Author's response to reviews

Title: Polidocanol versus hypertonic glucose for sclerotherapy treatment of reticular veins of the lower limbs: study protocol for a randomized controlled trial

Authors:

Matheus Bertanha (matheus.fameca@ig.com.br)
Carlos EP Lucio Filho (carloseduardofilho@ymail.com)
Jamil VO Mariúba (jamil_mariuba@hotmail.com)
Rafael EF Pimenta (pimentamed36@yahoo.com.br)
Rodrigo G Jaldin (rgibin@uol.com.br)
Marcone L Sobreira (mlsobreira@gmail.com)
Andrei Moroz (moroz@fcaar.unesp.br)
Regina Moura (rmoura@mbe.unesp.br)
Hamilton A Rollo (hrollo@mbe.unesp.br)
Winston B Yoshida (winston@mbe.unesp.br)

Version: 5
Date: 14 July 2014

Author's response to reviews: see over
Letter to Reviewer:

Study protocol

MS: 1860974408128689

Polidocanol versus hypertonic glucose for sclerotherapy treatment of reticular veins of the lower limbs: study protocol for a randomized controlled trial

Matheus Bertanha, Carlos EP Lucio Filho, Jamil VO Mariúba, Rafael EF Pimenta, Rodrigo G Jaldin, Marcone L Sobreira, Andrei Moroz, Regina Moura, Hamilton A Rollo and Winston B Yoshida

I would like to thank the reviewer George Thanassoulis for your considerations. It could be observed that with their relevant comments, the work presents itself with better quality than the previously sent. In a way, we believe that some of the presented errors were committed by the expression fails. Others however, more related to the outcomes were now corrected. In this way, we present a clearly work, which will facilitate the compilation of final results. Thus, we appreciate the suggestions very relevant correction.

Detailing:

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

1- The major issue with this protocol is the inadequate description of the outcomes. The authors state that "efficacy" will be the primary outcome but provide no details as how this will be defined. There are similar issues with some of the secondary outcomes. Please add a section to the protocol entitled "Outcomes" and clearly delineate what the primary outcome will be and how it will be measured using with sufficient detail to ensure that this study could be reproduced by another group. In particular, the scoring of excellent, very good, good, bad, very bad needs further clarification. How are these judgements made? There are also 2 ways to define efficacy: a subjective "eyeball" score and a sophisticated image analysis technique. Which is the primary outcome? Please also clarify how the image analysis will be scored to produce a measurable outcome.

1- We agree with your argument to promote the changes in the text and suitability of the protocol to facilitate analysis of the final results. We replace the term Analysis of Results for Outcomes. We parted the primary outcome (efficacy analysis by the naked eye) of the secondary outcomes (safety), beyond comparison of the method of analysis to the naked eye with the method of analyse that use a software standardized. We also created a more direct way to analyze the results of the score, scoring in centimeters areas examined with the naked eye by independent referee. Certainly, this way anyone can reproduce the experiment without an interpretation bias and is possible to identify how we calculate the work sampling. We also created two new annex that summarizes the scores of efficacy and security (Annex 5 and 6).
Primary endpoint - treatment efficacy: The analysis of the primary endpoint (efficacy) will be based on the ability of the treatment in promoting the disappearance of reticular veins after 60 days of the treatment (D60). The quantification of efficacy will be performed by visually analyzing the results, which is the traditional evaluation method commonly mentioned in scientific articles [2]. For this, a photographic collection previously prepared, containing the pretreatment photograph (D0) and the sixtieth day photograph (D60), will be handed to two external physician referees (blinded to which treatment each patient received). The referees will convert the values of the photographic measurements into centimeters. The referees will then assign scores for each treatment, in order to qualify the final result based on a rating scale: 5 (excellent - total disappearance of the treated reticular vein), 4 (very good - less than or equal to 1 cm of residual treated reticular vein), 3 (good - greater than 1 cm and less than or equal to 3 cm of residual treated reticular vein), 2 (regular - greater than 3 cm and less than or equal to 5 cm of residual treated reticular vein), 1 (bad - greater than 5 cm and less than or equal to 9 cm of residual treated reticular vein), and 0 (very bad - greater than 9 cm or no disappearance of reticular treated vein) (Annex 5). The referees will be trained initially with 10 randomized patients to converge analyzes before starting the real evaluation.

