Contemporary Clinical Trials Communications 19 (2020) 100618

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: http://www.elsevier.com/locate/conctc

A prospective controlled randomized multicenter study to evaluate the severity of compensatory sweating after one-stage bilateral thoracic sympathectomy versus unilateral thoracic sympathectomy in the dominant side

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ARTICLE INFO

Keywords:
Hyperhidrosis
Sweating
Sympathectomy
Compensatory sweating
Thoracic surgery
Video-Assisted

ABSTRACT

Objective: To evaluate the contribution that unilateral thoracic sympathectomy in dominant side or two-stage bilateral thoracic sympathectomy can have as strategies to reduce the incidence of compensatory sweating after sympathectomy for palmar hyperhidrosis.

Methods: This is a prospective, controlled, randomized multicenter trial of 200 participants with palmar hyperhidrosis, which will be randomized into two arms: (a) one-stage bilateral thoracic sympathectomy (control arm); or (b) unilateral thoracic sympathectomy in dominant side (intervention arm). At six months the participants submitted to unilateral procedure can make the contralateral surgery if they wanted it, creating a third group called two-stage bilateral sympathectomy. Participants will be evaluated for the degree of sweating by the Hyperhidrosis Disease Severity Scale (HDSS) and of quality of life questionnaires.

Results: 96 participants out of the 200 proposed have been included so far, with 48 participants randomized to each arm. From the sample 61 (63.5%) are female, with a mean age of 24 (20–32) years. There were exclusive palmar hiperhydrosis in 14 cases (14.5%), palmar and plantar hyperhidrosis in 36 (37.5%) cases, palmar and axillar hyperhidrosis in 12 (12,5%) cases and palmar-axillary-plantar hyperhidrosis in 34 (35,4%) cases. The age at the beginning of the disease was childhood (78%), with mean of time of disease 15 (11–22) years.

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https://doi.org/10.1016/j.conctc.2020.100618
Received 2 March 2020; Received in revised form 27 June 2020; Accepted 12 July 2020
Available online 15 July 2020

Conclusions: If one or both hypothesis: (a) unilateral sympathectomy in dominant hand is a satisfactory treatment; b) two-stage bilateral sympathectomy causes less compensatory sweating than in one stage are confirmed there is a chance that surgical therapy for palmar hyperhidrosis can be changed for better.

1. Introduction

Hyperhidrosis is a common clinical condition defined as a somatic disorder characterized by excessive sweating in certain regions. Palmar hyperhidrosis is a condition of greater importance when compared to other locations due to the affective, social and professional problems they cause in the patient. It is often associated with plantar and axillary hyperhidrosis [1–3].

The procedure commonly used for the treatment of palmar hyperhidrosis is one-stage (under the same anesthetic act) bilateral thoracic sympathectomy by videothoracosocopy [4–6].

The most frequent complication is compensatory sweating (CS), which occurs mainly in the trunk, with a 30–90% incidence and unknown pathophysiology; it is the most important complication due to the possibility of significantly affecting patients' postoperatively quality of life [7–10].

The wide variability of CS incidence can be affected by several factors like heterogeneous patient populations, a variety of sympathetic denervation techniques, or more important to a lack of objective methodology for defining CS [6,11,12]. In order to reduce the incidence of CS, some authors have studied the two-stage operative treatment, which consists of the initial approach of the dominant limb followed by contralateral limb surgery at a later time. Although the mechanism of CS is still uncertain, one hypothesis for a possible good response to the staggered treatment is that by delaying the second approach, Kuntz communicating fibers and accessory fibers are allowed to regenerate, so that after the second procedure a definitive thermoregulatory effect can be achieved [13].

One study showed that in the group undergoing two-stage treatment the rate of CS was 4.3% whereas in those patients treated by one-stage bilateral sympathectomy the rate was 19.1%, with no difference in relapse or complication rates [14].

This benefit was maintained over the long term (after 3 years), and the rate of CS persisted at the same levels, ie, in patients treated at two surgical times the rate was 4% while single-time surgical treatment had a rate of CS of 19% [15].

Another study showed similar results, with six-fold lower CS rates in the two-stage group (12.2% versus 71.1%) and similar improvement in symptomatology (with a satisfaction rate of 96.7% versus 97.2%) [16].

