PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Protocol for a multicentric, double-blind, randomised controlled trial of hyperbaric-oxygen therapy (HBOT) versus sham for treating Vaso-Occlusive Crisis (VOC) in sickle cell disease (SCD) in patients aged 8 years or older (HBOT-SCD study).

Authors

Stirnemann, Jerome; Serratrice, jacques; Mann, Tamara; Louge, Pierre; Christophe, Combescure; Samii, kaveh; Pignel, Rodrigue; Agoritsas, Thomas; Ansari, Marc; Cannas, Giovanna; Chalandon, Yves; Cimasoni, Laurent; Cougoul, Pierre; Desgraz, Benoit; Gervaix, Alain; Grosgurin, Olivier; Joffre, Thierry; Lae, Claude; Magnan, Marie-Anne; Menager, Etienne; Momo Bona, Annie; Panchard, Marc-Alain; Pellegrini, Michel; Reny, Jean-Luc; Riu, Beatrice; Sahyoun, Cyril; Boet, Sylvain

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Schiavo, Simone**
Affiliation	**University of Toronto**
Date	**29-Feb-2024**
COI	**none**

Overall, very well designed study, solid rationale, clear process and interventions, detailed and sound sample size and statistical analysis. Definitely an important study with potential for changes in guidelines and clinical practice for SCD. Worth publication; there are several points for which I'd like to have some details or clarifications (see attached).

Overall, very well designed study, solid rationale, clear process and interventions, detailed and sound sample size and statistical analysis. Definitely an important study with potential for changes in guidelines and clinical practice for SCD. Worth publication; there are several points for which I'd like to have some details or clarifications.

As the editor recommended, the protocol relates to a multicentre study that is already ongoing/recruiting at one of the sites, so the dates of the study should be included as per journal request?

The major points warranting clarifications are related to:

- Title
- More recent literature and references on the hematology part of the Intro
- Exclusion criteria: the transfusions, and their role in excluding the patient at different

timepoints and for different reasons; TCD; stroke.
- Safety outcomes
- Moving detailed descriptive paragraphs from Methods

See below the details.

Title

- It could be misleading, should be clearer that this is a protocol, and not the presentation of the results of this study.
- The last part, "after 8 years old" is not clear and should be rewritten (e.g., 8 years of age and older, or, after the age of 8, or, in patients aged 8 and older, or, in patients 8 years old and greater/older, or similar).
- The name "HBO-Sickle Cell study" will be used at the end of this paper, in Discussion, pg 15; it could be worth thinking of using this catchy name in the title.

Strengths box

- "*accessibility of HBO in countries with high sickle cell prevalence would be straightforward*", supporting evidence?

INTRO

- Line 9-10 "reducing life…//thalassaemia", please rephrase as the meaning/message is unclear.
- Line 13, reference # 1 seems old, and other causes of death in SCD seem to be the leading ones (e.g., infections, chronic and acute heart disease, stroke).
- Line 13: the abbreviation ACS is confusing, as the same of the more famous, well-known and world-recognized "acute coronaric syndrome"
- Line 14-15, ACS definition; any ref? such as *Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. N Engl J Med 2000;342:1855-1865*

Physiopathology

- Ref 2, old reference and relative to endothelium adherence more than hemolysis.
- line 25, CVO, abbreviation inconsistent with the previous, VCO.
- Line 32, remove "promoting"
- Line 32, perpetual, meaning vicious?
- Ref 17 and 18, missing year of publication

Usual care

- It could be useful to have a guideline cited, in addition to the one already there, #19; or is ref 19 a guideline per se? Also, the link provided in ref 19 is not working.
- I would highlight the message of how many new agents are currently being studied, and that despite the recent advances, VOC remains an issue, thus suggesting even further the importance of HBOT.
- I'd also stress more the concept of the impossible transfusions (line 47-50), that makes HBO even more an invaluable therapeutic asset/offer.

HBO

- Line 58, Add a reference about indications, such as ECHM or UHMS guidelines.

Rational

- Pg 5, line 25, "favourable issue for a number of patients", unclear; does it mean favourable outcomes?
- Line 27, "recognized indication of HBOT" should be "for HBOT"
- Ref # 37 is missing year and editor.

METHODS

Setting, pg 6

- Line 49, "On the Geneva site", "at the Geneva site"

Design, pg 5-6

- Pg 5, line 58, missing the word "trial" before "(RCT)".
- Pg 6, line 37-42, this can be simplified by just saying for example "Patients enrolled will receive a second (and third) session, either HBOT for the intervention arm, or sham for the sham arm", or similar sentence.
- Line 49-52, this can be better explained; my understanding is that if a patient doesn't meet the inclusion/exclusion criteria (such as > 2 l/min O2), they will not be recruited, and they will receive HBO as per standard of care at the institution; is this correct?
- line 45-46 (no session if VAS<2), this should be better explained. Is it because is not clinically relevant? Is it a pre-decided design of the study, and of so, based on what? Otherwise, it could result in a bias, excluding patients who improve.
- Line 47, transfusion. It's unclear if a transfusion is allowed before starting HBO without excluding the patient; I guess so, given that it's stated that "transfusion may be given" but also "the second session will be cancelled" (and also given that it will not be mentioned in Exclusion Criteria). This will be even more confusing when later, in *Methods-standard of care to all patients*, a transfusion is "considered as a treatment failure".

