




BMJ Open Efficacy of umbilical cord mesenchymal stem cell transfusion for the treatment of severe AKI: a protocol for a randomised controlled trial

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ABSTRACT

Introduction Acute kidney injury (AKI) is a common and severe clinical problem that is associated with high mortality, a long hospital stays and high healthcare resource consumption. Approximately a quarter of AKI survivors will develop chronic kidney disease. Mesenchymal stem cells (MSCs) are multipotent stem cells with antiapoptotic, immunomodulatory, antioxidative and proangiogenic properties. Therefore, MSCs have been considered as a potential new therapy for the treatment of AKI. Several clinical trials have been performed, but the results have been inconsistent. This trial investigated whether MSCs can improve renal recovery and mortality in patients with severe AKI.

Methods and analysis One hundred subjects suffering from severe AKI will participate in this patient-blinded, randomised, placebo-controlled, parallel design clinical trial. Participants will be randomly assigned to receive two doses of MSCs or placebo (saline) on days 0 and 7. Urinary biomarkers of renal injury and repair will be measured using commercially available ELISA kits. The main outcome measures are changes in renal function levels within the first 28 days following MSC infusion.

Ethics and dissemination The study was approved by the Ethics Committee of the Chinese PLA General Hospital. The findings of the study will be disseminated through public and scientific channels.

Trial registration number NCT04194671.

INTRODUCTION

Acute kidney injury (AKI) is a global public health issue characterised by a sudden loss of kidney function, which has an important impact on morbidity and mortality.^{1–3} Higher serum creatinine is associated with an increased risk for mortality in patients with AKI. Patients with severe AKI, that is, those with either a doubling of baseline creatinine within 48 hours or a urine output of less than 0.5 mL/kg/hour for more than 12 hour, are more likely to die than patients with mild AKI.^{4–6} A variety of factors, such as surgery, hypoxia, drugs, sepsis, inflammation,

Strengths and limitations of this study

- The main strength of our study is the number of treatments (two infusions), which may improve the efficacy of mesenchymal stem cells.
- The second strength is the rigorous design of inclusion and exclusion criteria for severe acute kidney injury to minimise sample heterogeneity to the greatest extent.
- The third strength is that our primary outcome measure is an objective measure of creatinine during the intervention period and follow-up periods to assess the change in renal function.
- A major limitation of this study lies in a small sample size due to the nature of exploratory clinical trials.

mechanical trauma, catheter-based interventions,⁷ haemodynamic instability and post-transplantation procedures, can cause AKI.⁸ AKI is mainly caused by ischaemia-reperfusion injury (IRI), infection, and drugs and AKI may progress to chronic kidney disease (CKD) or even end-stage renal disease.^{9 10} Approximately, 25% of AKI survivors will develop CKD.¹¹ The effects of treatments for AKI, including symptomatic and supportive treatments, remain insufficient. Therefore, it is important to develop an effective treatment strategy for treating severe AKI.

The pathogenesis of AKI includes acute tubular injury, reactive oxygen species (ROS) generation, inflammatory response activation, tubular epithelial cell apoptosis, inflammatory cell infiltration and extensive release of proinflammatory cytokines.^{12–16} Therefore, reducing the immune response and ameliorating kidney tissue damage is a potential therapeutic approach for AKI.

Mesenchymal stem cells (MSCs) have been used in cell-based therapies for many human diseases.¹⁷ The therapeutic effects of MSCs

Table 1 The characteristics of all clinical trials registered at clinicalTrial involving MSC-treated AKI

