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

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Research

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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 $\geq 0.1$. 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.
| Author, year | n  | Type of animal | Type of injury                  | MSC type                | Number of MSC | Route of delivery | Endpoint(s) for this meta-analysis |
|--------------|----|----------------|-------------------------------|-------------------------|--------------|-------------------|-----------------------------------|
| Herrera 2004 | 24 | Mice           | Glycerol-induced              | BM-MSCs                 | $1 \times 10^6$ | Intravenous injection | Scr                               |
| Bi 2007      | 12 | Mice           | Cisplatin-Induced             | BM-MSCs                 | $2 \times 10^5$ | Intravenous injection or intraperitoneal injection | Scr, BUN                          |
| Sun 2008     | 40 | Rat            | Glycerol-induced              | BM-MSCs                 | $2 \times 10^6$ | Abdominal aorta injection | Scr, BUN                          |
| Qian 2008    | 6  | Rat            | Glycerol-induced              | BM-MSCs                 | $1 \times 10^4$ | Intravenous injection | Scr                               |
| Magnasc 2008 | 22 | Rat            | Adriamycin-induced            | BM-MSCs                 | $3 \times 10^6$ | 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                 | $5 \times 10^6$ | Intraperitoneal injection | Scr, BUN                          |
| Kim 2012     | 17 | Rat            | Cisplatin-induced             | AD-MSCs                 | $5 \times 10^5$ | Intravenous 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.
| Author, year | n  | Type of animal | Type of injury | MSC type       | Number of MSC | Route of delivery | Endpoint s for this meta-analysis |
|--------------|----|----------------|----------------|----------------|---------------|-------------------|----------------------------------|
| Zickri 2012  | 30 | Rat            | Adriamycin-induced | hUC-MSCs | $5 \times 10^5$ | Intravenous injection | Scr                              |
| Sarhan 2014  | 19 | Rat            | Adriamycin-induced | BM-MSCs | $4 \times 10^6$  | Intravenous injection | Scr, BUN, UAE, renal pathology, MDA, GSH |
| Moustafa 2016| 80 | Rat            | Cisplatin-induced  | BM-MSCs | $5 \times 10^6$  | Intravenous injection, intrarterial or kidney subcapsular injection | Scr, MDA, GSH, SOD |
| Elhusseini 2016| 40 | Rat            | Cisplatin-induced  | AD-MSCs | $5 \times 10^6$  | Intravenous injection | Ccr, renal pathology, MDA, GSH, SOD |
| Anan 2016    | 13 | Rat            | Adriamycin-induced | BM-MSCs | $1 \times 10^6$  | Intravenous injection | Scr, BUN, SOD |
| Gad 2017     | 24 | Rat            | Methotrexate-induced| BM-MSCs | $2 \times 10^6$  | Intraperitoneal injection | Scr, BUN, MDA, GSH |
| Rashed 2018  | 20 | Rat            | Streptozotocin-induced| BM-MSCs | $1 \times 10^6$  | Intravenous injection | Scr, BUN, UAE, Ccr |
| Elbaghdady 2018| 20 | Rat            | Cadmium chloride-induced| BM-MSCs | $2 \times 10^6$  | Intravenous injection | Scr |
| Danjuma 2018 | 16 | Rat            | Rifampicin-induced | BM-MSCs | $2.5 \times 10^6$ | Intravenous 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.
| Author, year | n  | Type of animal | Type of injury | MSC type | Number of MSC | Route of delivery | Endpoint(s) for this meta-analysis |
|-------------|----|----------------|---------------|----------|---------------|------------------|-----------------------------------|
| Putra 2019  | 10 | Rat            | Gentamicin-induced | hUC-MSCs | $1 \times 10^6$ | Intraperitoneal injection | Scr, BUN, renal pathology |
| Cetinkaya 2019 | 17 | Rat            | Aristolochic acid-induced | hAMSC | $6 \times 10^5$ | Intravenous injection | Scr, BUN |
| Selim 2019  | 70 | Rat            | Cisplatin-induced | AD-MSCs; BM-MSCs | $4 \times 10^6$ | Intravenous injection | Scr, BUN |
| Mata-Miranda 2019 | 10 | Mice           | Cisplatin-induced | mESCs | $1 \times 10^6$ | Intraperitoneal injection | Scr |
| Vazquez-Zapien 2019 | 19 | Mice           | Cisplatin-induced | mESCs | $1 \times 10^6$ | Intraperitoneal injection | Scr |
| Minocha 2019 | 3  | Rat            | Cisplatin-induced | AFSC | $2 \times 10^6$ | Intravenous injection | Scr, BUN |
| Sun B 2019  | 10 | Rat            | Cisplatin-induced | USC | $2 \times 10^6$ | Intravenous injection | Scr |
| Sun 2019    | 6  | Rat            | Cisplatin-induced | BM-MSCs | - | Renal parenchyma injection | Scr, BUN |
| Zhang 2020  | 9  | Rat            | Cisplatin-induced | USC | $5 \times 10^6$ | 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; 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.
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 |

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        |
|-----------------------------|------------|---------|----------|---------|-------------------------|----------|
| 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|
| 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 lipopolysaccaride-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**
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.

