Induction Therapy With Mesenchymal Stem Cells in Kidney Transplantation: A Meta-Analysis

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Abstract

Objective The aim of this meta-analysis was to evaluate the therapeutic effects of mesenchymal stem cells (MSCs) versus other regimens as induction therapy in kidney transplantation patients.

Methods PubMed, Embase, EBSCO, Ovid and the Cochrane Library were searched to identify prospective clinical trials which compared MSCs with other regimens as induction therapy in renal allograft.

Results Four studies with five cohorts were contained, including a total of 301 patients. The pooled results revealed that the MSCs therapy had a lower 1-year infection rate (RR=0.73, 95% CI: 0.58–0.93, P=0.01), espeicially for 1-year opportunistic infection rate (RR=0.59, 95% CI: 0.37–0.93, P=0.02). There were no significant differences between the two protocols regarding 1-year acute rejection (AR) rate (RR=0.69, 95% CI: 0.42–1.14, P=0.15), 1-year graft survival rate (RR=0.99, 95% CI: 0.95–1.03, P=0.74), delayed graft function (DGF) rate (RR=0.72, 95% CI: 0.34–1.50, P=0.38) and renal graft function at 1 month (MD=2.4, 95% CI: -7.41– 12.22, p=0.63), 3 months (MD=0.91, 95% CI: -4.17– 5.98, p=0.73), 6 months (MD=-1.41, 95% CI: -5.69– 2.87, p=0.52), 12 months (MD=1.25, 95% CI: -3.89– 6.4, p=0.63) post surgery. Subgroup analysis demonstrated 1-year AR rate, DGF rate and renal graft function at 12 month post surgery did not reach to a significant difference between low-dose calcineurin inhibitors (CNIs) group with standard-dose CNIs group, indicating successful CNIs withdrawal in combination with MSCs treatment. Meanwhile, when applied MSCs as an alternative standard induction therapy regimen, all of those outcomes mentioned above were also comparable with those in MSCs plus standard induction therapy group.

Conclusion Induction therapy of MSCs has similar inducing immune tolerance effects on the recipients in kidney transplantation compared with that of other regimens. However, regarding the long term effect, as represented by 1-year infection rate, 1-year opportunistic infection rate and CNIs withdrawl, MSCs therapy has a significant advantage.

Introduction

Kidney transplantation is still the best choice for the treatment of end-stage renal disease (ESRD). Due to the development in tissue type matching and immunosuppressive agents, the concern for acute rejection (AR) has been effectively prevented. However, adverse effects related with current immunosuppressive drugs have become new challenges which should be overcome. The long-term utilization of regular immunosuppressive drugs including corticosteroids, calcineurin inhibitors (CNIs), antimetabolites, and sometimes lymphodepletion can significantly increase the risk of some important adverse effects, such as nephrotoxicity, infection, tumorigenicity, diabetes and cardiovascular diseases, influencing long-term graft outcomes and even sometimes life threat [1–5]. Despite great effort in drug innovations, these drawbacks mentioned above are still not well resolved and failed to substantially decrease the hazards for long-term graft survival over the past two decades [6]. Exploring for novel immunosuppressive strategies to achieve graft tolerance and minimize adverse effects is of great importance.

Stem cell-based therapies have been emerged as novel approaches to induce immune tolerance for organ transplantation in the last ten years [7]. Among them, MSCs have proposed as a promising candidate. MSCs are a type of stem cells which hold self-renewal, regeneration, proliferation, and three-lineage differentiation ability. Meanwhile, the absence of HLA-DR expression on its surface makes it a low immunogenicity agent [8]. Functionally, by paracrine/endocrine actions such as secretion of cytokines and growth factors, MSCs are able to interact with several key factors in both the innate and adaptive immune system, acting immunoregulatory roles [9]. These evidence accompanied with the clinical effectiveness in the treatment of graft-versus-host disease (GVHD) drove the exploration of regarding MSCs as an immunomodulatory therapy in kidney transplantation [10].

During last decade, MSCs has been performed as induction therapy in some kidney transplantation patients, but the results are controversial. Some researches demonstrated the beneficial effects of MSCs treatment in decreasing the ratio of memory/effector CD8(+) T cells, promoting faster renal function recovery or reducing incidence of opportunistic infections [11–13]. Whereas, others suggested MSCs were not advantage over traditional regimens [14–16]. There even existed a study indicating a deleterious role of MSCs in inducing immune tolerance [17]. Whether MSCs can become an effective induction protocol is still in contradiction. In this meta-analysis, we included all available clinical trials related with the application of MSCs as induction therapy in kidney transplantation. By summarizing these articles, we intend to provide an up-to-date view of this innovative induction regimen, make it possible to minimize the induction, maintenance immunosuppressive drugs and inducing a better prognosis for those patients.

Materials And Methods

Search strategy

We conducted a search on PubMed, Embase, EBSCO, Ovid and the Cochrane Library for related articles from 1970. The last date for the search was June 1th, 2020. The search headings used were as follows: “mesenchymal stem cells”, “mesenchymal stromal cells”, “renal transplantation” and “kidney transplantation”. The above terms and their combinations were also searched. All clinical trials which compared mesenchymal stem cells with other regimens as induction therapy in kidney transplantation were identified. There were no language restrictions on inclusion in this meta-analysis. References within the included articles were also searched by hand. The abstracts of the articles were independently analyzed by two of the authors (L.F. Zhao and C.X. Hu) to ascertain inclusion criteria conformity. Disagreements between these two investigators were was determined by consensus.

Inclusion criteria

We included all clinical trials which meet all of the following criteria: (1) the study was a trial of adult kidney transplantation. (2) the study compared the injection of MSCs versus other regimens as induction therapy. (3) matched baseline characteristics of patients in the two groups. (4) the trial assessed at least

three of the following outcomes: 1-year AR rate, 1-year infection rate and renal graft function at 12 month post surgery. (5) follow-up time ≥ 1 year.

Exclusion criteria

Studies enrolling paediatric patients were excluded. Studies enrolling patients with ABO blood

incompatibility kidney transplantation were excluded.

Data extraction

Data extraction was performed of all included trials by the two reviewers (L.F. Zhao and C.X. Hu) independently. Disagreements between these two reviewers were solved by discussion. We extracted data from each study including first authors, year of publication, design of the trial, population characteristics, cases, duration of follow-up, interventions, MSCs type, MSCs doses and maintenance immunosuppressants.

Outcomes of interest

The following reported outcomes were used to compare the therapeutic effects of MSCs with other regimens for induction therapy in kidney transplantation:

(1) 1-year AR rate. (2) 1-year graft survival rate. (3) 1-year infection rate. (4) 1-year opportunistic infection rate. (5) Delayed graft function (DGF) rate. (6) Renal graft function at 1, 3, 6, 12 month post surgery.

Quality assessment

The quality of RCTs were assessed using modified Jadad scoring system, including randomized adequately (2 = described in detail with proper method of randomization, 1 = randomized but not detail reported, 0 = not randomized), allocation concealment (2 = described in detail with proper method of allocation concealment (7), 1 = stated but no detail information, 0 = not proper), blinding (2 = Double-blind,1 = single-blind, 0 = open-label), completeness of follow-up (1 = reported numbers and reasons, 0 = not reported), as well as intention-to-treat (ITT) analysis. The maximum score is 7 points, more than 4 points represents high quality of this study.

Meanwhile, the quality of cohort studies was assessed using the Newcastle–Ottawa scale (8), including selection (0 to 4 points), comparability (0 to 1 points), and outcome (0 to 3 points). The maximum score is 8 points, representing the highest methodological quality.

