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Original Article

Characterization of dynamical changes in vital signs during allogeneic human umbilical cord-derived mesenchymal stem cells infusion

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ABSTRACT

Human umbilical cord-derived mesenchymal stem cells (hUC-MSCs), a kind of adult stem cell, were studied for clinical applications in regenerative medicine. To date, the safety evaluations of intravenous infusion of allogeneic hUC-MSCs were focused on fever, infection, malignancy, and death. However, the characteristics of dynamical changes in vital signs during hUC-MSCs infusion are largely unknown. In this study, twenty participants with allogeneic hUC-MSCs transplanted (MSC group) and twenty sex- and age-matched individuals with cardiovascular disease who treated with the equal volume of 0.9% normal saline were recruited (NS group). Heart rate, respiratory rate, oxygen saturation, systolic and diastolic blood pressure, and temperature were monitored at intervals of 15 min during infusion. Adverse events were recorded during infusion and within seven days after infusion. No adverse events were observed during and after infusion in both groups. Compared with the baseline, the mean systolic blood pressure (SBP) levels were significantly decreased at 15 min, 30 min, 45 min and 60 min in the MSC group (all $P < 0.05$) during infusion. In addition, SBP changed significantly from baseline during hUC-MSCs infusion when compared with that of NS group ($P < 0.05$). Repeated measures analysis of variance confirmed difference over time on the SBP levels ($P < 0.05$). Our results showed that the process of allogeneic hUC-MSCs intravenous infusion was safe and the vital signs were stable, whereas a slight decrease in SBP was observed.

1. Introduction

In recent years, stem cell transplantation has emerged as a promising treatment, which is characterized by repairing injury, regulating immunity, and controlling inflammation. Mesenchymal stem cells (MSCs), a kind of adult stem cell, exert anti-inflammatory, immunomodulatory and pro-regenerative properties [1], were studied extensively for clinical applications. Up to now, MSCs have been proposed in more than 1000 clinical trials [2], which are administrated to patients with diabetes, Crohn's disease, bronchopulmonary dysplasia, multiple sclerosis, liver failure, chronic autoimmune urticaria, and so on.

MSCs can be isolated from umbilical cord blood and tissue, adipose tissue, placenta, and bone marrow [3–6]. In recent years, umbilical cord-derived MSCs (UC-MSCs) have received more attention due to their low immunogenicity and convenience of

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preparation. Over 60 clinical studies involving human umbilical cord-derived MSCs (hUC-MSCs) have been registered [7]. Various approaches, such as intravenous infusion, localized injection, intra-arterial injection, and intraperitoneal injection, have been exploited to transplant MSCs in different diseases. Intravenous infusion was utilized by many of the available clinical trials due to, probably, ease of operation and less invasion. At present, the clinical studies on MSCs-based therapy are mainly focused on the therapeutic efficacy and safety. To date, the safety evaluation of intravenous infusion of hUC-MSCs were focused on the immediate events (fever, acute infusional toxicity), acute and chronic system complications, infection, and longer term adverse events (malignancy, death) [8]. For example, Riordan et al. reported the mild inflammation, swelling, and/or redness at the infusion site in two subjects with autism spectrum disorder after allogeneic hUC-MSCs infusion [9]. Result from Zhang et al. showed that four of the forty-one patients with Crohn's disease experienced fever after hUC-MSCs infusion [10]. Other studies revealed no adverse reactions in patients with COVID-19, relapse remitting multiple sclerosis, neuromyelitis optica and primary immune thrombocytopenia after hUC-MSCs infusion [11–13]. However, the characteristics of dynamical changes in vital signs during hUC-MSCs infusion are largely unknown.

Some studies have shown that intravenous infusion may increase accumulation of MSCs within filtering organs such as the lung, liver, or spleen [14,15]. It is possible that MSCs become passively arrested in capillaries or microvessels including arterioles and postcapillary venules, which may alter blood flow [16,17] and increase the risk of thrombotic events, such as pulmonary embolism [18,19]. In this context, the aim of this study was to evaluate the safety and the dynamic changes of heart rate, respiratory rate, blood pressure, oxygen saturation (SpO_2) and temperature during hUC-MSCs infusion.