Registration number	Status	Study title	Interventions	Country
NCT01275612	Withdrawn	Mesenchymal stem cells in cisplatin-induced acute renal failure in patients with solid organ cancers	MSC infusion	Italy
NCT00733876	Completed	Allogeneic multipotent stromal cell treatment for acute kidney injury following cardiac surgery ²⁶	Multipotent stromal cells	USA
NCT01602328	Terminated	A study to evaluate the safety and efficacy of ac607 for the treatment of kidney injury in cardiac surgery subjects ²⁷	AC607	USA
NCT03015623	Active, not recruiting	A study of cell therapy for subjects with acute kidney injury who are receiving continuous renal replacement therapy ²⁹	SBI-101	USA
NCT04194671	Not yet recruiting	Clinical trial of mesenchymal stem cells in the treatment of severe acute kidney injury	Mesenchymal stem cells	China
NCT04445220	Recruiting	A study of cell therapy in COVID-19 subjects with acute kidney injury who are receiving renal replacement therapy	SBI-101	USA

AC607, a kind of allogeneic MSCs products; AKI, acute kidney injury; MSC, mesenchymal stem cell; SBI-101, an extracorporeal stromal cell therapeutic.

are due to paracrine effects. MSCs have been proposed to have immunomodulatory, anti-inflammatory, antioxidative, antiapoptotic and reparative properties.^{18 19} MSCs significantly attenuate acute IRI in an animal model.^{20–25} Therefore, the clinical application of MSCs for AKI treatment is promising.¹⁷

Several clinical studies have been conducted (table 1).^{26–29} The results from clinical trials of MSC therapy for AKI following cardiac surgery suggested that MSC therapy prevented the deterioration of renal function after cardiac operation, reduced hospital stay and the need for readmission and improved long-term outcomes of renal function.^{26 28} However, another clinical trial demonstrated that allogeneic MSC transfusion after cardiac surgery did not decrease the time to recovery of kidney function.²⁷ Given that it is still not known whether MSCs can improve the renal function of patients with AKI and because severe AKI has a high mortality, these results prompted us to design a randomised clinical trial (RCT) to test the safety and efficacy of MSC therapy for AKI.

METHODS AND ANALYSIS

Study design

We designed a patient-blinded, randomised, parallel placebo-controlled clinical trial among patients with severe AKI; we will randomly assign patients to receive either MSCs at a dose of 1×10^6 cells/kg or placebo at day 0 and day 7. The total number of cells will be no more than 1×10^8 per person. This single-centre study will be conducted in the Department of Nephrology, the First Medical Centre, Chinese PLA General Hospital, Chinese PLA Institute of Nephrology, Beijing, China. An overview of the study is presented in figure 1. Any methodological changes in the study design or sample size, which may potentially affect the patients' safety or efficacy results, will be validated by the ethics committee before implementation.

Study participants

Participants who meet the following criteria will be included: (1) severe AKI, defined as a more than twofold increase in serum creatinine level compared with baseline creatinine level within 48 hours and/or urinary output consistently $<0.5 \text{ mL/kg/hour}$ over 12 hours; the lowest serum creatinine value in the 3 months preceding inclusion was taken as the baseline value. If data are not available, the serum creatinine baseline value was estimated using the Modification of Diet in Renal Disease study (MDRD) equation assuming that estimated glomerular filtration rate (eGFR) was $75 \text{ mL/min} \times 1.73 \text{ m}^2$; (2) age between 18 and 65 years; (3) willingness to give written informed consent or having a legally acceptable representative willing to provide consent and (4) ability to comply with procedures and study visit schedule, including post-discharge follow-up.

