective treatment.

There are two main types of surgeries: excisional surgeries and pexy surgeries.

Within excisional surgeries, Milligan-Morgan excisional hemorrhoidectomy[3], described in 1937, is still considered the standard technique for treating grade III-IV haemorrhoids. It consists of excising the haemorrhoidal bundles, leaving cutaneous-mucosal bridges and the surgical wounds open. Multiple studies have demonstrated its high efficacy in resolving symptoms and long-term control of haemorrhoidal symptoms. However, as the surgical wounds are made in the anoderm, an area with a high number of sensory nerve endings, there is significant and severe postoperative pain during the first two weeks. Additionally, excessive scarring of the surgical wounds may occur, leading to anal stenosis; fortunately, this complication is infrequent, although highly disabling.

Within pexy surgeries, transanal haemorrhoidal dearterialization (THD)[4], which consists of identifying the haemorrhoidal vascular pedicles using transanal Doppler ultrasound and ligating them, combined with haemorrhoidal mucopexy, is the most commonly performed technique. Since there are no surgical wounds in the anoderm, postoperative pain is less and there is no possibility of anal stenosis. However, as it does not directly address the pathophysiological mechanisms that led to the descent, its long-term efficacy regarding recurrence is theoretically lower than that of excisional techniques.

Many studies have shown favourable results for the Milligan-Morgan hemorrhoidectomy, which is currently considered the standard technique, and some have evaluated the results of the THD technique [5]. However, there are very few studies comparing the two techniques[6]. Several meta-analyses [7-8] include comparative studies between excisional and pexy techniques; however, none were found comparing the Milligan-Morgan hemorrhoidectomy with the THD technique. One of the main problems when comparing different techniques in haemorrhoidal surgery is the lack of validated tools to quantify the improvement of haemorrhoidal symptoms and thus compare different studies. Only in 2019 was a validation tool proposed to evaluate symptoms and improvement after surgery: the "Hemorrhoidal Disease Symptom Score (HDSS) and Short Health Scale in Hemorrhoidal Disease (SHS-HD)"[9]. The validation of this scale is intrinsic to this study, as recently endorsed in an external publication [10].

Our primary objective is to compare the efficacy of transanal haemorrhoidal dearterialization (THD) with Milligan-Morgan excisional hemorrhoidectomy in our setting, using the new validation scale, to determine which technique may be considered the treatment of choice.

BACKGROUND

Surgery is considered the only effective treatment for grade III and IV haemorrhoids. The first surgical techniques were described in the early twentieth century, although there are records of surgical treatment for haemorrhoids dating back to the Egyptian era and the Chinese Empire.

All initially described surgical techniques were excisional and, although highly effective, entail considerable morbidity. The high-intensity postoperative pain experienced by patients in the first weeks is the main drawback of surgical indication. Paradoxically, the initial treatment of haemorrhoids (grades I and II) is not surgical, and medical or instrumental treatments (banding or sclerotherapy) in these early stages are very effective and with very low morbidity. However, patients do not seek medical attention in these early stages due to fear of the postoperative pain of excisional surgeries, often recounted by family or friends. As a result, patients eventually consult at very advanced and highly symptomatic stages. In summary, the popular fear of postoperative pain from excisional surgeries prevents patients from benefiting from less invasive treatments.

In 1998, Dr. Longo[11] proposed a completely novel pathophysiological mechanism for haemorrhoidal disease. Haemorrhoidal syndrome was caused by laxity of the connective tissue anchoring the haemorrhoids in the anal canal and consequent anal and rectal mucosal prolapse. He described a surgical technique based on excising the surrounding mucosa above the haemorrhoidal bundles to reposition and fix them in their anatomical position, thus initiating pexy surgeries. As the surgery is performed in the rectal mucosa, which lacks pain receptors, the main benefit for the patient is reduced postoperative pain. However, as it does not address the pathophysiological mechanism, the chances of recurrence (haemorrhoids prolapsing again) and thus clinical failure are higher than with excisional surgeries. In 2014, Dr. Ratto[4] described a new pexy technique called transanal haemorrhoidal dearterialization (THD), which, in addition to pexy of the haemorrhoidal bundles, includes Doppler-guided dearterialization to significantly reduce vascular flow and, theoretically, decrease the chances of recurrence.

CURRENT STATUS

Milligan-Morgan hemorrhoidectomy and the THD technique are theoretically indicated for the same condition: grade III-IV haemorrhoids. Due to insufficient scientific evidence regarding the superiority of one technique over the other, clinical criteria must be used for selection. In routine clinical practice, the choice of surgical technique depends mainly on the surgeon’s preferences, experience with a given technique, or the availability of the method at the hospital. Pexy techniques require specific disposable materials and are therefore more expensive than classical excisional techniques.

