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Original Research

Five sessions of hyperbaric oxygen for critically ill patients with COVID-19-induced ARDS: A randomised, open label, phase II trial

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ABSTRACT

Background: Few treatment options exist for patients with COVID–19–induced acute respiratory distress syndrome (ARDS). Data on the benefits and harms of hyperbaric oxygen treatment (HBOT) for this condition is limited.

Objective: To evaluate benefits and harms of HBOT in patients with COVID-19 induced ARDS.

Methods: In this open-label trial conducted at three hospitals in Sweden and Germany, patients with moderate to severe ARDS and at least two risk factors for unfavourable outcome, were randomly assigned (1:1) to medical oxygen 100 %, 2·4 Atmospheres absolute (ATA), 80 min (HBOT) adjuvant to best practice or to best practice alone (Control). Randomisation was stratified by sex and site. The primary endpoint was ICU admission by Day 30.

Results: Between June 4, 2020, and Dec 1, 2021, 34 subjects were randomised to HBOT (N = 18) or Control (N = 16). The trial was prematurely terminated for futility. There was no statistically significant difference in ICU admission, 5 (50 %) in Control vs 13 (72 %) in HBOT. OR 2·54 [95 % CI 0·62-10·39], p = 0·19.

Harms: 102 adverse events (AEs) were recorded. 16 (94 %) subjects in the HBOT group and 14 (93 %) in the control group had at least one AE. Three serious adverse events (SAEs), were at least, possibly related to HBOT. All deaths were unlikely related to HBOT.

Conclusions: HBOT did not reduce ICU admission or mortality in patients with COVID–19–induced ARDS. The trial cannot conclude definitive benefits or harms. Treating COVID–19–induced ARDS with HBOT is feasible with a favourable harms profile.

1. Introduction

Coronavirus disease 2019 (COVID–19) causes acute lung injury (ALI), that within 1–2 weeks, can progress into acute respiratory distress syndrome (ARDS) due to a hyperactivation of the innate immune system, commonly known as a "cytokine storm", if not resolved [1]. Despite

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major advances and better understanding of individual differences in the immune response depending on age, sex, comorbidities, and other factors, there is a need for alternative treatments to restore homeostasis and a dysregulated innate immune system [2].

1.1. Current guidelines and recommendations

More than 5000 potential drugs have been evaluated, for preventing development of severe disease, reducing mortality, targeting viral replication, and/or the innate immune system. Some drugs have shown benefits, but others were unfortunately detrimental. The WHO living guideline is regularly updated with recommendations on best practice. Dexamethasone, IL-6 blockers and Baricitinib have strong recommendations in favour, for severe and critical cases, per late 2023 [3]. Much of the evidence, so far, has been generated from open-label trial platforms, such as RECOVERY, DISCOVERY and SOLIDARITY trial platforms. Dexamethasone reduce 28–day mortality. The benefit is greatest for patients on invasive mechanical ventilation based on data from the RECOVERY trial [4]. The RECOVERY platform has also identified the IL-6 inhibitor tocilizumab as an effective treatment that decreases mortality and improves hospital discharge, even for severe cases on mechanical ventilation [5]. Corticosteroids (Dexamethasone), alone or in combination with IL-6 inhibitors (tocilizumab) and Janus Kinase (JAK) inhibitors (baricitinib), probably reduce mortality. All three are now strongly recommended by WHO for patients with severe or critical COVID-19. With moderate to strong evidence [3]. A recent systematic review and meta-analysis, including 8 RCTs with 19 819 patients, suggests that neutralising antibodies casirivimab-imdevimab are safe and effective for patients at risk of developing severe and critical COVID-19 [5]. The WHO guidelines have a strong recommendation against the antiviral monoclonal antibodies casirivimab-imdevimab due to lack of specificity for the new Omicron variants. It is also recommended against the use of anti-viral drugs such as remdesivir and lopinavir-ritonavir in critical cases [3]. Current recommendations highlights the difficulty in specifically targeting the virus and the most effective drug to date is paradoxically a non-precision drug: low dose Dexamethasone [4].

1.2. Previous clinical trials with HBOT for COVID-19

Despite advances in management of severe and critical cases of COVID-19, there is still significant mortality and morbidity [6]. HBOT was provided as “compassionate use” for COVID–19 [7]. Some evidence from small case series and prospective cohorts, suggests that HBOT is safe and potentially effective [8–10]. Four RCTs, with 225 patients have been published. Two RCTs, (n = 90) including patients with severe hypoxemia (SpO2 < 90 %) but excluding ARDS, compared “mild hyperbaric oxygen therapy” at 1·45 atm absolute (ATA), 5 sessions of 90 min, with standard of care. The Revitalair 430 technology can deliver close to 100 % oxygen but use an oxygen extractor, which also extracts and concentrates argon from air. Both studies show a shorter time to correct hypoxemia in the treatment group versus control group. One also a decrease in inflammatory markers [11,12]. Two RCTs, (n = 106) with HBOT 2·0–2·4 ATA, 5–10 sessions of 60–90 min, with or without air–-breaks, shows an increase in oxygen saturation and decrease in inflammatory markers in the HBOT group compared to the control group at ten days [13,14]. The trial by Siewiera et al. is the only previous RCT that specifically included ARDS patients [14]. Another RCT, (n = 29) that is not peer-reviewed but available as a preprint, included patients with hypoxemia (SpO2<94 % and did not exclude ARDS), treated with HBOT 2·2 ATA, 8 sessions of 60 min without air breaks, twice daily for four days, suggests that HBOT is safe and can improve oxygenation, attenuate inflammation and improve the clinical status of severely ill COVID–19 patients [15].

