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Adolescent idiopathic scoliosis: a prospective randomised trial protocol comparing clinical and radiological outcomes in minimally invasive surgery versus standard posterior spinal fusion in a single-centre, the Rizzoli Orthopaedic Institute, Bologna, Italy

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ABSTRACT

Introduction Minimally invasive spine surgery (MISS) has been shown to be safe and effective in adolescent idiopathic scoliosis (AIS) correction, even though there is no consensus on which treatment provides the best results.

Methods and analysis The present study will be a randomised controlled trial with allocation 1:1. We will enrol 126 patients with Cobb≤70° undergoing AIS surgery. Patients will be divided into two groups, according to a randomisation list unknown to the surgeons. Group 1 will be treated with posterior spine fusion and group 2 with MISS. MISS technique: two midline noncontiguous skin incisions of 3 cm in length, 3–4 segments (6–8 pedicles screws) instrumented per skin incision, uniplanar and polyaxial pedicle screws inserted bilaterally on each side of the proximal and distal levels, rod translation manoeuvre and C–D manoeuvre performed on the distal part. Clinical and radiological follow-ups will be performed for 5 years. Values of Cobb angles degrees will be collected to study the correction rate of the structural major curve. Postoperative and preoperative anterior-posterior (AP) direct radiography will be compared with the last follow-up examination. Operative time, preoperative haemoglobin (Hb) and second postoperative day Hb, full length of hospitalisation, time to achieve verticalisation and time to remove the drainage will be recorded. Numeric Rating Scale (NRS) medium score will be assessed immediately after surgery and during the whole postoperative rehabilitation treatment to estimate pain reduction. Complications will be collected postoperatively and throughout the whole follow-up period. Moreover, questionnaires will be administered at follow-up (NRS, Scoliosis Research Society-22 and Oswestry Disability Index) for the clinical assessment.

Ethics and dissemination The study protocol has been approved by the local ethic committee Area Vasta Emilia Romagna Centro. Written informed consent will be collected for all the participants. Findings of this study will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number NCT05860673.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a prospective, randomised controlled trial comparing the results of two different surgical techniques for the treatment of adolescent idiopathic scoliosis.
⇒ Patients are analysed clinically as well as with objective measures, X-rays and CT examination.
⇒ Patient baseline characteristics and disease-related factors are investigated to define the aspects that make different individuals benefiting from each surgical approach.
⇒ Pain assessment is evaluated in terms of pain with the Numeric Rating Scale, although we cannot exclude environmental influencing factors on symptoms.

INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is the most common spinal deformity, it is a structural multiplanar disorder, affecting patients aged 10 years to maturity, and it has a high prevalence of 2%–3% worldwide.[1] Untreated severe cases can lead to important complications, such as back pain, increased disability and socioeconomic effects on work and marital status, up to increased mortality rates related to cardiopulmonary diseases.[2] Rapidly progressive cases need surgical correction at a young age, with the primary goals of correcting deformity, restoring balance and achieving a solid arthrodesis.[3] Traditional

open posterior instrumentation and fusion have been used for decades to correct AIS, although it implies a major invasive surgery for these young patients. This technique is typically performed using a large midline incision with extensive subperiosteal stripping of the posterior elements and is associated with significant blood loss, significant postoperative pain, wound infection and poor cosmetics.[4]

Minimally invasive spine surgery (MISS) has been proposed as a potential mean of improving these shortcomings. MISS was first performed in adult deformity correction and is associated with important benefits such as reduced intraoperative blood loss, muscle attachment sparing and shorter hospital stay.[5] However, the current literature about MISS for AIS treatment is relatively scarce and there is no consensus regarding the best surgical approach for AIS.[6] Controversial findings have shown the benefits and safety of MISS, while other reports claim that the gold standard for AIS correction remains the classic posterior spine fusion (PSF).[7–9] A previous retrospective study, conducted in our unit,[10] collected 111 patients with Lenke type 1–6 AIS who were treated with MISS or PSF, with a 2-year clinical and radiological follow-up. There was no significant difference between the two groups in terms of radiographic and clinical features, so that MISS appeared to be a safe and suitable alternative to PSF for AIS patients with curves<70°. However, nowadays, no high-level study directly compared the two approaches. A randomised controlled trial (RCT) would provide the high-level evidence necessary to clarify the controversial evaluations of the pros and cons of the two treatments, guiding surgeons in the most appropriate choice when managing patients affected by AIS.