Sample size, pg 6

- Line 59-60, I commend the use of a clinically relevant outcome rather than just a statistically significant one.

Study phase, pg 7

- Line 21, "adapted", unclear; does it mean suitable/appropriate?

Patient population, pg 7

- Line 31 "or over" is unclear, should be "or more" or "or older".
- Line 31, It states "with or without ACS"; if ACS does not impact the screening/inclusion, why is it necessary to specify it? We could just remove the detail entirely.
- Line 32, "level 3 analgesia" is introduced for the first time here in Methods, It could be defined in Intro - Usual care.

Inclusion/Exclusion, pg 8 Box

1 – inclusion

- "Age 8 or over", same as above

- "level 2 analgesic" concept should be introduced earlier (in Intro).
- "legal guardian 8", unclear; despite understanding what the authors mean, this should be better explained/rephrased.

Box 1 – exclusion

- "contraindication for HBOT established by a physician…"; this should be defined somewhere in details, otherwise without criteria there is a risk of unintended selection bias based on the specific HBO physician assessing the patient. I guess a simple list of "standard" contraindications as per ECHM/UHMS suffices.
- What is the rationale for excluding TCD anomaly? A PFO under HBOT does not influence/worsen any outcome, given they're breathing oxygen; is the worry due to the nitrogen load for the sham group? If so, the sham group wouldn't be really a sham group.
- What is the rational for excluding previous stroke?

Recruitment

- I'd suggest to explicitly identify and describe the recruitment procedure, to avoid missing patients; for example
    - Who recruits - is there a research team that gets notified, or directly the physician; which physicians will recruit, ER or HBO?
    - How the recruiter knows about a potential patient - is there a system to notify the team such as email, EMR automatic notification, ER doctor calling the HBO doctor or what else?
    - Who actually discusses the study with eligible patients, and obtain consent? (This was mentioned in Methods - Study Design)
    - Who collects the data (e.g., VAS, analgesic regimen and doses)

Randomization

- System used to randomize should be specified (protocol and sequence generation, concealment – maybe not necessary given the HBO team is not blinded, but if so better to explain it.
- Size of randomized group (1:1?) - this was actually mentioned in sample size.

Intervention

- line 13-27: it seems a description of the standard chamber operation, so it should go in Intro rather than Methods. But if it was stated as "The increase in pressure will be achieved by introducing…", then it's a description of the Method, and can stay here. It should also include a very brief description of devices used (masks with on-demand valve? Rather than just oxygen mask), and presence or not of inside attendant.
- line 24: "Conventional treatment (standard of care) will be applied also to the Sham, so should be either moved from this section *Intervention Group*, or repeated/mentioned into the *Sham Group* section.
- Line 29-35, being a hyperbaric physician, I perfectly understand the process described, but for a general reader, it could be better specified the protocol 20x3 + air breaks; and possibly in Intro if felt necessary to describe in details or to explain the rationale.
- Also, 10-minute compression + 10 deco + 20x3 O2 + 2 air breaks (and not 3), equals 90 minutes, not 95. This is also consistent with the vast majority of HBO protocols, usually described as 90 minutes - even though in North America these usually refer to 90 minutes of O2, for a total of 120 minutes per session.

Sham

- As above, the full description of the rationale and validation should go in Intro, and

should specify the respiratory devices used to administer the air are the same of those used to administer oxygen in the intervention arm.
- Validation: the cited validated procedure (ref # 41) from the same group, as well as other papers, suggest additional blinding measures to increase the sham fidelity and involuntary unblinding (e.g., heating/colling system, blinding internal gauges, instructions to operators/attendants, separate days/hours for sham); consider adding those details here, keeping in mind their feasibility in other centers.
- If the timing (95 min vs 90 min) of the intervention arm will be reviewed, the timing of the sham will need to be reviewed accordingly.
- "avoid any adverse event", mild ear barotrauma is still possible though. Or not. Any ref?

Blinding

- The questionnaire description appears in this section for the first time, and should be described earlier elsewhere.

Unblinding

Criteria for discontinuing

- A detailed description of side effects and relative literature should not be in Methods
- Pg 11, line 9, respiratory depression; unclear to the reader why the risk of resp depression should trigger caution; it could be nice to explain the rationale (CO2 retention, vasodilation) (and not in Methods though)

Standard of care

- Why excluding patient receiving transfusions only for some indications (VOC vs non-VOC)? If confirmed, it should be among the exclusion criteria.
- Transfusion, "considered as a treatment failure"; for *treatment* I think to the study intervention (HBO); if so, this is even more confusing, and it should be described earlier, maybe even under "Criteria for discontinuing interventions".

