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FULL LENGTH ARTICLE

Phase I trial of human umbilical cord-derived mesenchymal stem cells for treatment of severe bronchopulmonary dysplasia

Yunqiu Xia [a,1], Tingyuan Lang [b,1], Yuqin Niu [c], Xian Wu [d], Ou Zhou [e], Jihong Dai [e], Lei Bao [f], Ke Yang [g], Lin Zou [h], Zhou Fu [e,g,*], Gang Geng [e,**]

[a] *Department of Dermatology, Ministry of Education Key Laboratory of Child Development and Disorders, National Clinical Research Center for Child Health and Disorders, China International Science and Technology Cooperation Base of Child Development and Critical Disorders, Children's Hospital of Chongqing Medical University, Chongqing 400014, China*
[b] *Department of Gynecologic Oncology, School of Medicine, Chongqing University Cancer Hospital, Chongqing University, Chongqing 400030, China*
[c] *The First Affiliated Hospital, School of Medicine, Shihezi University, Shihezi, Xinjiang 832008, China*
[d] *Department of Respiratory Medicine, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China*
[e] *Department of Respiratory Medicine, Children's Hospital of Chongqing Medical University, Chongqing 400014, China*
[f] *Department of Neonatology, Children's Hospital of Chongqing Medical University, Chongqing 400014, China*
[g] *Chongqing Engineering Technology Research Center of Stem Cell Therapy, Children's Hospital of Chongqing Medical University, Chongqing 400014, China*
[h] *Center for Clinical Molecular Medicine, Children's Hospital of Chongqing Medical University, Chongqing 400014, China*

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KEYWORDS
Bronchopulmonary dysplasia;
Dose escalation;

Abstract Severe bronchopulmonary dysplasia (BPD) is a chronic lung disorder that primarily affects premature babies with extremely low birth weight and involves in multiple organ system; no effective pharmacotherapy for this disease exists, and mortality remains high. Based on the evidence from previous preclinical studies and phase I clinical trials, this study aims to

* Corresponding author. Department of Respiratory Medicine, Children's Hospital of Chongqing Medical University, Chongqing 400014, China.
** Corresponding author.
E-mail addresses: fuzhoucqmu@126.com (Z. Fu), 285544470@qq.com (G. Geng).
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[1] These authors contributed equally to this work.

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Human umbilical cord-derived mesenchymal stem cells;
Intravenous treatment;
Phase I trial

test the safety of intravenous application of a single dose of human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) in patients with severe BPD. The Mesenchymal Stem cells for Bronchopulmonary Dysplasia Treatment (MSBDT) trial is a single center, open-label, dose-escalation phase I clinical trial. Severe BPD patients were enrolled in Children Hospital of Chongqing Medical University, Chongqing, China. The first six patients were treated with low-dose hUC-MSCs (1×10^6 cells/kg) and the next seven patients were treated with high-dose hUC-MSCs (5×10^6 cells/kg). This study is registered with ClinicalTrials.gov, number NCT03558334. No prespecified infusion-associated adverse events, immediate complication, respiratory or cardiovascular compromise were observed during infusion and 24 h after infusion. No significant changes in safety laboratory values were observed. One death event occurred in the low-dose group on study day 10, and one death event occurred in the high-dose group on study day 24, while, after review in detail, the two cases are not believed to be infusion-associated events. In conclusion, intravenous application of a single dose of hUC-MSCs was tolerated in thirteen patients with severe BPD.

Introduction

Bronchopulmonary dysplasia (BPD) was first recorded by Northway and colleagues in 1967 as a chronic lung disease in preterm infants who exhibits respiratory distress syndrome.[1] With development of modern medicine, BPD treatment and management are more difficult as less mature and lower birthweight of the patients as well as the worse pathological signs, such as arrested lung development.[2,3] Although development of perinatal medicine, including antenatal steroids, gentle or non-invasive ventilation, and pulmonary surfactant replacement therapies, and drugs, such as vitamin A, steroids, caffeine, and anti-inflammatory agents, for BPD treatment, the situations of BPD patients are not significantly changed,[4,5] which leads to an urgent requirement of revolutionary treatment strategies.

Recently, mesenchymal stem cells (MSCs)-based therapy has been recognized as a promising and innovative therapeutic and preventive strategy for BPD; the advantages of MSCs include self-renewal and differentiation, low immunogenicity, and anti-inflammatory properties, etc.[6,7] Although MSCs could be isolated from multiple types of tissues, MSCs from fetal appendages, such as umbilical cord, possess higher proliferative activity in most cases.[8,9] Evidence from hyperoxia-induced lung injury neonatal rat model suggests that intravenous and intratracheal routes are the most effective methods for MSCs-based BPD treatment.[10] One phase I clinical trial was conducted in which 1×10^7 and 2×10^7 MSCs/kg were given intratracheally to BPD patients and no related adverse events were observed.[11,12] However, due to inadequate number of participants, the therapeutic efficacy of intratracheal administration of MSCs for BPD has not been proved yet.[13] Rare studies have been conducted for intravenous infusion of MSCs for BPD treatment. So far only one phase I clinical trial from Nguyen LT and colleagues suggested the safety of intravenous administration of MSCs for BPD treatment in which two intravenous doses of MSCs (1×10^6 MSCs/kg) were given by intravenous infusion, however, only four patients were enrolled.[14] Therefore, in this study, we performed a single center, open-label, dose-escalation phase I clinical trial to assess the safety of intravenous infusion of human umbilical cord-derived MSCs (hUC-MSCs) for treatment of severe BPD and to determine the maximum tolerated dose up to a dose of 5×10^6 cells/kg.