Objectives and trial design

The aim of this study is to provide clear indications with a high level of evidence to guide the choice of surgical approach for the treatment of AIS. This study protocol foresees an RCT study design to analyse and compare the outcomes in AIS patients treated with MISS technique versus PSF technique through clinical and radiographic evaluations. The study will be an RCT with allocation 1:1. A software will generate the randomisation in blocks of 6, the randomisation list will be unknown to the surgeons involved. AIS patients will be divided into two groups. Group 1 will be treated with MISS and group 2 will be treated with PSF. A total of 126 patients undergoing spine surgery for AIS will be included and a clinical and radiological follow-up will be performed.

METHODS AND ANALYSIS

Study setting

The study is a single-centre RCT, with all activities related to the study performed in a single site, the IRCCS Rizzoli Orthopaedic Institute, Bologna, Italy. This trial protocol has been approved by the local ethic committee (prot 0016554, protocol version 1 (07 November 2022)).

Based on preliminary data obtained from our case studies, we hypothesise that MISS is a safe and effective procedure for AIS patients with a deformity Cobb<70°. Randomisation will allow the comparison of the two approaches in homogeneous patients selected for AIS with the same clinical and radiological characteristics, thus removing the selection bias correlated to the surgeon indication and experience, which affects the current literature evidence on this topic. This study, the first of its kind, will provide a better understanding of the potential of the MISS surgical approach for AIS, and it will offer elements that can help its development and application in clinical practice. MISS will be compared with PSF to quantify advantages and disadvantages in terms of scoliosis correction capacity, operative time, blood loss, length of stay and postoperative pain.

Patient and public involvement

Patients have not been directly involved in planning the research questions, outcome measures or the design of the study. Yet, the need for this study was inspired by the interaction with patients, collecting their experiences with this type of major surgery and trying to improve their experience by investigating the possibility to treat their condition successfully with a less invasive approach.

Eligibility criteria

AIS patients will be recruited according to the following criteria.

Inclusion criteria

1. Male or female patients, aged between 12 and 25 years. The most suitable age limit could usually be considered 18 years old. However, some patients receive the indication or the possibility to be operated sometimes after this deadline for several reasons, despite the AIS diagnosis. In this light, the age limit has been broadened to 25 years, although to avoid biases in the study, only patients still showing signs of sufficient flexibility are foreseen, with the major curve thus being suitable for MIS technique, as underlined in the following criteria number 4.
2. Site of scoliotic curve: thoracic and/or lumbar.
3. Preoperative radiographic range between 40° and 70° Cobb of the main scoliotic curve. Conventionally, surgery for AIS is indicated for curves>40°, although 40° may represent borderline cases, since a measurement error of 5° is commonly acknowledged. Considering the surgical choice is more complex than that simple number, as it would be based on the finding of the rotational component prevailing over the angular component, and most operated scoliosis are rather close to the upper limit of the range. Still, a prudential approach could be either to include only those >45°, or to have a measurement from two separate independent operators to confirm indications around the lower 40° limit. As this study has been approved with the 40° cut-off and is currently ongoing, this parameter was kept