2. Materials and methods

2.1. Study design and participants

In 2020, the East Hospital Cell Therapy Registry (EHCTR) was launched to collect clinical characteristics of patients who underwent the cell therapy. Infusion related side effects, clinical response to the cell therapy, and disease outcomes were also recorded. In this study, a total of twenty participants with allogeneic hUC-MSCs transplanted were recruited (MSC group). The total number of hUC-MSCs for each participant was $60–80 \times 10^6$. In addition, twenty sex- and age-matched individuals with cardiovascular disease who treated with the equal volume of 0.9% normal saline (NS) after coronary angiography were also included (NS group) in this study. Participants with acute infection, heart failure, respiratory failure, hemorrhage, and shock were excluded. This study was approved by the Institutional Review Board of Shanghai East Hospital in accordance with the principles of the Helsinki Declaration [No.2020 (061)]. Written informed consent was obtained from each participant.

2.2. Allogeneic human umbilical cord mesenchymal stem cells

Human umbilical cord samples were collected from healthy pregnant women of Shanghai East Hospital, and written informed consent was obtained from every donor before sample collection. The protocol was reviewed and approved by the Ethics Committee of Shanghai East Hospital.

hUC-MSCs were prepared in accordance with current Good Manufacturing Practices (GMP) standards for clinical translation. The donor was screened for infectious diseases including human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), and syphilis. Umbilical cord was disinfected in 75% ethanol for two times, and the umbilical arteries and vein were removed. Umbilical cord was dissected into 3–4 cm small pieces, placed in a T75 flask (Thermo Fisher Scientific,156499), and incubated at 37 °C in a humidified tissue culture incubator containing 5% CO_2 and 95% O_2. After being cultured for 4–6 h, the αMEM (Gibco, C12571500BT) supplemented with 5% UltraGro-advanced (Helios, HPCFDCRL50) was added, with a change of culture medium every five days. After 10 days in culture, the cord pieces were removed from culture and the adherent cells were trypsinized (Tryple-Express, Gibco, 12604021) and passaged into a new flask for further expansion.

The Passage5 (P5) hUC-MSCs were sterile and qualified for aerobe, mycoplasma and endotoxin testing. The P5 hUC-MSCs were characterized by MSC markers with flow cytometry. The results showed that ≥95% of cells expressed CD73, CD90, CD105, while the expression of CD11, CD19, CD31, CD34, CD45 and HLA-DR was 2% or less. hUC-MSCs were evaluated for tumorigenicity and tri-lineage differentiation potential such as adipogenesis, chondrogenesis, and osteogenesis. Before the transplantation, the P5 hUC-MSCs were suspended in normal saline (containing 5% human albumin).

2.3. Study procedures

Demographic data from the participants were collected such as gender, age, personal histories of hypertension, diabetes, hyperlipidemia, cardiovascular disease, and disease of respiratory system. Each participant experienced a basic physical examination. Height and weight were measured with light clothes and bare feet. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Heart rate, respiratory rate, SpO_2, systolic and diastolic blood pressure were measured with Philips InterlliVue MX450. The oral temperatures were also measured.

According to National High Blood Pressure Education Program, hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg and/or taking an anti-hypertensive medication [20].

The infusion was from the participants' peripheral veins in the hand. The infusion rate was 15 drops/minute for the first 15 min and thereafter 60 drops/minute until the end of treatment. Heart rate, respiratory rate, SpO_2, systolic and diastolic blood pressure, and temperature were monitored at intervals of 15 min during infusion. In addition, adverse events including general disorders (e.g. fever, chills, rash, headache, chest pain, cough, dyspnea, pruritis and/or redness at the infusion site, abdominal distention, abdominal pain, diarrhea, nausea, vomiting, and confusion), infusional toxicity (e.g. embolism, anaphylaxis, pulmonary edema, and phlebitis), infection, organ dysfunction (e.g. arrhythmia, heart failure, and stroke), and death were recorded during infusion and within seven days after infusion. Clinical observation and management of adverse events were performed by experienced clinicians throughout the infusion.