1.3. Rationale and hypothesis

HBOT has well known anti-inflammatory and immunomodulating effects and seems rational, but there is still a big gap of knowledge regarding potential harms, underlying mechanisms, timing and dosing to attenuate the uncontrolled inflammation in severe COVID–19 [16–18]. The overall hypothesis in our trial was that HBOT could reduce mortality, increase hypoxia tolerance and prevent organ failure in patients with severe COVID–19 by attenuating the inflammatory response.

1.4. Objectives

The primary objective was to evaluate if HBOT reduced the number of ICU admissions compared to best practice for severe COVID–19. Main secondary objectives were to evaluate if HBOT reduced the load on ICU resources, morbidity, and mortality, and to evaluate if HBOT mitigated the inflammatory response in severe COVID–19. Other secondary objectives, in selection, were to evaluate harms associated with HBOT for severe COVID–19 patients and staff.

To the best of our knowledge this is the first RCT conducted in compliance with International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use–Good Clinical Practice (ICH-GCP) on HBOT including critical COVID–19 patients with moderate to severe ARDS.

2. Methods

2.1. Trial design

This was an investigator initiated, randomised, controlled, parallel-arms, open-label, international multicentre, phase II clinical trial that was conducted at three hospitals: Blekingesjukhuset, Karlskrona, Karolinska University Hospital, Solna, both in Sweden and Krankenhaus St. Josef, Regensburg in Germany. The sponsor was Karolinska Institutet. The trial was monitored by independent organisations in Sweden and Germany before, during and after the trial. An independent data safety monitoring board (DSMB) reviewed the safety data at the predetermined interim analysis of the first 20 subjects without any major remarks on the safety of the trial. The DSMB was composed of three experts in their respective disciplines of medicine, clinical trial methodology and conduct. The members of the DSMB, meeting plan and responsibilities are specified in the original protocol, all details can be read in the DSMB Charter (Appendix A), and open minutes (Appendix A). The protocol includes Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [19]. The full protocol is available with open access [17], and available in Supplementary Table 1 Appendix A. The results from the interim safety analysis has been published [20]. The decision to terminate the trial prematurely for futility was made by the sponsor approximately one year after the last inclusion in each country based on slow inclusion rate due to changes in disease severity and best practice. A graphical summary of the trial design is depicted in Fig. 1.

2.2. Ethics and regulations

The trial was conducted in accordance with the Declaration of Helsinki, national legislations and in compliance with ICH-GCP. The protocol was approved by The National Institutional Review Board in Sweden (EPM), Dnr: 2020–01705 and Ethics Commission Münster in Germany, no: 2020–648-f-S. Approved by the Swedish Medical Products Agency (Läkemedelsverket), Dnr 5.1–2020–36673 and German Medical Product Agency (Bundesinstitut für Arzneimittel und Medizinprodukte) (BFArM), Vnr: 4044756. The trial was registered online prior to initiation on ClinicalTrials.gov, NCT04327505 and on EU Clinical Trials Register, EudraCT number: 2020–001349–37. All subjects signed an informed consent form compliant with ICH–GCP, including information of dissemination and data sharing. The trial was monitored by the

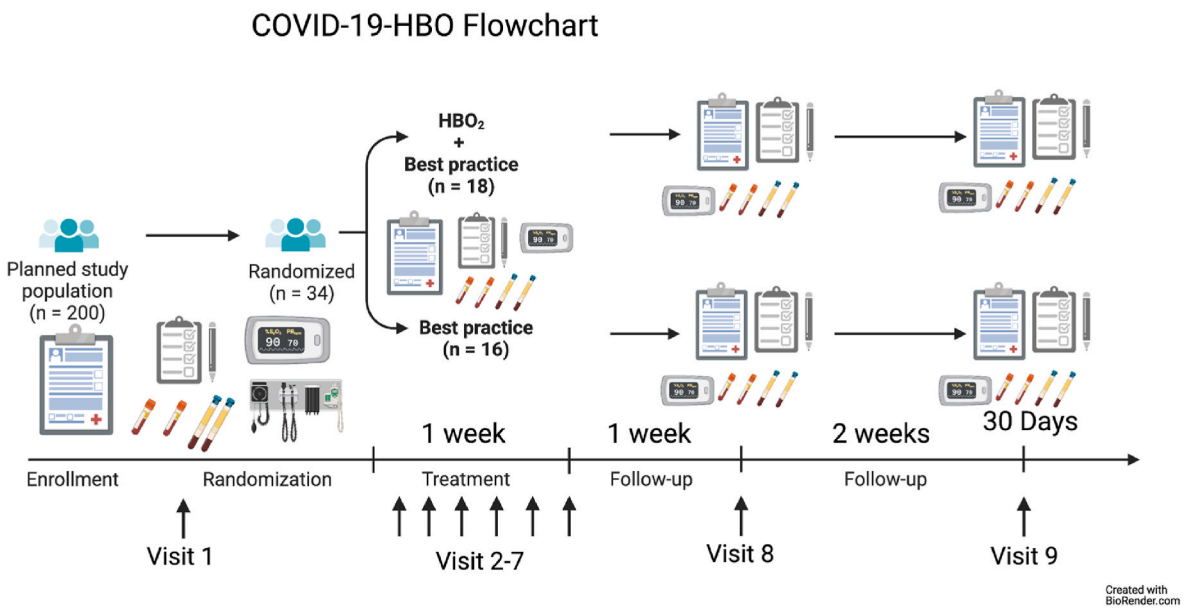

Fig. 1. Trial design. The subjects were followed every day for seven days and then Day 14 and Day 30.