OBJECTIVES

Secondary, pg 12

- Line 35, a new concept of 1-year follow-up is introduced here for the first time, and it should be mentioned earlier (e.g., in Study Design).
- In *Intro- Rationale* (pg 5), it was mentioned the aim for the study is HBO efficacy and safety. There is mention of safety here, but there is no indication of how this objective will be assessed.

OUTCOMES

Main Outcome, could be called just Primary outcome, which is also consistent with the "analysis of the primary outcome" on pg 14 – statistical methods.

Secondary main

- Is this another (the second) primary outcome, or a secondary outcome? As morphine dose is listed among the secondary objectives, but then here this outcome is called "main", which is a bit confusing. This could just easily be another primary outcome, used along with the first one (difference in VAS before/after) to measure the primary objective (HBO efficacy).
- Compared to before HBO or to other patients?

Other outcomes

- Meaning “Secondary outcomes”?
- “in the absence of painkillers level III”, as previously mentioned, a definition of WHO levels should be described in Intro, otherwise is not clear what these terminated VOC are referring to.
- Patient satisfaction via a questionnaire: which one, which questions? It could be briefly described somewhere else.
- HBO Safety was previously reported as a secondary aim/objective; outcomes to measure it are missing though; unless you mean safety of this approach measured as complications (ACS, priapism, stroke). Probably, HBO side effects would suffice? To be rephrased to clarify.
- Outcome # 3 (accumulated dose…or readiness for discharge) and outcome # 15 (readiness for discharge): is it a duplicate or else?

At some point, it would be nice to clarify who will be performing the study’s assessment and/or collecting the data (ED physician, HBO physician, research team?); this was clear and indicated for the first VAS, under *Study Design*, but not for all other secondary outcomes here described.

STATISTICAL

Primary outcome

- Line 41 “adjusted for the centre and the hourly dose…” is unclear as missing a “for”: “adjusted for the centre and for the hourly dose…”
- - line 44, “and the baseline VAS”, unclear, probably missing “for” the VAS.

Secondary outcomes

- is actually the (second) primary (composite) outcome, see comments above.

Other outcomes

- Should be just “secondary outcomes”
- Pg 14, Line 14, “using similar statistical methods than for the primary outcome”: “than” is not clear, and makes the sentence confusing; I think it means “using similar methods used for the primary outcomes”, but it could misinterpreted as “using similar methods among them, rather than the one used for the primary outcome”. Please rephrase; if my interpretation is correct, it could be easier to mention something like “using the same 95% confidence interval used for the primary outcome”.
- line 25, “than”, same as above.
- There is no statistical considerations details of several “other outcomes” (accumulated dose of parenteral opioid, absence of opioid use, time to discontinuation of IV opioids, pain location, transfusions, complications, patient’s satisfaction, readiness to discharge, costs). While, for some, it’s quite obvious, being just a descriptive issue, it could be worth mentioning them for all of the outcomes.
- I noticed in hindsight, that there is a Table at the end mentioning some details of the above outcomes; this should be cited in Outcomes or Statistical analysis, before Discussion, so it’s easier for the reader to avoid getting lost, as I did when reading the Outcomes and their statistical analysis.

Table 1

- Main outcome: Pain Network, add reference.
- “VAS and CPS range from 0 to 3”, it should be clear that’s just for CPS.
- “Reduction of VAS > 30% with painkillers doses inferior or equal to those of standard

treatment"; unclear what is the standard treatment, as in the description of the outcome (pg 13) it was much clearly stated "a reduction >30% compared with H0.

- VOC recurrences; there was no mention in the paper of these (new) timepoints, at 3 and 6 months.
- Safety outcomes, according to the "usual grading"; which grading specifically?

References

- Check details (e.g., year, editor) for some references, e.g. 37, 43, etc.

Reviewer 2

Name Forni, Gian Luca

Affiliation Centro della Microcitemia, delle Anemie Congenite e dei Disordini del Metabolismo del Ferro

Date 04-Apr-2024

COI no

Exploring the possibility of treating VOCs and preventing its complications through a non-invasive system is certainly to be encouraged. The protocol is well designed and is based on observations reported in a previous pilot study. Reducing the use of opioids represents a very important objective although as a general observation, which goes beyond this

review, their use seems excessive to me and more space should be given to a type of multimodal analgesia in the meantime to obtain results from new approaches

VERSION 1 - AUTHOR RESPONSE

Reviewer 1 comments :

Overall, very well designed study, solid rationale, clear process and interventions, detailed and sound sample size and statistical analysis. Definitely an important study with potential for changes in guidelines and clinical practice for SCD. Worth publication; there are several points for which I'd like to have some details or clarifications.
As the editor recommended, the protocol relates to a multicentre study that is already ongoing/recruiting at one of the sites, so the dates of the study should be included as per journal request?
The major points warranting clarifications are related to:

- Title
- More recent literature and references on the hematology part of the Intro
- Exclusion criteria: the transfusions, and their role in excluding the patient at different timepoints and for different reasons; TCD; stroke.
- Safety outcomes
- Moving detailed descriptive paragraphs from Methods

See below the details.