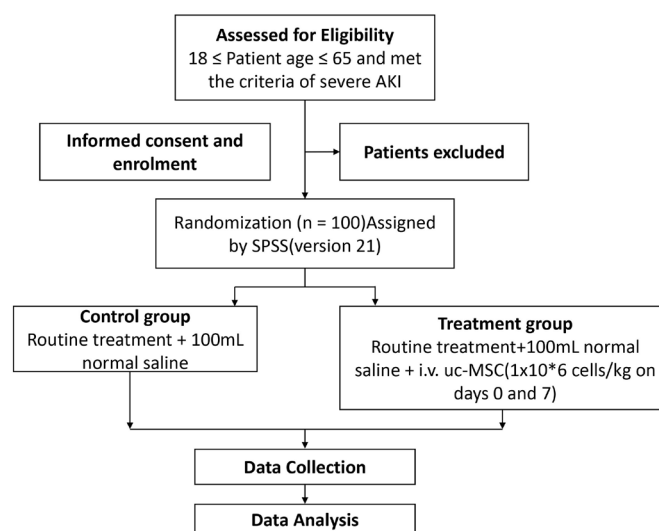


Figure 1 Flowchart of the efficacy of uc-MSC transfusion for patients with severe AKI. AKI, acute kidney injury; uc-MSC, umbilical cord mesenchymal stem cell.

Participants who meet any of the following criteria will be excluded: (1) AKI due to renal obstruction, glomerulonephritis, lupus nephritis, antineutrophil cytoplasmic antibody-related nephritis, antiglomerular-basement membrane antibody-mediated nephritis, cryoglobulinemia, thrombotic microangiopathy and purpura nephritis; (2) pregnancy or lactation; (3) allergic constitution; (4) previous haematopoietic stem cell transplantation or solid organ transplantation; (5) a history of benign or malignant tumours; (6) life expectancy less than 3 months; (7) known end-stage liver disease; (8) uncontrollable infection; (9) aged younger than 65 years old with an eGFR less than 60 mL/min/1.73 m²; (10) severe pulmonary dysfunction; (11) severe cardiac dysfunction, left ventricular ejection fraction less than 40%, or severe arrhythmia; (12) haemodynamic instability; (13) organ failure affecting more than two non-renal organs; (14) vasculitis of any cause; (15) a history of chronic systemic infection of any cause; (16) investigator belief that the subject may need to increase the vasopressor dose to achieve and/or maintain haemodynamic stability; (17) systemic immunosuppressive therapy that has not been stabilised for more than 4 months, or, in the case of chronic corticosteroid therapy, a dose of >15 mg/day of prednisone or the equivalent within the past 30 days; (18) platelet count <25 000/μL or other severe haematological abnormalities causing the subject to be at risk of death; (19) mechanical ventilation requirements and (20) participation in other clinical trials.

Ethics and informed consent

The current trial was approved by the Ethics Committee of the Chinese PLA General Hospital in April 2019 (file number: S2019-067-01). This study is registered at ClinicalTrials.gov. Informed consent (see online supplemental file 1) received prior to study inclusion by the investigating physician is required for this type of study according to Chinese law. Precautions will be taken to ensure the confidentiality of participants' information during and after the clinical study.

Randomisation and allocation concealment

The present study will be a patient-blinded parallel RCT. Subjects will be numbered in chronological order. A random number sequence generated by SPSS V.21.0 before study commencement will be used for patient randomisation. These generated numbers will be stored in opaque sealed envelopes which are sequentially numbered, and once generated, the list will remain unchanged. Independent drug administrators will store the envelopes, which will be concealed from participants and care providers until data analyses. Patients will be randomised 1:1 to either the MSC treatment group or the placebo control group according to their assigned random number.

Intervention

The recruitment of participants will take place in the Department of Nephrology of the Chinese PLA General Hospital. Investigators will explain the study protocol to potential participants in detail. If the patient decides to participate in this study, they will be required to sign a consent form. The efficacy and safety of MSCs will be compared between the treatment group and the control group. The control group will receive only 100 mL normal saline, while the treatment group will receive MSCs+100 mL normal saline. Patients in both groups will receive conventional therapy as recommended by the attending physician according to the KDIGO Clinical Practice Guideline for AKI, including the removal of reversible causes, the maintenance of a stable internal environment, nutritional support, anti-infective treatment, the prevention and treatment of complications, rehydration and renal replacement therapy (RRT). Passage 4 umbilical cord MSCs (uc-MSCs) will be used. These MSCs will be manufactured by a Good Manufacturing Practice-certified company in China (Regend Therapeutics). Patients in the treatment group will receive two intravenous infusions at a dose of 1×10^6 cells/kg on days 0 and 7. The maximum dose of MSCs per person will not exceed 1×10^8 cells. The length of the infusion will be more than 30 min. During the infusion, vital signs will be monitored continuously. The timing of treatment will be as soon as possible, and ideally within 72 hours of a clinical diagnosis of severe AKI. We will allocate other medications continuously used to treat concurrent diseases, and their volume and dosing will remain unchanged throughout the therapeutic intervention. Medication administration will be recorded in a case report form (CRF). The criteria for discontinuing the allocated interventions for a given trial participant were: (1) serious adverse events (SAEs); (2) serious deviations occurred in implementation and (3) China Food and Drug Administration's suspension of trials for some reason.