Materials and methods

Study design and participants

The MSCs for bronchopulmonary dysplasia treatment (MSBDT) trial is a single center, open-label, dose-escalation phase I clinical trial of intravenous administration of hUC-MSCs in patients with severe BPD at Children Hospital of Chongqing Medical University, Chongqing, China. A detailed protocol is provided in Data S1. Severe BPD is defined by (1) for infants who were born at $<$ 32 weeks (treatment with oxygen $>$21% for at least 28 days): need $\geq$30% oxygen and/or positive pressure (positive-pressure ventilation (PPV) or nasal continuous positive airway pressure (NCPAP)) ventilation at 36 weeks postmenstrual age (PMA) or discharge, whichever comes first; (2) for infants who were born at $\geq$ 32 weeks (treatment with oxygen $>$21% for at least 28 days): need $\geq$30% oxygen and/or positive pressure (PPV or NCPAP) ventilation at 56 days postnatal age or discharge, whichever comes first.[15] Patients were excluded if they have the following: (1) age $>$1 year; (2) no dyspnea or BPD-related changes in pulmonary imaging; (3) concurrent cyanotic or acyanotic congenital heart diseases; (4) abnormal laboratory test (three-fold); (5) severe pulmonary hypertension; (6) severe respiratory tract malformation; (7) chromosome anomalies; (8) severe congenital infection; (9) severe active infection; (10)

Table 1 MSBDT inclusion and exclusion criteria.

Inclusion criteria
For infants who were born at < 32 weeks
Time point of assessment
- Treatment with oxygen >21% for at least 28 days
- 36 weeks' PMA or discharge, whichever comes first
Criteria
- $FiO_2 \geq 30\%$
- and/or positive pressure (PPV/NCPAP)
For infants who were born at ≥ 32 week
Time point of assessment
- Treatment with oxygen >21% for at least 28 days
- 56 days' postnatal age or discharge, whichever comes first
Criteria
- $FiO_2 \geq 30\%$
- and/or positive pressure (PPV/NCPAP)
Exclusion criteria
- Age >1 year
- No dyspnea or BPD-related changes in pulmonary imaging
- Concurrent cyanotic or acyanotic congenital heart diseases
- Abnormal laboratory test (liver and kidney functions tests, cardiac markers, hematology and immunity tests) (three-fold change)
- Severe pulmonary hypertension (diagnosed with an echocardiogram)
- Severe respiratory tract malformation (Pierre-Robin syndrome, tracheobronchomalacia, vascular ring syndrome, congenital tracheal stenosis, tracheo-esophageal fistula, pulmonary emphysema, pulmonary sequestration, congenital pulmonary dysplasia, congenital pulmonary cyst, congenital spasm, etc.)
- Chromosome anomalies (Edward syndrome, Patau syndrome, Down syndrome, etc.)
- Severe congenital infection (herpes simplex, toxoplasmosis, rubella, syphilis, AIDS, etc.)
- Severe active infection (c-reactive protein (CRP) > 30 mg/dL, suffer sepsis, septic shock, etc.)
- Surgery within 72 h before/after infusion
- Surfactant administration within 24 h before infusion
- Severe intracranial hemorrhage
- Hormone treatment within 7 days of infusion

surgery within 72 h before/after hUC-MSCs infusion; (11) surfactant administration within 24 h before hUC-MSCs infusion; (12) severe intracranial hemorrhage; (13) hormones treatment. The details of inclusion and exclusion criteria are given in Table 1 and our previous report.[16]

Informed consent was obtained from parents of each patient after discussion. To make sure the patients were stable before infusion, a 2-h period of bedside observation was performed once informed consent was gained. To obtain baseline stability criteria, another 2-h bedside observation was performed before infusion. The thirteen-patient dose-escalation protocol was selected which was approved by the Institutional Review Board of Children Hospital of Chongqing Medical University (Chongqing, China). This study is registered with ClinicalTrials.gov, number NCT03558334.

Procedures

The first six patients were assigned to receive low-dose hUC-MSCs (1×10^6 cells/kg); the next seven patients were assigned to receive high-dose hUC-MSCs (5×10^6 cells/kg). The dose of 5×10^6 cells/kg was selected as the final target dose based on our previous research.[16] The safety of the first patient of each cohort and the complete first cohort were reviewed before enrolment of the rest patients or escalation of the dose.