Title

- It could be misleading, should be clearer that this is a protocol, and not the presentation of the results of this study.

We have clarified this point in the title.

- The last part, "after 8 years old" is not clear and should be rewritten (e.g., 8 years of age and older, or, after the

age of 8, or, in patients aged 8 and older, or, in patients 8 years old and greater/older, or similar).

We have clarified this point in the title.

- The name "HBO-Sickle Cell study" will be used at the end of this paper, in Discussion, pg 15; it could be worth thinking of using this catchy name in the title.

We have added of "HBOT-SCD study".

Strengths box

- "*accessibility of HBO in countries with high sickle cell prevalence would be straightforward*", supporting evidence?

We have removed this sentence (which remains questionable) from the 'Strengths box'. Indeed, there are hyperbaric centres in the Carribean and in many African countries (Ivory Coase, Cameroon, Algeria, Morocco, Tunisia, Egypt, South Africa, Senegal, etc.). However, not the entire population of these countries has access to these infrastructures. Companies are working on mobile and easily installed hyperbaric chambers, which could be a solution in the future.

We added, in the discussion: "An introduction of mobile and easy installed hyperbaric chambers could then be considered in these countries."

INTRO

- Line 9-10 "reducing life…//thalassaemia", please rephrase as the meaning/message is unclear.

Clarified: "Severe forms of SCD include haemoglobin SS resulting from the inheritance of HbS, Sβ_0-thalassaemias due to co-inheritance of HbS with the β_0-thalassemia mutation or other forms of co-inheritance of HbS with other β-globin gene mutation such as hemoglobin C (SC form) or β_+-thalassaemias (Sβ_+)."

- Line 13, reference # 1 seems old, and other causes of death in SCD seem to be the leading ones (e.g., infections, chronic and acute heart disease, stroke).

We rephrased to clarify and used a new reference : "Due to accompanying acute complications (as VOC and ACS), with or without infections and chronic complications (such as stroke, pulmonary hypertension, chronic lung disease or nephropathy), SCD is associated with a reduced life expectancy and a median age of death of 43 years (IQR 31.5-55 years) (1)."

- Line 13: the abbreviation ACS is confusing, as the same of the more famous, well-known and world-recognized "acute coronaric syndrome"

It is indeed a bit confusing but ACS is the abbreviation used in most articles and on sites such as "Up to Date" (https://www.uptodate.com/contents/acute-chest-syndrome-acs-in-sickle-cell-disease-adults-and-children). We therefore propose to keep this abbreviation which was initially defined in our manuscript. However, we added a glossary to help to understand all the abbreviations.

- Line 14-15, ACS definition; any ref? such as *Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. N Engl J Med 2000;342:1855-1865*

We added this reference as suggested.

Physiopathology

- Ref 2, old reference and relative to endothelium adherence more than hemolysis.

You are right. We removed this old reference et added a more recent reference about physiopathology of SCD (Sunnd, 2019). The haemolysis usually leads to endothelial dysfunction.

- line 25, CVO, abbreviation inconsistent with the previous, VCO.

Changed

- Line 32, remove "promoting"

Removed

- Line 32, perpetual, meaning vicious?

Yes, changed

- Ref 17 and 18, missing year of publication

Corrected

Usual care

- It could be useful to have a guideline cited, in addition to the one already there, #19; or is ref 19 a guideline per se? Also, the link provided in ref 19 is not working.

We changed reference with international guidelines in English.

- I would highlight the message of how many new agents are currently being studied, and that despite the recent advances, VOC remains an issue, thus suggesting even further the importance of HBOT.

We added a paragraph about chronic treatment of SCD : (1)" The recent availability of L-glutamine, crizanlizumab

and voxelotor provides an alternative or additional alternative to hydroxyurea, which remains the first choice for disease-modifying therapy (1).
Overall survival rates remain high for individuals with SCD who have undergone allogeneic hematopoietic stem cell transplantation using matched sibling donors. Newer approaches to graft-versus-host (GVHD) prophylaxis and the incorporation of post-transplant cyclophosphamide have improved engraftment rates, reduced GVHD and have allowed for alternative donors for individuals in the absence of a HLA-matched sibling. Despite progress in this field, the increase in world SCD prevalence means management of VOCs remains a real and persistent problem, requiring the identification of alternative treatments outside of opioid and transfusion therapy."

- I'd also stress more the concept of the impossible transfusions (line 47-50), that makes HBO even more an invaluable therapeutic asset/offer.

We specified: " Alloimmunisation remains an extremely frequent consequence of the use of erythrocytes transfusion which, consequently, excludes the possibility of further transfusions or exchange transfusions as a therapeutic option in certain patients ; some patients become impossible to transfuse and HBOT is then an ultimate treatment offered in case of CV."