Secondary endpoint – treatment safety: Treatment with sclerotherapy presents simple events and often self-limiting adverse effects such as pain during and after the procedure, haematomas, edemas, phlebitis, and small pigmentation on the path of the vein, the former being the most unwanted by the doctor. There are also scarce reports of more serious complications, such as deep vein thrombosis [15]. To evaluate the pain inflicted in the act of the treatment, the data obtained through the “Patient Satisfaction Questionnaire” will be directly analyzed (Annex 3).

To evaluate the occurrence of post procedure pain, phlebitis, haematoma, and the possibility of major complications, the data will be collected at the 7th day visit (D7) directly by the physician. In addition, any suspected deep vein thrombosis will be investigated immediately using ultrasound. To evaluate irregular skin hyperpigmentation, which is a later complication, the photograph taken 60 days after the treatment (D60) will then be evaluated by the referees, using these possible scores: 5 (excellent – it was not identified hyperpigmentation), 4 (very good – it was identified with only one point of hyperpigmentation with up to 1cm in length), 3 (good – 2 to 3 points of hyperpigmentation were identified with up to 1 cm in length), 2 (regular – 4 to 5 points of hyperpigmentation were identified with up to 1cm in length or one hyperchromatic line with up to 5cm in length), 1 (bad – more than 5 points of hyperpigmentation were identified with up to 1cm or one hyperchromatic line with more than 5cm and less than 9cm in length), and 0 (very bad – a hyperchromatic line larger than 9cm in length was identified or the total extension of the vein presenting hyperpigmentation) (Annex 6).

The photographs will be objectively analyzed by an experienced person in image analysis using the ImageJ® free software, which will measure the reticular veins before treatment begins - pre-treatment (D0) and post-treatment (D60). This new analysis of efficacy has the goal of trying to produce an automated and direct method for this type of image, compared with the traditional manual method. Briefly, the contour of the total length of the reticular vein is highlighted by the person using the software, which measures it in pixels. A 2x2 cm square image is also measured in pixels using the software, after which is possible to convert pixels to cm. Finally, the same score of efficacy previously described will be applied (Annex 5). In the end of the study, we will try to correlate the two analyses so as to simplify future research. The results will then be delivered to a professional statistician for analysis.
2- “Please also clarify the treatment intervention. How many reticular veins can be treated in the study treatment session? Although the authors state that 30 injections are allowed, is the size of the area treated standardized? Could treatments over large areas have different efficacy than over smaller defined areas?”

2- For a better understanding of the area to be treated in the research, we created a new topic defined as Treatment area. We developed a schematic drawing to represent the measures more visual and practical way for the reader (annex 2). This figure became the object area best defined study. It was done because it is actually on this site that we found highest frequency of reticular veins in clinical practice, then thereby there are not bias of anatomical position. Also was more clearly defined the form of application execution and the minimum and maximum size of the vein. We believe that there is no bias of performing treatment, because all of them were performed by the same experienced physician. We think the length and the number of treated veins do not interfere with the outcome, because a smaller vein will receive lower volume of medication, proportionally, that was better described in the section - Session Treatment (Day zero - D0). Regardless of the medication used (blind), the initial visual result (D0) must be same for all patients treated, with total and immediate disappearance of the vein.

“Treatment Area

The treatment area was defined as follows: looking sideways at the selected lower member, with the anatomical point of reference of the fibular head, a longitudinal imaginary line is drawn over it. This line measures 25cm proximally and 15cm distally, starting from the fibular head. Two more lines are drawn parallel to the first one, one at 7.5 cm anterior and another at 7.5cm posterior, defining the limited area for treatment (600cm²) (Annex 2). In this area, one or two reticular veins, measuring from 10cm - 20cm in total length will be treated, through a minimum of 10 and a maximum of 30 punctures, with 5ml in maximum volume of medication for all the treatment.”