In 1999, Dohayan et al. evaluated the outcome of a series of 120 patients who underwent unilateral sympathectomy on dominant limbs and who eventually underwent surgery on the contralateral limb if they were dissatisfied with the outcome. Most patients were satisfied with unilateral surgery, as only 40% decided to sympathectomy the other limb. The degree of CS was lower than in patients operated on both sides (27% versus 42%) [17].

In 2015, Ravari et al. conducted a prospective study evaluating the outcome of a series of 52 patients undergoing unilateral sympathectomy alone and noting that there was complete resolution in all dominant limbs. In the contralateral limb, 46% of patients had complete resolution. CS was present in 34% of patients [18].

Even though, to the best of our knowledge, there is no prospective randomized trial addressing this issue.

1.1. Trial objectives

We hypothesized that participants having in mind the possibility to reduce the risks of compensatory sweating may be satisfied with unilateral sympathectomy in the dominant side. In addition, we hypothesized that participants undergoing bilateral two-stage surgery may have a lower occurrence of compensatory sweating than those undergoing bilateral one-stage surgery. The primary purpose of the trial is to compare the intensity of compensatory sweating in participants with palmar hyperhidrosis treated by one-stage bilateral thoracic sympathectomy with those submitted to unilateral thoracic sympathectomy in dominant side.

Furthermore, the secondary purposes are (a) to compare the intensity of compensatory sweating in participants undergoing one-stage bilateral thoracic sympathectomy with those undergoing two-stage bilateral thoracic sympathectomy; (b) to compare the intensity of compensatory sweating in participants undergoing two-stage bilateral thoracic sympathectomy with those undergoing unilateral thoracic sympathectomy in the dominant side; (c) to evaluate the postoperative quality of life of participants treated for palmar hyperhidrosis by one-stage bilateral sympathectomy, two-stage bilateral sympathectomy and unilateral sympathectomy in dominant side; (d) and to evaluate whether sympathetic resection of the 4th thoracic ganglion causes changes in cardiac autonomic physiology.

2. Material and methods

2.1. Study design

The study is a prospective, controlled, randomized multicenter trial of 200 participants with palmar hyperhidrosis, which will be randomized to one of two arms: (a) one-stage bilateral thoracic sympathectomy (control arm); or (b) unilateral thoracic sympathectomy in dominant side (intervention arm). The diagram was shown in Fig. 1. Both groups will be followed for six months, when they will be evaluated for the degree of sweating by the Hyperhidrosis Disease Severity Scale (HDSS) and application of quality of life questionnaires. The heart rate variability will be analyzed by 24-h Holter recordings obtained before endoscopic thoracic sympathectomy and two weeks after the procedure. At six months the participants submitted to unilateral sympathectomy will be able to make the contralateral procedure if they wanted it, creating a third comparison group called two-stage bilateral sympathectomy.

1SBS: one-stage bilateral sympathectomy; USDS: unilateral sympathectomy in dominant side; 2SBS: two-stage bilateral sympathectomy.

This study was approved by the IRB and is registered at Plataforma Brasil with CAAE 00273818.4.1001.0068 and has a ClinicalTrials.gov Identifier: NCT03921320. All participants provided written informed consent.

2.2. Sample size

Two hundred participants will be included with palmar hyperhidrosis according to the inclusion criteria. The number of participants who will be recruited for this study was initially based on data from Cubuk S et al. [19] where it was found that 20% of patients who had undergone unilateral sympathectomy did not wish to perform contralateral complementation surgery. Based on this information the sample was calculated for two situations:

a)for the comparison of compensatory sweating between 1SBS versus USDS groups, the calculation was based on data from Youssef T et al. [16] who described incidence of compensatory sweating of 71.1% in patients undergoing bilateral sympathectomy versus 12.2% in patients undergoing exclusive unilateral sympathectomy.

b) for the comparison of compensatory sweating between groups 1SBS versus 2SBS the calculation was based on data from Ibrahim M et al. [14] who reported that compensatory sweating occurred in 19% in the group undergoing bilateral sympathectomy at one time and in 4% in those undergoing bilateral sympathectomy at two times.

The final number of participants (n = 200) corresponds to the minimum sample size results plus a value of 20% to ensure that the number of participants in each subgroup (1SBS, USDS and 2SBS) is representative to the point of reliable estimation, and to not compromise the final results with possible follow-up losses of participants.