HBO

- Line 58, Add a reference about indications, such as ECHM or UHMS guidelines.

Added

Rational

- Pg 5, line 25, "favourable issue for a number of patients", unclear; does it mean favourable outcomes?

We changed "issue" to "outcomes"

- Line 27, "recognized indication of HBOT" should be "for HBOT"

Changed

- Ref # 37 is missing year and editor.

Thank you. Updated and corrected.

METHODS

Setting, pg 6

- Line 49, "On the Geneva site", "at the Geneva site"

Sentence modified.

Design, pg 5-6

- Pg 5, line 58, missing the word "trial" before "(RCT)".

OK

- Pg 6, line 37-42, this can be simplified by just saying for example “Patients enrolled will receive a second (and third) session, either HBOT for the intervention arm, or sham for the sham arm”, or similar sentence.

Modified as suggested.

- Line 49-52, this can be better explained; my understanding is that if a patient doesn’t meet the inclusion/exclusion criteria (such as > 2 l/min O2), they will not be recruited, and they will receive HBO as per standard of care at the institution; is this correct?

Yes, it’s correct. We clarified this sentence as suggested: “In certain strictly defined circumstances and only for patients needing more than 2 l/min of oxygen, patients will not be recruited in the RCT, but could receive HBOT out of protocol, as per usual practice in the institution.”

- line 45-46 (no session if VAS<2), this should be better explained. Is it because is not clinically relevant? Is it a pre-decided design of the study, and of so, based on what? Otherwise, it could result in a bias, excluding patients who improve.

We do not know if 1, 2 or 3 sessions of HBOT are necessary to treat VOC. After a first session, if patient has a VAS<2 without opioid, we can consider that the VOC is over; if so, there is no need to continue HBOT/sham sessions. To clarify, we added in the manuscript: “These sessions will be cancelled if the patient’s VAS score ≤ 2 without morphine treatment. In this case, we can consider that the VOC is finished.”

- Line 47, transfusion. It’s unclear if a transfusion is allowed before starting HBO without excluding the patient; I guess so, given that it’s stated that “transfusion may be given” but also “the second session will be cancelled” (and also given that it will not be mentioned in Exclusion Criteria). This will be even more confusing when later, in *Methods-standard of care to all patients*, a transfusion is “considered as a treatment failure”.

Transfusion therapy is often an ultimate treatment for VOC. Therefore, to avoid bias, we elected to exclude patients who received blood transfusion during VOC. If this transfusion is performed just before the 1st session, this indeed excludes inclusion (and we added this in the exclusion criteria). If the transfusion is performed after the first session, “ the specific effect of the HBOT cannot be evaluated ” and the HBOT/sham intervention will be interrupted for the patient.

Sample size, pg 6

- Line 59-60, I commend the use of a clinically relevant outcome rather than just a statistically significant one.

Thank you for this comment!

Study phase, pg 7

- Line 21, “adapted”, unclear; does it mean suitable/appropriate?

Changed for appropriate.

Patient population, pg 7

- Line 31 “or over” is unclear, should be “or more” or “or older”.

Changed.

- Line 31, It states “with or without ACS”; if ACS does not impact the screening/inclusion, why is it necessary to specify it? We could just remove the detail entirely.

Removed.

- Line 32, “level 3 analgesia” is introduced for the first time here in Methods, It could be defined in Intro/Usual care.

A point is added in Introduction/Usual Care : “Home-based management of a VOC is usually based on WHO classification level one and two analgesics (1: nonsteroidal anti-inflammatory drugs or acetaminophen, 2: codeine, tramadol). When VOC management is impossible with these analgesics, WHO classified level three analgesics are introduced (3: morphine or its derivatives e.g, fentanyl, oxycodone, buprenorphine or hydromorphone).”

Inclusion/Exclusion, pg 8

Box 1 – inclusion

- “Age 8 or over”, same as above

Changed

- “level 2 analgesic” concept should be introduced earlier (in Intro).

Done

- “legal guardian 8”, unclear; despite understanding what the authors mean, this should be better explained/rephrased.

“ consent and signature of legal guardian is required for minor patients or those under guardianship ”

Box 1 – exclusion

- “contraindication for HBOT established by a physician…”; this should be defined somewhere in details, otherwise without criteria there is a risk of unintended selection bias based on the specific HBO physician assessing the patient. I guess a simple list of “standard” contraindications as per ECHM/UHMS suffices.

“The contraindication for HBOT established by a physician responsible for hyperbaric medicine, as per ECHM/UHMS guidelines, e.g. untreated pneumothorax, eustachian tube dysfunction, claustrophobia or other usually contraindications (2).”

- What is the rationale for excluding TCD anomaly? A PFO under HBOT does not influence/worsen any outcome, given they’re breathing oxygen; is the worry due to the nitrogen load for the sham group? If so, the sham group wouldn’t be really a sham group.