Articles retrieved for review from PubMed, Embase, ISI Web of Science, and Cochrane Library: 785

751 articles were excluded:
- Letters/case reports/reviews/clinical studies/editorials/meta-analysis/systematic reviews: 237
- Preliminary results not on MSC or kidney disease: 341
- Kidney disease not induced by toxicant: 173

Potentially relevant studies retrieved for more detailed evaluation: 34

7 studies excluded:
- Did not provide the detailed data for case or control group: 3
- Therapeutic regimen for kidney disease including other agents with undefined effects: 4

Studies included in the meta-analysis: 27
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.
### Table 1: Effect of MSC on BUN

| Study or Subgroup          | MSC  | Control | Mean Difference | IV, Random, 95% CI |
|----------------------------|------|---------|-----------------|--------------------|
| **2.1.1 2-3 days**         |      |         |                 |                    |
| Bi 2007                    | 40   | 2.5     | 6               | 75                 |
| Bruno 2009                 | 149.32 | 14.32   | 10              | 149.32             |
| Kim 2012                   | 64   | 16.79   | 10              | 132                |
| Sun 2008                   | 21   | 4       | 5               | 36                 |
| Sun 2019                   | 16   | 4       | 4               | 67                 |
| Vazquez-Zapion 2019        | 40.8 | 2.16    | 19              | 50                 |
| **Subtotal (65% CI)**      | 56   | 53      | 22.6%           | -25.06 [-37.49,-12.67] |
| Heterogeneity: Tau² = 214.65; Chi² = 80.05, df = 5 (P < 0.00001); P = 94% |
| Test for overall effect: Z = 3.96 (P < 0.00001) |

| **2.1.2 4-5 days**         |      |         |                 |                    |
| Bruno 2009                 | 52.8 | 14      | 8               | 145                |
| Elopoulos 2010             | 62.5 | 18.6    | 15              | 138                |
| Foroudan 2020              | 23.33| 3.89    | 6               | 33.33              |
| Mnocha 2019                | 133.32 | 16.67   | 3               | 140                |
| Putra 2019                 | 14.102 | 1.32   | 36              | 33.846             |
| Sun 2008                   | 10   | 3       | 5               | 17                 |
| Sun 2019                   | 8    | 0.5     | 10              | 18.8               |
| **Subtotal (65% CI)**      | 52   | 52      | 26.3%           | -24.37 [-31.66,-17.07] |
| Heterogeneity: Tau² = 74.47; Chi² = 235.53, df = 6 (P < 0.00001); P = 97% |
| Test for overall effect: Z = 6.54 (P < 0.00001) |

| **2.1.3 6-8 days**         |      |         |                 |                    |
| Bi 2007                    | 52.5 | 5       | 6               | 83.75              |
| Bruno 2009                 | 40.9 | 12.27   | 8               | 94.07              |
| Elopoulos 2010             | 20.86 | 8.88   | 15              | 28.8               |
| Mnocha 2019                | 79.68 | 14      | 13              | 131.99             |
| **Subtotal (65% CI)**      | 32   | 42      | 14.0%           | -33.44 [-59.37,-7.51] |
| Heterogeneity: Tau² = 657.41; Chi² = 96.14, df = 3 (P < 0.00001); P = 97% |
| Test for overall effect: Z = 2.53 (P = 0.01) |

| **2.1.4 13-15 days**       |      |         |                 |                    |
| Bruno 2009                 | 32.72 | 6.14    | 6               | 53.17              |
| Elopoulos 2010             | 31.08 | 2.23    | 15              | 22.65              |
| Putra 2019                 | 10   | 1.2     | 5               | 30.768             |
| Rashied 2018               | 62.23 | 3.9     | 10              | 84.06              |
| **Subtotal (65% CI)**      | 46   | 46      | 16.5%           | -13.40 [-32.34,5.54] |
| Heterogeneity: Tau² = 358.68; Chi² = 414.98, df = 3 (P < 0.00001); P = 99% |
| Test for overall effect: Z = 1.39 (P = 0.17) |

| **2.1.5 >=28 days**        |      |         |                 |                    |
| Anan 2016                  | 33   | 15.88   | 5               | 60                 |
| Cotinkaya 2019             | 36.14 | 19.95   | 5               | 64.50              |
| Danjuma 2018               | 28.4 | 1.16    | 4               | 30.58              |
| Gad 2017                   | 22.93 | 2.88    | 8               | 57.11              |
| Magnras 2008               | 48   | 16      | 4               | 42                 |
| Sarhan 2014                | 169.94 | 84      | 11              | 261.18             |
| Selim 2019                 | 54.16 | 1.08    | 10              | 78.08              |
| **Subtotal (65% CI)**      | 47   | 46      | 20.4%           | -19.85 [-33.35,-6.35] |
| Heterogeneity: Tau² = 241.51; Chi² = 246.16, df = 6 (P < 0.00001); P = 98% |
| Test for overall effect: Z = 2.88 (P = 0.004) |

| Total (95% CI)             | 223  | 239     | 100.0%          | -22.60 [-27.15,-18.04] |
| Heterogeneity: Tau² = 117.61; Chi² = 1177.76, df = 27 (P < 0.00001); P = 99% |
| Test for overall effect: Z = 9.72 (P < 0.00001) |
| Test for subarous differences: Chi² = 2.05, df = 4 (P = 0.73), P = 0% |

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**Figure 4**

Effect of MSC on BUN.
Figure 5

Publication bias.