At our centre, Milligan-Morgan hemorrhoidectomy is routinely performed, as we do not yet have the material for the THD technique. Before presenting this trial, a budget proposal had already been made by the General Surgery Department to purchase the necessary materials. However, the principal investigator has surgical experience with the

THD technique, as it is performed at another hospital. The principal investigator's clinical impression is that the THD technique's long-term efficacy in terms of quality of life is inferior to that of the Milligan-Morgan hemorrhoidectomy.

Currently, several proposed clinical trials aim to assess the efficacy of THD compared to other surgical techniques. However, few proposals are comparing THD with Milligan-Morgan hemorrhoidectomy:

- https://clinicaltrials.gov/ct2/show/NCT01244672?cond=Hemorrhoids&draw=4&rank=48

Purpose of the study: to compare the frequency and severity of postoperative pain between THD and Milligan-Morgan hemorrhoidectomy.

- https://clinicaltrials.gov/ct2/show/NCT02061176?cond=Hemorrhoids&draw=4&rank=51

Purpose of the study: to compare long-term results, at one year, of THD versus Milligan-Morgan hemorrhoidectomy.

3. HYPOTHESES AND OBJECTIVES

3.1. Hypotheses

Primary hypothesis: In the surgical treatment of grade III-IV haemorrhoids, transanal haemorrhoidal dearterialization is less effective, in terms of quality of life, than Milligan-Morgan hemorrhoidectomy one year after surgery.

Secondary hypothesis: The transanal haemorrhoidal dearterialization technique presents fewer early and late postoperative complications than Milligan-Morgan hemorrhoidectomy.

3.2. Objectives

3.2.1. Main Objective

The primary objective is to compare the efficacy of transanal haemorrhoidal dearterialization (THD) with that of Milligan-Morgan excisional hemorrhoidectomy.

Efficacy will be assessed by measuring patient satisfaction and improvement in haemorrhoidal symptoms, comparing symptoms before surgery with those present one year after surgery. The Hemorrhoidal Disease Symptom Score (HDSS) and the Short Health Scale in Hemorrhoidal Disease (SHS-HD) (see Annexe III) will be utilised as assessment tools.

3.2.2. Secondary Objectives

Secondary objectives are:

A. To compare the incidence of early postoperative complications in both techniques:

- Postoperative pain
- Acute urinary retention
- Postoperative bleeding
- Postoperative infection

B. To compare the incidence of late postoperative complications in both techniques:

- Delayed healing
- Fecal incontinence
- Anal stenosis

4. STUDY DESIGN

4.1. Study Type and Design

This is a single-centre, prospective, open, randomised clinical trial.

Randomisation will be performed using the OxMaR system and software (Oxford Minimisation and Randomisation), a free online software available since 2014 and recently adapted to Spanish [1]. The allocation method corresponds to the minimisation method associated with 20% simple randomisation. This system follows the CONSORT guidelines.

4.2. Patient Selection and Sample Size Calculation

4.2.1. Inclusion Criteria

The study population consists of patients attending the General and Digestive Surgery Department of Hospital Universitari Son Llàtzer, with the following inclusion criteria:

- Age over 18 years
- Grade III-IV haemorrhoids
- Indications for surgical treatment
- A signed written informed consent

4.2.2. Exclusion Criteria

Patients must not meet any of the following exclusion criteria:

- Acute haemorrhoidal disease (thrombosis)
- Previous surgery on haemorrhoids
- Coexistence of anal fissure
- Coexistence of perianal fistula
- Coexistence of rectal or anal prolapse
- Inflammatory bowel disease
- Anal or colorectal cancer

4.2.3. Withdrawal Criteria

The investigator must withdraw patients from the trial if any of the following occur:

- Death
- Withdrawal of informed consent
- Loss to follow-up

The reason and date of withdrawal must be recorded in the Case Report Form (CRF).

4.2.4. Sample Size Calculation

Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 25 subjects are required in the first group and 25 in the second to detect as statistically significant the difference between two proportions, expected to be 0.99 for group 1 and 0.7 for group 2. A total of 50 patients is required. An estimated 30% loss to follow-up is anticipated, considering various difficulties that may arise during recruitment (failure to sign informed consent, loss of information during the trial, etc.). The arcsine approximation was used.

4.2.5. Study Duration

The duration of the trial will be determined by the favourable reports from the Research Committee of Hospital Universitari Son Llàtzer and the Ethics Committee of the Balearic Islands until the required sample size is reached.