The recognised presentation of neurological oxygen toxicity during hyperbaric oxygen treatment is an oxygen toxicity seizure (Paul Bert Effect). “Due to the particular sensitivity of sickle cell patients to seizure, the study’s HBOT protocol limits pressure to 2.0 ATA with 100% oxygen, in order to decrease the risk of seizure. In children, transcranial Dopplers are carried out regularly and abnormalities (>200cm/sec) are an exclusion criterion to limit the possible risk of seizure disorders.” We have moved this information which was described below.

- What is the rational for excluding previous stroke?

It is the same for patients with a history of stroke who could be more sensitive to neurological toxicity of oxygen.

Recruitment

- I'd suggest to explicitly identify and describe the recruitment procedure, to avoid missing patients; for example
  - o Who recruits - is there a research team that gets notified, or directly the physician; which physicians will recruit, ER or HBO?
  - o How the recruiter knows about a potential patient - is there a system to notify the team such as email, EMR automatic notification, ER doctor calling the HBO doctor or what else?
  - o Who actually discusses the study with eligible patients, and obtain consent? (This was mentioned in Methods - Study Design)

We added more details about inclusion procedure: "Potential patients will be identified on their arrival by the triage nurse or treating physician who will inform the hyperbaric physician of their arrival. The hyperbaric physician and/or research nurse will then verify the patient's inclusion and exclusion criteria. The hyperbaric physician is responsible for giving information concerning the study and obtaining the patient's /legal representative's informed consent. The patient will then be transferred to the HD, next to the ED. There, the HD team will carry out the randomisation and be responsible for giving the treatment/sham according to randomised arm."

- o Who collects the data (e.g., VAS, analgesic regimen and doses)

" Data will be collected by research personnel from their respective participating centres. The data will be entered into the eCRF (REDCap software)."

Randomization

- System used to randomize should be specified (protocol and sequence generation, concealment – maybe not necessary given the HBO team is not blinded, but if so better to explain it.
- Size of randomized group (1:1?) - this was actually mentioned in sample size.

We added/regrouped in the 'Randomisation' part: "Randomisation will be triple blinded: the patient, research team and treating physician will not be aware of the randomisation arm, only the HD team.

To preserve the blinding, the randomisation blocks are completely random and the randomisation list created by a researcher completely external to the protocol. The size of randomised group is 1:1 (same numbers of subjects in the two groups)."

Intervention

- line 13-27: it seems a description of the standard chamber operation, so it should go in Intro rather than Methods. But if it was stated as "The increase in pressure will be achieved by introducing…", then it's a description of the Method, and can stay here. It should also include a very brief description of devices used (masks with on-demand valve? Rather than just oxygen mask), and presence or not of inside attendant.

We moved the description of the standard chamber in introduction and include here only precisions about intervention.

- line 24: "Conventional treatment (standard of care) will be applied also to the Sham, so should be either moved from this section *Intervention Group*, or repeated/mentioned into the *Sham Group* section.

We moved this information to before for the two groups.

- Line 29-35, being a hyperbaric physician, I perfectly understand the process described, but for a general reader, it could be better specified the protocol 20x3 + air breaks; and possibly in Intro if felt necessary to describe in details or to explain the rationale.

We propose to keep the section on compression and decompression times in this methods section, but have we moved the rationale to the introduction.

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- Also, 10-minute compression + 10 deco + 20x3 O2 + 2 air breaks (and not 3), equals 90 minutes, not 95. This is also consistent with the vast majority of HBO protocols, usually described as 90 minutes - even though in North America these usually refer to 90 minutes of O2, for a total of 120 minutes per session.

Yes, you are right. Changed to 90 minutes We
added a figure to clarify.

Sham

- As above, the full description of the rationale and validation should go in Intro, and should specify the respiratory devices used to administer the air are the same of those used to administer oxygen in the intervention arm.

We moved the full description of the rationale and validation of the sham in introduction.

- Validation: the cited validated procedure (ref # 41) from the same group, as well as other papers, suggest additional blinding measures to increase the sham fidelity and involuntary unblinding (e.g., heating/colling system, blinding internal gauges, instructions to operators/attendants, separate days/hours for sham); consider adding those details here, keeping in mind their feasibility in other centers.

The detailed description of the SHAM procedure has been published elsewhere (3). We precised: "… and as described, additional measures, as faster compression with ventilation during the fictitious compression time, heating at compression and cooling at decompression."

- If the timing (95 min vs 90 min) of the intervention arm will be reviewed, the timing of the sham will need to be reviewed accordingly.

OK, modified.

- "avoid any adverse event", mild ear barotrauma is still possible though. Or not. Any ref?

We modified the sentence: "The sham group (control group) will avoid only mild potential adverse effects of pressurisation as mild ear barotrauma."

Blinding

- The questionnaire description appears in this section for the first time, and should be described earlier elsewhere.

We moved the 'Blinding' part in 'randomisation'.

we added in the 'study design' chapter: "Patient satisfaction and their impression of receiving the treatment or sham will be documented after the first session, using a questionnaire."