The hUC-MCSs were obtained from Vcanbio Cell & Gene Engineering Corp., Ltd (Tianjin, China).[17] The freshly produced hUC-MSCs were shipped under 4 °C to the clinical sites within 6 h. The hUC-MSCs were maintained in room temperature for 30 min to 1 h before administration. The total volume of the hUC-MSCs infusion was 20 mL regardless of dose. The viability of infused hUC-MSCs was checked by trypan blue exclusion before infusion. The viability of all infused hUC-MSCs was ≥85%.

After clinical stability observation, the infusion was initiated using a standard set; the infusion rate was controlled by a trained investigator (5 mL/kg per hour). A bedside observation was implemented during infusion and 6 h after start of hUC-MSCs infusion for observation any signs of adverse reaction. Gentle respiratory support was given for each patient according to the therapeutic strategy from committee on fetus and newborn.[18] The detailed information about on-study measurements and data collection are reported in our previous publication.[16]

Any changes in vital signs including respiratory or cardiovascular parameters, such as body temperature, respiratory rate, heart rate, mean arterial pressure, and saturation of peripheral oxygen (SpO_2), were closely

Table 2 Prespecified infusion-associated events.

Any of the following occurring within 6 h of mesenchymal stem cell infusion:
- Worsening hypoxemia
- Acute cardiac events
- Pulmonary embolism
- Anaphylaxis
- Clinically significant laboratory test abnormalities
- Cardiac arrest or death within 24 h post-infusion

monitored during infusion and 24 h after start of infusion in order to avoid any cases of transient obstruction of the pulmonary microcirculation and monitor safety. Prespecified infusion-associated events are listed in Table 2. All serious adverse events were recorded, analyzed and independently evaluated by Data Safety Monitoring Board (DSMB), which is composed of physicians and statistician with clinical trial experience, to determine whether they were related to hUC-MSCs infusion. In addition, safety laboratory values, including peripheral blood cell counts, hemoglobin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, myoglobin, cardiac troponin I (cTnI), creatine kinase-MB, serum IgG, IgM, IgA, IgE, and complement C3 and C4, were also measured on day 7 after hUC-MSCs infusion for safety monitoring.

The lung injury score (LIS) and Silverman-Andersen Sore were used to evaluate severity of lung injury and respiratory distress, respectively. LIS is composed of chest radiograph, PaO_2:FiO_2, positive end-expiratory pressure (PEEP), and static compliance of respiratory system, which is aim to assess lung injury severity.[19,20] Silverman-Andersen score is composed of upper chest retraction, lower chest retraction, xiphoid retraction, nasal dilatation, and grunt, which is aim to assess breathing performance of premature infants.[21] The detail schedule of examination and observation is given in Figure 1.

Outcomes

Because MSBDT study was one of the first trials to evaluate intravenous infusion of hUC-MSCs in patients with severe BPD, the primary objective of this study was to evaluate the safety and tolerability of the intravenous hUC-MSCs infusion for severe BPD treatment. The incidence of all serious and non-serious adverse events was reported. The secondary objective was to measure standard respiratory endpoints, including LIS and Silverman-Andersen Sore.

Statistics

The data are presented as mean ± SD. Student's *t*-test (two-tailed) and one-way ANOVA were used for *p*-value calculation and $P < 0.05$ was considered as statistical significance.

Role of the funding source

The sponsors had no role in the study design and data collection, analysis and interpretation. The corresponding authors have full access to the data and the final responsibility of publication.

Results

The workflow of MSBDT study was given in Figure 1: six patients received the low-dose (1×10^6 cells/kg) and seven patients received the high-dose (5×10^6 cells/kg) hUC-MSCs. Baseline characteristics of the patients were given in Table 3. All the patients were severe BPD patients and clinical variables were similar at baseline.

As shown in Table 4 and Figure 2—4, all patients well tolerated the hUC-MSCs infusion and there were no prespecified infusion-associated adverse events. No immediate complication, respiratory or cardiovascular compromise were observed during infusion and 24 h after infusion (Table 4). Almost all vital signs values, including body temperature, respiratory rate, heart rate, mean arterial pressure, and SpO_2, obtained within 24 h of infusion (infusion and immediate post-infusion period) were in normal ranges (Fig. 2). No significant changes in safety laboratory values, including the number of white blood cells, red blood cells, blood platelet, as well as the levels of hemoglobin, ALT, AST, blood urea nitrogen, creatinine, myoglobin (Mb), cardiac troponin I (cTnI), creatine kinase-MB (CK-MB), immunoglobulin G (IgG), IgA, IgM, IgE, and complement C3 and C4, were observed for any of the dosing groups (Fig. 3, 4).

Two patients died at 24 h after infusion; the mortality rate is 15.38% (two of thirteen patients). One death event occurred in the low-dose group on day 10 after infusion, and another death event occurred in the high-dose group on day 24 after infusion; after review in detail, the two cases were not believed to be infusion-associated events.