2.4. Statistical analysis

Data were presented as mean (standard deviation), median (interquartile range), or number (%), as appropriate. The normality of continuous variables was assessed using the Shapiro–Wilk test. Continuous variables with approximately normal distribution were tested by student's t-test, while those with skew distribution were analyzed by Wilcoxon rank sum test and categorical variables were analyzed by Pearson's chi-squared test. For comparison of repeated measurement data, repeated measures analysis of variance (ANOVA) was performed with each vital sign as the dependent

variable and group as a between-subject factor in the analysis. In addition, the effect of time and the interaction between group and time was evaluated with repeated measures ANOVA. Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA). In addition, GraphPad Prism 8.0 software was used (San Diego, California, USA). All reported *P* values were two-tailed and $P \leq 0.05$ were considered statistically significant.

3. Results

3.1. Demographics

From September in 2020 to December in 2022, a total of forty participants (i.e. twenty participants with hUC-MSCs infusion and twenty sex- and age-matched participants with NS infusion) were including the final analysis. The demographic details and clinical characteristics of the participants were summarized in Table 1. Baseline characteristics including heart rate, respiratory rate, SBP, DBP, and temperature were comparable between two groups, except that the NS group had a higher SpO_2 ($P < 0.001$) and a higher occurrence of cardiovascular disease ($P < 0.001$) as seen in Table 1.

3.2. Adverse events

No obvious side effects including general disorders (e.g. fever, chills, rash, headache, chest pain, dyspnea, abdominal pain, diarrhea, vomiting, and confusion), infusional toxicity (e.g. embolism, anaphylaxis, pulmonary edema, and phlebitis), infection, and other adverse events were observed during and after infusion in both groups.

3.3. Characteristics of SBP and DBP within and between two groups during infusion

First, we analyzed the dynamical changes of blood pressure during infusion. Sixteen participants in the MSC group and seventeen participants in the NS group were normal blood pressure at baseline, respectively. The number of participants with sustained normal blood pressure in the MSC group during infusion was higher than that of the NS group (14/16 vs. 8/17, $P = 0.032$) (Table 2).

Next, we analyzed the changes from baseline of blood pressure during infusion. Compared with the baseline, the mean SBP levels were significantly decreased at 15min, 30min, 45 min, and 60min in the MSC group (all $P < 0.05$). In addition, SBP changed significantly from baseline in the MSC group when compared with the NS group at 15min (MSC group difference value -4.30 ± 7.81 vs. NS group difference value 1.85 ± 10.47, $P < 0.05$), 30min (MSC group difference value -4.70 ± 6.36 vs. NS group difference value 1.30 ± 7.85, $P < 0.05$), and 45min (MSC group difference value -5.35 ± 10.05 vs. NS group difference value 2.00 ± 11.84, $P < 0.05$) (Table 3, Fig. 1 d). Interestingly, our subgroup analysis in participants with cardiovascular disease revealed that SBP was also significantly reduced at 15min in the MSC group during infusion when compared with the NS group (Supplementary Table S1, Table S2, Table S3).

There was no significant change from baseline in DBP at each point of time in the MSC group compared with the NS group (Table 3).

Repeated measures ANOVA confirmed difference over time on the SBP (group, $F = 3.23$, $P = 0.080$; time, $F = 2.44$, $P = 0.049$; group * time, $F = 2.04$, $P = 0.091$). There were no effects of interaction between time and group on the SBP and DBP (Table 4).

3.4. Characteristics of SpO_2 within and between two groups during infusion

The mean SpO_2 value at each point of time was above 95% during infusion in both groups (Fig. 1 f).