Karolinska Trial Alliance in Sweden and by Zentrum für Klinische Studien (ZKSE) in Germany, through experienced monitors qualified in ICH GCP, applicable national and international regulations, and the Declaration of Helsinki, per the trial's monitoring plan. In Sweden the trial was also audited by the Swedish Medical Products Agency (Läkemedelsverket) without any critical remarks at the end of the trial (Dnr 6.3.1–2022–037011).

2.3. Participants

Adult patients 18–90 years old, hospitalised for severe COVID–19 with moderate to severe ARDS, with ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) below 26·7 kPa (200 mmHg), based on arterial blood gas (ABG) measurement, with at least two risk factors for increased risk of ICU admission or mortality and likely to need intubation within seven days of admission to hospital were included. Exclusion criteria included severe chronic obstructive pulmonary disease (COPD) (GOLD class III–IV), pulmonary fibrosis more than 10 % and contraindications for HBOT. All inclusion/exclusion criteria are listed in the published protocol. Patients were screened in the hospital wards by study personnel. Before any study specific interventions took place, the patients were provided with verbal and written information about the trial and signed an informed consent form.

2.4. Randomisation

Eligible subjects were randomised in a 1:1 allocation, stratified by site and sex, in blocks of eight (blinded to all study personnel) to either HBOT or Control with a computer-generated sequence using RANDOMIZE.NET. The block size was set up by an independent clinical research associate (CRA)

2.5. Trial procedures and interventions

The trial consists of nine visits over 30 days. Visit 1 includes medical history, concomitant medication, physical examination, drawing blood tests including ABG and biobanking. Visit 2 to 7 include registration of national early warning score (NEWS) and Adverse Events (AEs) and drawing blood tests during the treatment period. Visit 8 and 9 are follow-up visits that include registration of NEWS and AEs and drawing blood tests. Subjects who were discharged from hospital was asked to come in to an out-patients clinic. Both groups received best practice treatment for COVID–19, including normobaric medical oxygen 100 % administrated as needed, low dose steroids and low molecular weight heparin. The HBOT group received, in addition to best practice, HBOT with medical oxygen 100 % at 2·4 ATA for 80–90 min, with two 5-min air–breaks, once a day, maximum five treatments within seven days from randomisation. The protocol allowed 1·6–2·4ATA, but all centres used 2·4ATA. All treatments in Sweden were delivered in monoplace chambers and treatments in Germany was delivered in a Multiplace chamber with attending staff inside. The first HBOT was given within 24 h from inclusion. A detailed description of all trial procedures is listed in the published protocol [17].

2.6. Outcomes

2.6.1. Primary endpoint

The proportion of subjects admitted to or selected for ICU (including ECMO), from day 1 to day 30, based on at least one of the following criteria at the discretion of the investigator:

i) Rapid progression over hours.
ii) Lack of improvement on high flow oxygen >40L/min or non-invasive ventilation with
fraction of inspired oxygen (FiO2) > 0·6.
iii) Evolving Hypercapnia or increased work of breathing, not responding to increased oxygen despite maximum standard of care available outside ICU.
iv) Hemodynamic instability or multi organ failure with maximum standard of care available outside ICU.

2.6.2. Main secondary efficacy endpoints

I. Proportion of subjects with 30–day mortality, all-cause mortality, from day one to day 30.
II. Time–to–Intubation, i.e., cumulative days free of invasive mechanical ventilation, from day one to day 30.
III. Time–to–ICU, i.e., cumulative ICU-free days, derived as the number of days from day one to ICU admission, where all ICU-free subjects are censored at day 30.
IV. Mean change in inflammatory response, from day one to day 30.

a. White blood cell count (WBCC)
b. Procalcitonin (PCT)
c. C–reactive protein (CRP)
d. Ferritin
e. D–Dimer
f. Lactate dehydrogenase (LDH)

VI. Overall Survival.

2.6.3. Safety endpoints

I. Number of subjects, proportion of subjects and number of events of AE.
II. Number of subjects, proportion of subjects and number of events of SAE.
III. Number of subjects, proportion of subjects and number of events of SADR.
IV. Mean change in PaO_2/FiO_2 before and after HBO compared to mean variance in PaO_2/FiO_2 in control group day one to day seven.
V. Mean change in NEWS before and after HBO compared to mean change in daily NEWS in control group day one to day seven.
VI. Number of negative events in staff associated with treatment of subject, (e.g. contact with aerosol from subject), number of events from day one to day 30 or last day in hospital if subject is discharged earlier, or at withdrawal.

A change in the safety endpoints IV and V was made due to lack of feasibility and change in risk assessment after ethical review and amendment to the protocol. All details including amendments are listed in the protocol. The initial protocol is previously published [17].

2.7. Statistics

The statistical plan is described in more detail in the protocol [17]. The primary endpoint, ICU admission, was defined by criteria for selection for ICU. We assumed that 50 % of the subjects would have at least one criterion during the trial. We aimed at reducing the ICU admission rate by 40 %, i.e. to an ICU admission rate of 30 %. To achieve 80 % power with type-I error rate of 0.05, a sample size of 93 subjects per group was required (two-sided) and the plan was to enrol 200 subjects.

