Nephroprotective effect of mesenchymal stem cells in therapy of kidney disease induced by toxicant

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Abstract

Background

Renal damage caused by drug toxicity is becoming more and more common in clinic. How to avoid and treat kidney damage caused by drug toxicity is essential to maintain patient health and reduce social economic burden. In this study, we performed a meta-analysis to assess the nephroprotective effect of mesenchymal stem cells (MSCs) in therapy of kidney disease induced by toxicant.

Methods

Cochrane Library, Embase, ISI Web of Science and PubMed databases were searched up to Dec 31, 2019 to identify the studies and extract the data to assess the efficacy of MSCs for kidney disease induced by toxicant using Cochrane Review Manager Version 5.3.

Results

27 studies were eligible and recruited for this meta-analysis. The results showed that the difference of Scr between MSCs treatment group and control group was notable for 2 days, 4 days, 5 days, 6–8 days, 10–15 days, ≥ 42 days (2 days: WMD = -0.88, 95%CI: -1.34, -0.42, $P = 0.0002$; 4 days: WMD = -0.69, 95%CI: -0.99, -0.39, $P < 0.00001$; 5 days: WMD = -0.46, 95%CI: -0.67, -0.25, $P < 0.0001$; 6–8 days: WMD = -0.51, 95%CI: -0.79, -0.22, $P = 0.0005$; 10–15 days: WMD = -0.38, 95%CI: -0.56, -0.20, $P < 0.0001$; ≥ 42 days: WMD = -0.22, 95%CI: -0.39, -0.06, $P = 0.007$). Furthermore, the difference of BUN between MSCs treatment group and control group was notable for 2–3 days, 4–5 days, 6–8 days, ≥ 28 days. The results also indicated that MSCs treatment can alleviate the inflammatory cells, necrotic tubule, regenerative tubules, renal interstitial fibrosis in kidney disease induced by toxicant.

Conclusion

MSCs might be a promising therapeutic agent for kidney disease induced by toxicant.

Background

Kidney injury includes acute kidney injury and chronic kidney disease and it is a common condition to be associated with the morbidity and mortality of patients. When the acute kidney injury is not alleviated in time, it will develop into chronic kidney disease. Toxicant-induced kidney injury is one of the most common causes for kidney disease, and it also causes substantial morbidity and retards drug development [1]. At present, renal damage caused by drug toxicity is becoming more and more common in clinic. How to avoid and treat kidney damage caused by drug toxicity is essential to maintain patient health and reduce social economic burden.

Mesenchymal stem cells (MSCs), being pluripotent mesenchymal cells present in various tissues with self-regeneration, have multilineage differentiation ability under an appropriate environment, and are easy to obtain; therefore, they are a promising therapeutic option for some diseases due to their unique properties of releasing some important bioactive factors [2–4]. Drug toxicity results in renal tubular epithelial cell damage or death, and can lead to renal interstitial inflammation which develops into renal interstitial fibrosis and renal loss. In previous, some studies found that MSCs can play a protective role against the injury of renal tubular epithelial cell and prevent the renal interstitial fibrosis[5–9]. In this study, we performed a meta-analysis to assess the nephroprotective effect of MSCs in therapy of kidney disease induced by toxicant.

Materials And Methods

Search strategy

We searched databases (Cochrane Library, Embase, ISI Web of Science and PubMed databases) up to Dec 31, 2019, for the following search corresponding terms: (mesenchymal stem cells OR MSC OR MSCs OR multipotent stromal cells OR mesenchymal stromal cells OR mesenchymal progenitor cells OR stem cells) AND (gentamicin OR aristolochic acid OR cisplatin OR adriamycin OR cadmium chloride OR methotrexate OR rifampicin OR glycerol OR streptozocin) AND (kidney injury OR renal failure OR kidney disease), only confined to English-language literature. An additional search was conducted among the eligible manual references of the cited articles.

Inclusion And Exclusion Criteria

Inclusion criteria:

Our meta-analysis includes studies analyzing the efficacy of MSCs treatment on the mice or rat with kidney disease.