The level of SpO_2 value in the NS group was higher than that of the MSC group during infusion. However, change from baseline in SpO_2 at each point of time was not significant in the MSC group compared with the NS group (Table 3, Fig. 1 f).

Repeated measures ANOVA confirmed difference between two groups on the SpO_2 (group, $F = 6.04$, $P = 0.019$; time, $F = 0.87$, $P = 0.484$; group * time, $F = 1.39$, $P = 0.242$). Furthermore, there was no effect of interaction between time and group on the SpO_2 (Table 4).

3.5. Characteristics of temperature within and between two groups during infusion

The mean temperature value at each point of time was below 37.0 °C during infusion in both groups (Fig. 1 c).

Temperature changed significantly from baseline in the MSC group compared with the NS group at 45min (MSC group difference value -0.04 ± 0.14 vs. NS group difference value 0.10 ± 0.26, $P < 0.05$). The mean temperature value was significantly increased at 60min compared with the baseline ($P < 0.05$) in the NS group (Table 3, Fig. 1 c).

Repeated measures ANOVA showed no effect of interaction between time and group on the temperature (Table 4).

Table 1
Clinical characteristics of the MSC group and NS group.

Demographics	MSC group n = 20	NS group n = 20	*P*
Age, years, mean (SD)	57.15 (8.69)	61.60 (11.65)	0.179
Gender, no. of male (%)	16 (80)	12 (60)	0.173
BMI, kg/m^2, mean (SD)	25.69 (3.75)	25.24 (2.87)	0.677
Baseline respiratory rate,/min, median (Q1, Q3)	18 (18, 20)	19 (18, 19)	0.718
Baseline HR, bpm, median (Q1, Q3)	72.5 (69.5, 79.5)	78.5 (74.0, 84.0)	0.233
Baseline SBP, mmHg, mean (SD)	129.70 (11.76)	131.00 (7.17)	0.675
Baseline DBP, mmHg, mean (SD)	80.30 (9.22)	79.05 (7.48)	0.641
Baseline SpO_2, %, median (Q1, Q3)	97 (96, 98)	100 (99, 100)	**<0.001**
Baseline T, °C, median (Q1, Q3)	36.80 (36.40, 37.00)	36.50 (36.50, 36.60)	0.134
Diagnoses, n (%)			
Diabetes Mellitus	8 (40)	5 (25)	0.317
Hypertension	6 (30)	11 (55)	0.114
Hyperlipidemia	2 (10)	3 (15)	0.637
Cardiovascular Disease	4 (20)	18 (90)	**<0.001**
Disease of respiratory system	4 (20)	1 (5)	0.157

BMI body mass index, DBP diastolic blood pressure, HR heart rate, MSC mesenchymal stem cell, NS normal saline, Q1 lower quartile, Q3 higher quartile, SBP systolic blood pressure, SD standard deviation, SpO_2 oxygen saturation, T temperature.

Table 2
The changes of blood pressure from normal baseline in two groups during infusion.

	MSC group n = 16	NS group n = 17	P[a]
Sustained normal (%)	14 (87.50)	8 (47.06)	0.032
Transient abnormal elevation (%)	2 (12.50)	7 (41.18)	
Sustained abnormal elevation (%)	0 (0.00)	2 (11.76)	

MSC mesenchymal stem cell, NS normal saline.
[a] Computed by Fisher's exact test.

3.6. Characteristics of heart rate and respiratory rate within and between two groups during infusion

The median respiratory rate and the mean heart rate were in the normal range at each point of time throughout the infusion in both groups (Fig. 1 a, b).

The heart rate and the respiratory rate did not change significantly from baseline at each point of time between two groups. The mean heart rate was significantly decreased at 30 min compared with the baseline ($P < 0.05$) in the MSC group (Table 3, Fig. 1 b).

There were no effects of interaction between time and group on the heart rate and the respiratory rate (Table 4).