The sample size calculation was done in nQuery version 7.

The primary and secondary endpoints were evaluated using the ITT population (Full Analysis Set), including all randomised subjects. We initially planned to use the non-responder imputation (NRI) for the missing data. As the trial was prematurely terminated, the NRI was only used for the primary endpoint. The secondary endpoints were analysed for observed cases only. The safety endpoints were evaluated using the Safety population that included all subjects who were randomised and had received at least one treatment.

The primary endpoint, the proportion of patients with ICU admission, was analysed using the Cochran Mantel-Haenszel test, adjusting for randomisation strata site and gender. Due to premature termination of the study which reduced the number of subjects available for evaluation, analysis was done for one stratification factor at the time, in two separate models.

The secondary endpoints, in terms of time-to-event variables, were presented with Kaplan-Meier statistics and tested between treatment arms using the Log-rank test. Median estimates were presented where median could be estimated, otherwise the mean estimates were presented.

The secondary endpoints, in terms of continuous variables, were evaluated using the Analysis of co-variance (ANCOVA) including the treatment and the strata of gender and site as fixed factors, and the baseline as a covariate in the models.

The primary endpoint and secondary endpoints were evaluated at the type I error rate of 0.05, using a two-sided test. There was no adjustment for multiplicity as there was only one primary endpoint. The secondary endpoints are to be interpreted as exploratory findings. IBM SPSS Statistics version 29 was used for statistical calculations. A p-value less than 0.05 was considered statistically significant.

The safety endpoints were summarised descriptively using the number of subjects, AE events, and percentage of patients reporting AEs by treatment group.

2.8. Role of funding sources

The trial was investigator initiated. The sponsor is Karolinska Institutet. The funding body had no role in the trial design, data collection, data analysis, data interpretation, or writing of the report. The Swedish Research Council (Vetenskapsrådet), grant number KBF 2019–00446.

3. Results

3.1. Subjects and setting

Between June 4th, 2020, and Dec 1st, 2021, 79 patients were assessed for eligibility, 34 subjects were randomly assigned to HBOT (N = 18) or Control (N = 16) at two centres in Sweden and one centre in Germany. One subject in each group was excluded from the safety analysis since they were not given treatment. Randomisations per site and group are listed in Supplementary Table 1. (Appendix A) The trial was stopped for futility by the sponsor due to slow inclusion rate with 34 randomised subjects and only primary, main secondary and safety endpoints are reported. Exploratory endpoints in a predefined sub study on inflammatory mechanisms will be reported separately. The CONSORT flowchart is depicted in Fig. 2.

3.2. Primary endpoint

ICU admission. There was no statistically significant difference between the treatment arms in the proportion of subjects selected for ICU. 5 (50 %) in Control vs 13 (72·2 %) in HBOT. Corrected for gender OR 2·54 [95 % CI 0·62–10·39], p = 0·19. The corresponding results corrected for site was OR 5·27 [95 % CI 0·85–32·63], p = 0·07. The listing of individual days from randomisation to ICU admission is available in Supplementary Table 2. (Appendix A).

3.3. Main secondary endpoints

Mortality. There was no statistically significant difference between treatment arms, in 30–day mortality, all–cause. Four subjects expired in the HBOT group on Day 1, 2, 8 and 25 respectively. One subject expired in the control group on Day 13. The overall survival was 77·8 % in the HBOT group vs 93·8 % in the control group, p = 0.19.

Time–to–Intubation. There was no statistically significant difference between the treatment arms in cumulative days free of invasive mechanical ventilation, from day 1 to day 30. 24·5 (95 % CI 19·8–29·3) for Control vs 25·3 (95 % CI 19·7–30·9) for HBOT, p = 0·94.

Time–to–ICU. There was no statistically significant difference between the treatment arms in cumulative ICU-free days, derived as the number of days from day 1 to ICU, where all ICU free subjects are censored at day 30. Median time 14.0 for Control vs 1.0 for HBOT, p = 0·21.

Inflammatory response. There was a statistically significant effect between the treatment arms in the mean change from the baseline (day One) to day 30 in C-reactive protein (CRP). There was no statistically significant difference in the mean change in the other inflammatory response from day One to day 30 (Table 2).

Table 2. ANCOVA F–statistics for the inflammatory markers: White blood cell count (WBCC), procalcitonin (PCT), C-reactive protein (CRP), Ferritin, D–Dimer and Lactate dehydrogenase (LDH).