Blinding

Similar opaque infusion bags with different marks and black infusion lines will be used for both groups to ensure identical appearances. Independent drug administrators who receive group information based on the random number will inform dosing nurse and investigators responsible for recruiting participants of the group allocation. Then, the mixture of drugs will be prepared, and the bags will be labelled as A or B by the dosing nurse in a separate room. The participants will be blinded to the intervention allocation and the statistical analysts. Investigators and the clinical team looking after the patient (doctors, nurses and so on) are unblinded. Unblinding conditions are only permissible in case of medical emergency.

Study outcomes

The primary outcome is the difference in the renal function (creatinine) between the two groups (MSC treatment group vs placebo control group) within 28 days after

receiving MSC/placebo treatment. These lab measurements were analysed at the Central Clinical Chemistry Laboratory, Chinese PLA General Hospital.

The secondary endpoints are as follows:

1. Overall survival within 28 days after receiving MSC/placebo treatment.
2. Overall survival within 3 months after receiving MSC/placebo treatment.
3. Dependence on RRT within 3 months after receiving MSC/placebo treatment.
4. Complete renal recovery within 3 months after receiving MSC/placebo treatment (complete recovery refers to survival, free of RRT and the serum creatinine (SCR) decreased to no more than 1.5 times of the baseline level. Baseline creatinine was defined as the lowest serum creatinine value in the 3 months preceding inclusion; if data are not available, the serum creatinine baseline value was estimated using the MDRD equation assuming that eGFR was $75 \text{ mL/min} \cdot 1.73 \text{ m}^2$).
5. Partial renal recovery within 3 months after receiving MSC treatment (partial recovery refers to survival, free of RRT and the SCR 1.5 times higher than the baseline level of creatinine).
6. ICU and hospitalisation duration of stay among survivors and those who died within 3 months after receiving MSC treatment.
7. Adverse events within 3 months after receiving MSC treatment.

Follow-up

The trial follow-up schedule is shown in [table 2](#). At the screening stage, the study participants will undergo assessment for the inclusion and exclusion criteria alongside a full medical history and physical examination. Follow-up visits will be conducted during hospitalisation and after discharge. In the intervention period (days 0–28), data will be recorded at 1, 3, 7, 14 and 28 days. After discharge, follow-up will take place during outpatient clinic visits at

Table 2 Follow-up schedule and assessments

	Enrolment	Intervention (28 days)						Follow-up		
	Admission	D 0	D 1	D 3	D 7	D 14	D 28	M 2	M 3	Y 3
Medical history-taking	X									
Physical examination	X	X	X	X	X	X	X	X	X	
Screening, entry standard audit	X									
Informed consent	X									
Randomisation	X									
Blood routine	X		X	X	X	X	X	X	X	
Blood biochemistry	X		X	X	X	X	X	X	X	
Urine test	X		X	X	X	X	X	X	X	
Coagulation function	X									
Serology tests	X									
Cardiac markers	X									
ECG	X									
MSC infusion	X				X					
PRA	X						X			
Tumour marker	X									
Sample collection	X			X	X		X			
SOFA	X									
APACHEII	X									
Risk factor assessment	X									
Aetiology assessment	X									
Concomitant diseases	X									
Renal replacement therapy	X	X	X	X	X	X	X			
Blood transfusion	X	X	X	X	X	X	X			
AEs and handling	X	X	X	X	X	X	X	X	X	
Tumorigenesis										X

AEs, adverse events; APACHE II, Acute Physiology and Chronic Health Evaluation II; MSC, mesenchymal stem cell; PRA, panel-reactive antibody; SOFA, Sequential Organ Failure Assessment.