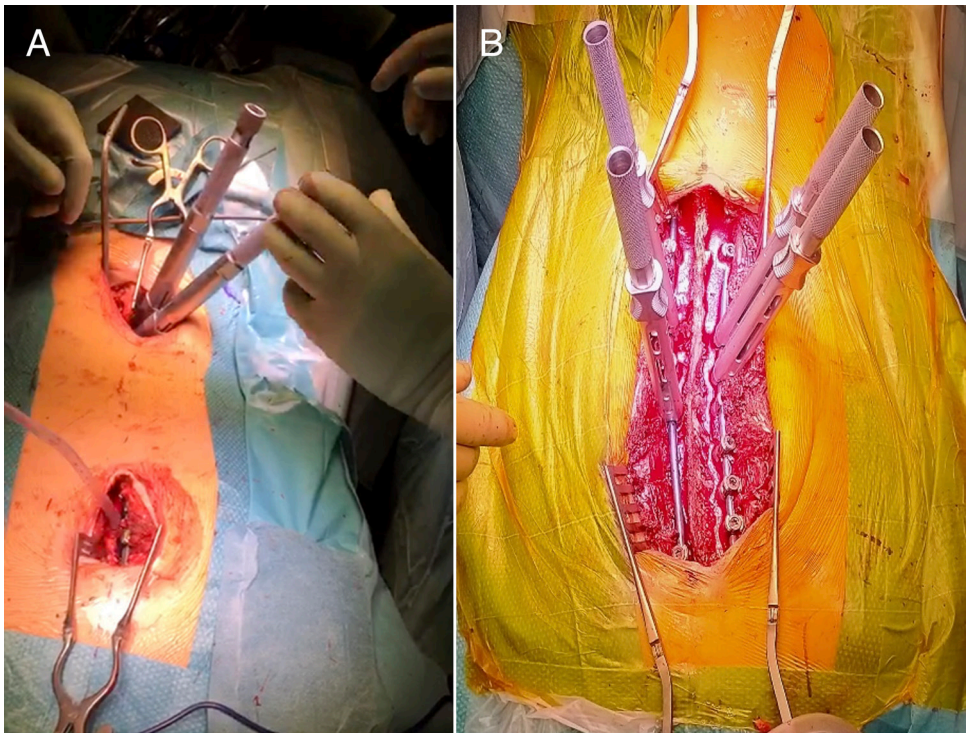

Figure 1 Surgical exposure in minimally invasive spine surgery (A) and posterior spine fusion (B).

for consistency within the study, also in consideration of the unlikely enrolment of borderline cases in our practice. However, we will consider carefully the study results also in light of this aspect, and we suggest that future studies should take the possible risks of enrolling borderline cases and consider a different cut-off.
4. Curve flexibility>50° on supine side-bending films.
5. Patients' ability and consent to participate in clinical and radiological follow-ups.
6. Parental consent for participants under the age of 18 years.

Exclusion criteria

1. Patients who already underwent surgery for scoliosis.
2. Cervical site of the scoliotic curve.
3. Different aetiology from AIS.
4. Unbalanced sagittal profile.
5. Patients unable to consent or perform follow-ups.
6. Pregnancy.

Surgical techniques

All patients will be treated by spine surgeons with established experience in scoliosis procedures.

Minimally invasive spinal surgery

This MISS technique is performed through two small midline skin incisions (5–6 cm of length) (figure 1A), followed by subcutaneous and muscular dissection to mobilise laterally the skin incisions. The muscles fibres are dissected from the bone with subperiosteal skeletonization. An adequate facetectomy is obtained at all levels instrumented with osteotomy and usually at one or two levels proximally for the distal incision and distally for the proximal incision. Three or four levels are instrumented for each incision. Resect facets are used as autograft to facilitate the arthrodesis. Uniplanar pedicle screws are used bilaterally and polyaxially screws are used for the proximal and distal levels, according to the 'free hand anatomic technique'. Two rods contoured with planned sagittal lordosis and kyphosis are passed from the proximal to the distal incision in cephalocaudal direction, passing below the fascia in the not exposed tract. The screws are capped as the rod passes on the tulip. Rod reduction devices can be used to facilitate the correct positioning of the screw heads. Rod translation manoeuvres are performed, as well as a Cotrel-Dubousset manoeuvre on the distal part. To do this, a temporary, slightly longer rod is applied on the contralateral side only in the distal tract and a derotation is performed using a rod wrench on the distal part of the temporary rod while obtaining a deformity reduction on the definitive rod. A reverse force is applied on the thorax of the patient during the manoeuvre. The definitive rod is locked, the temporary rod removed, and the positioning of the rod on the contralateral side is repeated with the same technique. Distraction and compression manoeuvres are performed as per conventional technique. Subfascial drain is not always used and removed 1 or 2 days after the surgery.