Statistical analysis

This meta-analysis followed the recommendations of the Cochrane Collaboration meta-analyses guideline [18]. Statistical analyses were performed using RevMan 5.1 statistical software (Cochrane Collaboration, Oxford, UK). Data were pooled using a fixed-effect model, unless they had significant heterogeneity, in which results were confirmed using a random-effect statistical model. For dichotomous outcomes, results were expressed as risk ratio (RR) with 95% confidence intervals (CI). For continuous outcomes, we expressed the results using the weighted mean difference (WMD) with 95% CIs. We also assessed the heterogeneity of results by calculating a chi-square test and evaluated the extent of inconsistency using the I^2 measure. I^2 values at > 25%, > 50%, and > 75% were defined as mild, moderate, and severe heterogeneity. $P < 0.05$ was considered statistically significant.

Results

Included studies

The electronic and manual search retrieved 928 citations. 865 citations were excluded after reading on basis of titles and abstracts. In the remaining 63 studies, there existed 13 case reports, 17 animal experiments, 22 reviews, three trial protocols. Besides, one study was an reanalysis of a former study, two studies reported the outcomes of co-fusion MSCs together with other stem cells and one study did not intend to inject MSCs as induction therapy. At last, four trials consisted of five cohorts which were Pan group, Sun group, Tan low-dose CNIs group and Tan standard-dose CNIs group [12–15], with a total of 301 patients, were included in this analysis (Fig. 1).

Study characteristics

The details of design of the trial, population characteristics, cases, duration of follow-up, interventions, MSCs type, MSCs doses and maintenance immunosuppressants were summarized in Table 1. Particularly, two cohorts compared the application of MSCs for induction treatment with anti–IL-2 receptor antibody (Tan standard-dose CNIs group and Tan low-dose CNIs group) [13], while the other three put MSCs plus standard induction therapy and standard induction therapy in comparison (Erpicum group, Pan group and Sun group) [12, 14, 15]. The cohorts in Pan group and Tan low-dose CNIs group tried to reduce the doses of CNIs during maintenance period, about 20% reduction in Tan low-dose CNIs group [13] and approximately 40% decrease in Pan group [15]. Four cohorts adopted two injection of transplanted MSCs, while the remaining one in Erpicum group tried to apply an one injection regimen. The specific timepoint of MSCs intervention also varied in different groups. Patients in Erpicum group received MSCs treatment at D3 ± 2 with the dose of approximately 1.5×10^6- 3×10^6 cells/kg. Pan group choose to inject 5×10^6 cells of MSCs during surgery, followed by 2×10^6 cells/kg at D30, while Sun group separately infused 2×10^6 cells/kg, 5×10^6 cells 30 min before surgery and during surgery. Both of Tan standard-dose CNIs group and Tan standard-dose CNIs group transplanted two doses of $1–2 \times 10^6$ cells/kg MSCs before surgery and at D14 post surgery. No infusion related adverse effects in all of these four cohorts [12–15]. Except for the study by Erpicum et al. and Sun et al. [12, 14], the remaining three cohorts all contained living-related donor kidney transplant recipients.

Table 1
Characteristics of included studies.

Author	Year	Design of the study	Population characteristics	Cases		Follow up	Interventions		MSCs type	MSCs doses
				Treatment group	Control group		Treatment group	Control group		
Erpicum(12)	2018	Single-centre, nonrandomized, controlled study	Deceased donor kidney transplant recipients	10	10	12 months	MSC + Anti–IL-2 receptor antibody (D0 + D4)	Anti–IL-2 receptor antibody (D0 + D4)	Allogeneic	One injection (1.5×10^6- 3×10^6 cells/kg D3 ± 2)
Pan (15)	2016	Single-centre, prospective, nonrandomized pilot study	Living-related donor kidney transplant recipients	16	16	24 months	MSCs + Cytoxan (200 mg/day D0-3)	Cytoxan (200 mg/day D0-3)	Allogeneic	Two injections (5×10^6 cells during surgery, 2×10^6 cells/kg D30)
Sun (14)	2018	Multi-center prospective RCT	Deceased donor kidney transplant recipients	21	21	12 months	MSC + ATG (50 mg/day D0-2)	ATG (50 mg/day D0-2)	Allogeneic	Two injections (2×10^6 cells/kg 30 min before surgery, 5×10^6 cells during surgery)
Tan low-dose CNIs (13)	2012	Single-centre, prospective RCT	Living-related donor kidney transplant recipients	52	51	12 months	MSCs	Anti–IL-2 receptor antibody (20 mg D0 + D4)	Autologous	Two injections ($1–2 \times 10^6$ cells/kg before surgery and D14)
Tan standard-dose CNIs (13)	2012	Single-centre, prospective RCT	Living-related donor kidney transplant recipients	53	51	12 months	MSCs	Anti–IL-2 receptor antibody (20 mg D0 + D4)	Autologous	Two injections ($1–2 \times 10^6$ cells/kg before surgery and D14)

RCT: Randomized control trial; MSCs: Mesenchymal stem cells; ATG: Antithymocyte globulin; CNIs: Calcineurin inhibitors; MMF: Mycophenolate mofetil

Quality assessment was analyzed in Table 2. All of the four included studies were regarded as high quality.

Table 2
Quality assessment of included studies.

Author	Randomized adequetely	Allocation concealment	Blinding	Completeness of follow-up	ITT analysis	Groups similar at baseline	Specific inclusion criteria	Modified jadad score	Quality
Tan (13)	2	0	1	1	no	yes	yes	4	high
Sun (14)	2	0	1	1	no	yes	yes	4	high
Author	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Quality
Erpicum (12)									high
Pan (15)									high
ITT: Intention to treat									

Meta-analysis of MSCs versus other regimens as induction therapy (Summarized in Table 3)

Table 3
Meta-analysis of MSCs versus other regimens as induction therapy

Outcomes	Number of sudies	Number of patients	RR/WMD	95% CI	P value	Heterogeneity P value (%)
1-year AR rate	5	301	0.69	0.42,1.14	0.15	0
1-year graft survival rate	4	269	0.99	0.95,1.03	0.74	0
1-year infection rate	5	301	0.73	0.58,0.93	0.01	3
1-year opportunistic infection rate	3	227	0.59	0.37,0.93	0.02	52
DGF rate	3	249	0.72	0.34,1.5	0.38	17
Renal graft function post surgery						
1 month	4	259	2.4	-7.41, 12.22	0.63	66
3 month	4	259	0.91	-4.17,5.98	0.73	0
6 month	4	259	-1.41	-5.69,2.87	0.52	47
12 month	5	301	1.25	-3.89,6.4	0.63	6
MSCs: Mesenchymal stem cells; AR: Acute rejection; DGF: Delay graft function; RR: Risk ratio; WMD: Weighted mean difference; CI: Confidence intervals						

Effect on 1-year AR rate

All of the five cohorts were undertaken to test the effectiveness of MSCs therapy on 1-year AR rate in a total of 301 patients [12–15]. In these cohorts, 152 patients were assigned to the MSCs group and 149 patients were assigned to the control group. An analysis of the treatment effect on 1-year AR rate was plotted in Fig. 2. Forest plots displayed the results of the meta-analysis for overall group (RR = 0.69, 95% CI: 0.42–1.14, P = 0.15) (Fig. 2). The results showed that there were no significant differences of 1-year AR rate between the two groups.

Effect on 1-year graft survival rate

Four cohorts assessed the effect on 1-year graft survival rate in a total of 269 patients [12–14]. 136 patients were assigned to the MSCs group and 133 patients were assigned to the control group.

An analysis of the treatment effect on 1-year graft survival rate was plotted in Fig. 3. Forest plots displayed the results of the meta-analysis for overall group (RR = 0.99, 95% CI: 0.95–1.03, P = 0.74). Our meta-analysis indicated that treatment with MSCs induced a comparable 1-year graft survival rate with the control group.