Unblinding

Criteria for discontinuing

- A detailed description of side effects and relative literature should not be in Methods

The description of side effects has moved in Introduction/HBOT.

- Pg 11, line 9, respiratory depression; unclear to the reader why the risk of resp depression should trigger caution; it could be nice to explain the rationale (CO2 retention, vasodilation) (and not in Methods though)

We tried to better explain, in 'Introduction': "However, combination of benzodiazepines with morphine should be considered with much caution like for any patient, due to the increased risk of respiratory depression (both drugs depress the brainstem areas responsible for regulating breathing in patients sometimes hypoxemic)."

Standard of care

- Why excluding patient receiving transfusions only for some indications (VOC vs non-VOC)? If confirmed, it should be among the exclusion criteria.

As explained before, transfusion therapy is often an ultimate treatment for VOC. Therefore, to avoid bias, we elected to exclude patients who received blood transfusion during VOC. If this transfusion is performed just before the 1st session, this indeed excludes inclusion (and we added this in the exclusion criteria). If the transfusion is performed after the first session, "the specific effect of the HBOT cannot be evaluated " and the HBOT/sham intervention will be interrupted for the patient.

- Transfusion, “considered as a treatment failure”; for *treatment* I think to the study intervention (HBO); if so, this is even more confusing, and it should be described earlier, maybe even under “Criteria for discontinuing interventions”.

We added than transfusion received for VOC/ACS will interrupt the intervention/sham in the chapter “Criteria for discontinuing interventions”.

So, we moved the chapter « standard of care » earlier.

OBJECTIVES

Secondary, pg 12

- Line 35, a new concept of 1-year follow-up is introduced here for the first time, and it should be mentioned earlier (e.g., in Study Design).

OK, added in Study design: ”After inclusion, patients will be followed up1 year (by telephone or medical file. ”»

- In *Intro- Rationale* (pg 5), it was mentioned the aim for the study is HBO efficacy and safety. There is mention of safety here, but there is no indication of how this objective will be assessed.

We added «… occurrence of adverse events »

OUTCOMES

Main Outcome, could be called just Primary outcome, which is also consistent with the “analysis of the primary outcome” on pg 14 – statistical methods.

OK

Secondary main

- Is this another (the second) primary outcome, or a secondary outcome? As morphine dose is listed among the secondary objectives, but then here this outcome is called “main”, which is a bit confusing. This could just easily be another primary outcome, used along with the first one (difference in VAS before/after) to measure the primary objective (HBO efficacy).

Yes, second primary outcome.

- Compared to before HBO or to other patients?

Comparison of number of patients in each group after intervention/sham.

Other outcomes

- Meaning “Secondary outcomes”?

OK

- "in the absence of painkillers level III", as previously mentioned, a definition of WHO levels should be described in Intro, otherwise is not clear what these terminated VOC are referring to.

Thank you. WHO levels have been described in introduction.

- Patient satisfaction via a questionnaire: which one, which questions? It could be briefly described somewhere else.

Detailed in the table 1:

"By questionnaire with questions about :

- satisfaction of reception, HBO team (communication, availability, privacy), local, security, comfort, information.
- Sensations (temperature, noise, pain).
- General impression of the management, the treatment and the feeling of having undergone "compression"

- HBO Safety was previously reported as a secondary aim/objective; outcomes to measure it are missing though; unless you mean safety of this approach measured as complications (ACS, priapism, stroke). Probably, HBO side effects would suffice? To be rephrased to clarify.

You are totally right. We added "occurrence of adverse event of HBOT/Sham".

- Outcome # 3 (accumulated dose…or readiness for discharge) and outcome # 15 (readiness for discharge): is it a duplicate or else?

Not a duplicate. "Accumulated dose of parenteral opioid equivalent from baseline until VOC resolution or until discharge".

At some point, it would be nice to clarify who will be performing the study's assessment and/or collecting the data (ED physician, HBO physician, research team?); this was clear and indicated for the first VAS, under *Study Design*, but not for all other secondary outcomes here described.

HBO physicians

"

The different outcomes will be identified in the patient's electronic charting system by the research team and entered into the eCRF. The specific outcomes (scores, biology, investigations) will be prescribed by the HD physician/research team and performed then documented by the clinical team in charge of the patient."

STATISTICAL

Primary outcome

- Line 41 "adjusted for the centre and the hourly dose…" is unclear as missing a "for": "adjusted for the centre and for the hourly dose…"

Added

- - line 44, "and the baseline VAS", unclear, probably missing "for" the VAS.

The sentence was unclear: “at the baseline VAS” was deleted.

Secondary outcomes

- is actually the (second) primary (composite) outcome, see comments above.