4. Discussion

In this study, no adverse events were observed during and after the allogeneic hUC-MSCs infusion which suggested that the approach of allogeneic hUC-MSCs intravenous infusion was safe. Our study demonstrated that the SBP rather than DBP was reduced (approximately 3.75–5.35 mmHg) during hUC-MSCs infusion. Nine of seventeen participants (52.94%) with normal blood pressure at baseline occurred hypertension during infusion in the NS group, which were higher than that of the MSC group (2/16, 12.5%). With

Table 3
Vital Sign Changes from baseline of two groups.

	Group	15min	30min	45min	60min
SBP, mmHg	MSC	−4.30 (7.81) [a]	−4.70 (6.36)[a]	−5.35 (10.05) [b]	−3.75 (9.40)
	NS	1.85 (10.47)	1.30 (7.85)	2.00 (11.84)	0.60 (8.86)
DBP, mmHg	MSC	−0.85 (5.22)	−3.40 (7.56)	−3.25 (8.45)	−1.95 (7.21)
	NS	−1.30 (5.43)	−0.70 (5.04)	−1.00 (7.93)	−1.30 (7.41)
T, °C	MSC	−0.07 (0.25)	−0.02 (0.17)	−0.04 (0.14) [a]	0.01 (0.13)
	NS	0.00 (0.17)	0.03 (0.19)	0.10 (0.26)	0.13 (0.24)
SpO_2, %	MSC	0.15 (1.09)	−0.05 (1.05)	−0.30 (0.80)	−0.40 (0.94)
	NS	−0.05 (0.89)	0.20 (0.70)	−0.25 (1.02)	0.05 (1.00)
Respiratory rate,/min	MSC	−0.05 (1.32)	−0.15 (0.81)	−0.25 (1.07)	−0.20 (1.44)
	NS	0.30 (0.92)	0.10 (0.97)	0.00 (0.92)	0.10 (1.29)
HR, bpm	MSC	−1.65 (4.72)	−2.10 (4.15)	−1.25 (5.10)	−1.35 (4.61)
	NS	0.55 (3.55)	0.15 (4.56)	−0.45 (4.98)	−1.15 (5.11)

DBP diastolic blood pressure, HR heart rate, MSC mesenchymal stem cell, NS normal saline, SBP systolic blood pressure, SpO_2 oxygen saturation, T temperature.
Vital Sign Changes from baseline are described as mean (standard deviation).
[a] Compared with NS group, Wilcoxon rank sum test showed $P < 0.05$.
[b] Compared with NS group, independent sample t test showed $P < 0.05$.