Exclusion criteria

(1) letters, case reports, reviews, clinical studies, editorials, meta-analysis and systematic reviews; (2) studies lacked the targeted indicators or number of case group or control group, and were conducted in humans; (3) the kidney disease was not induced by toxicant, and (4) the therapeutic regimen for kidney disease including other agents with undefined effects.

Outcome Measures

We filter the following outcomes associated with the efficacy of MSCs treatment from the recruited studies: serum creatinine (Scr), blood urea nitrogen (BUN), urinary albumin excretion (UAE),

malondialdehyde (MDA), L-Glutathione (GSH), CAT, superoxide dismutase (SOD), and renal pathology. Also, we conducted a mutual consensus when met with disagreements.

Quality Assessment

Two investigators evaluate the methodological quality with The Cochrane Handbook for Interventions independently. We assessed the following sections of every investigation: selection bias, attrition bias, performance bias, detection bias, reporting bias, and other bias. Each item was classified as unclear, high risk or low risk.

Statistical analysis

Review Manager Version 5.3 was applied to explore whether MSCs treatment can acquire a good efficacy on kidney disease induced by toxicant and STATA 12.0 were used to test the publication bias.

Heterogeneity of variation among individual studies was quantified and described with the I^2 . The fixed effect model was used if the p -value of the the heterogeneity test was ≥ 0.1 . Otherwise, the random effects model will be applied to pool the outcomes. Besides, to compute the continuous variables, we analyze weighted mean differences (WMDs) for the mean values. We also calculated 95% confidence intervals (95% CI) for the included studies using the Mantel-Haenszel (M-H) method. Additionally, we evaluate the publication bias with Begg's rank correlation test as well as Egger's linear regression method among the studies. A p -value < 0.05 was considered as statistical significance.

Results

Search results

The databases mentioned above were searched for this meta-analysis, and we only recruited these studies in mice or rat for evaluation of therapeutic efficiency of MSCs treatment on kidney disease induced by toxicant. Twenty studies [10–36] were eligible and recruited for this meta-analysis, and the flowchart of inclusion of studies is presented in Fig. 1. The included study characteristics are shown in Table 1.

Table 1
Characteristics of the studies included in this meta-analysis.

Author, year	n	Type of animal	Type of injury	MSC type	Number of MSC	Route of delivery	Endpoints for this meta-analysis
Herrera 2004	24	Mice	Glycerol-induced	BM-MSCs	1×10^6	Intravenous injection	Scr
Bi 2007	12	Mice	Cisplatin-Induced	BM-MSCs	2×10^5	Intravenous injection or intraperitoneal injection	Scr, BUN,
Sun 2008	40	Rat	Glycerol-induced	BM-MSCs	2×10^6	Abdominal aorta injection	Scr, BUN,
Qian 2008	6	Rat	Glycerol-induced	BM-MSCs	1×10^4	Intravenous injection	Scr
Magnasco 2008	22	Rat	Adriamycin-induced	BM-MSCs	3×10^6	Intravenous injection	Scr, BUN, UAE, renal damage score
Bruno 2009	16	Mice	Glycerol-induced	BM-MSCs	-	Intravenous injection	Scr, BUN, MDA, GSH, SOD, renal damage score
Eliopoulos 2010	10	Mice	Cisplatin-induced	BM-MSCs	5×10^6	Intraperitoneal injection	Scr, BUN
Kim 2012	17	Rat	Cisplatin-induced	AD-MSCs	5×10^5	Intravenous injection	Scr, BUN
Zickri 2012	30	Rat	Adriamycin-induced	hUC-MSCs	5×10^5	Intravenous injection	Scr
Sarhan 2014	19	Rat	Adriamycin-induced	BM-MSCs	4×10^6	Intravenous injection	Scr, BUN, UAE, renal pathology, MDA, GSH
Moustafa 2016	80	Rat	Cisplatin-induced	BM-MSCs	5×10^6	Intravenous, intra-arterial or kidney sub capsular injection	Scr, MDA, GSH, SOD