Posterior spinal fusion

The standard open technique involves an extended midline incision along the entire thoracolumbar spine (figure 1B). Paravertebral muscles are incised and spread apart to expose the posterior vertebral structures. Pairs of pedicle screws are infixed freehand after facetectomies

are performed. Several osteotomies are made to mobilise the vertebral metameres at the apex of the deformity, at this point correction in carried out through derotation manoeuvres. The obtained correction is fixed with preshaped rods, which subsequently are connected to screws and tightened to nuts with a dynamometer. Almost all thoracolumbar levels are included into the arthrodesis.

Outcomes

The primary outcome is to document AIS correction in terms of primary curve Cobb degree 1 year after surgery. The secondary outcomes are:

- Surgical correction in terms of Cobb degrees of the primary curve at the coronal plane at other follow-ups, to document any changes in the curve over time (postoperative, 2, 6, 24 and 60 months).
- Numeric Rating Scale (NRS) Score at baseline, 2, 6, 12, 24 and 60 months of follow-up.
- Scoliosis Research Society-22 (SRS-22) Score at postoperative time, 2, 6, 12, 24 and 60 months of follow-up.
- Oswestry Disability Index (ODI) Score at postoperative time, 2, 6, 12, 24 and 60 months of follow-up.
- Screw malposition rate will be evaluated by a CT scan performed at 6-month follow-up, and the Brantigan score will be applied to document screw fusion.
- Incidence of mechanical complications, such as break or implant mobilisation or junctional kyphosis.
- Differences in terms of operative time, blood loss, length of stay, drug use and postoperative NRS pain.

Additionally, operative time, preoperative haemoglobin (Hb) and second postoperative day Hb, full length of hospitalisation, time to achieve verticalization and time to remove the drainage will be recorded. NRS Score will be assessed immediately after surgery and during the whole postoperative rehabilitation treatment to estimate pain reduction. The medication regimen will be standardised involving administration of morphine on the first postoperative day, as well as prophylactic antibiotic therapy standardised with Cefazolin. The patient will be able to walk, if no complication will arise, from the first postoperative day.

Participant timeline and recruitment

Properly trained medical staff belonging to the Hospital Spine Unit will identify the subjects who meet the inclusion criteria, who will sign the informed consent and answer evaluation questionnaires. Enrolled patients who have provided written consent will be placed in one of the two arms of the study according to the randomisation list. The two arms will be:

- MISS arm: patients treated with the MISS.
- PSF arm: patients treated with the traditional open technique.

Patients' enrolment will start in June 2023.

Patients will undergo an outpatient visit and X-rays evaluation before surgery and then will be evaluated at hospital discharge and subsequent clinical follow-ups (2, 6, 12, 24 and 60 months after surgery). At this time, questionnaires will be administered (NRS, SRS-22 and ODI) for the clinical assessments and any adverse events will be assessed.

With regard to the questionnaire choice, we chose the SRS-22 Score based on the international society on scoliosis orthopaedic and rehabilitation treatment (SOSORT) 2016 guidelines, which indicate that the SRS-22 Questionnaire is responsive to changes in the postsurgical period.[11 12] However, while this is an accepted questionnaire for this kind of studies, the SRS-30 Score could be used as well as a suitable score for this type of study protocol.

Moreover, with regard to the use of ODI, while the use of this score is accepted by the literature in this field,[13 14] other suitable options for evaluating these patients may include the EQ-5YL Score as well.

The purpose of this radiological evaluation is to quantify the correction and stability of the correction over time (see figures 2 and 3 for the different radiographic pattern before and after surgery).

Allocation

A total of 126 eligible patients are allocated to undergo MISS or PSF, in a 1:1 ratio (63 patients for each group). The randomisation list is computer generated and will have blocks of six. The list will be kept by research staff members dedicated to the study organisation and monitoring with no direct involvement in the surgery procedures. The randomisation list is covered by password and accessible only by staff members with no direct involvement in the study.