Agreed

Other outcomes

- Should be just “secondary outcomes”

Changed

- Pg 14, Line 14, “using similar statistical methods than for the primary outcome”: “than” is not clear, and makes the sentence confusing; I think it means “using similar methods used for the primary outcomes”, but it could misinterpreted as “using similar methods among them, rather than the one used for the primary outcome”. Please rephrase; if my interpretation is correct, it could be easier to mention something like “using the same 95% confidence interval used for the primary outcome”.

Changed

“The difference in VAS pain scores between H0 and H24, the difference in hourly doses of morphine between before and after HBOT and the difference in biomarkers (LDH, CRP) between before and after HBOT will be reported in each arm using the same two-sided 95% confidence interval used for the primary outcome.”

- line 25, “than”, same as above.

“The frequency of patients with a reduction in VAS pain score of 30% or more from H6 to H24 and the frequency of patients with VAS<2 (in absence of painkillers of level III) at each visit will be reported with the Clopper- Pearson exact 95% confidence interval in each study arm as for the second primary outcome.”

- There is no statistical considerations details of several “other outcomes” (accumulated dose of parenteral opioid, absence of opioid use, time to discontinuation of IV opioids, pain location, transfusions, complications, patient’s satisfaction, readiness to discharge, costs). While, for some, it’s quite obvious, being just a descriptive issue, it could be worth mentioning them for all of the outcomes.

“A comparative description can be provided of other outcomes (accumulated dose of parenteral opioid, absence of opioid use, time to discontinuation of IV opioids, pain location, transfusions, complications, patient’s satisfaction, readiness for discharge, costs).”

- I noticed in hindsight, that there is a Table at the end mentioning some details of the above outcomes; this should be cited in Outcomes or Statistical analysis, before Discussion, so it's easier for the reader to avoid getting lost, as I did when reading the Outcomes and their statistical analysis.

Yes. "All outcomes are detailed in the Table 1."

Table 1

- Main outcome: Pain Network, add reference.

We added a reference in text for the primary outcome (4) and a link to our pain network (Réseau douleur à Genève aux HUG - HUG).

- "VAS and CPS range from 0 to 3", it should be clear that's just for CPS.

Clarified

- "Reduction of VAS > 30% with painkillers doses inferior or equal to those of standard treatment"; unclear what is the standard treatment, as in the description of the outcome (pg 13) it was much clearly stated "a reduction >30% compared with H0.

OK

- VOC recurrences; there was no mention in the paper of these (new) timepoints, at 3 and 6 months.

Recurrences of VOC during the following year is indicated in the text. We deleted the number of patients with VOC at 3, 6 and 12 months.

- Safety outcomes, according to the "usual grading"; which grading specifically?

"Mild (tolerable), Moderate (interferes with daily activity) or Severe (daily activities impossible)."

References

- Check details (e.g., year, editor) for some references, e.g. 37, 43, etc.

Reviewer: 2

Comments to the Author:

Exploring the possibility of treating VOCs and preventing its complications through a non-invasive system is certainly to be encouraged. The protocol is well designed and is based on observations reported in a previous pilot study. Reducing the use of opioids represents a very important objective although as a general observation, which

does beyond this review, their use seems excessive to me and more space should be given to a type of multimodal analgesia in the meantime to obtain results from new approaches.

Thank you !!

1. Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. J Hematol Oncol. 2022;15(1):20.
2. Gawdi R, Cooper JS. Hyperbaric Contraindications. StatPearls. Treasure Island (FL) ineligible companies. Disclosure: Jeffrey Cooper declares no relevant financial relationships with ineligible companies.2024.
3. Louge P, Pignel R, Serratrice J, Stirnemann J. Validation of sham treatment in hyperbaric medicine: a randomised trial. Diving and hyperbaric medicine. 2023;53(1):51-4.
4. Dampier CD, Smith WR, Wager CG, Kim HY, Bell MC, Miller ST, et al. IMPROVE trial: a randomized controlled trial of patient-controlled analgesia for sickle cell painful episodes: rationale, design challenges, initial experience, and recommendations for future studies. Clin Trials. 2013;10(2):319-31.

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Schiavo, Simone**
Affiliation	**University of Toronto**
Date	**04-Nov-2024**
COI	

Great work.

Thanks for all the replies to the comments.

See additional minimal comments below; otherwise, for publication.

- revised version: pg 1 of 34 (or pg 36 of 84), line 49: after obtaining consent

- throughout the paper: cvo=voc

- pg 6/34, line 59: HD, means HBO? or just explain the acronym after it's first use.

- Pg 12/34, box 1 the words "exclusion criteria" are repeated twice

- In Study design (pg 9), and in Randomization (pg 13), treatment time is 95 min, should be 90 as in Abstract?

- in Randomization (pg 14, line 3), triple blinded it says patient, research team and physician; Vs in Study Design (pg 9, line 24), it said patient, statistician, physician; please correct as necessary.

- Intervention group, pg 14, lines 54 and line 59: it first says “during pressurization patients will breathe FiO2 1” (line 54), but then it says “compression will be performed in air”; please adjust one or the other.

- Pg 14, line 59, “on air/oxygen” instead of “in air/oxygen”