4.3. Study Development (Stages) and Response Evaluation

4.3.1. Main and Secondary Variables

All necessary variables for the correct conduct of the trial are listed below. Since the primary objective is to assess efficacy in terms of patient quality of life, the main variables are those derived from the Hemorrhoidal Disease Symptom Score and the Short Health Scale for Hemorrhoidal Disease, collected at the initial anamnesis and one year after surgery.

- Demographic variables: extracted from the hospital's electronic medical record.

  - Age (years)
  - Sex (1.male; 2.female)

- Clinical variables: extracted from the anamnesis performed during the clinical visit and recorded in the electronic medical record. None of the variables collected modifies standard clinical practice.

a) Related to the patient's history:

- Body Mass Index (BMI) (numeric)
- Bowel movement frequency: number of bowel movements per week (numeric)
- Use of laxatives (1.yes; 2.no)
- Straining during defecation (1.yes; 2.no)
- Stool characteristics: numeric according to Bristol classification (1-7, normal value 4)

- Number of deliveries (numeric)
- Difficult deliveries (0.not applicable; 1. yes; 2.no)
- Passive anal intercourse (1.yes; 2.no)
- Previous proctologic surgery: specify (1.yes; 2.no)
- Faecal incontinence: numeric according to Wexner scale (0-20, normal value 0)
- Urinary incontinence (1.yes; 2.no)

b) Related to haemorrhoidal disease:

- Anamnesis (HDSS and SHS-HD applied):

  - Proctalgia:

    - Intensity (scale 1-7, SHS-HD)
    - Frequency (scale 1-5, HDSS)

  - Pruritus: frequency (scale 1-5, HDSS)

  - Rectal bleeding: frequency (scale 1-5, HDSS)

  - Soiling: frequency (scale 1-5, HDSS)

  - Prolapse: frequency (scale 1-5, HDSS)

  - Symptom interference with daily activity (scale 1-7, SHS-HD)

  - Concern caused by symptoms (scale 1-7, SHS-HD)

  - General sense of well-being (scale 1-7, SHS-HD)

- Physical examination

  - Perianal scars (1.yes; 2.no)

  - Skin tags:

    - Number (numeric)
    - Position (1-12, clock-face distribution, 12 is anterior)
    - Association with haemorrhoidal bundle (1.yes; 2.no)

  - Perineal descent (1.yes; 2.no)

  - Basal sphincter tone (scale 1-5, normal value 4)

  - Sphincter tone on contraction: numeric(scale 1-10,normal value 8)

  - Haemorrhoidal bundles:

    - Number (numeric)
    - Position (1-12, clock-face distribution, 12 is anterior)
    - Grade (1.III; 2.IV)

c) Related to the surgical procedure

- Common to both procedures
    - Type of anaesthesia (1.general; 2. regional; 3.local)
    - Patient position (1.lithotomy; 2.jackknife)
    - Primary surgeon category (1.senior; 2.junior)
    - Surgery schedule (1.morning; 2.afternoon)
- Milligan-Morgan technique
    - Anaesthetic infiltration (1.yes; 2.no)
    - Number of bundles excised (total number)
    - Identify each excised bundle
        - Bundle position (1-12, clock-face distribution, 12 is anterior)
        - Pedicle treatment (1.electrocoagulation; 2. transfixing suture; 3.sealer)
        - Mucosal fixation (1.yes; 2.no)
    - Hemostatic agent (1.yes; 2.no)
    - Shaving (1.yes; 2.no)
- THD technique
    - Number of sutures (numeric)
    - Suture position (1-12, clock-face distribution, 12 is anterior)
    - Hematoma (1.yes; 2.no)
    - Hemostatic agent (1.yes; 2.no)

d) <u>Related to hospital admission</u>

- Same-day surgery protocol discharge (1.yes; 2.no). If no, complete the following variable:
- Reason for not same-day surgery discharge (0.not applicable; 1. not candidate; 2. pain; 3. urinary retention; 4. bleeding; 5. nausea; 6. anaesthetic problems)

- <u>Postoperative variables</u>

a) <u>7-day follow-up:</u>

- Postoperative pain
    - Visual Analogue Scale (VAS) (1-10)
    - Number of analgesics taken in the first seven days (numeric)

- Time needed to return to work (numeric, in calendar weeks)

- Acute urinary retention: need for bladder catheterisation (1.yes; 2.no)
- Postoperative bleeding

  - Emergency visit (1.yes; 2.no)

  - Blood transfusion (1.yes; 2.no)

  - Reoperation (1.yes; 2.no)