The sample size calculation for the two cases was carried out with the aid of MINITAB Release 14.12.0 Statistical Software using 80% power and 0,05 level of significance.

2.3. Study eligibility

Enrolled 200 participants with hyperhidrosis palmar were men or women aged in rage of 18–60 years old at randomization, who had a body mass index of 28 or less and dominant right hand. The participants could have palmar hyperhidrosis exclusively or also associated with axillary and/or plantar hyperhidrosis. All participants should agree with the proposed treatment by signing the consent form. The exclusion criteria were previous thoracic surgical interventions, presence of comorbidities such as cardiac, metabolic, infectious or neoplastic diseases, and pregnancy. The details of inclusion and exclusion criteria for this trial were described in Table 1.

2.4. Study sites

A total of 11 centers throughout Brazil participated in the study. The coordinator center, Heart Institute (InCor) FMUSP, is a tertiary public university hospital with 500 beds located in Sao Paulo, southwest of Brazil. There are ten other public university hospitals distributed in other Brazil States: Amazonas, Rio Grande do Norte, Ceara, Pernambuco, Bahia, Distrito Federal, Mato Grosso do Sul, Minas Gerais e Rio de Janeiro. It's important to highlight that the distance between the sites located farther north and farther south is 2408 miles to make clear that the sites are geographically distributed and that all country regions are well represented. The full list of participating hospitals and investigators was shown in Appendix 1.

2.5. Data collection

All data will be collected through REDCap. Eligible participants were determined by a local investigator based on the inclusion and exclusion criteria during a medical consultation. Once the conditions for participation in the study were accepted, the participants underwent preoperative evaluation with clinical history, physical examination and complementary exams. This process corresponds to the routine evaluation of patients with hyperhidrosis who are candidates for surgical treatment in the study centers. In centers where possible, a 24-h preoperative Holter examination to measure heart rate variability (HRV) in time and frequency domains will be part of this evaluation. Since it is not possible to guarantee that all centers will have conditions to make this evaluation, it is expected that only part of the participants will undergo this type of assessment.

Then participants will be objectively assessed for sweating intensity in 18 selected areas of the body using the HDSS hyperhidrosis severity scale, as well as the HidroQOL and Horn quality of life questionnaires will be applied.

Table 1
Inclusion and exclusion criteria of the trial.

Criteria	Definition
Inclusion	1. Age between 18 and 60 years old; 2. Body mass index of 28 or less; 3. Dominant right hand; 4. Having exclusive palmar hyperhidrosis or palmar hyperhidrosis associated with axillary and/or plantar hyperhidrosis; 5. Agreement with the proposed treatment by signing the consent form.
Exclusion	1. Presence of craniofacial or generalized hyperhidrosis; 2. Previous thoracic surgical interventions; 3. Presence of other comorbidities such as cardiac, metabolic, infectious or neoplastic diseases; 4. Pregnancy.

2.6. Evaluation instruments

The Hyperhidrosis Disease Severity Scale (HDSS), that was translated and validated to Portuguese, will be used to measure the severity of hyperhidrosis and compensatory sweating in other areas of the body. This instrument is composed of a single question that can be answered with four different degrees of sweat tolerance and interference in the patient's daily life. Score 1 indicates absence of excessive sweating; score 2 moderate hyperhidrosis, with 3 and 4 corresponding to severe hyperhidrosis. Studies have shown a good correlation with gravimetric indices where a two-point reduction in scale indicates an 80% drop in sweat production [20,21].

Quality of life will be assessed using two instruments developed specifically for patients with hyperhidrosis. The questionnaire called