2 months and 3 months for both study groups. We will establish contact via telephone and ask whether tumours occurred after hospital discharge for 3 years.

Blood and urine sample collection

Urine and blood samples for the biomarker assay will be collected at enrolment and on days 3, 7 and 28. The samples will be frozen at -80°C immediately after processing until use. We plan to use these samples to detect kidney injury biomarkers, renal repair biomarkers, inflammatory markers, immunomodulatory factors and fibrosis markers.

Sample size

Due to the exploratory nature of the study, no sample size calculation was performed. Assuming a 20% dropout rate, the final sample size is set to 50 participants in each group.

Clinical assessments and data collection

Clinical information, including age, medical history, comorbidities, Sequential Organ Failure Assessment score, Acute Physiology and Chronic Health Evaluation II score and the severity of AKI, will be documented within the clinical information system of the hospital after enrolment. The type and duration of RRT, the use of vasoactive drugs and the number of blood products will be recorded at all interviews from the beginning of the study by the investigating physician. Vital signs, including breathing, body temperature, pulse, blood pressure and adverse events, used for safety assessment, will be measured during human MSC infusion. Any adverse events, such as fever, itching, headache, vomiting and weakness, will be reported to the Medical Ethics Committee of the Chinese PLA General Hospital within 15 days.

Routine blood, urine test, biochemical, renal function (serum creatinine, blood urea nitrogen and cystatin C (CysC) levels), panel-reactive antibody, cardiac markers (creatinine kinase, lactate dehydrogenase, phosphocreatine kinase isoenzyme), blood coagulation, ECG, tumour marker and serological tests will be performed. These routine lab measurements were analysed at the Central Clinical Chemistry Laboratory, Chinese PLA General Hospital.

For cases withdrawn from the study or dropped out for follow-up, the investigator should actively take measures to complete the last test as much as possible in order to analyse its efficacy and safety and take corresponding treatment measures. For all dropped cases, we will document the reason for the case drop on the CRF.

Confidentiality

Information will be entered into a standardised electronic CRF from the clinical information system of the hospital, stored in Department of Nephrology, the First Medical Centre, Chinese PLA General Hospital with a password protected hard disk. All data will be handled and processed anonymously to ensure the confidentiality

of the individuals. Only the researchers will have access to the final trial dataset.

Statistical analysis

Statistical analyses will be performed using SPSS V.21. If the disease progressed rapidly after randomisation so that the patient receives only one infusion or no infusion, we will still include them for the primary analysis, as allocation to MSC treatment or placebo control arm could influence the likelihood that patients receive a transfusion. Continuous variables will be summarised as means with SD if normally distributed and medians with first and third quartiles otherwise. We will use the one-sample Kolmogorov-Smirnov test to check whether the data are normally distributed. For the effectiveness analysis, missing data will be imputed using last observation carried forward, and for patients with missing data due to death, missing data will be imputed using the worst possible value (in the dataset). For the safety analysis, it will be conducted with the raw data. Because of the small sample sizes, we considered subgroup analyses were less suitable in the present study. We planned no subgroup analyses prespecified based on baseline characteristics. However, a posthoc subgroup analysis will only be analysed if there was no difference between the two groups, in order to provide the basis for our next research. Due to the exploratory nature of the study, a forInterventionsmal data monitoring committee or interim analyses were not considered. However, data monitoring will be conducted by the research team regularly.