Effect on 1-year infection rate

All of the five included cohorts reported 1-year infection rate, including 301 patients in total [12–15]. As shown in Fig. 4, 152 patients were assigned to the MSCs group and 149 patients were assigned to the control group. During the 1-year follow up, the infection rate in the MSCs group was significantly lower than control group (RR = 0.73, 95% CI: 0.58–0.93, P = 0.01). Particularly, in the field of opportunistic infection, MSCs treatment revealed additional protective effects as compared with control group (RR = 0.59, 95% CI: 0.37–0.93, P = 0.02) (Fig. 5). This evidence suggested that induction therapy with MSCs could effective reduce the infection rate after kidney transplantation.

Effect on DGF rate

Three cohorts of the four involving 249 patients have been published on the effect of MSCs therapy on DGF rate in adult kidney transplantation patients [13, 14]. 126 patients were assigned to the MSCs group and 123 patients were assigned to the control group.

An analysis of the effect of treatment on DGF rate was plotted in Fig. 6. Forest plots displayed the results of the meta-analysis for overall group (RR = 0.72, 95% CI: 0.34–1.50, P = 0.38). According to our meta-analysis in which the weight of individual studies was taken into account, there were no significant differences of DGF rate between the two groups.

Effect on renal graft function post surgery

Renal graft function post surgery was assessed at 1, 3, 6, 12 months post surgery. At every evaluation point, renal graft function was comparable between the two groups (Fig. 7–10). In details, (MD = 2.4, 95% CI: -7.41– 12.22, p = 0.63) at 1 month (Fig. 7), (MD = 0.91, 95% CI: -4.17– 5.98, p = 0.73) at 3 months (Fig. 8), (MD=-1.41, 95% CI: -5.69– 2.87, p = 0.52) at 6 months (Fig. 9) and (MD = 1.25, 95% CI: -3.89– 6.4, p = 0.63) at 12 months (Fig. 10). Our meta-analysis demonstrated an equal therapeutic effects for renal graft function in MSCs group and control group.

Subgroup analysis between low-dose CNIs group with standard-dose CNIs group

In order to evaluate whether MSCs could induce successful CNIs withdrawl,we conducted a subgroup analysis.

Effect on 1-year AR rate between low-dose CNIs group with standard-dose CNIs group

68 patients were assigned to the low-dose CNIs group and 84 patients were assigned to the standard-dose CNIs group. An analysis of the treatment effect on effect on 1-year AR rate between standard-dose CNIs group with low-dose CNIs group was plotted in Fig. 11. Forest plots displayed the results of the meta-analysis for low-dose CNIs group (RR = 0.57, 95% CI: 0.27–1.17, P = 0.12), standard-dose CNIs group (RR = 0.84, 95% CI: 0.42–1.67, P = 0.61). Test for subgroup differences was not significant (P = 0.59).

Effect on DGF rate between low-dose CNIs group with standard-dose CNIs group

52 patients were assigned to the low-dose CNIs group and 74 patients were assigned to the standard-dose CNIs group. An analysis of the effect of treatment on DGF rate between low-dose CNIs group with standard-dose CNIs group was plotted in Fig. 12. Forest plots displayed the results of the meta-analysis for low-dose CNIs group (RR = 0.98, 95% CI: 0.26–3.71, P = 0.98), standard-dose CNIs group (RR = 0.62, 95% CI: 0.26–1.52, P = 0.3). Test for subgroup differences was not significant (P = 0.58).

Effect on renal graft function at 12 months post surgery between low-dose CNIs group with standard-dose CNIs group

68 patients were assigned to the low-dose CNIs group and 84 patients were assigned to the standard-dose CNIs group. An analysis of the treatment effect on renal graft function at 12 months post surgery between low-dose CNIs group with standard-dose CNIs group was plotted in Fig. 13. Forest plots displayed the results of the meta-analysis for low-dose CNIs group (MD=-2.96, 95% CI: -11.12– 5.21, p = 0.48), standard-dose CNIs group (MD = 4.03, 95% CI: -2.60– 10.66, p = 0.23). Test for subgroup differences was not significant (P = 0.19).

Subgroup analysis between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group

Another question was the impact of MSCs alternative standard induction therapy on the AR rate, DGF rate and renal graft function at 12 month post surgery. Subgroup analysis were performed.

Effect on 1-year AR rate between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group

105 patients were assigned to the MSCs alternative standard induction therapy group and 47 patients were assigned to the MSCs plus standard induction therapy group. An analysis of the treatment effect on 1-year AR rate between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group was plotted in Fig. 14. Forest plots displayed the results of the meta-analysis for MSCs alternative standard induction therapy group (RR = 0.64, 95% CI: 0.37–1.10, P = 0.10), MSCs plus standard induction therapy group (RR = 1.00, 95% CI: 0.30–3.32, P = 1.00). Test for subgroup differences was not significant (P = 0.50).

Effect on DGF rate between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group

105 patients were assigned to the MSCs alternative standard induction therapy group and 21 patients were assigned to the MSCs plus standard induction therapy group. An analysis of the effect of treatment on DGF rate between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group was plotted in Fig. 15. Forest plots displayed the results of the meta-analysis for MSCs alternative standard induction therapy group

(RR = 1.09, 95% CI: 0.44–2.72, P = 0.85), MSCs plus standard induction therapy group (RR = 0.29, 95% CI: 0.07–1.22, P = 0.09). Test for subgroup differences was not significant (P = 0.13).

Effect on renal graft function at 12 months post surgery between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group

105 patients were assigned to the MSCs alternative standard induction therapy group and 47 patients were assigned to the MSCs plus standard induction therapy group. An analysis of the treatment effect on renal graft function at 12 months post surgery between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group was plotted in Fig. 16. Forest plots displayed the results of the meta-analysis for MSCs alternative standard induction therapy group (MD = 4.61, 95% CI: -2.56– 11.79, p = 0.21), MSCs plus standard induction therapy group (MD=-2.31, 95% CI: -9.7– 5.08, p = 0.54). Test for subgroup differences was not significant (P = 0.19).

Discussion

To our knowledge, this is the first meta-analysis for MSCs therapy as induction treatment in kidney transplantation. The results from our meta-analysis showed that the infusion of MSCs as induction therapy was safe and effective, in some aspects was even superior to standard induction regimens.

First of all, the infusion of MSCs as induction therapy was safe. It was reported that, despite the low expression of HLA molecules on their surface and the inherent immunosuppressive properties, injection of allogeneic MSCs still bear the risk to active recipients' immune responses and induce the development of donor-specific antibodies [19, 20]. Embolism has also been reported in some cases [21]. In our meta-analysis, during the period of MSCs infusion, no related adverse effects happened in all of the five included cohorts, indicating the tolerance of MSCs injections.

Second, the infusion of MSCs as induction therapy was effective. There still existed concern that the infusion of MSCs would cause damage to the grafted kidney based on the undesirable results by Perico et al. in 2011. Perico et al. were the pioneers to attempt the application of MSCs in patients undergoing kidney transplantation. However, both of the two patients receiving MSCs treatment in their study experienced transient serum creatinine increasing during 7–14 days after MSCs infusion, dampening expectations of this regimen [17]. According to our meta-analysis, a major difference between the above mentioned study conducted by Perico et al. and those studies included in our research was the timepoint of MSCs infusion. Perico et al. tried to injected MSCs at 7 days after surgery, rather than pre- or peri-transplant infusion. After surgery, those infused MSCs would follow the graft originated inflammatory stimulus into the kidney, turned into a pro-inflammatory type rather than an immunoregulatory type which localized in lymphoid organs when injected pre-transplant [22]. One of the patient in their study undertook graft biopsy, and presented with focal interstitial inflammatory cells infiltration and deposition of complement C3 without signs of AR, much like engraftment syndrome which was commonly seen in bone marrow transplantation patients, also verifying this explanation [23]. In our meta-analysis, all of the five included cohorts choose to inject the first dose of MSCs pre- or peri-transplant. Compared with standard induction regimens, utilization of MSCs as induction therapy did not increase the risk of AR or DGF (Fig. 2, Fig. 6). Meanwhile, 1-year graft survival rate, renal graft function at 1, 3, 6, 12 month post surgery were all comparable between these two groups (Fig. 3, Fig. 7–10). Moreover, in subgroup analysis, after replacement of anti-IL-2 receptor antibody with MSCs, the outcomes still remained the same (Fig. 14–16). These evidence suggested the equal efficacy of MSCs with standard induction regimens in inducting renal graft immune tolerance. MSCs could be an alternative choice for induction treatment in kidney transplantation patients.