And

“Treatment (Day zero - D0)

The treatment area, as described above, will be photographed before starting the treatment (pretreatment) to prevent a possible temporal bias regarding the condition of the patient’s illness. The photograph will be performed with a high definition camera (D7000 Nikon) in a standard patient position, where she will stay on a platform, laterally, 1.5m away from the camera, with adequate lighting and with a black background.
Treatment technique: After the photographs are taken, the two groups will be treated similarly in order to eliminate all the reticular veins in the area of the selected lower limb. All the procedure will be performed by one physician only. The techniques of conventional sclerotherapy will be respected with careful injections in order to prevent leakage of fluid into the subcutaneous tissue. It is important to note that applications will be held until the vein becomes imperceptible to the physician. The volume injected per puncture will not exceed 1ml of medication. A 3mL luer-lok plastic syringe BD® will be used with a 13x4 Terumo® needle (27 G1/2). Punches will be covered with a cotton ball approximately 0.3cm in diameter, fixed with a rectangular piece of microporous tape of approximately 2x3cm immediately after the application to avoid leakage of applied fluid and blood. After the treatment is complete, the treated area will be submitted to elastic compression using a 1.5m long lightweight elastic band (Atadress®), for one day [19].

All of the data regarding the treatment will be stored, such as the volume of injected medication necessary for primary disappearance of all reticular veins in the pre-defined local of the lower limb, the number of dressings necessary to cover all punctures, the location of the treated areas, possible allergic reactions, and the presence of minimum varicose veins in the treated area. Also, a form will be given to the patient to fill regarding the level of discomfort that the disease causes, the level of pain that was caused by the treatment, and asking if the pain was caused by the needle, by the liquid, or both (Annex 3). Patients will receive an instruction sheet for maintenance after the procedure, which will be carefully explained until the patient fully understands it (Annex 4). All patients will receive one tube of post procedure cream to treat initial blemishes, containing sodium heparin 0,5% and the recommendation to use this cream two times per day for two weeks.”

3- “The authors state: "The treated area will be photographed with a D7000 Nikon high definition camera in a standard predefined patient position (patient standing on a platform, laterally, 1.5 m away from the camera)." Will this be before or after the initial treatment? Isn’t a baseline pre-treatment picture needed? The way this is written implies that the picture will be taken after the treatment.”

3- There was a failure of expression, because there is no sense in comparing the pictures without an initial pre-treatment photo. We rewrite this sentence and change its position in the text to better your understanding.

4- “Without a clearer description of the outcomes, the adequacy of the sample size cannot be judged.”
4- The answers to the questions and suggestions were given and I hope that will be enough for publication. The calculation of sample size was performed by the statistical staff of our institution, following the limitations proposed by the local research ethics committee.

Minor issues not for publication

The writing needs to be improved and I suggest the authors consider further editing of their manuscript to improve the language and style. I have highlighted a few areas (not an exhaustive list) that should be addressed:

1. “It’s also common seen in dermatologic and vascular surgery practice with various symptoms. Even so it is still poorly understood.[4] The sclerotherapy is considered to be the treatment of choice for many patients and is performed by physicians because it is a simple, minimally invasive procedure which avoids surgery.[5, 6] Please rephrase above. Please also avoid contractions (i.e. it's).”

2. “The diluents may be distilled water, air, or a range of glucose concentrations. There is a word missing”

3. “This is especially true when polidocanol if used in unusual concentrations and volumes which increases the risk of other complications such as chest pain, cough, scotoma, and gas embolization. Moreover, to date, it’s not discarded that it may cause anaphylaxis.[14-16]. If should be replaced by is. There are several contractions that must be revised.”

4. “This study is a trial is a single-center, prospective, randomized, triple-blind trial. Please rephrase”

5. “Patients will be obtained from a convenience sample generated from the patients’ spontaneous desire to treat mild varicose veins ”Obtained” should be "recruited"

6. “These patients will be pooled in an electronic database and, later on, they will be invited by phone call to attend an outpatient evaluation. Please clarify. I don't think "pooled" is the right term.”

7. “With the end of the treatments and visits for clinical evaluation, the collected data will be plotted in an excel spreadsheet... Plotted is not the correct term”

1 – 7. We perform all the corrections and we submit the text to an expert in English.