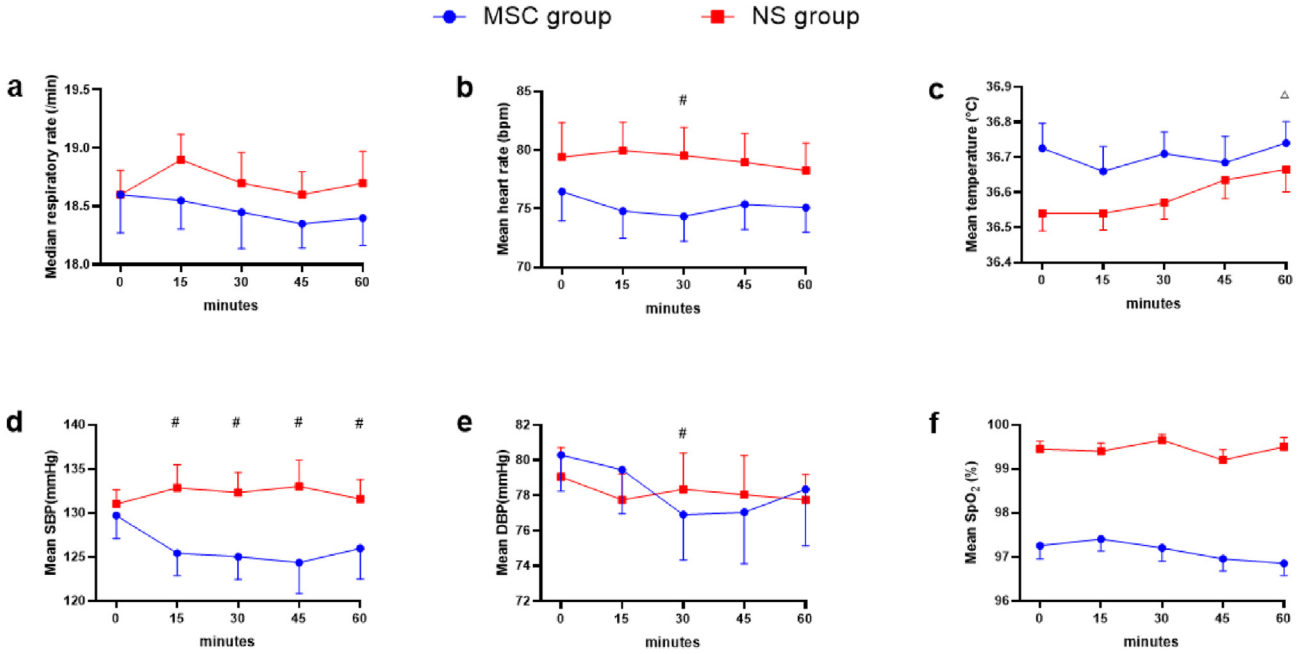

Fig. 1. Vital signs through 60 min according to the groups. Data were shown as median or mean. I bars indicated standard errors. Data of vital signs including respiratory rate, heart rate, temperature, SBP, DBP, and SpO_2 at each point of time during infusion in two groups were described in a, b, c, d, e, and f, respectively. The data in MSC group were color-coded "blue circle" and the data in NS group were color-coded "red square". # indicated significant difference compared with the baseline in MSC group ($P < 0.05$). △ indicated significant difference compared with the baseline in NS group ($P < 0.05$). DBP diastolic blood pressure, MSC mesenchymal stem cell, NS normal saline, SBP systolic blood pressure, SpO_2 oxygen saturation.

Table 4
Comparison of vital signs with-in and between two groups.

Variables	Source	*F*	*P*
SBP, mmHg	group	3.23	0.080
	time	2.44	**0.049**
	time*group	2.04	0.091
DBP, mmHg	group	0.01	0.939
	time	1.14	0.339
	time*group	0.69	0.600
SpO_2, %	group	6.04	**0.019**
	time	0.87	0.484
	time*group	1.39	0.242
T, °C	group	2.27	0.140
	time	0.87	0.484
	time*group	1.39	0.242
Respiratory rate,/min	group	0.64	0.429
	time	0.31	0.872
	time*group	0.33	0.859
HR, bpm	group	1.54	0.222
	time	1.46	0.218
	time*group	1.35	0.253

HR heart rate, DBP diastolic blood pressure, SBP systolic blood pressure, SpO_2 oxygen saturation, T temperature.