Third, but the most important, our meta-analysis demonstrated a lower infection incidence in MSCs group. The RR for 1-year infection rate was 0.73 (95% CI: 0.58–0.93, P = 0.01) in the MSCs group as compared with standard induction therapy group (Fig. 4). In term of opportunistic infection, result remained the same (RR = 0.59, 95% CI: 0.37–0.93, P = 0.02) (Fig. 5). One major doubt for the application of MSCs in kidney transplantation patients was whether such an expensive therapy was suitable to be used to merely prevent AR, an event which has already been well controlled by conventional immunosuppressive drugs. Results from our research provided another meaningful advantage for its application. The attention of the transplant community has turned from the inhibition of rejection reaction to long-term event-free survival [9]. Infection was an important part. Contrast with a small samples former study by Reinders et al. that demonstrated a high opportunistic viral infection risk [24], our data providing evidence that patients who received MSCs infusion developed less infections than those in control group. The different immune state of patients might account for this contradiction, for those paitent in Reinders's study all had signs of rejection or interstitial fibrosis/tubular atrophy (IF/TA) before MSCs infusion.

Last, according to our meta-analysis, strategy with MSCs successfully reduced total dosage of CNIs during maintenance period. Lifelong intake of immunosuppressive drugs which were necessary to circumvent graft rejection inevitably imposed increasing risks of morbidity and mortality in kidney transplantation recipients. An interesting concept to make use of MSCs as induction therapy was indented to minimize immune suppression, especially during maintenance period. Animal experiments showed that combination therapy with MSCs contributed to a subtherapeutic dose of rapamycin in promoting graft tolerance [25]. Subgroup analysis in our meta-analysis also revealed that none of the 1-year AR rate, DGF rate and renal graft function at 12 month post surgery in low-dose CNIs group were different with those in standard-dose CNIs group, suggesting the successful CNIs withdrawl (Fig. 11–13).

Despite the promising future, some limitations in our meta-analysis should also be mentioned. First, the sample in our meta-analysis is still not large enough. Only four studies with five cohorts contained a total of 301 patients are available to be included in the meta-analysis. We still need more well-designed, multi-centre, large-samples RCTs to further discuss this issue. Second, the follow-up time is still not long enough. Most patients in our study are followed up for one year. The short follow-up time is insufficiency to get a tough conclusion. Last but not the lease, the risk of tumor formation is not analyzed in our research, nor in those original articles. The concern for the development of tumor is a major hurdle for translation into clinical settings. Although no study right now reported the de novo formation of tumor after MSCs infusion in humans, this caution should always be kept an eye on.

In conclusion, our meta-analysis demonstrated a similar, even better, inducing immune tolerance effect of MSCs therapy on the recipients in kidney transplantation as compared with that of other regimens. Some ongoing clinical trials will provide more evidence about the long-term risks and benefits of MSCs therapy. We believe a promising future of MSCs as induction therapy in kidney transplantion and call for more studies in this field.

Declarations

Ethical approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of Supporting Data

Not applicable

Competing Interests

The authors declare no competing interests.

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Authors' Contributions

L.F. Zhao and J.H. Chen contributed to the conception of this manuscript. L.F. Zhao and C.X. Hu were responsible for the literature review, data extraction and analysis. L.F. Zhao, F. Han, D.J. Chen, J. Cheng, J.Y. Wu and W.H. Peng drafted and revised the manuscript. All authors read and approved the final manuscript.