- Postoperative infection
  - Fever: measured once daily, at the same time, for 7 days. Considered positive if over 38°C (1.yes; 2.no)
  - Emergency visit (1.yes; 2.no)
  - Antibiotics (1.yes; 2.no)

b) <u>1-month and 3-month follow-up:</u>

- Faecal incontinence, Wexner classification: interval one week before follow-up (0-20, normal value 0)
- Anal stenosis (1.yes; 2.no)
- Complete healing (0.not applicable; 1. yes; 2.no)

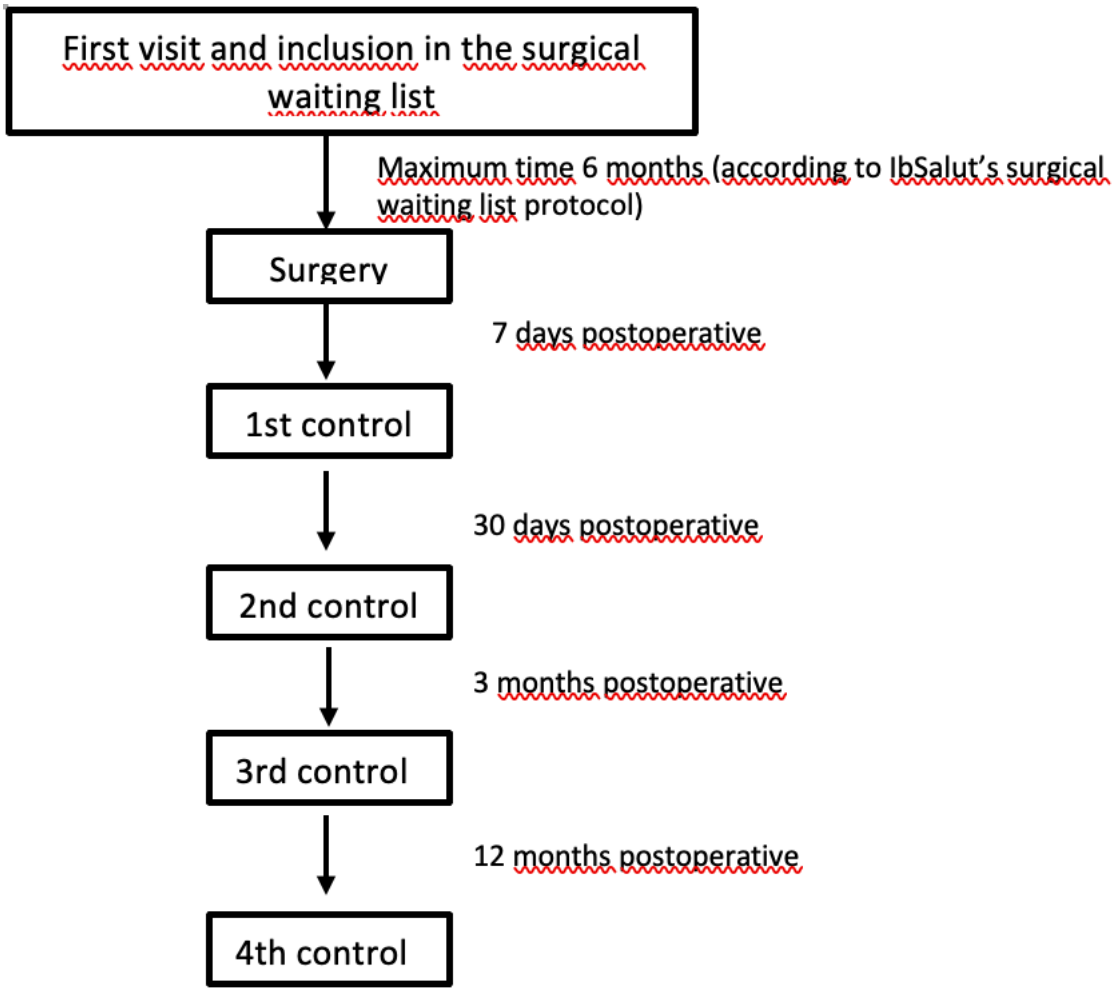
c) 1-year follow-up:

- Faecal incontinence, Wexner classification: interval one week before follow-up (0-20, normal value 0)
- Anal stenosis (1.yes; 2.no)
- Complete healing (1.yes; 2.no; 3.not applicable)
- Repeat variables used in the Hemorrhoidal Disease Symptom Score and Short Health Scale in Hemorrhoidal Disease, as described above.

4.3.2. Study Development: Work Plan and Data Collection

The entire trial will be conducted at Hospital Universitari Son Llàtzer.