For continuous variables, such as hospital length of intensive care unit (ICU) stay and total hospital length of stay, we will use non-parametric tests to analyse the differences between groups. Continuous variables such as creatinine, GFR, CysC, urine volume, urea nitrogen and all kinds of biomarkers are repeat-measurement data. We will develop a statistical analysis plan in consultation with a statistician, taking into account the repeated nature of the measurements. Data for categorical variables, including the survival of patients with severe AKI at 28 days and 3 months after receiving MSC, RRT dependence at 3 months, complete recovery rate, partial recovery rate and the incidence of adverse events, will be presented as proportions and compared using a χ^2 test.

Patient and public involvement

The development of the research questions and outcome measures were not informed by patients' priorities, experience or preferences. Patients and public will not be involved in the design nor recruitment and conduct of study. Results will be disseminated to all study participants after study completion. The burden of the intervention was not assessed by the patients themselves.

Safety consideration

All necessary procedures and precautions will be taken to maximise participant safety. First, patients with higher potential risks will be excluded based on the exclusion



criteria. Second, an infusion time of more 30 min was chosen to minimise the risk of infusion-related adverse effects. Third, during the infusion, vital signs will be continuously monitored. Fourth, once an adverse event occurs, SAEs considered to be related to the study procedure will be submitted to the principal investigator within 24 hours and to the ethics committee within 15 days of the completion of treatment. Then, the ethics committee will report the event to the Food and Drug Administration and the Provincial Health and Family Planning Commission of China. The patient will be followed up until the event has stabilised. No independent auditing of trial conduct is planned.

ETHICS AND DISSEMINATION

The study protocol and trial documents including the consent form and participant information sheet have been approved by the Ethics Committee of the Chinese PLA General Hospital. The findings of the study will be disseminated through scientific peer-reviewed journals as well as research conferences.

DISCUSSION

Severe AKI is associated with high mortality in patients. MSC therapy has shown the most attractive results in both preclinical and clinical research. At present, there are only three clinical trials registered in ClinicalTrials.gov of MSCs in the treatment of severe acute renal injury. Two of them have been completed, and one is recruiting subjects. Due to the opposite conclusions of the two trials and scarce evidence, more clinical trials are required to verify these inconsistent conclusions. Our study was designed to define the effects of uc-MSCs on severe AKI.

A strength of this study is that we will include only patients with AKI caused directly by renal tubular epithelial cell damage, and not those with AKI caused by glomerular or vascular disease, to ensure the homogeneity of the study sample. We will also exclude patients who are severely ill due to damage to other organs that may aggravate the patient's condition and possibly result in a higher mortality rate, which may mask the genuine action of MSCs.

A novel aspect of this study is the two intravenous infusions of MSCs on days 0 and 7. When cells are injected into an injured environment, they face a harsh internal environment, including ROS and anoikis, which contribute to MSC apoptosis.^{30–32} Additionally, cell accumulation in the lung, liver and spleen leads to a small number of cells surviving to engraft injured kidneys. Due to the high risk of pulmonary embolism in bed-ridden patients, who are too ill to receive a large volume of cells that could accumulate in the lungs, a dose of 10^6 MSCs per 1 kg will be used in this trial, which is half the number administered in other clinical trials. At the same time, considering the need for a sufficient dose of cells, an additional infusion will be conducted to increase the possibility of a good

curative effect. MSCs will be administered by intravenous infusion, which is different from previous research. Compared with arterial infusion, intravenous infusion is more convenient and more easily accepted by patients.

Finally, our primary outcome measure is an objective measure of creatinine during the intervention period and follow-up periods to assess the change in renal function. The selection of these objective measures will make it possible to monitor continuous and dynamic changes in renal function and differences between the two groups.

However, the main limitation of our trial should be noted. A small sample size due to the nature of exploratory clinical trials needs to be further explored in the future.

TRIAL STATUS

Patient recruitment started on 31 December 2021 and will be completed on 31 December 2022.

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