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Figures

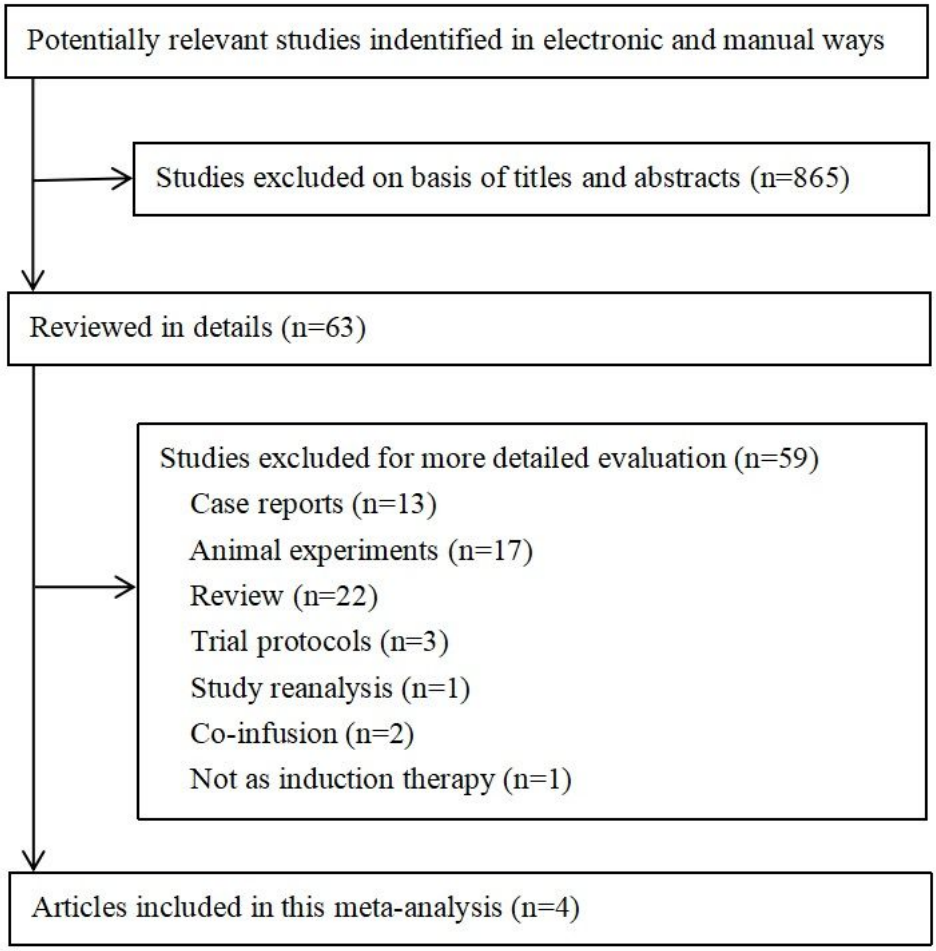

Figure 1

Flowchart of meta-analysis

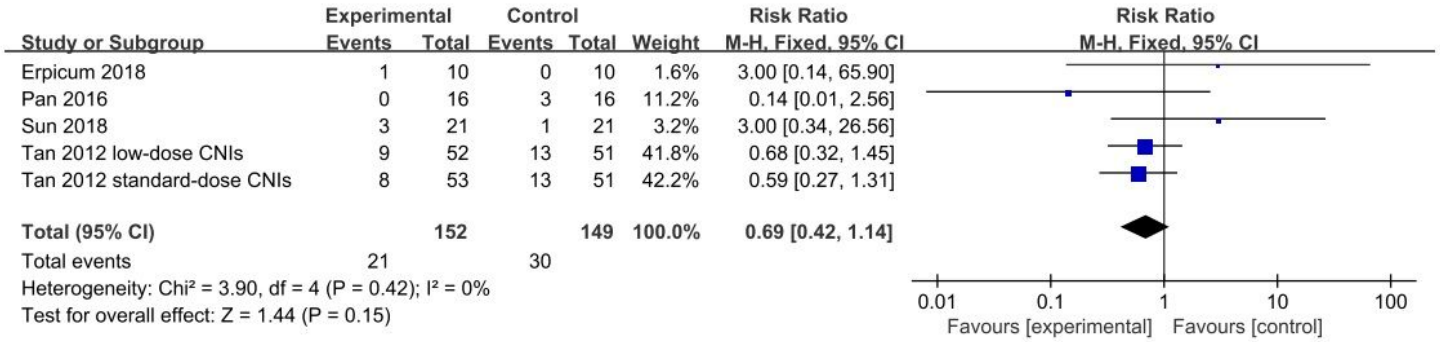

Figure 2

Effect on 1-year AR rate

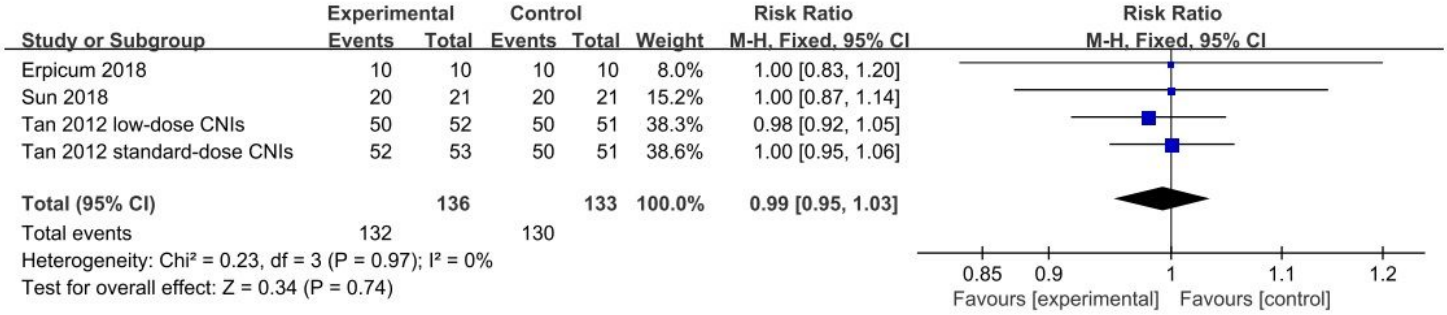

Figure 3

Effect on 1-year graft survival rate

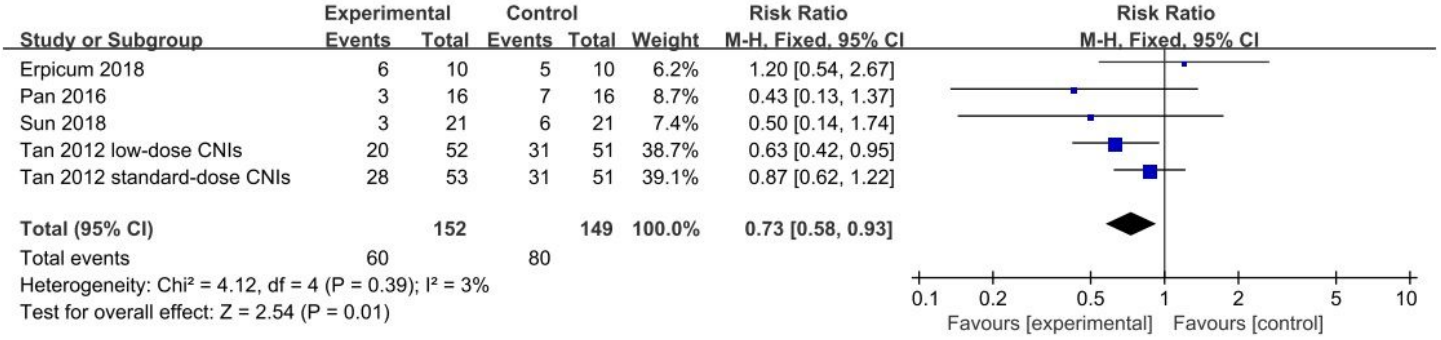

Figure 4

Effect on 1-year infection rate

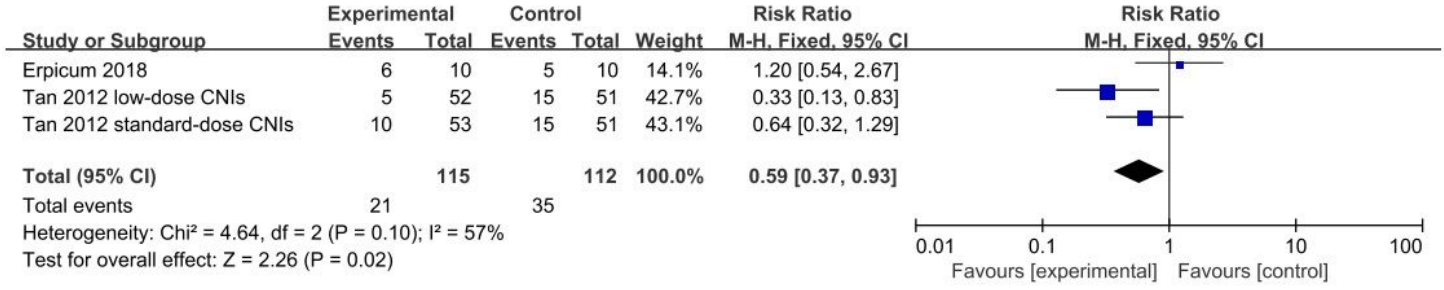

Figure 5

Effect on 1-year opportunistic infection rate

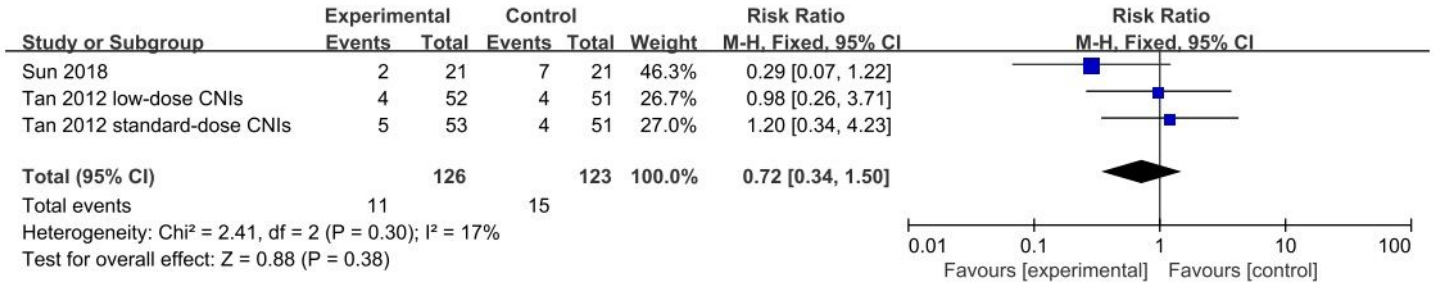

Figure 6

Effect on DGF rate