Data collection methods

Data are first collected on paper-based case report forms (CRFs), with the help of research trained orthopaedic residents and subsequently trained data analysts process the data into electronic form for statistical analysis. Baseline and follow-up X-rays spine are coded and stored at the Rizzoli Orthopaedic Institute to ensure data quality control. Operative data are collected electronically by the respective surgeons shortly after surgery.

Data management

Study data are stored in a password-protected spreadsheet on a server hosted at the Rizzoli Orthopaedical Institute. Data transfer is encrypted with all data deidentified. Only trained research personnel specifically dedicated to the data handling can access the database and ensure the correspondence of the electronic data with the original paper-based questionnaires and medical charts.

Statistical methods

Based on a power analysis considering the Cobb degree correction at 1 year, with a difference between the two techniques of 5° considered to be not clinically relevant, a population of 100 patients, 50 per group, has been determined to have a 90% power and a CI of 5°. Considering a possible dropout of 20%, we expect to enrol 126 patients (63 per group).

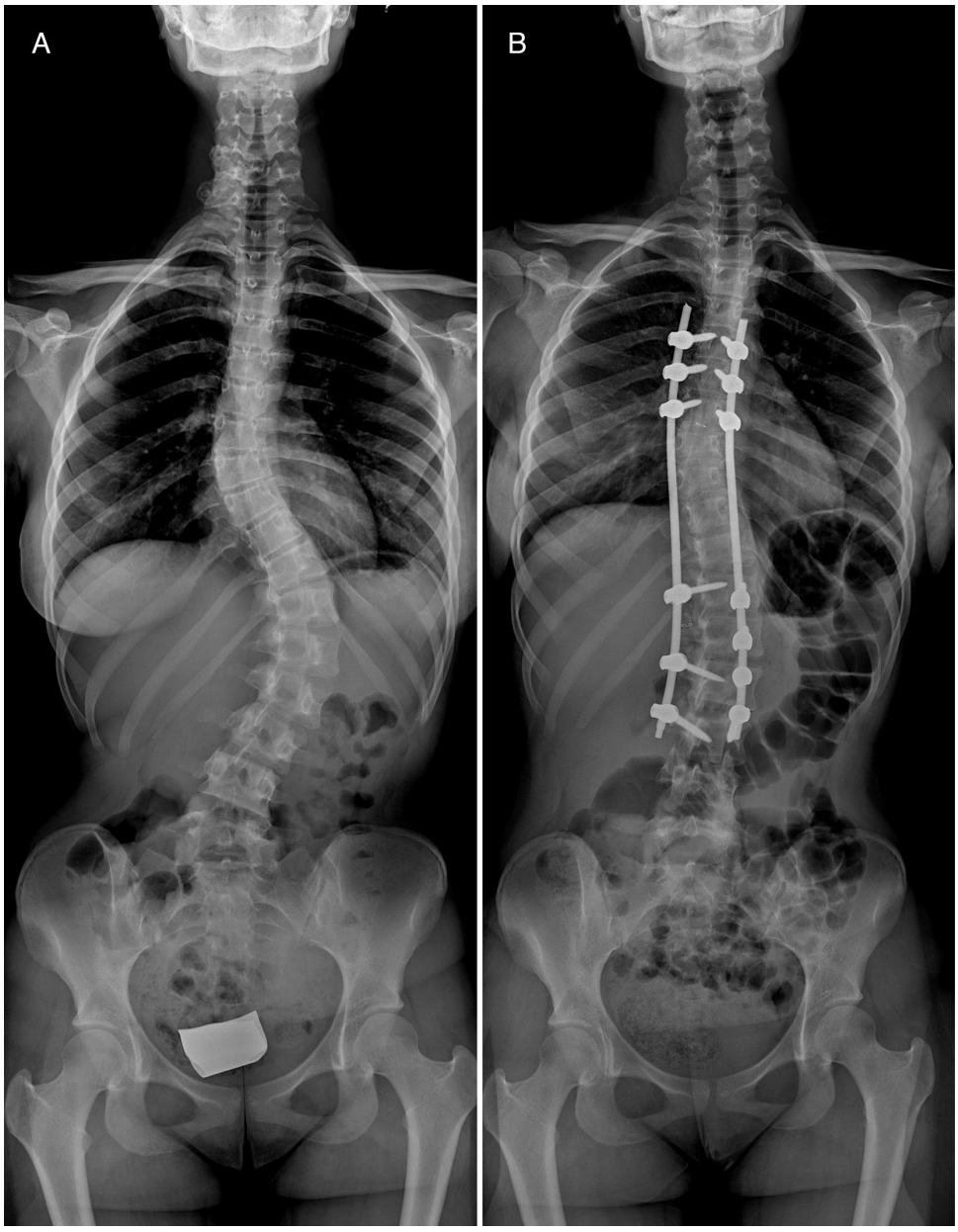

Figure 2 (A) Preoperative and (B) postoperative X-rays of a case of adolescent idiopathic scoliosis treated with minimally invasive spine surgery.

For these trials, the objective is not to demonstrate that MISS is superior to the PSF, but rather to demonstrate that is clinically not inferior or no worse compared with the control. The null (H0) and alternative (H1) hypotheses for non-inferiority trials may take the form as follows:

H0: Treatment A (MISS) is inferior in terms of the mean response mA−mB≤−dNI.

H1: Treatment A (MISS) is non-inferior in terms of the mean response mA−mB>−dNI.

The non-inferiority limit, dNI, is defined to be the difference that is clinically acceptable for us to conclude that there is no difference between treatments. So the difference between the group used to design the sample size must be a value 'considered to be not clinically relevant'.

Continuous and normally distributed variables will be expressed in terms of mean and SD, those not normally distributed will be expressed in terms of median and range. Dichotomous or categorical variables will be expressed in terms of frequency and percentage incidence. The normality of the distribution will be verified using Shapiro-Wilk test. Levene's test will be used to verify the homogeneity of variances (homoskedasticity) between the compared groups. Sidak's test and Friedman test will be used to compare changes over time in the primary and secondary outcomes. One-way analysis of variance will be used to verify the difference between the two groups in homoskedastic outcomes, while for non-homoskedastic outcomes, the non-parametric Mann-Whitney test will be used. Pearson's χ^2 test will be used to verify the difference in the frequency of categorical outcomes between groups, even between small subgroups. Spearman's rank correlation will be used to evaluate the influence of continuous variables on continuous outcomes.