blood pressure controlled by a combination of cardiac output and vascular resistance, imbalance of either or both two variables can give rise to hypotension or hypertension. Compared with DBP, SBP is more appropriate to be used as a predictor of cardiovascular mortality and morbidity [21,22]. Interestingly, an in vivo study reported that the spontaneously hypertensive rats receiving bone marrow-derived MSCs with endothelial growth medium showed a reduction in blood pressure without altering heart rate [23]. Studies showed that MSCs had an elevated capacity to secret many bioactive factors, such as fibroblast growth factor-2, vascular endothelial growth factor, placental growth factor, hepatocyte growth factor [24], which could regulate vasomotion. An in vitro study found that hepatocyte growth factor inhibited the release of endothelin-1, a potent vasoconstrictor [25]. Grover et al. found that the pulmonary arteries of fetal lambs receiving the vascular endothelial growth factors occurred acute vasodilation [26]. Another study reported that hydrogen sulfide, an endogenously secreted from hUC-MSCs [27], promoted dilation of ex vivo mesenteric arteries from mice [28]. These evidences suggested that bioactive factors secreted by MSCs had a vasodilatory effect. Considering the unchanged heart rate and respiratory rate in our study, the reason of the SBP reduction may result from the MSCs-related vasodilation. We also noticed a decrease in SBP during the infusion of allogeneic hUC−MSCs in participants with cardiovascular disease. Currently, MSCs are receiving extensive attention as a potential treatment for cardiovascular disease. The primary therapeutic advantages of MSCs for cardiovascular disease encompass enhanced left ventricular fraction and endothelial function, as well as diminished fibrosis in scarred tissues. These improvements are attributed to factors like immune response modulation and paracrine signaling [29–32]. Increased endothelial function can consequently result in improved vasomotor responses, such as enhanced vasodilation [33]. However, the specific mechanisms underlying the observed reduction in SBP during allogeneic hUC-MSCs intravenous infusion remain unclear. Further research is needed to understand these mechanisms.

In our study, we found that the SpO_2 values in the NS group were higher than the MSC group. Nevertheless, the SpO_2 values were in the normal range and no anoxic symptoms were happened throughout the hUC-MSCs infusion. It should be noted that the participants in the NS group received the oxygen via nasal cannula after coronary angiography. A study reported that the oxygen saturation increased in participants who received oxygen via nasal cannula for 30 min when compared with the no oxygen enhancing group [34].

In this study, we also found that there was no fever in the participants throughout the hUC-MSCs infusion. One meta-analysis reported that there was a significant association between MSCs and transient fever but no significant increased risk of infection for the MSCs as compared to the control group [8]. The mechanisms for fever are not clear but could be related to the preparations of MSCs. First, the use of dimethylsulfoxide as a cryopreservative has been a potential concern with MSCs therapy to have toxic side effects and can cause hypersensitivity reactions [35]. Second, the use of fetal bovine serum for culturing MSCs has been criticized for potentially introducing zoonotic contamination and also potentially increasing the immunogenicity of the MSCs [36]. However, our study confirmed that the use of human albumin and the absence of the cryopreservation during the preparations of hUC-MSCs could be the important reasons to reduce the risk of fever.

However, this study have some limitations. Firstly, this study is a single-center, nonblinded, observational study, and the sample size is small. Secondly, the observation only focuses on the process of allogeneic hUC−MSCs intravenous infusion and further double-blind, large sample, and prospective studies are needed to evaluate the long-term safety associated with hUC-MSCs infusion. Thirdly, this study showed a slight decrease in SBP during the allogeneic hUC-MSCs intravenous infusion. However, we did not measure hypertension-related hormones in this study, which is an area that would be valuable to explore further.

5. Conclusions

Despite a slight decrease in SBP was observed during the allogeneic hUC-MSCs intravenous infusion in our study, heart rate, respiratory rate, DBP, SpO_2, and temperature were not changes. In addition, no adverse events were observed during and after the allogeneic hUC-MSCs infusion. Further studies with follow-up will be required to clear the specific mechanism of the MSCs -related SBP reduction.

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Authors' contributions

All authors were involved in data interpretation, participated in manuscript preparation, and approved the final version for submission. In addition, Zhongmin Liu and Congrong Wang performed study design; Yue Wang, Congrong Wang, and Haiping Yu planned the initial draft of the manuscript; Jinfang Xu assisted with data analyses; and Rong Zhu, Yiqi Shi, Changqin Xu, Yan Li, Hua Wang, Peichen Shen, and Yue Wang were involved in study conduct and data acquisition.

Ethics approval and consent to participate

All participants provided informed consent. This study was approved by the Institutional Review Board of Shanghai East Hospital in accordance with the principles of the Helsinki Declaration [No.2020 (061)].

Consent to publish

Consent to publish has been received from all participants.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.reth.2023.07.007.

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