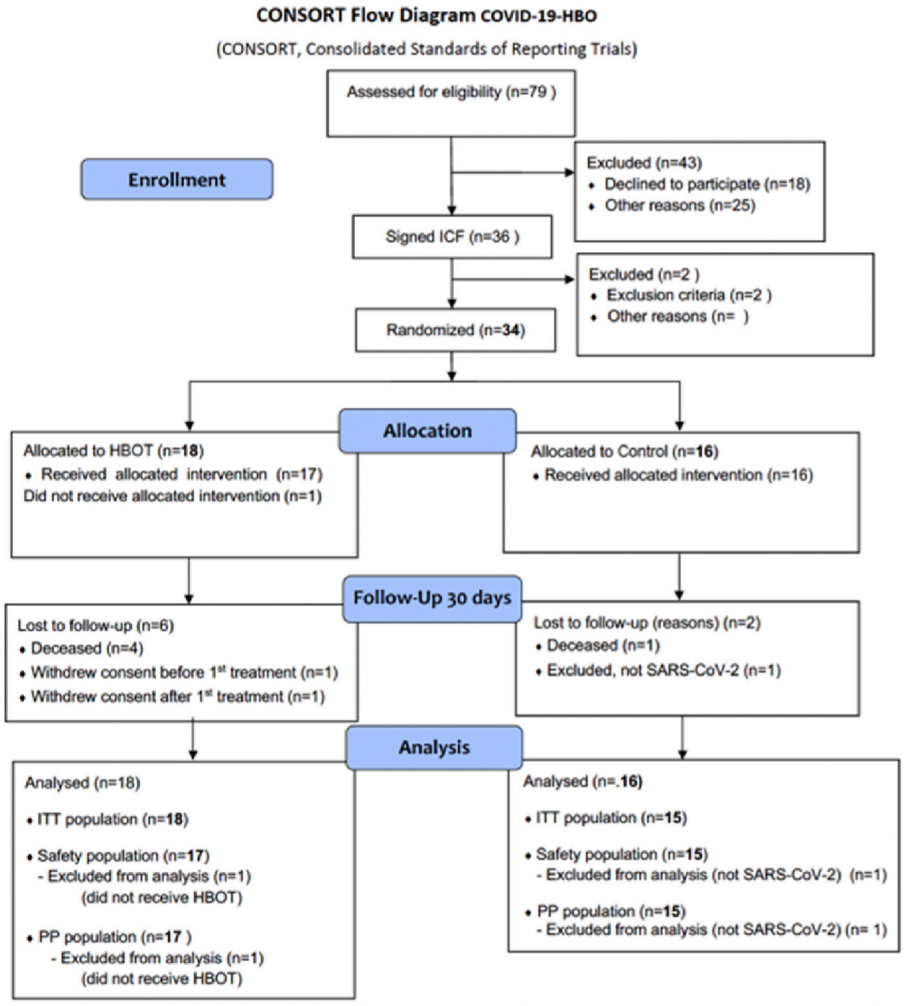

Fig. 2. CONSORT flowchart.
Fig. 2. CONSORT flowchart. The diagram shows the number of subjects in each group, allocation, analysis and reason for exclusion in analysis.

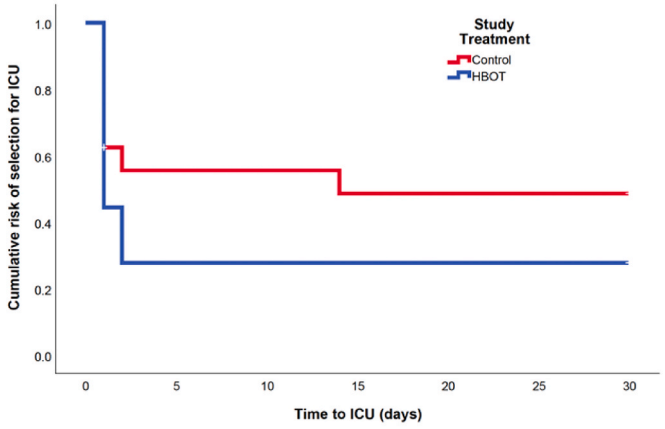

Fig. 3. Time–to–ICU
Fig. 3. Kaplan–Meier curve describing cumulative risk for ICU selection. Log rank χ_2 1·589, p = 0·207.

3.4. Safety endpoints

There were 102 AEs reported in the study. The AEs and SAEs were more commonly reported in the control group, but severe AEs were more common in the HBOT group. Four subjects expired in the HBOT group and one in the control group, but all deaths were assessed as unrelated to HBOT (Table 3). By system organ class (SOC), not surprisingly the most common SOC was Respiratory, thoracic and mediastinal disorders (25 in Control vs 18 in HBOT) and by preferred term (PT) the most common AE was hypoxia (18 in Control vs 15 in HBOT). Interestingly, pneumomediastinum and pneumothorax were more common in the control group, five vs only one in the HBOT group. SOC Infections and infestations was also more common in the control group, seven vs three in the HBOT group. Details of all AEs are listed in Supplementary Table 3 (Appendix A). No negative events in staff associated with treatment of subjects were reported.

Table 3. Number of subjects with at least one AE, proportion of subjects and number of events of AEs. N (%) AEs. Data are presented by severity of AEs and assessment of relationship to HBOT.

There were no signs of harms in the safety variables NEWS and PaO_2/FiO_2, in fact the HBOT group recovered faster compared to the Control group with significant Treatment × Time interaction (Table 4, Fig. 5).

4. Discussion

The aim of this trial was to evaluate the benefits and harms with HBOT compared to best practise for severe COVID–19 patients. Since the trial was prematurely terminated the study was inconclusive to meet the criteria in the power calculation. Exploratory, some results are worth discussing. There was no statistically significant difference between the