Note: BM-MSCs: bone marrow mesenchymal stem cells; hAMSCs: human amnion-derived mesenchymal stem cells; hUC-MSCs: human umbilical cord-mesenchymal stem cells; AD-MSCs: adipose tissue-derived mesenchymal stem cells; mESC: mouse embryonic stem cells; AFSCs: amniotic fluid stem cells; USC: urine-derived stem cells; Scr: serum creatinine; BUN: blood urea nitrogen; UAE: urinary albumin excretion; Ccr: creatinine clearance rate; MDA: malondialdehyde; GSH: L-Glutathione; SOD: superoxide dismutase.

Author, year	n	Type of animal	Type of injury	MSC type	Number of MSC	Route of delivery	Endpoints for this meta-analysis
Elhusseini 2016	40	Rat	Cisplatin-induced	AD-MSCs	5×10^6	Intravenous injection	Ccr, renal pathology, MDA, GSH, SOD
Anan 2016	13	Rat	Adriamycin-induced	BM-MSCs	1×10^6	Intravenous injection	Scr, BUN, SOD
Gad 2017	24	Rat	Methotrexate-induced	BM-MSCs	2×10^6	Intraperitoneal injection	Scr, BUN, MDA, GSH
Rashed 2018	20	Rat	Streptozotocin-induced	BM-MSCs	1×10^6	Intravenous injection	Scr, BUN, UAE, Ccr
Elbaghdady 2018	20	Rat	Cadmium chloride-induced	BM-MSCs	2×10^6	Intravenous injection	Scr
Danjuma 2018	16	Rat	Rifampicin-induced	BM-MSCs	2.5×10^6	Intravenous injection	Scr, BUN
Putra 2019	10	Rat	Gentamicin induced	hUC-MSCs	1×10^6	Intraperitoneal injection	Scr, BUN, renal pathology
Cetinkaya 2019	17	Rat	Aristolochic acid induced	hAMSC	6×10^6	Intravenous injection	Scr, BUN
Selim 2019	70	Rat	Cisplatin-induced	AD-MSCs; BM-MSCs	4×10^6	Intravenous injection	Scr, BUN
Mata-Miranda 2019	10	Mice	Cisplatin-induced	mESCs	1×10^6	Intraperitoneal injection	Scr
Vazquez-Zapien 2019	19	Mice	Cisplatin-induced	mESCs	1×10^6	Intraperitoneal injection	Scr
Minocha 2019	3	Rat	Cisplatin-induced	AFSC	2×10^6	Intravenous injection	Scr, BUN
Sun B 2019	10	Rat	Cisplatin-induced	USCs	2×10^6	Intravenous injection	Scr

Note: BM-MSCs: bone marrow mesenchymal stem cells; hAMSCs: human amnion-derived mesenchymal stem cells; hUC-MSCs: human umbilical cord-mesenchymal stem cells; AD-MSCs: adipose tissue-derived mesenchymal stem cells; mESCs: mouse embryonic stem cells; AFSCs: amniotic fluid stem cells; USCs: urine-derived stem cells; Scr: serum creatinine; BUN: blood urea nitrogen; UAE: urinary albumin excretion; Ccr: creatinine clearance rate; MDA: malondialdehyde; GSH: L-Glutathione; SOD: superoxide dismutase.

Author, year	n	Type of animal	Type of injury	MSC type	Number of MSC	Route of delivery	Endpoints for this meta-analysis
Sun 2019	6	Rat	Cisplatin-induced	BM-MSCs	-	Renal parenchyma injection	Scr, BUN
Zhang 2020	9	Rat	Cisplatin-induced	USCs	5×10^6	Subcutaneous injection	Scr, Ccr, renal pathology
Foroutan 2020	6	Rat	Cisplatin-induced	BM-MSCs	-	Intraperitoneal injection	Scr, BUN
Note: BM-MSCs: bone marrow mesenchymal stem cells; hAMSCs: human amnion-derived mesenchymal stem cells; hUC-MSCs: human umbilical cord-mesenchymal stem cells; AD-MSCs: adipose tissue-derived mesenchymal stem cells; mESCs: mouse embryonic stem cells; AFSCs: amniotic fluid stem cells; USCs: urine-derived stem cells; Scr: serum creatinine; BUN: blood urea nitrogen; UAE: urinary albumin excretion; Ccr: creatinine clearance rate; MDA: malondialdehyde; GSH: L-Glutathione; SOD: superoxide dismutase.							