In term of the mean LIS, no changes were observed in both dosing groups (Fig. 5A), while Silverman Andersen Score declined (improved) in both dosing groups (Fig. 5B). The greatest decrease in Silverman Andersen Score was observed on day 1 (high-dose group: from 4.86 to 3.42 [−29.63%]; low-dose group: from 5.17 to 4.33 [−16.25%]) and small decreases were observed between day 1 and day 7 in both groups (Fig. 5B). The decreases in Silverman Andersen Score between baseline and day 1 were statistically significant in both groups, and a greater decrease was observed in the high-dose group (Fig. 5B).

Discussion

In this study, we demonstrated that intravenous application of a single dose of hUC-MSCs (1×10^6 cells/kg and

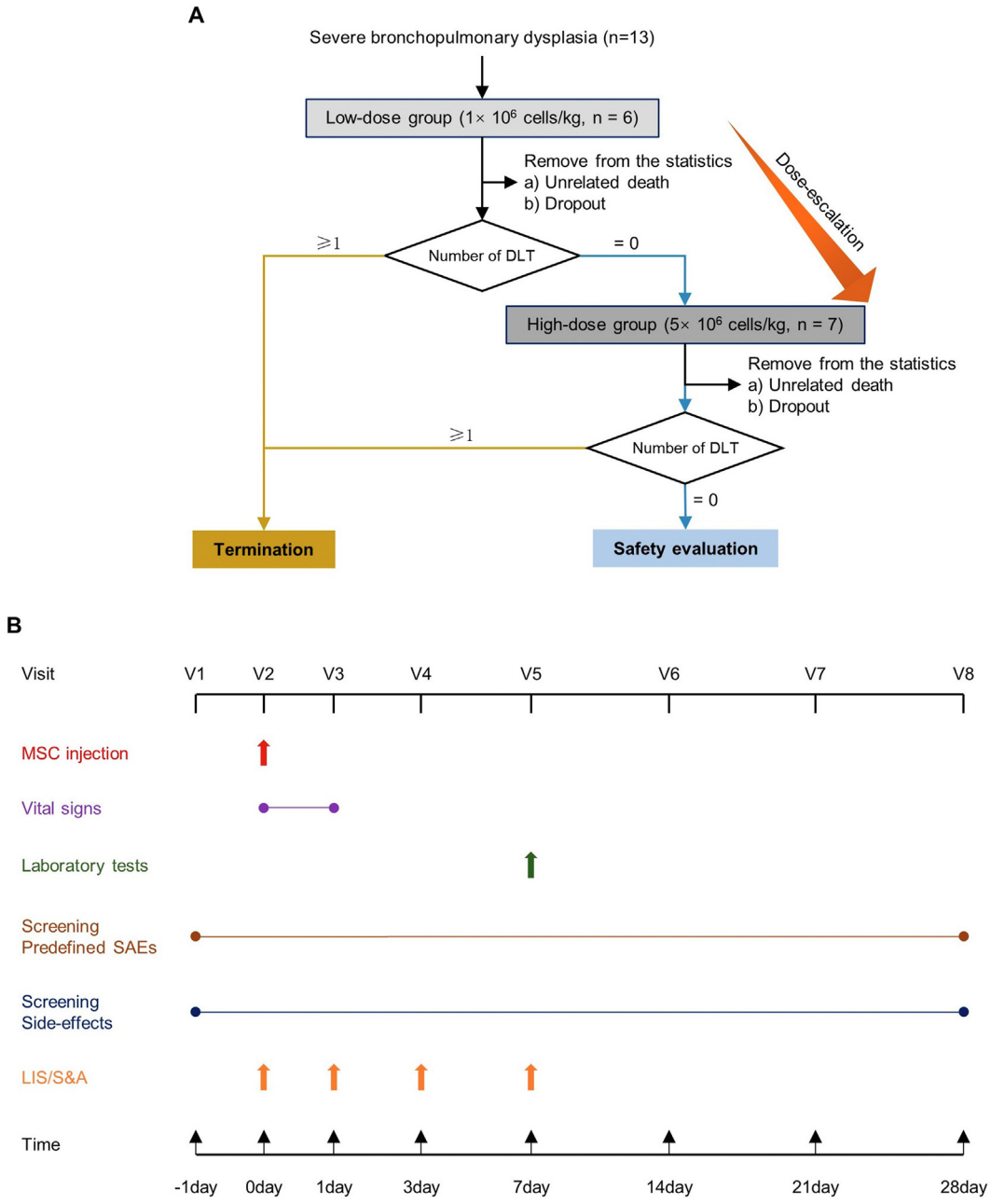

Figure 1 Workflow of MSBDT trial. The Mesenchymal Stem cells for Bronchopulmonary Dysplasia Treatment (MSBDT) trial is a single center, open-label, dose-escalation phase I clinical trial. The first six severe BPD patients were treated with low-dose hUC-MSCs (1×10^6 cells/kg) and the next seven patients were treated with high-dose hUC-MSCs (5×10^6 cells/kg). Patients were visited seven times (V1—V8) to assess the safety and tolerability of intravenous transplantation of hUC-MSCs. LIS, S&A score, and PaO_2 were recorded four times(V2—V5) to explore the efficacy. Abbreviations: DLT: dose limited toxicity; LIS: lung injury score; MSBDT: The mesenchymal stem cells for bronchopulmonary dysplasia treatment; MSC: mesenchymal stem cell; PaO_2: partial pressure of oxygen; SAE: serious adverse event; S&A: Silverman Andersen score.