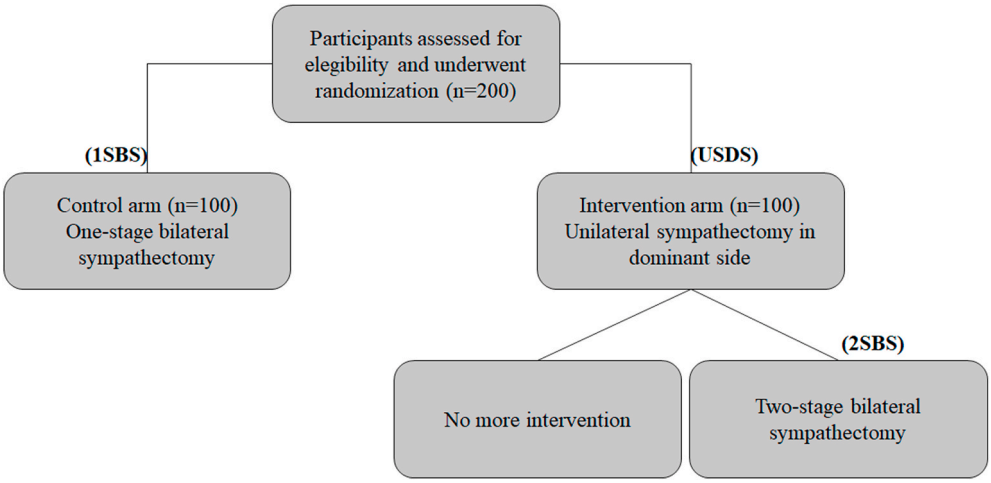

Fig. 1. Diagram of the trial.

Hyperhidrosis Quality of Life Index (HidroQOl©), in which the variables address everyday situations in which hyperhidrosis may interfere and are organized in a protocol with 18 questions, divided into two domains: activities of daily life (with 6 questions) and psychosocial life (with 12 questions). Answers are scored at three points: very = 2; a little = 1; and no, not at all = 0. The point scale ranges from 0 to 36 [22].

Another instrument is the questionnaire described by Horn et al., which was developed in the Portuguese language of Brazil according to the methodology recommended in the literature. It consists of 10 closed questions whose answers were uniformly structured so that each question has four alternatives according to the impact on quality of life: "nothing", "a little", "very", "very much" and their scores range from 0 to 40 [23].

2.7. Randomization

The nature of the intervention prevents the blinding of participants and surgical teams but after preoperative evaluation participants will be randomized to be allocated into two surgical arms:

Control arm: one-stage bilateral thoracic sympathectomy (OBS).

Intervention arm: unilateral thoracic sympathectomy in dominant (USD).

The type of randomization employed is the simple one, with each center having its own randomization table. These tables were generated electronically through a web-based program that ensures confidentiality and were then uploaded to the REDCap randomization module.

2.8. Surgical intervention

The surgical technique to be employed has already been described in detail elsewhere [24].

After general anesthesia the participant is placed on the operating table in a semi-sitting position at 60° (beach position). Axillary incisions will be made on the right side of the lateral chest wall through which a video camera and electrocautery will be introduced. Then, the sympathetic chain is identified and the nerve segment thermoablation is contained between the upper edge of the 4th arch and the lower edge of the 5th costal arch, corresponding to the 4th sympathetic ganglion. After revision of hemostasis, pulmonary hyperinflation is performed until complete expansion of the lung. In the bilateral group, the same procedure will be performed in the sympathetic chain of the contralateral hemithorax. With satisfactory postoperative evolution, the participant may be discharged on the same day or on the first day after surgery.

From the 6th postoperative month, participants in the dominant unilateral group may, if they consider that the result obtained was not satisfactory, be submitted to contralateral surgery, called two-stage bilateral sympathectomy.

2.9. Follow-up procedures

The return of postoperative control will be between the 7th to the 15th postoperative day with chest X-ray to check for possible pleural or surgical complications. Response to treatment in terms of intensity of palmar hyperhidrosis after surgery as well as the presence and intensity of compensatory sweating will be assessed by HDSS application at 60th PO and also after 6 months of surgery, on participant's outpatient return or through of telephone interview. In addition, in the 6th postoperative month the quality of life questionnaires, HidroQOl© and Horn, will be applied again.

During the postoperative period participants will also be observed regarding the appearance of possible complications. These complications will be recorded and analyzed to assess whether there is correlation with the surgery performed.

2.10. Endpoints

The primary outcome is compensatory sweating and it was defined as the difference in the sum of all values attributed to the 18 body areas (except the hands) of the HDSS in the postoperative period subtracted from those same areas in the preoperative.

The palmar hyperhidrosis severity is defined by the sum of the values attributed to both hands in HDSS.

The efficacy of sympathectomy is evaluated by the difference of the sum of values attributed to both hands in pre and postoperative periods.