Quality Assessment Of Included Studies

In the recruited studies, the methodological quality was considered as acceptable, for the result that most of the domains of the recruited investigations were ranked as unclear risk of bias or low risk of bias. Unclear risk of bias mostly detected in performance bias and selection bias. Low risk of bias was mostly occurred in detection bias, reporting bias, and attrition bias. Figure 2 showed the summary of the risk of biases of the recruited investigations.

Scr

26 studies [10–15, 17–36] was included to assess the effect of MSCs on Scr, three for 2 days, four for 3-day, five for 4 days, six for 5-day, seven for 6–8 days, ten for 10–15 days, six for 28–30 days, and six for ≥ 42 days, and the results showed that the difference between MSCs treatment group and control group was notable for 2 days, 4 days, 5 days, 6–8 days, 10–15 days, ≥ 42 days (2 days: WMD = -0.88, 95%CI: -1.34, -0.42, $P = 0.0002$; 4 days: WMD = -0.69, 95%CI: -0.99, -0.39, $P < 0.00001$; 5 days: WMD = -0.46, 95%CI: -0.67, -0.25, $P < 0.0001$; 6–8 days: WMD = -0.51, 95%CI: -0.79, -0.22, $P = 0.0005$; 10–15 days: WMD = -0.38, 95%CI: -0.56, -0.20, $P < 0.0001$; ≥ 42 days: WMD = -0.22, 95%CI: -0.39, -0.06, $P = 0.007$; Fig. 3 and Table 2). However, the difference between MSCs treatment group and control group was not notable for 3 days and 28–30 days (3 days: WMD = -0.09, 95%CI: -0.25, -0.06, $P = 0.24$; 28–30 days: WMD = -0.59, 95%CI: -1.22, -0.05, $P = 0.07$; Fig. 3 and Table 2).

Table 2
Meta-analysis of the efficacy of MSC in therapy of renal injury induced by toxicant

Indicators	Time point	Studies	Q test	Model	OR/WMD	P
		Number	P-value	selected	(95%CI)	
Scr	2 days	3	0.001	Random	-0.88 (-1.34, -0.42)	0.0002
	3 days	4	0.0004	Random	-0.09 (-0.25, 0.06)	0.24
	4 days	5	0.0002	Random	-0.69 (-0.99, -0.39)	< 0.00001
	5 days	6	< 0.00001	Random	-0.46 (-0.67, -0.25)	< 0.0001
	6–8 days	6	< 0.00001	Random	-0.51 (-0.79, -0.22)	0.0005
	10–15 days	10	< 0.00001	Random	-0.38 (-0.56, -0.20)	< 0.0001
	28–30 days	6	< 0.00001	Random	-0.59 (-1.22, 0.05)	0.07
	≥ 42 days	6	< 0.00001	Random	-0.22 (-0.39, -0.06)	0.007
BUN	2–3 days	6	< 0.00001	Random	-25.08 (-37.49, -12.67)	< 0.0001
	4–5 days	7	< 0.00001	Random	-24.37 (-31.66, -17.07)	< 0.00001
	6–8 days	4	< 0.00001	Random	-33.44 (-59.37, -7.51)	0.01
	13–15 days	4	< 0.00001	Random	-13.40 (-32.34, 5.54)	0.17
	≥ 28 days	7	< 0.00001	Random	-19.85 (-33.35, -6.35)	0.004
UAE	-	3	0.72	Fixed	-22.66 (-26.41, -18.90)	< 0.00001
MDA	-	4	0.41	Fixed	-17.21 (-20.38, -14.04)	< 0.00001
GSH	-	4	< 0.00001	Random	4.62 (2.74, 6.50)	< 0.00001

Note: Scr: serum creatinine; BUN: blood urea nitrogen; UAE: urinary albumin excretion; Ccr: creatinine clearance rate; MDA: malondialdehyde; GSH: L-Glutathione; SOD: superoxide dismutase.