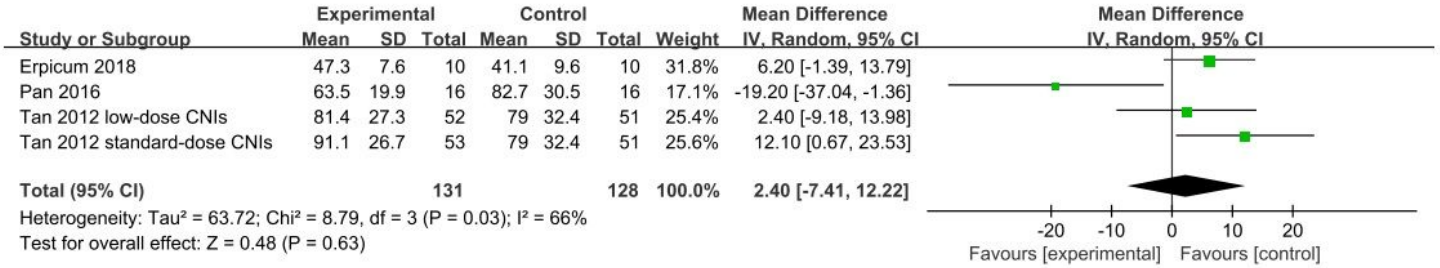

Figure 7

Effect on renal graft function at 1 month post surgery

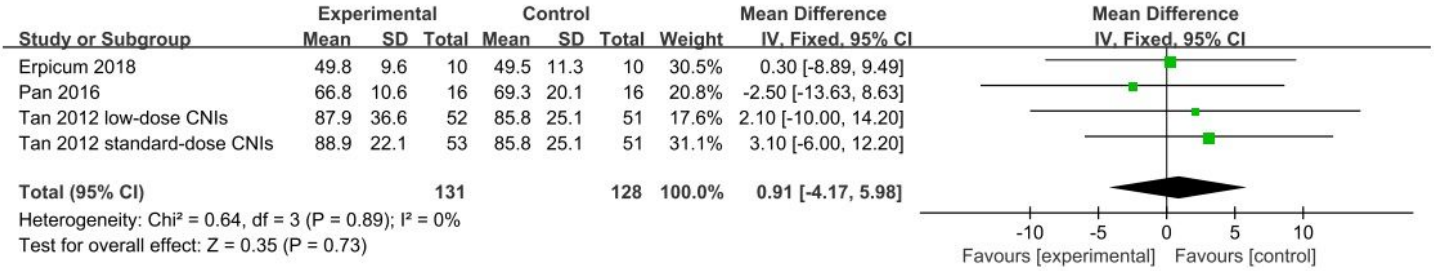

Figure 8

Effect on renal graft function at 3 months post surgery

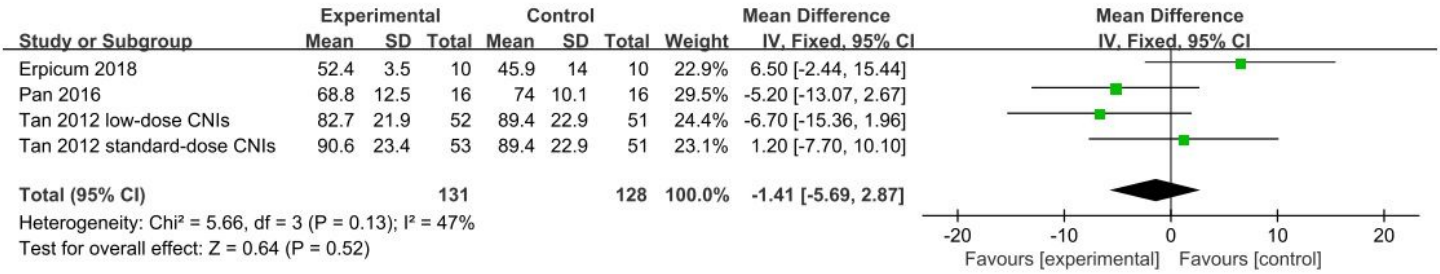

Figure 9

Effect on renal graft function at 6 months post surgery

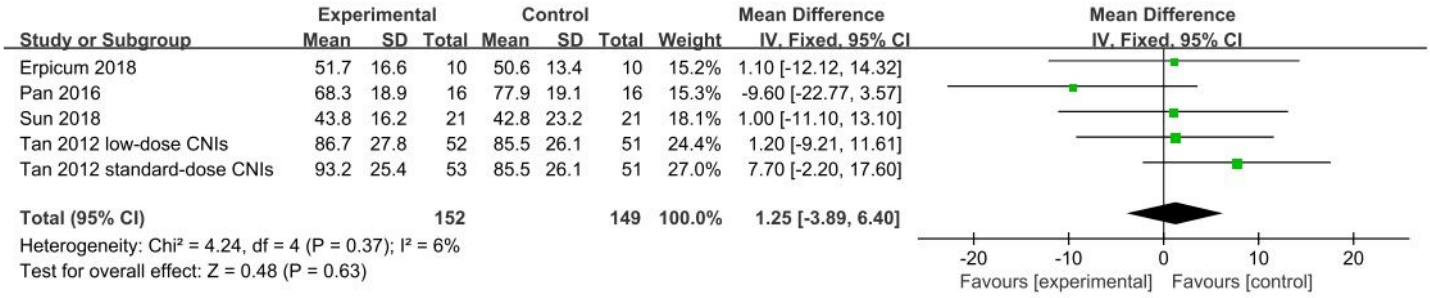

Figure 10

Effect on renal graft function at 12 months post surgery

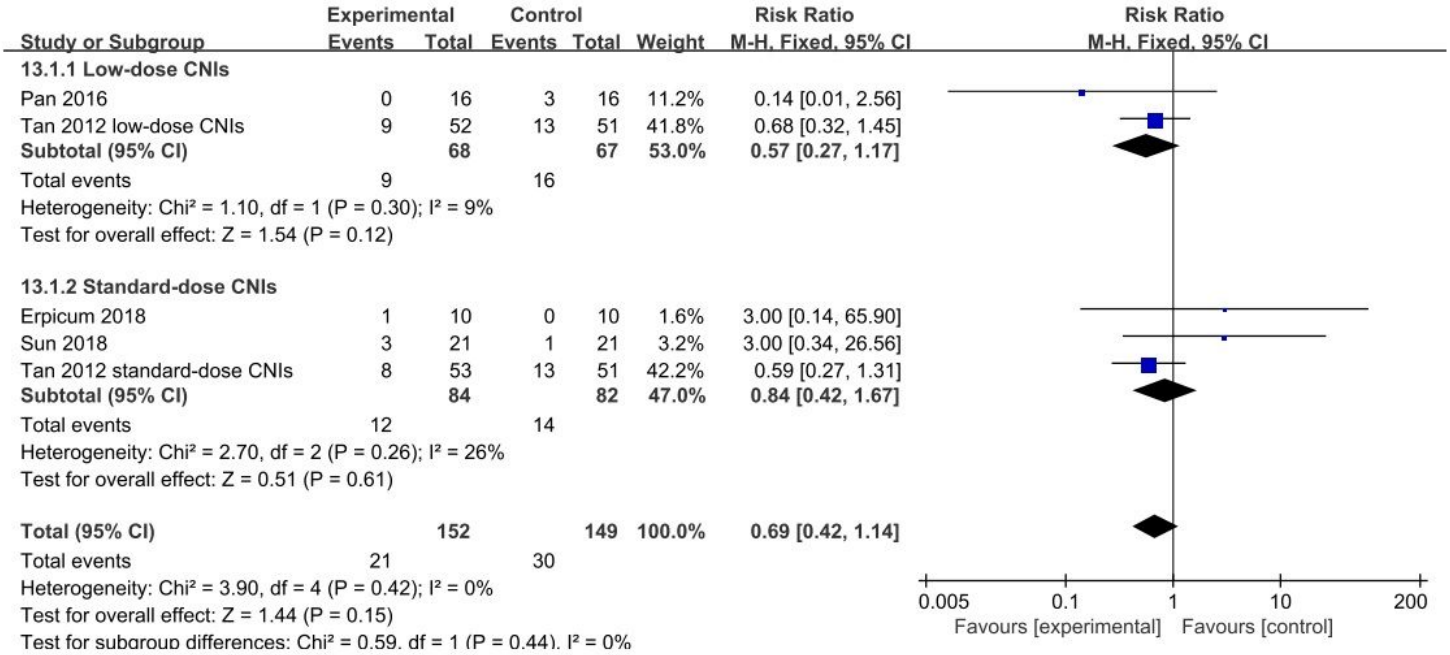

Figure 11

Effect on 1-year AR rate between low-dose CNIs group with standard-dose CNIs group