2.11. Data entry & storage

REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources [25,26].

The study has no data obtained through paper format. All data collected by the study personnel are directly entered, stored and managed using REDCap electronic data capture tools hosted at Hospital das Clinicas, University of Sao Paulo. At each clinical site, authorized research coordinators have REDCap access to enter and edit data only for the participants at their site. REDCap automatically maintains an audit trail of all users and all activity. The database is incrementally archived.

2.12. Statistical methods

In the evaluation of primary endpoint, unpaired Student t-test (or the non-parametric alternative, the Mann-Whitney test) and analyses of covariance (ANCOVA) (with adjustment for pre-treatment measure), will be used to determine unadjusted and adjusted differences between groups. Unadjusted and adjusted means (with 95%CI) will be presented. Otherwise, if there are strong deviations for ANCOVA application a non-parametric alternative will be used. All assumptions for ANCOVA, including homogeneity of regression slopes, equality of variances and normality of residuals, will be checked.

In not completely randomized group comparisons, to manage possible baseline differences between the two groups generalized linear models will be applied. Linear correlation will be conducted according to Pearson's correlation coefficient or Spearman 's correlation coefficient when appropriate. The correlation coefficient will be reported with 95% confidence level and interpreted as follows: Very strong linear correlation $|r| = 0.9–1.0$; strong $|r| = 0.7–0.9$; moderate $|r| = 0.4–0.7$; weak $|r| = 0.2–0.4$; very weak $|r| = 0.0–0.2$.

Comparisons between two groups will be assessed using the Student t-test, or the Mann-Withney test if appropriate for quantitative variables, and Chi-square test or Fisher's exact test for categorical variables. Normally distributed quantitative variables will be presented as mean ± standard deviation and non-normally distributed quantitative variables as median (interquartile range (IQR)).

Normality will be assessed with visual inspection of histograms and application of Shapiro-Wilk test. All the hypothesis tests will be two-sided with a p-value <0.05 being considered statistically significant. Statistical analyzes will be performed using the Statistical Package for Social Sciences version 21 (SPSS 21.0 for Windows) software.

2.13. Safety monitoring

All participants will be instructed to report any injuries to study staff within 24 h of the event occurring. Adverse events will be recorded on case report forms during follow-up visits. Reports of adverse events may be forwarded to a designated researcher contact point at any time.

Adverse events will be monitored until properly resolved or explained.

2.14. Search termination or suspension criteria

If significant risks or damages are found to the participant, this research may be suspended or terminated at any time by joint decision of the researcher and the ethics committee of the institution.

3. Results

The participant recruitment process began in March 2019 and it is estimated to be completed at June 2020. There are 96 participants out of the 200 proposed so far. From the sample 61 (63.5%) are female and 35 (37.5%) male, with a mean age of 24 (20–32) years. Fourteen (14.5%) participants had isolated palmar hyperhidrosis, 12 (12.5%) palmar and axillary hyperhidrosis, 36 (37.5%) palmar and plantar hyperhidrosis, and 34 (35.4%) palmar-axillary-plantar hyperhidrosis. Disease onset was prevalent in childhood (78%), with a mean disease duration of 15 (11–22) years.

The randomization was for dominant unilateral surgical procedure in 48 cases and one-stage bilateral in 48 cases. The total score of HDSS scale resulted in 31 (26–36) points in the unilateral group and 32 (27–38) points in the bilateral group. Quality of life by the Horn questionnaire averaged 21 (16–25) points in the unilateral group and 19 (15–24) in the bilateral group, and by the HidroQol questionnaire averaged 27 (21–31) points in the unilateral group and 28 (22–31) in the bilateral group, showing a similar distribution of the sample between the groups preoperatively.

The compensatory sweating comparison between the groups did not show statistical difference, which may be due to partial results and still small sample. Results regarding the two-stage bilateral sympathectomy are still being analyzed. Recruiting can be completed at March 2020.

4. Discussion

One difficulty in this study was to recruiting the investigators. The main reason is that in the field of thoracic surgery, most public hospitals in Brazil have a large number of cases of lung cancer waiting for surgery. In these hospitals it would be pointless to propose a protocol in which cases of sympathectomy will compete for operating rooms with cases of cancer.