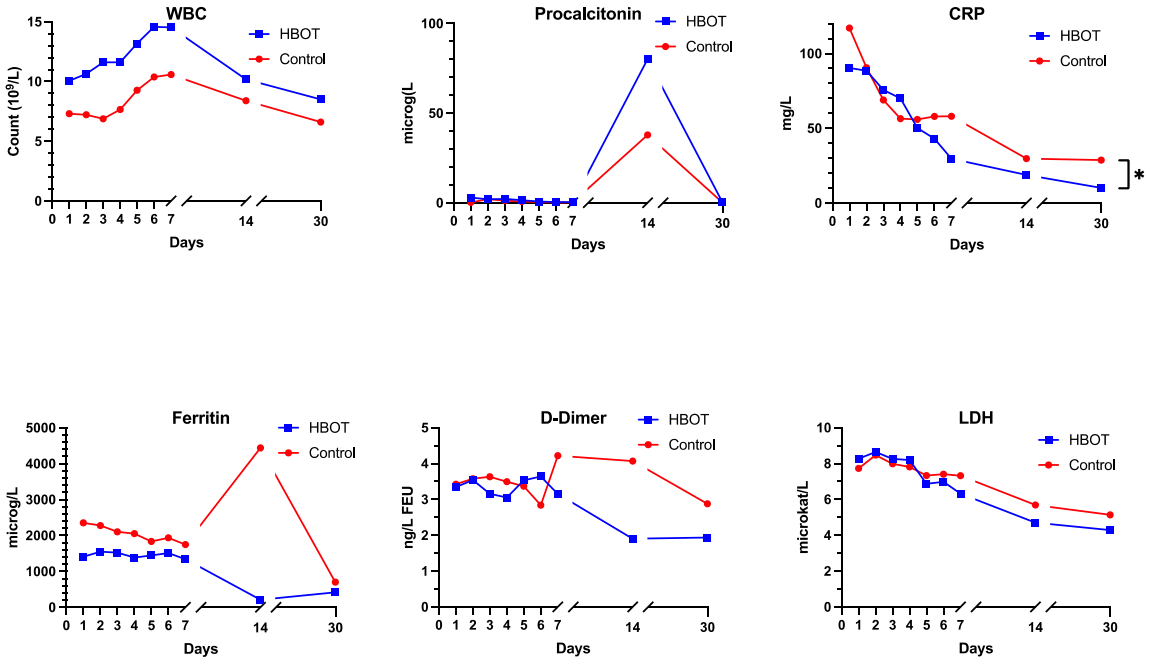

Fig. 4. Inflammatory markers

Fig. 4. Mean value plot of the trajectory of inflammatory markers (mean) over time, day 1 to day 30. * indicates $p < 0{\cdot}05$ in ANCOVA interaction (Treatment x Time).

Table 1
Patient characteristics.

Characteristics	HBOT (N = 18)	Control (N = 16)	Total (N = 34)
Age	66·6 (10·3)	64·1 (8·5)	65·4 (9·5)
Male	10 (56 %)	9 (56 %)	19 (56 %)
Female	8 (44 %)	7 (44 %)	15 (44 %)
White ethnicity	17 (94 %)	16 (100 %)	33 (97 %)
BMI	28·7 (4·2)	28·8 (5·2)	28·7 (4·6)
Risk factors (number)	2·8 (0·9	3·3 (0·9)	3·0 (1·0)
Above 50 years old	18 (100 %)	16 (100 %)	34 (100 %)
Disease severity			
PaO_2/FiO_2	16·0 (9·4)	19·1 (5·6)	17·5 (7·8)
NEWS	5·5 (1·7)	5·6 (1·9)	5·6 (1·8)
Comorbidity			
Hypertension	13 (72 %)	8 (50 %)	21 (62 %)
Cardiovascular disease	2 (11 %)	2 (12 %)	4 (12 %)
Diabetes Type 1	1 (6 %)	1 (6 %)	2 (6 %)
Diabetes Type 2	2 (11 %)	2 (11 %)	4 (11 %)
Active or cured cancer	2 (11 %)	9 (56 %)	11 (32 %)
Rheumatoid arthritis	3 (17 %)	0 (0 %)	3 (9 %)
Psoriasis arthritis	1 (6 %)	0 (0 %)	1 (3 %)
Asthma/COPD	1 (6 %)	5 (31 %)	6 (18 %)
Smoking	1 (6 %)	0 (0 %)	1 (3 %)
Treatment limitations			
DNR	1 (6 %)	1 (6 %)	2 (6 %)
Not for intubation	1 6 %)	0 (0 %)	1 (3 %)
Concomitant medications			
Dexamethasone/ Betamethasone	16 (89 %)	16 (100 %)	32 (94 %)
LMWH	17 (94 %)	16 (100 %)	33 (97 %
Remdesivir	5 (56 %)	6 (75 %)	11 (32 %)
Rituximab	1 (6 %)	0 (0 %)	1 (6 %)
Tocilizumab	2 (11 %)	1 (6 %)	3 (9 %)
Casirivimab/Imdevimab	1 (6 %)	0 (0 %)	1 (3 %)
Methotrexate	1 (6 %)	0 (0 %)	1 (3 %)

Table 1. Data is presented as number and percentage (%) or mean and standard deviation (SD). Abbreviations BMI, body mass index; PaO_2/FiO_2, partial pressure of arterial oxygen (kPa)/fraction of inspired oxygen ratio; NEWS, national early warning score; COPD, chronic obstructive pulmonary disease; DNR, do not resuscitate, LMWH, low molecular weight heparin.

Table 2
Inflammatory response.

ANCOVA F statistics for Inflammatory response (Treatment x Day)				
Dependent variable	Numerator df	Denominator df	F	Sig.
WBCC	8	22·22	0·92	0·52
Procalcitonin	8	11	1·86	0·17
CRP	8	21·78	2·56	0·04
Ferritin	8	24·24	2·28	0·06
D–Dimer	8	15	1·88	0·14
LDH	8	9·72	1·04	0·47

Table 3
AE overview (safety population).