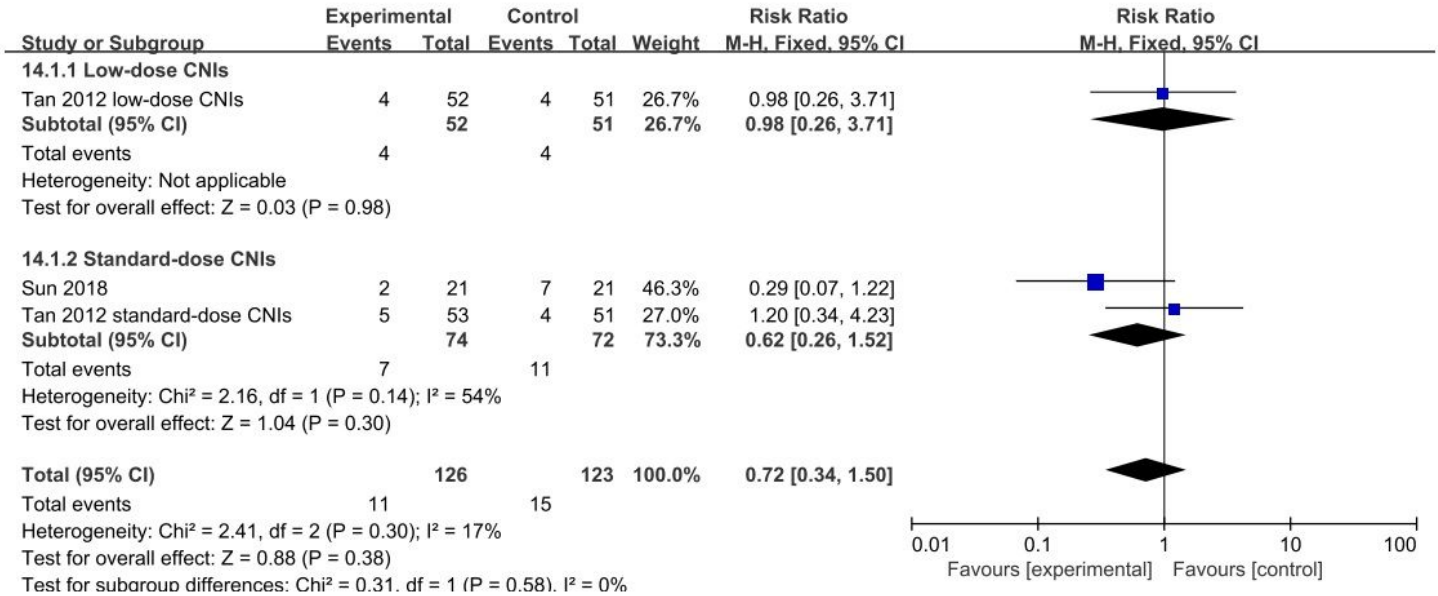

Figure 12

Effect on DGF rate between low-dose CNIs group with standard-dose CNIs group

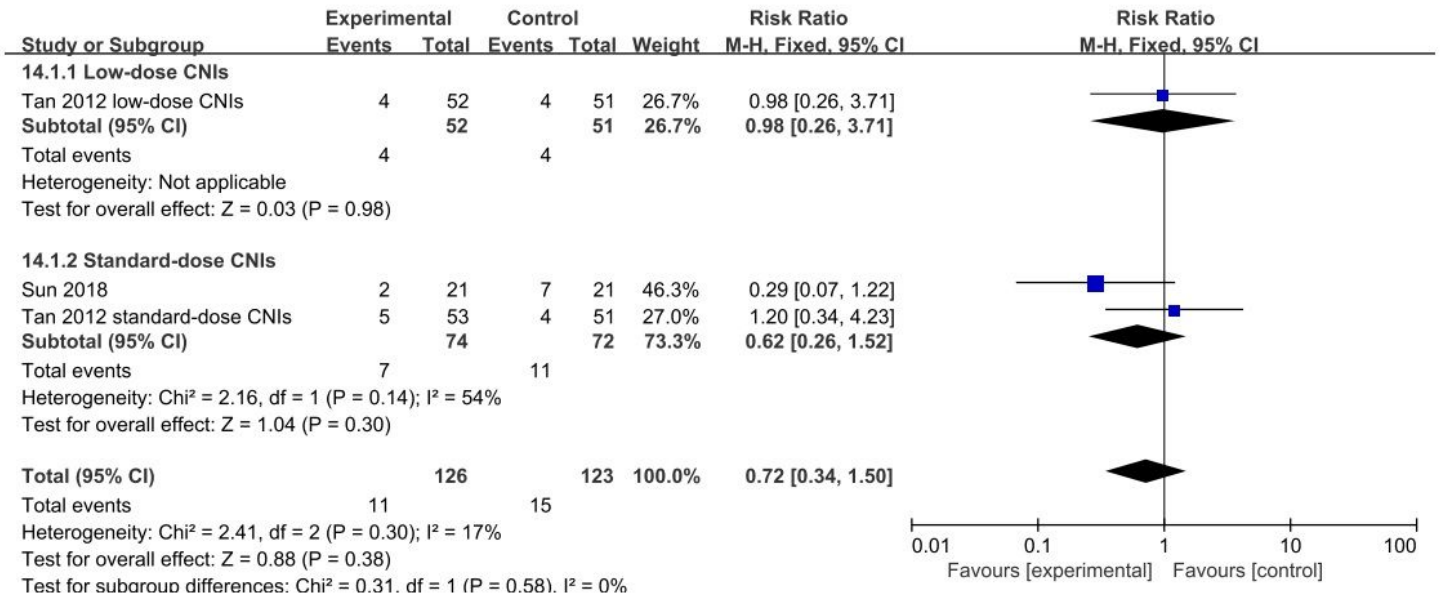

Figure 13

Effect on renal graft function at 12 months post surgery between low-dose CNIs group with standard-dose CNIs group