SCHEDULE



WORK PLAN

FIRST VISIT	SURGICAL INTERVENTION	FOLLOW-UPS
Anamnesis and physical examination to select grade III-IV haemorrhoids with surgical indication	Random assignment of surgical procedure	FOLLOW-UP 1: Fill in the data sheet corresponding to follow-up 1
Select patient according to inclusion and exclusion criteria	Fill in the surgical procedure data sheet	FOLLOW-UP 2: Fill in the data sheet corresponding to follow-up 2
Explain the trial to the patient and, if accepted, sign the specific informed consent	Fill in the hospital admission data sheet	FOLLOW-UP 3: Fill in the data sheet corresponding to follow-up 3
Fill in the data sheet for the first visit		FOLLOW-UP 4: Fill in the data sheet corresponding to follow-up 4

TASK DISTRIBUTION

- First visit: conducted in person by either investigator

- Surgical intervention: performed by the principal investigator, with the secondary investigator prioritised as first assistant

- Follow-ups 1, 2, 3, and 4: conducted in person by either investigator. Exceptionally, follow-ups 2 and 3 may be performed by telephone.

5. DATA ANALYSIS: STATISTICS

A descriptive analysis of all variables will be performed. For categorical variables, overall percentages and frequencies will be estimated. Normality tests and graphs will be used to determine if quantitative variables follow a normal distribution. Normally distributed variables will be expressed as mean ± standard deviation; those not normally distributed will be expressed as median and interquartile range. To describe significance and associations between variables after intervention, parametric and non-parametric tests will be used as appropriate (paired Student's t-test or Wilcoxon test for quantitative variables, paired ANOVA or Friedman test for qualitative variables). Correlations will be examined using Spearman or Pearson correlation, and a multivariate analysis will be performed to assess the effect of other confounding factors. A p-value <0.05 will be considered significant. SPSS v. 23 software will be used for data analysis.

6. ETHICAL ASPECTS

6.1. General Considerations

The trial will be conducted by Good Clinical Practice guidelines and the International Council for Harmonisation (ICH) guidelines.

6.2. Patient Information and Type of Informed Consent

Each participant must provide written consent voluntarily before the trial begins to be included. Investigators must ensure that patients receive adequate verbal and written information regarding the nature, purpose, and possible consequences of the trial, in a language that is understandable to them. Subjects must also be informed of their complete freedom to withdraw consent at any time without any penalty. They will be allowed to ask questions and given time to consider their decision.

The patient information and informed consent to be provided for the trial are in Annexes I and II. The investigator will keep the signed and dated informed consent form for all subjects included in the clinical trial.

6.3. Confidentiality

To ensure confidentiality, patients recruited for the trial will be randomised and assigned an entry code that is accessible only to the investigators, with prior notification to the patient reflected in the signed informed consent.

Data will be retained for the duration of the trial and a maximum period of two years in case of audits.

The processing, communication, and transfer of subjects' data will be carried out in accordance with Organic Law 3/2018, of December 5, on the protection of personal data and guarantee of digital rights (LOPD-GDD).

7. PRACTICAL CONSIDERATIONS: LIMITATIONS

7.1. Data Collection, Handling, Processing, and Corrections

All patient data generated in this trial will be collected in the CRF, which is specifically designed to capture the necessary clinical data.

Limitations of the trial include its single-centre design and the fact that a single surgeon performs all surgeries. It was decided that the principal investigator would operate on all patients because the THD technique has never been performed by other surgeons in the department. Thus, their learning curve could interfere with the results.

Additionally, the efficacy of one technique over the other, as determined by patient quality of life, is intrinsically subjective. However, the scales used for assessment have recently been validated and standardised [8].

The principal investigator will be responsible for properly archiving and maintaining all data and documentation related to the trial's conduct.

7.2. Publication Conditions

The information obtained from this trial will be analysed jointly, and before publication, it must be reviewed by all participating investigators.

8. SCIENTIFIC RELEVANCE AND APPLICABILITY

Although multiple studies have attempted to compare the various treatments available for hemorrhoidal disease, few studies specifically compare these two techniques, and none exist in the Balearic Islands.

Moreover, most publications assess efficacy based on the somewhat subjective impression of surgical results, whereas recent trends in the literature emphasise the need for assessment using quality-of-life scales [10].

This trial will provide data in our setting comparing both techniques based on efficacy criteria, as measured by patient quality of life. Additionally, if the proposed hypothesis is confirmed, it will allow us to conduct further studies to identify which patient subgroups may benefit from each technique.

9. FUNDING

This is not applicable in our case, as the material used for the trial is already available for routine clinical practice.

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