Indicators	Time point	Studies	Q test	Model	OR/WMD	P
SOD	-	3	< 0.00001	Random	5.42 (2.92, 7.93)	< 0.0001
Renal pathology						
Inflammatory cells	-	4	< 0.00001	Random	-2.66 (-3.83, -1.49)	< 0.00001
Necrotic tubule	-	2	< 0.00001	Random	-2.58 (-4.75, -0.40)	0.02
Regenerative tubules	-	2	-	Fixed	6.00 (3.45, 8.55)	< 0.00001
Renal interstitial fibrosis	-	3	< 0.00001	Random	-5.82 (-7.41, -4.23)	< 0.00001
Note: Scr: serum creatinine; BUN: blood urea nitrogen; UAE: urinary albumin excretion; Ccr: creatinine clearance rate; MDA: malondialdehyde; GSH: L-Glutathione; SOD: superoxide dismutase.						

BUN

17 studies [10–14, 17, 18, 20, 21, 23, 25–28, 31–33, 35, 36] was included to assess the effect of MSCs on BUN, six for 2–3 days, seven for 4–5 days, four for 6–8 days, four for 13–15 days, and seven for ≥ 28 days, and the results indicated that the difference between MSCs treatment group and control group was notable for 2–3 days, 4–5 days, 6–8 days, ≥ 28 days (2–3 days: WMD = -25.08, 95%CI: -37.49, -12.67, $P < 0.0001$; 4–5 days: WMD = -24.37, 95%CI: -31.66, -17.07, $P < 0.00001$; 6–8 days: WMD = -33.44, 95%CI: -59.37, -7.51, $P = 0.01$; ≥ 28 days: WMD = -19.85, 95%CI: -33.35, -6.35, $P = 0.004$; Fig. 4 and Table 2). However, the difference between MSCs treatment group and control group was not notable for 13–15 days (WMD = -13.40, 95%CI: -32.34, 5.54, $P = 0.17$; Fig. 4 and Table 2).

Urinary Albumin Excretion

Three studies [21, 25, 26] were recruited into the meta-analysis for the assessment of MSCs on UAE. The results showed that the MSCs group had lower UAE than the control group (WMD = -22.66, 95%CI: -26.41, -18.90, $P < 0.00001$; Table 2).

Oxidative Stress

In this meta-analysis, four studies [16, 18, 22, 26] were included for the assessment of MDA, four [16, 18, 22, 26] for GSH, three [10, 16, 22] for SOD. The results indicated that the difference between MSCs treatment group and control group was notable for MDA, GSH, SOD (MDA: WMD = -17.21, 95%CI: -20.38,

-14.04, $P < 0.00001$; GSH: WMD = 4.62, 95%CI: 2.74, 6.50, $P < 0.00001$; SOD: WMD = 5.42, 95%CI: 2.92, 7.93, $P < 0.0001$; Table 2).

Assessment Of Renal Pathology

Four studies [16, 23, 26, 34] for inflammatory cells, two studies [16, 26] for necrotic tubule, two studies [16, 26] for regenerative tubules and three studies [16, 26, 34] for renal interstitial fibrosis were included into this meta-analysis. The results indicated that the difference of inflammatory cells, necrotic tubule, regenerative tubules, renal interstitial fibrosis between MSCs treatment and control group was significant (inflammatory cells: WMD=-2.66, 95%CI: -3.83, -1.49, $P < 0.00001$; necrotic tubule: WMD=-2.58, 95%CI: -4.75, -0.40, $P = 0.02$; regenerative tubules: WMD = 6.00, 95%CI: 3.45, 8.55, $P < 0.00001$; renal interstitial fibrosis: WMD=-5.82, 95%CI: -7.41, -4.23, $P < 0.00001$; Table 2).