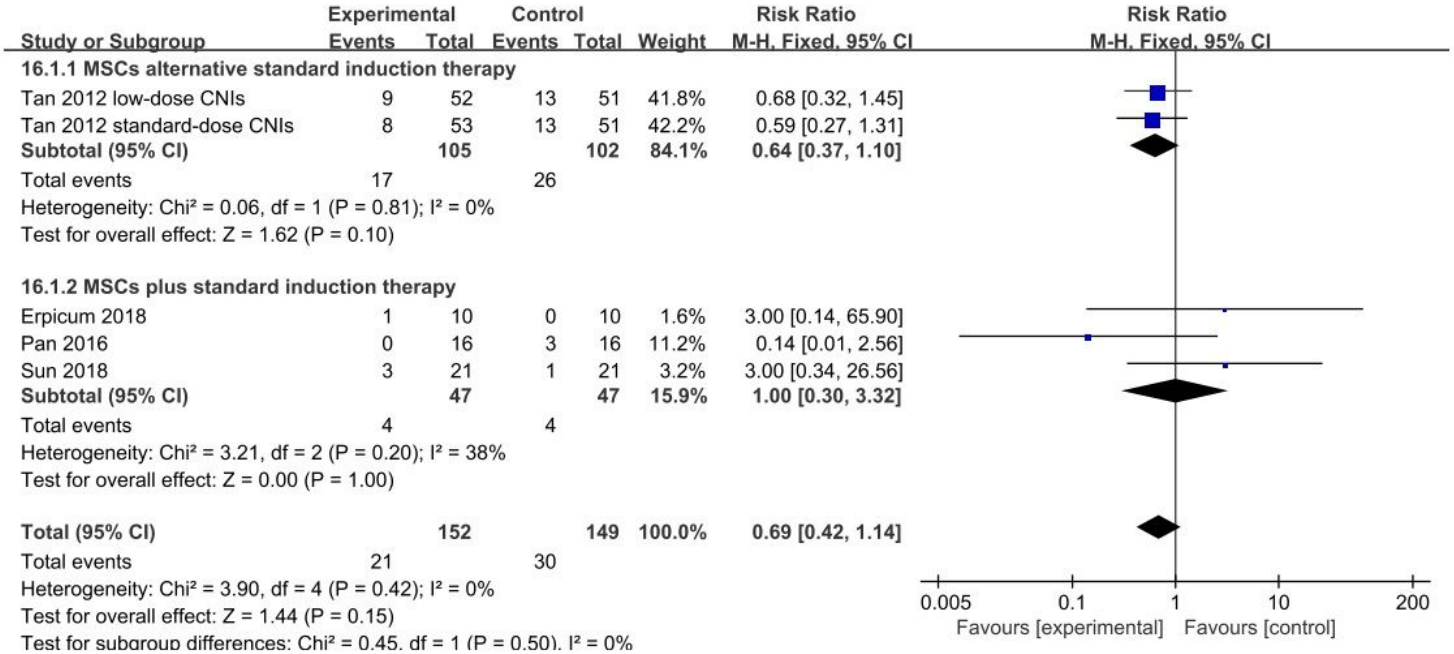

Figure 14

Effect on 1-year AR rate between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group

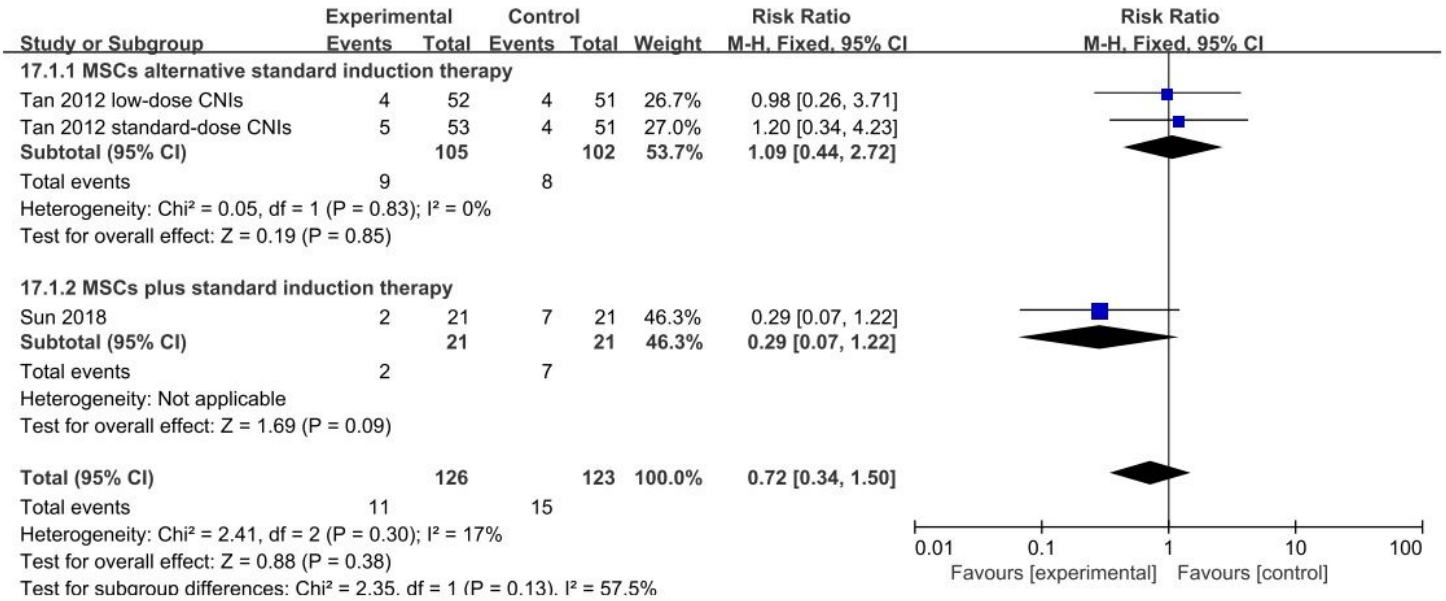

Figure 15

Effect on DGF rate between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group

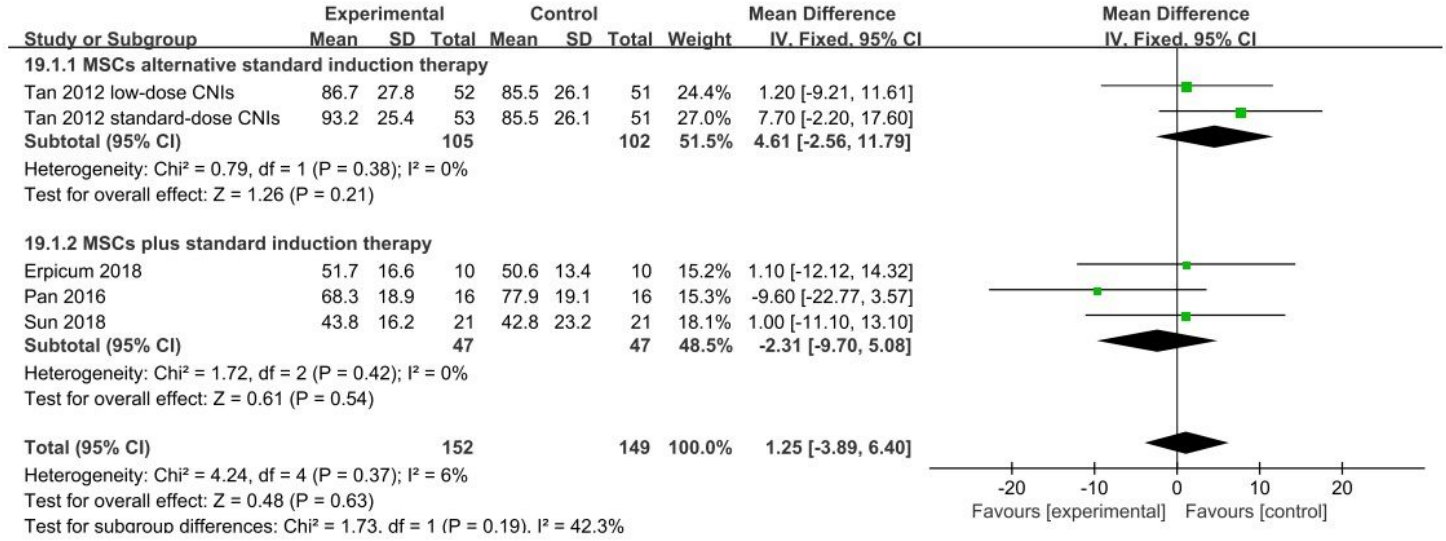

Figure 16

Effect on renal graft function at 12 months post surgery between MSCs alternative standard induction therapy group with MSCs plus standard induction therapy group