5×10^6 cells/kg) was well tolerated in thirteen patients with severe BPD in this phase I trial. No immediate clinical instability, prespecified infusion-associated adverse events and dose-limiting toxicity were observed. The severe adverse events reported in this trial were not believed to be related to hUC-MSCs infusion. Thus, the results of this trial suggest that intravenous infusion of both doses of hUC-MSCs is safe in patients with severe BPD.

Two serious adverse events occurred (two of thirteen patients died) in this study; the mortality was 15.38%. Geetha O and colleagues reported that the expected mortality in patients with moderate-severe BPD is 67% and overall mortality of BPD is 19%.[4] Thus, the mortality observed in this study is lower than the expected mortality. Furthermore, both events occurred after day 10, which suggests that these two serious adverse events are not related to hUC-MSCs infusion.

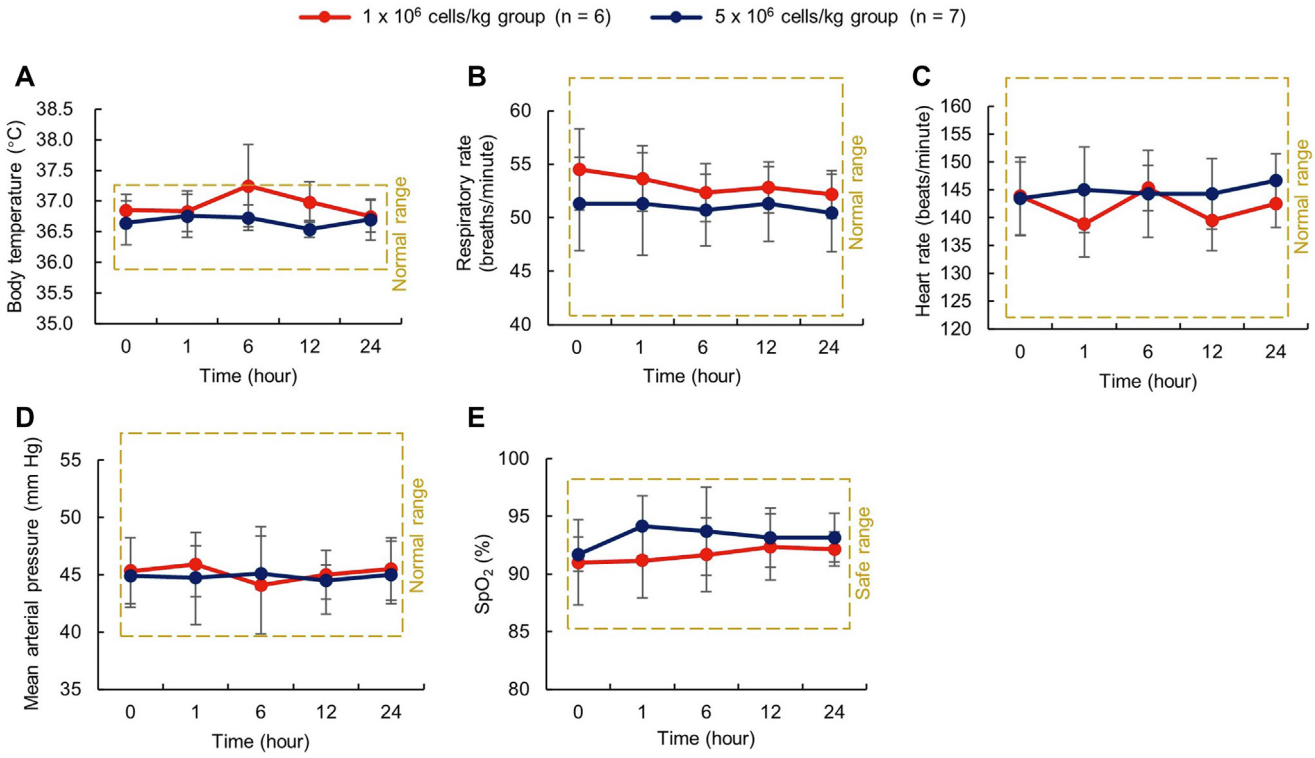

Figure 2 Vital signs during and after hUC-MSCs infusion. Mean ± SD values in each dosing group for **(A)** body temperature (°C), **(B)** respiratory rate (breaths/minute), **(C)** heart rate (beats/minute), **(D)** mean arterial pressure (mm Hg), and **(E)** oxygen saturation (SpO_2%) at base line, 1, 6, 12 and 24 h from start of hUC-MSCs infusion.

Table 3 Clinical characteristics of study subjects.