Group	Control (N = 15)	HBOT (N = 17)
	n (%) AEs	n (%) AEs
Adverse Events	14 (93 %) 57	16 (94 %) 45
Serious Adverse Events	8 (53 %) 17	8 (47 %) 12
Severe Adverse Events	4 (27 %) 5	7 (41 %) 9
Deaths	1 (7 %)	4 (24 %)
Life–threatening	1	3
Persistent or significant disability/incapacity	0	3
Initial or prolonged hospitalization	5 (33 %) 11	6 (35 %) 8
Congenital anomaly/birth defect	0	0
Relationship to IMP – Related (n)	0	1
Relationship to IMP – Possible (n)	0	2
Action taken regarding IMP/IMD (discontinued) (n)	0	3

treatment arms in ICU admission. The standard ICU criteria to evaluate selection for ICU admission were used. The subjects were selected by at least one of the following criteria:

1. Rapid progression over hours.
2. Lack of improvement on high flow oxygen >40L/min or non–invasive ventilation with fraction of inspired oxygen (FiO2) > 0·6.

Table 4
PaO_2/FiO_2 and NEWS.

Variable	HBOT		Control			
	n	LSD (SE)	n	LSD (SE)	F	p-value
NEWS						
Day 7	12	−1·19 (0·81)	14	−0·73 (0·75)	0.17	0·68
Day 14	11	−2·69 (1·06)	13	−0·57 (0·98)	2.15	0·16
Day 30	10	−3·80 (0·86)	13	−1·61 (0·86)	3.60	0·072
PaO_2/FiO_2						
Day 7	11	13·75 (5·40)	11	3·31 (5·40)	1.81	0·19
Day 14	10	23·74 (3·48)	8	11·50 (3·90)	5.35	0·035
Day 30	8	31·93 (4·20)	10	23·50 (3·74)	2.16	0·16

Table 4. Least square mean changes in NEWS and PaO_2/FiO_2 by treatment group. ANCOVA, adjusted for baseline levels, site and gender.

3. Evolving Hypercapnia or increased work of breathing not responding to increased oxygen despite maximum standard of care available outside ICU.
4. Hemodynamic instability or multi organ failure with maximum standard of care available outside ICU.

Due to the overwhelming number of patients during the pandemic many patients fulfilling ICU criteria were treated outside the ICU. Patients were treated in ordinary wards with high flow oxygen >40L/min if no other signs of exhaustion or organ failure were present and in high dependency units with non-invasive ventilation well above FiO2 0·6 and low dose vasopressors. The fact that many severely hypoxic patients were subjectively unaffected, described as "happy hypoxia" or "silent hypoxia" [21] also contributed to the inclusion of "ICU patients", further impairing the power of the trial. The inclusion spanned over three waves in different hospitals. Karlskrona included eight subjects during first and second wave (alpha and delta), Karolinska 23 subjects, mostly during the second wave (delta) and Regensburg included their three patients during the third wave (omicron). The substantial differences complicate the ability to draw definitive conclusions from the results. It should be noted that all subjects with fatal outcomes in the trial were concomitantly treated off-label with monoclonal antibodies and the deaths were assessed as unlikely related to HBOT. Two subjects were not on Dexamethasone and one subject was not on LMWH in the HBOT group. These factors may have contributed to the outcome.

There were more ICU admissions and more deaths in the HBOT group which may be an indication of harms, although all deaths were assessed as unlikely related to HBOT. It is possible that benefits and harms are dependent on the severity of the disease, dose and timing of HBOT. On the other hand, the HBOT group showed numerically less AEs, SAEs and a trend towards lower NEWS, higher $PaO_2/PFiO_2$ and a shorter hospital length of stay. Even though no firm conclusions can be drawn from our small sample size, an interesting finding was that the only pneumothorax was in the control group. Another such finding was the four cases of pneumomediastinum in the control group vs only one in the HBOT group. The trend that we observed in our trial with better oxygenation and faster recovery in the HBOT group compared with Control is consistent with previously published trials [11–14]. Keller and Cannellotto excluded ARDS in their trials, so the patient populations are completely different from ours [11,12]. Toledo–Orozco did not specify ARDS but the baseline peripheral saturation was above 90 % without oxygen, suggesting that this also was a different population [13]. Despite this, Toledo–Orozco reports 10 deaths that occurred after randomisation but before first treatment (six in the HBOT group and four in Control group), these subjects were excluded from the final analysis and no harms were reported [13]. Siewiera used a similar protocol with the same inclusion and exclusion criteria as ours, hence their population is comparable. They have not yet fully reported on benefits and harms, but the reported preliminary data is consistent with the previous findings of improved oxygenation and a decrease in inflammatory markers. Three subjects expired in Siewiera's trial, all in the Control group [14].

In summary, none of the previous trials were conducted in compliance with ICH–GCP and the reporting of benefits and harms are incomplete which makes it difficult to assess if there is a reporting bias. The risk of bias in the study design, small studies, poor understanding of mechanisms and an inexplicit definition of how HBOT should be defined may be a reason why HBOT rarely figure in summaries of potential drugs or interventions, despite registration as clinical trials [22,23]. Although larger well designed clinical trials are warranted to evaluate benefits and harms of HBOT, there is a consistent beneficial trend in all trials that has been reported. HBOT seems to have an anti-inflammatory effect that improves oxygenation in individuals with severe and critical COVID-19. HBOT has a favourable profile of harms and may be beneficial in the intervention strategies for ARDS regardless of underlying causative agents.