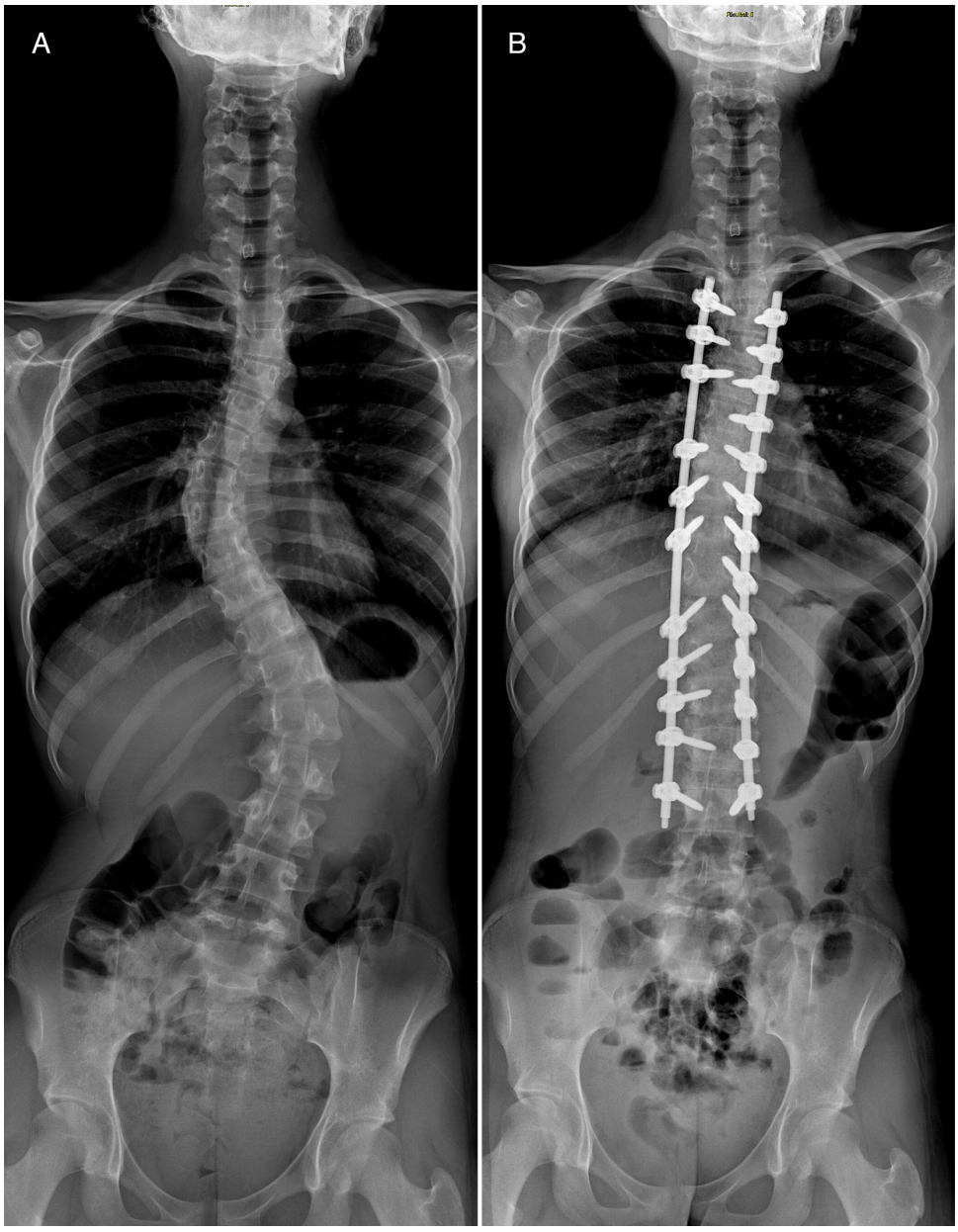

Figure 3 (A) Preoperative and (B) Postoperative X-rays of a case of adolescent idiopathic scoliosis treated with posterior spinal fusion technique.

Generalised linear models will be used as multivariate analyses to evaluate the combined impact of baseline variables on outcomes. Possible adverse events will be analysed using Kaplan-Meier survival analysis. For all tests, a p value of 0.05 will be used as limit of significance.

Data monitoring

A central project data manager is tasked to perform data quality control on all collected data. Electronic data are kept in a secure electronic database. This remains password protected and with access given only to the study investigators unless otherwise authorised by the study team.

Access to data

Only members of the research team who need to contact study patients, enter data or perform data quality control have access to patient information. According to the ethic committee, we will share aggregated data anonymously. No individual deidentified participant data will be available.

Data will be shared in accordance to the law in place by the time when the RCT will be concluded.

Dissemination policy

This trial is produced according to the Standard Protocol Items: Recommendations for Interventional Trials international standards. The results will be disseminated through peer-reviewed publications and will be submitted for presentation at national and international conferences.

ETHICS AND DISSEMINATION

The study protocol has been approved by the local ethic committee 'Area Vasta Emilia Romagna Centro'. Written

informed consent will be collected for all the participants. Findings of this study will be disseminated through peer-reviewed publications and conference presentations.

Scientific relevance and broader impact

This study provides a detailed method of minimally invasive surgical treatment for scoliosis and can offer clear indications on the potential and limitations of the MISS technique. The aim of this study is to better quantify advantages and disadvantages of MISS versus the traditional more invasive approach, including factors related to patient and disease which may lead to better results with either PSF or MISS.

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Contributors BM and CC wrote the manuscript and together with FV will conduct the trial and is the guarantor. GF supervise the trial. AG is the principal investigator of this study. All authors read and approved the final protocol.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

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