However, sometimes these facilities have other limitations, such as the lack of beds in intensive care, which means that minor surgeries have to be performed to avoid missing surgical hours. Thus, when selecting investigators and sites, it is not enough do it solely on the basis of their willingness to participate, it is also necessary to analyze the hospital situation in relation to these scheduling problems.

Because of this, in the tenth month after the trial initiation it was necessary to exclude five centers that were unable to include participants. Unfortunately, this is a not a rare problem. There is considerable literature reporting results from studies in which numerous study sites failed to meet enrollment, or failed to enroll any subject at all [27–29].

But to substitute these centers instead of relying solely in investigators enthusiasm to participate it was made a broader arrangement. Together with the Teaching, Research and Innovation Department of the Brazilian network of federal public hospitals (Ebserh) we selected facilities in which not only the investigators were qualified but the hospital direction agreed to collaborate with the research.

There is some data in literature showing that 16% of protocol amendments in general are due to changes in inclusion/exclusion criteria problems [30].

Another point of concern in this study is related to the inclusion criteria. The study is accepting participants with palmar, palmar and axillary, and palmar and plantar hyperhidrosis. In three of the first cases included in the protocol the participants submitted to the unilateral sympathectomy of the dominant hand requested to be submitted to the contralateral surgery not because of complaints of her left hand but because of her left axilla. This fact made us aware that we probably should have not included in the trial participants with axillary sweating since these cases can contaminate our results not because of poor hands outcomes but because of axilla outcomes, which is not being studied.

In this case we will consider classifying participants with axillary sweating as a factor for exclusion segment by post factum casualty. If this situation occurs, the same number of axillary sweating cases excluded will be substituted by participants that can have palmar or palmar and plantar, but without axillary sweating [31].

For the comparison of the CS of participants undergoing one-stage bilateral with those undergoing two-stage bilateral sympathectomy; and in participants undergoing two-stage bilateral with those undergoing unilateral sympathectomy in the dominant side, two subgroups that are not randomized, therefore not entirely comparable, generalized linear models analysis will be utilized.

5. Limitations

The main limitation of this study stems from the fact that we are using self-report measures of disability rather than objective functional or biological assessments. Accurate quantitative measurement of sweating is not feasible because besides the flow of sweating is not constant throughout the day there is also no instrument that's use is practical enough to be incorporated into the clinical routine. Consequently, the instruments to assess outcomes are indirect instruments such as HDSS and quality of life questionnaires. Although HDSS is detailed in the assessment of ten body areas (twenty considering each side separately), and the questionnaires were designed specifically for cases of hyperhidrosis, their results derive from responses that will depend on subjective assessment and participant's memory.

Another point that may limit study results is the level of surgical resection that will be performed in the sympathetic chain. Although there is no consensus on the optimal level of resection for the treatment of palmar hyperhidrosis, it is known that more proximal resections such as R2 tend to achieve better results (dryer hands) but in turn cause more compensatory sweating [32].

For this study we decided that the level of surgical resection of the sympathetic chain would be R4, which is what we use in our clinical practice. In our view, this is the break-even point for this type of surgery and is the most beneficial for participants in reducing palmar sweating without triggering excessive compensatory sweating. However, choosing this resection level may not help the results in terms of protocol.

One of the protocol hypotheses is that a percentage of participants undergoing sympathectomy of the dominant (right) side will not require contralateral (left side) surgery as a way to reduce the chance of presenting compensatory sweating. Since we are using R4 resection, that usually triggers little compensatory sweating, these participants will not have the stimulus (compensatory sweating) to avoid contralateral surgery.

The literature shows that are many groups that employ R2 resections for treating palmar hyperhidrosis probably because they favored more dried hands and don't care so much about the consequences of compensatory sweating. If instead of R4 we were using the R2 resection, there is a chance that more patients would present compensatory sweating after the unilateral sympathectomy and would avoid the contralateral surgery.

6. Strengths

This study design was useful because with this sample of participants it will be possible to test two different strategies, the two main hypothesis, aimed to reducing the compensatory sweating that occurs after sympathectomy: a) that only unilateral sympathectomy are considered feasible, practical, and acceptable; and b) that bilateral surgery in two

different times produces less compensatory sweating than in one time.