Patient ID	Gestational age (weeks)	Birth weight (kg)	Sex	Prenatal steroid	Postnatal steroid	Pulmonary surfactant	Oxygen and/ or respiratory support	Apgar score at 1 min
Low-dose group								
A1	30.8	1.21	male	Y	N	Y	Intubation	10
A2	27.1	0.97	male	Y	Y	Y	NCPAP	5
A3	30.7	1.44	male	N	N	Y	NCPAP	7
A4	27.6	1.08	male	Y	Y	Y	Nasal cannula > 2 L/min	7
A5	27.0	1.10	female	Y	N	Y	Intubation	7
A6	30.1	1.40	male	Y	Y	Y	Nasal cannula > 2 L/min	4
High-dose group								
B1	30.8	1.39	male	Y	Y	Y	Nasal cannula > 2 L/min	9
B2	30.0	1.30	male	Y	Y	Y	Nasal cannula > 2 L/min	8
B3	28.7	0.95	male	Y	N	N	Intubation	4
B4	30.8	1.15	male	Y	N	Y	Nasal cannula > 2 L/min	5
B5	29.0	1.14	male	Y	N	Y	Nasal cannula > 2 L/min	7
B6	30.0	0.85	male	Y	N	Y	NCPAP	7
B7	29.3	1.50	male	Y	Y	Y	Intubation	5

NCPAP: Nasal continuous positive airway pressure; Apgar score: Apgar stands for "Appearance, Pulse, Grimace, Activity, and Respiration."

The improvements in Silverman Andersen Score, a system for evaluating breathing performance of premature infants,[21] in both groups were observed on day 1 and this effect was sustained at least 7 days. The decrease in the high-dose group is greater than that in the low-dose group, which suggests that increased doses of hUC-MSCs might increase clinical benefit. On the other hand, no changes in LIS,[19,20] a commonly utilized measure of acute lung injury severity, were observed in this study, which indicates that the effect of the interventions used in this study may not