The basic mechanism of HBOT is induction of oxidative stress which modulates the immune response [24], but the optimal dose and timing is not established [25–27]. It is possible that the induction of the immune response may lead to a transient deterioration before resolving which could be detrimental for critically ill patients. Intubation was regarded as an SAE in our trial, and we did not continue treatment for intubated subjects. Future trials should investigate benefits and harms on intubated subjects with ARDS [28]. However, to justify clinical trials on critically ill patients, trials with HBOT should be conducted in compliance with ICH–GCP. HBOT above 1.4 ATA with 100 % oxygen is a

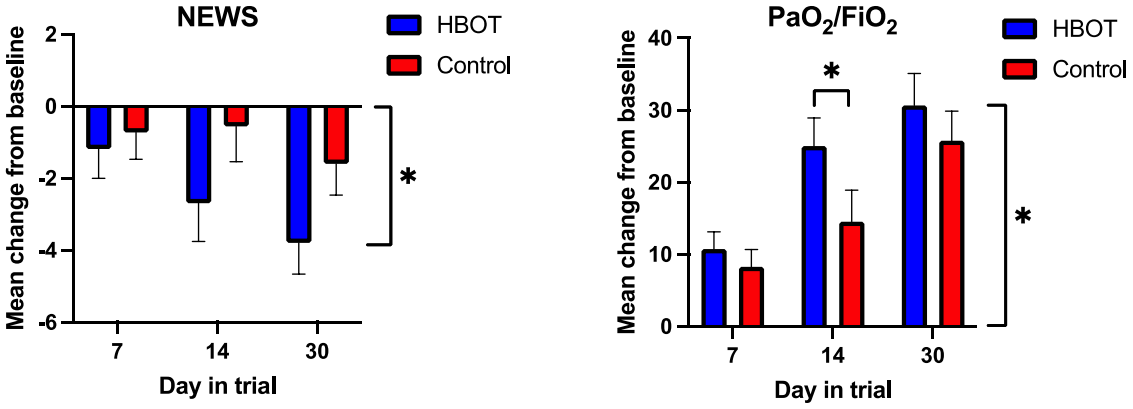

Fig. 5. Safety endpoints NEWS and PaO_2/FiO_2
Fig. 5. Least square mean changes in NEWS and PaO_2/FiO_2 at Day 7, 14 and 30. * indicates $p < 0.05$.

pharmalogical intervention and should be regarded as such by competent authorities, clinicians and researchers conducting clinical trials.

5. Conclusions

HBOT is a feasible treatment option for patients with critical COVID-19 and moderate to severe ARDS. HBOT has a favourable profile of harms for this condition. The trial was prematurely terminated for futility and could not definitely conclude benefits or harms of HBOT for patients with COVID–19-induced ARDS.

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Availability of data and materials

An anonymised list of all adverse events, the full protocol, the DSMB charter and open minutes are available as supplementary material. Anonymised data on subject level will be available upon reasonable request. A full description of the intended use of the data must be sent to the corresponding author for review and approval. Participant consent for data sharing is conditioned and new ethics approval may be required.

CRediT authorship contribution statement

Anders Kjellberg: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Johan Douglas:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation. **Michael T. Pawlik:** Writing – review & editing, Validation, Resources, Project administration, Investigation. **Adrian Hassler:** Writing – review & editing, Validation, Investigation. **Sarah Al-Ezerjawi:** Writing – review & editing, Validation, Investigation. **Emil Boström:** Writing – review & editing, Investigation. **Lina Abdel-Halim:** Writing – review & editing, Validation, Investigation. **Lovisa Liwenborg:** Writing – review & editing, Validation, Investigation. **Anna-Dora Jonasdottir-Njåstad:** Writing – review & editing, Validation, Investigation. **Jan Kowalski:** Writing – review & editing, Software, Formal analysis, Data curation. **Sergiu-Bogdan Catrina:** Writing – review & editing, Resources, Funding acquisition. **Kenny A. Rodriguez-Wallberg:** Writing – review & editing, Funding acquisition. **Peter Lindholm:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

KRW disclose funding from the Swedish Research Council, grant number KBF 2019–00446 for the current trial. JK disclose consulting fee for statistical work in this trial. For a full disclosure, please see Appendix A.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2024.107744.

Abbreviations

ABG	Arterial Blood Gas
AE	Adverse Event = any untoward medical occurrence
ANCOVA	Analysis of Covariance
ARDS	Acute Respiratory Distress Syndrome
ATA	Atmosphere Absolute (pressure) 1ATA = 101.3 kPa
BMI	Body Mass Index
COPD	Chronic Obstructive Pulmonary Disease
COVID–19	Corona Virus Disease 2019
CRA	Clinical Research Associate
CRF	Case Report Form
DNR	Do Not Resuscitate
DSMB	Data Safety Monitoring Board
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonization–Good Clinical Practice
ICU	Intensive Care Unit
IL-	Interleukin
ITT	Intention-to-treat = including all data from all subjects who have participated in the study
HBOT	Hyperbaric Oxygen Treatment
LHWH	Low Molecular Weight Heparin
MPA	Medical Products Agency
NEWS	National Early Warning Score
PBMC	Peripheral Blood Mononuclear Cells
PaO2/FiO2	Partial pressure of oxygen in arterial blood/Fraction of inspired oxygen
SAE	Serious Adverse Event = serious untoward medical occurrence
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SpO2	Saturation of peripheral Oxygen

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