Publication bias

The publication bias was tested in this meta-analysis, and a funnel plot generated used STATA 12.0 for the primary outcome, and Begg's test and Egger's test suggested that publication bias was found (Egger's: $P = 0.000$, Begg's: $P = 0.000$; Fig. 5).

Discussion

We reviewed all the included studies and included the various of Scr, BUN, urinary albumin excretion, oxidative stress, renal pathology to assess the nephroprotective effect of MSCs in therapy of kidney disease induced by toxicant. We found that MSCs treatment can reduce the Scr levels at 2 days, 4 days, 5 days, 6–8 days, 10–15 days, ≥ 42 days in animal models of kidney disease induced by toxicant. Furthermore, MSCs treatment also can reduce the levels of BUN at 2–3 days, 4–5 days, 6–8 days, ≥ 28 days. We also found that MSCs group had lower UAE than the control group. In previous, MSCs treatment can reduce the levels of Scr, BUN, proteinuria in lupus nephritis in mice [37]. Chen et al [38] found that MSCs have ameliorated ischemia/reperfusion injury-induced acute kidney injury in rats and can reduce the Scr levels. Xiu et al [39] found that MSCs transplantation can significantly download the concentration of BUN and SCr, and prevent the event of the tissue injury, and reduced mortality after lipopolysaccharide-induced acute kidney injury.

MSCs treatment group got a higher level of GSH, SOD, and a lower level of MDA when compared with control group. El-Metwaly et al [40] found that MSCs can increase the GSH level and reduce the MDA level in lung tissue of acute lung injury rats. Zhang et al [41] reported that MSC effectively reduced the level of MDA, and increased SOD in the lung tissue of acute lung injury rats. Liu et al [42] reported that MSC significantly increased the activity of glutathione (GSH), and reduced the levels of MDA in rats induced by unilateral ureteral obstruction.

Furthermore, our study indicated that the MSCs treatment can alleviate the inflammatory cells, necrotic tubule, regenerative tubules, renal interstitial fibrosis in kidney disease induced by toxicant. In previous, there were some studies indicated that MSCs treatment can alleviate the renal pathological changes in unilateral ureteral obstruction rat or mice [8, 9, 43].

However, some limitations were also found in this meta-analysis. First, the small sample size was found for the recruited studies. The dose of MSCs administered and the type of MSCs were not exactly same. Publication bias was found in this meta-analysis, and the results should be re-assessed in the future. Furthermore, there were different animal types (mouse and rat). These limitations mentioned above may affect the robust of our results.

Conclusions

The MSCs treatment can reduce the Scr levels at 2 days, 4 days, 5 days, 6–8 days, 10–15 days, ≥ 42 days, and reduce the BUN levels at 2–3 days, 4–5 days, 6–8 days, ≥ 28 days. The results also indicated that MSCs treatment can alleviate the inflammatory cells, necrotic tubule, regenerative tubules, renal interstitial fibrosis in kidney disease induced by toxicant.

Abbreviations

MSCs: mesenchymal stem cells; Scr: serum creatinine; BUN: blood urea nitrogen; UAE: urinary albumin excretion; MDA: malondialdehyde; GSH: L-Glutathione; SOD: superoxide dismutase; WMDs: Weighted mean differences; CI: confidence intervals; M-H: Mantel-Haenszel.

Declarations

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Availability of data and materials

Not applicable.

Authors' contributions

TBZ contributed to the conception and design of the study. TBZ, SJL and CLL were responsible for collection of data and performing the statistical analysis and manuscript preparation. WSL and HZZ were responsible for checking the data. All authors were responsible for drafting the manuscript, read and approved the final version.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flow diagram of the selection process.

Figure 2

A: Aggregate Risk of bias graph for each experimental animal studies; B: Risk of bias summary.

Figure 3

Effect of MSC on Scr.

Figure 4

Effect of MSC on BUN.

Figure 5

Publication bias.