Another strength of this study design is that it avoids what has been classified as "an explanatory or efficacy trial". There are some believes that such trials optimized to determine efficacy were performed with relatively small samples of highly selected participants at sites with experienced investigators and, they could be overestimating benefits and underestimating harm.

As a consequence, there is an increasing emphasis on trials designed to show the real-world effectiveness of the intervention in broad patient groups, and we believe that is what is happening with this study. This can be confirmed by looking at its characteristics in terms of recruitment of investigators and participants, the intervention and its delivery, the nature of follow-up and the nature and analyses of outcomes. In all these items the present study meet the requirements expressed on PRECIS-2 (Pragmatic-Explanatory Continuum Indicator Summary) tool [33], which enables it to be classified as "pragmatic design", which main objective is to provide evidence for adoption of the intervention into real world clinical practice [34].

Another study strength is that is has a strong representativeness in terms of geography and consequently in ethnic and climate aspects. As this is a research that basically evaluates sweating changes that may be influenced by ethnic and climatic factors, we believe it is important that different patient profiles and different climatic regions of the country are represented. Brazil is a country of continental dimensions and has in its history of colonization the presence of different ethnicities. In addition, from north to south the country also has important differences in its climate. The fact that the distance between the northern and southern participating centers is 2408 miles confirms that geographically there is good representativeness, which makes that these factors will have less impact in the results.

7. Conclusions

This project which design has the characteristics of what is called a pragmatic trial, is a multicentric, prospective, controlled, randomized study which aim is to test strategies that can decrease compensatory sweating after sympathectomy for palmar hyperhidrosis. The study has two null hypotheses: a) unilateral sympathectomy in dominant hand is a satisfactory treatment; b) the incidence of compensatory sweating is decreased if bilateral sympathectomy is done in two instead of one surgical procedure.

The therapy been employed is the videothoracoscopic thoracic sympathectomy that according to randomization is done bilateral or unilateral. Study endpoints are the intensity of residual hyperhidrosis the operated areas (hands) and of compensatory sweating after sympathectomy, as well as quality of life of these participants after surgeries. Recruitment of 200 participants will conclude approximately in June 2020.

If the study succeeds to confirm one or both hypothesis there is a strong chance that surgical therapy for hyperhidrosis, a condition that affects about 2,8% of population can be changed for better.

Study status

The study is still recruiting participants. It is estimated that recruiting can be completed at June 2020. Miguel Tedde, MD (tedde@usp.br) is the study contact.

Funding

This trial will be conducted with no external funding.

Author's contributions

NNH is a doctoral fellow on the study who assists with data management and analyses and has reviewed and edited the manuscript.

MLT is principle investigator of the study who conceptualized the research design and drafted and edited the manuscript.

NW helped conceptualize the research plan, will assist with interpretation of data, and has reviewed the manuscript.

WWSA helped conceptualize the research plan, will assist with interpretation of data and has reviewed the manuscript.

HAO is a site investigator involved in data collection and reviewed the manuscript.

HPCF is a site investigator involved in data collection and reviewed the manuscript.

AMRL helped conceptualize the research plan and measures regarding nutritional assessment as MH's K23 mentor and reviewed the manuscript.

FLW is a site investigator involved in data collection and reviewed the manuscript.

MRSM is a site investigator involved in data collection and reviewed the manuscript.

STLFP is a site investigator involved in data collection and reviewed the manuscript.

CEBW provided guidance in recruiting investigators and sites and reviewed the manuscript.

PMPF provided consultation regarding appropriate research design and reviewed the manuscript.

Declaration of competing interest

The authors declared no conflict of interest.

Acknowledgements

The authors wish to thank Mr. Aristides T Correa by assistance with sample size calculation and Mrs. Julia Fukushima and Mr. Frederico Rafael Moreira for their contributions to the study design and statistical support.

Appendix 1. : List of study sites and investigators

Coordination center	City	Investigator
Heart Institute, (InCor) Hospital de Clinicas da Universidade de Sao Paulo	São Paulo (SP)	**Miguel L. Tedde, MD, PhD** Nelson Wolosker, MD, PhD Niura Noro Hamilton, MD Jose R Milanez de Campos, MD, PhD Gabriela Lovece Paulo Manuel Pego-Fernandes, MD, PhD
Hospital – participating sites	**City**	Investigator
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