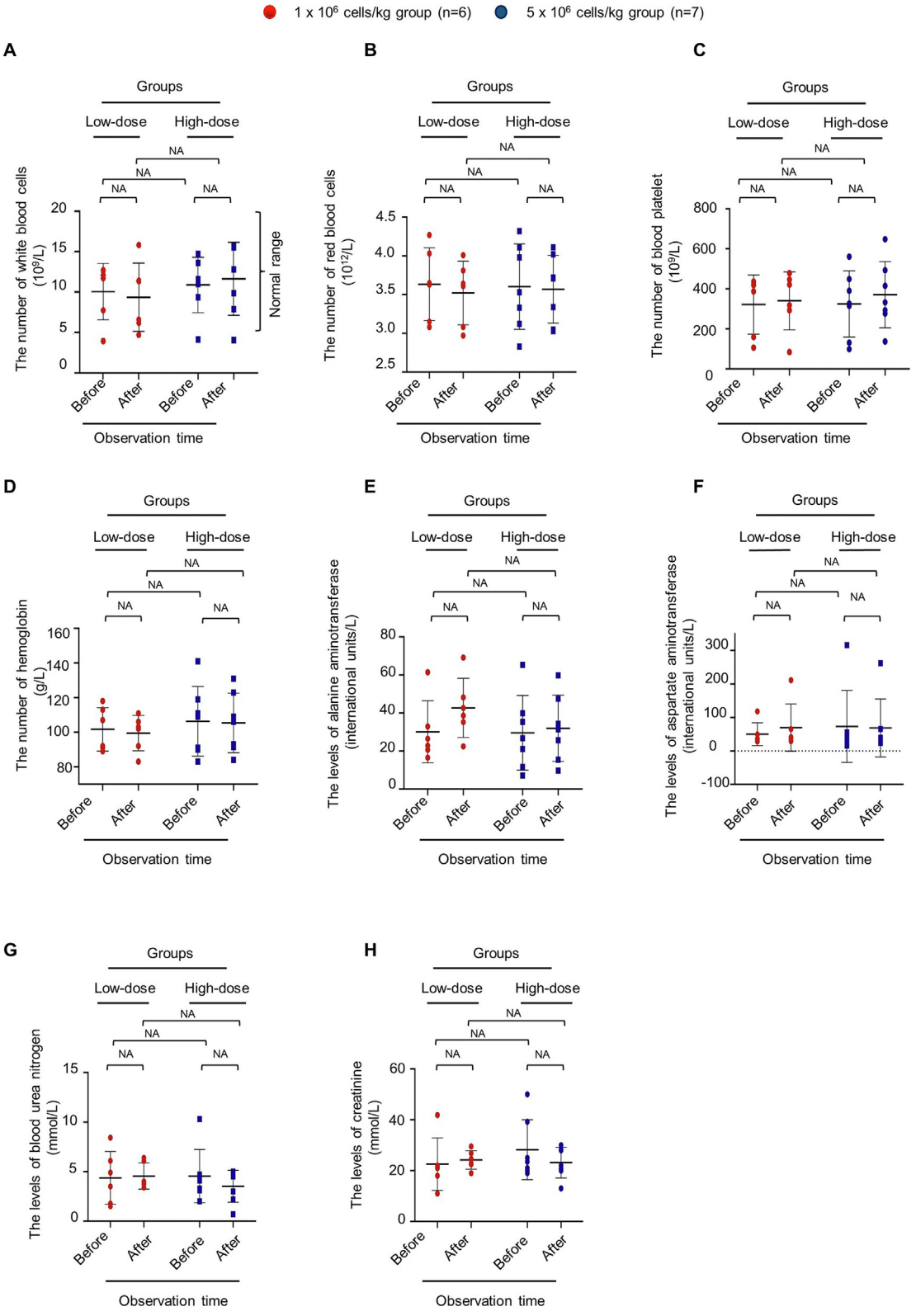

Figure 3 Safety laboratory values before and after hUC-MSCs infusion (part 1). Mean ± SD values in each dosing group for the number of **(A)** white blood cells (10^9/L), **(B)** red blood cells (10^{12}/L), **(C)** blood platelet (10^9/L), as well as the levels of **(D)** hemoglobin (g/L), **(E)** ALT (international units/L), **(F)** AST (international units/L), **(G)** blood urea nitrogen (mmol/L) and **(H)** creatinine (mmol/L) at base line and 7 days from start of hUC-MSCs infusion.

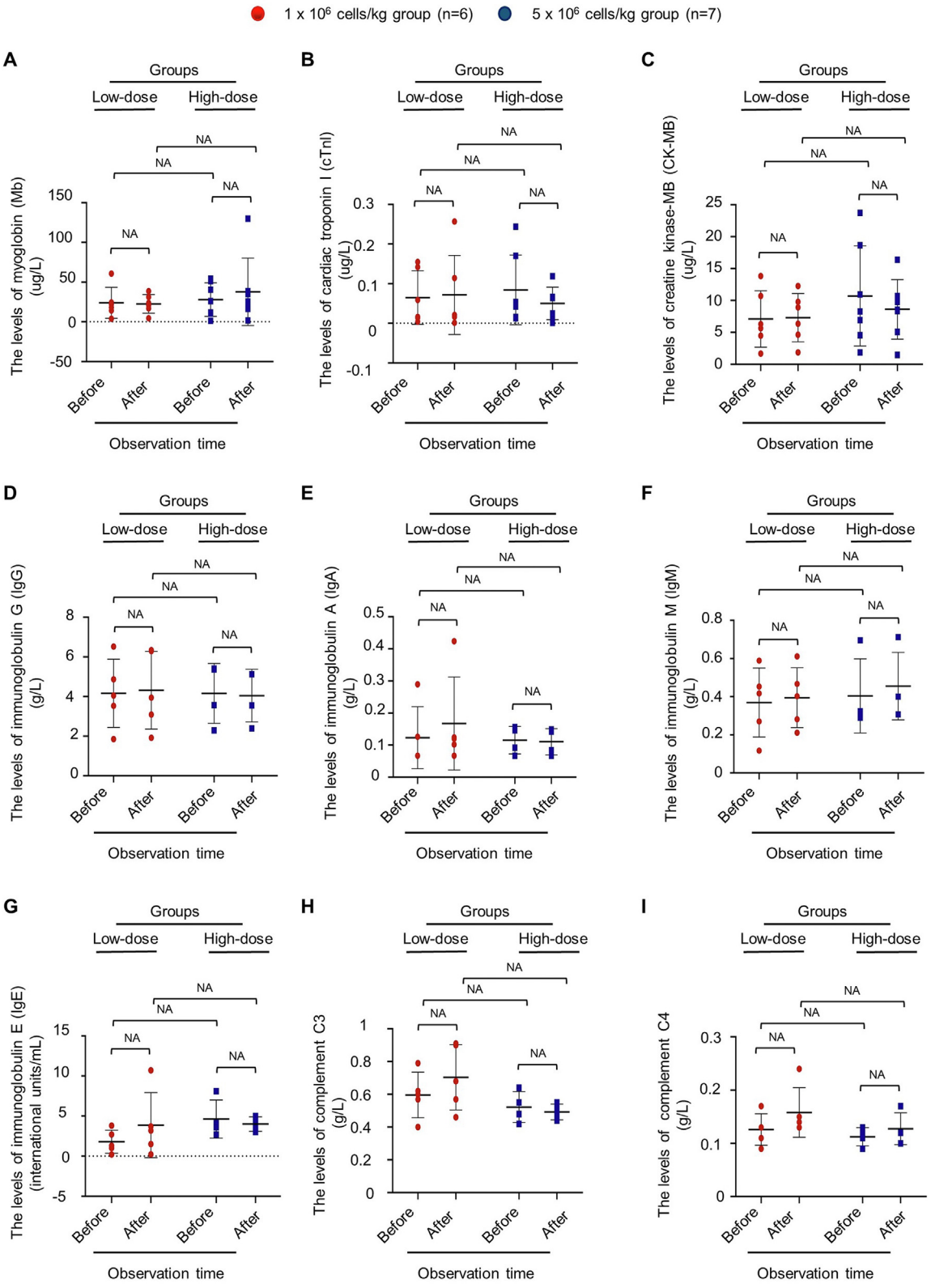

Figure 4 Safety laboratory values before and after hUC-MSCs infusion (part 2). Mean ± SD values in each dosing group for the levels of **(A)** myoglobin (μg/L), **(B)** cardiac troponin I (μg/L), **(C)** creatine kinase-MB (μg/L), **(D)** immunoglobulin G (g/L), **(E)** immunoglobulin A (g/L), **(F)** immunoglobulin M (g/L), **(G)** immunoglobulin E (international units/mL), **(H)** complement C3 (g/L) and **(I)** complement C4 (g/L) at base line and 7 days from start of hUC-MSCs infusion.

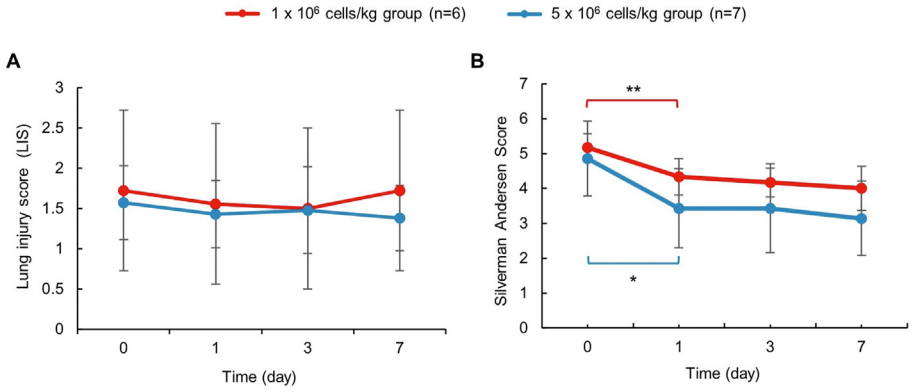

Figure 5 Lung injury score (LIS) before and after hUC-MSCs infusion. **(A)** Mean ± SD values of LIS and **(B)** Silverman Andersen Score in each dosing group at baseline, 1, 3 and 7 days from start of hUC-MSCs infusion. LIS is composed of chest radiograph, PaO_2:FiO_2, positive end-expiratory pressure (PEEP), and static compliance of respiratory system, which is aim to assess lung injury severity. Silverman-Andersen score is composed of upper chest retraction, lower chest retraction, xiphoid retraction, nasal dilatation, and grunt, which is aim to assess breathing performance of premature infants.

Table 4 Serious adverse events of study participants.

Adverse events	MSC groups	
	Low-dose group (1×10^6/kg)	High-dose group (5×10^6/kg)
Mortality No.		
<24 h	0	0
24 h ∽ 4 weeks	1	0
4 ∽ 12 weeks	0	1
Prespecified infusion-associated events	None	None
Other adverse events	None	None

be effective enough for ameliorating lung injury severity, at least in 7 days after infusion. However, given the absence of a control group in this study, the conclusion cannot be made. The effectiveness of hUC-MSCs infusion for BPD treatment should be investigated by a phase II study with large sample size and long-term follow up.

Investigation of the effectiveness resulted from different application routes of MSCs is important for further translation. Studies in animal models demonstrated that efficient delivery can be made by intratracheal, intravenous and intraperitoneal injection. Chang YS and colleagues performed a preclinical study and showed that intratracheal application of MSCs ameliorated lung injury at doses fourfold lower than intravenous application.[22] Subsequently, a phase I and a phase II studies were performed by the same team and the safety of intratracheal application of MSCs was demonstrated.[11–13] In addition, the results from another phase I early intervention study from Powell SB and colleagues also demonstrated the safety of the intratracheal application of MSCs for BPD treatment.[23]

However, investigation of the safety of intravenous application of MSCs was also important. First, one of the biggest challenges for BPD treatment is severe BPD in premature babies, especially these with extremely low birth weight, so that multiple organ systems are involved.[24] Thus, intravenous application of MSCs may be beneficial for not only BPD, but also other conditions.[25] Second, intravenous application of MSCs might be more helpful for preventing vessel loss and improvement of vessel remodeling.[26]

Furthermore, avoiding freeze-thaw cycle is important for MSCs preparation. In this study, all hUC-MSCs were freshly produced and the average cell viability was ≥85%. While, according to the study conducted by Wilson JG and colleagues, the average cell viability declined to 56% after freeze-thaw [27].

Conclusion

In conclusion, intravenous application of a single dose of hUC-MSCs (1×10^6 cells/kg and 5×10^6 cells/kg) was well tolerated in thirteen patients with severe BPD in this phase I trial. No immediate clinical instability, prespecified infusion-associated adverse events and dose-limiting toxicity were observed. The severe adverse events reported in this trial were not believed to be related to MSCs infusion. Thus, the results of this trial suggest that intravenous infusion of both doses of hUC-MSCs is safe in patients with severe BPD.

Funding

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Conflict of interests

All authors declare that there are no conflicts of interest related to the contents of this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.02.001.

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