REVIEW ARTICLE

Efficacy and safety of ketoconazole combined with calmodulin inhibitor in solid organ transplantation: A systematic review and meta-analysis

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Abstract

What is known and objective: Calcineurin inhibitors (CNIs) can significantly improve the results of solid organ transplantation regarding graft and patient survival. However, the high cost, chronic nephrotoxicity and other side effects are major challenges for the long-term use of these drugs. Ketoconazole can significantly increase the plasma concentration of CNIs by inhibiting the activity of the cytochrome P450 enzyme. The combination of ketoconazole-CNIs can reduce the cost of medication for patients by reducing the dosage of CNIs, but its safety is still controversial. Therefore, this study was designed to assess the safety and efficacy of this combination.

Methods: We performed a systematic literature search in PubMed, Embase, Cochrane Library and *clinicaltrials.gov* for randomized controlled trials on ketoconazole and CNI (cyclosporin or tacrolimus) co-administration in solid organ transplantation. Two authors independently selected studies, assessed the risk of bias and extracted data. The meta-analysis was performed in RevMan 5.3 provided by the Cochrane Collaboration. PROSPERO registration number: CRD42019118796.

Results and discussion: Five relevant trials with 326 patients were included. Compared with the controls, ketoconazole combined with CNIs can significantly reduce the dose of CNIs in patients receiving solid organ transplantation (WMD = −203.04 mg/day; 95% CI: −310.51 to −95.57, P = .0002). There was no significant difference in serum creatinine between the experimental group and the control group (WMD = −0.19 mg/mL; 95% CI: −0.52 to 0.14, P = .26). In addition, there was no significant difference in the number of rejections between the two groups (OR = 0.58; 95% CI: 0.27 to 1.22, P = .15).

What's new and conclusion: The co-administration of ketoconazole and CNIs can significantly reduce the dose of CNIs. This combination may be safely used as a

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Ting Xue and Ting Yang are contributed equally to this work.

CNI-sparing agent from the time of solid organ transplantation with low-dose keto-conazole, based on the findings of this review.

1 | WHAT IS KNOWN AND OBJECTIVE

Since the introduction of calcineurin inhibitors (CNIs), there has been a significant improvement in the results of solid organ transplantations. However, solid organ transplantation programmes are greatly hindered by financial problems, especially due to costly newer immunosuppressive medications, such as tacrolimus. These CNIs increase the financial burden on patients. In addition, chronic nephrotoxicity and other side effects are major challenges for the long-term use of these drugs.

Ketoconazole can significantly increase the plasma concentration of CNIs (cyclosporin or tacrolimus) by inhibiting the activity of cytochrome P450 enzyme. Therefore, it reduces the dosages of CNIs. The combination of ketoconazole-CNIs (cyclosporin or tacrolimus) can reduce the cost of medication for patients by reducing the dosage of CNIs. Diltiazem also blocks the metabolism of cyclosporine by cytochrome oxidase. In a prospective, randomized trial of diltiazem in patients with cardiac transplants, the results showed that diltiazem can reduce the dose of cyclosporine, thereby reducing the cost of treatment with cyclosporine.[1] At the same time, diltiazem can also reduce the development of coronary artery disease in heart transplantation.[2] However, the effect was not seen until days 4 to 7 with diltiazem. In contrast to diltiazem, ketoconazole exhibits a cyclosporine-sparing effect earlier. The dose of cyclosporine should be reduced as early as only one day after the start of ketoconazole therapy.[3] Moreover, diltiazem reduces the dose of CNIs,[4,5] and even low-doses of ketoconazole can reduce the dose of CNIs.[5]

However, the safety of ketoconazole combined with CNIs has been controversial in clinical practice, especially regarding the hepatotoxicity of ketoconazole. Some reports showed that the number of rejections was significantly higher in the ketoconazole group than in the control group, and the incidence of adverse reactions was higher in the ketoconazole group.[4,6] The combination of ketoconazole-CNIs can reduce the cost of medication for patients, but its safety is still controversial. To the best of our knowledge, no meta-analysis has investigated this issue. Therefore, this study was designed to assess the safety and efficacy of this combination by meta-analysis.

2 | METHODS

2.1 | Literature search

We performed a systematic literature search in PubMed, Embase, Cochrane Library and *clinicaltrials.gov* for randomized controlled trials (RCTs) on ketoconazole combined with CNI (cyclosporin or tacrolimus)

therapy for solid organ transplantation until 15 May 2018. The following keywords and subject terms were used in the search: 'keto-conazole', 'calcineurin inhibitor', 'sirolimus', 'everolimus', 'cyclosporine A', 'CsA', 'tacrolimus', 'FK506' and their derivative words.

2.2 | Study selection and data extraction

Two authors selected the studies independently. Any disagreements were resolved by consensus. The titles and abstracts were scanned to exclude any trials that were clearly irrelevant in the first stage. To determine whether trials contained information on the topic of interest in the second stage, the full texts of the relevant articles were read.

The inclusion criteria consisted of the following: (a) the study design was an RCT; (b) the study focused on solid organ transplant patients; (c) the study compared ketoconazole-CNI and CNI treatment groups; and (d) the study reported at least one of the following outcomes: serum creatinine (SCr) or the dose of CNIs, the number of rejections and other side effects.

The exclusion criteria were as follows: (a) no control group; (b) clinical trials in healthy people; (c) the treatment time of the experimental and control groups was not parallel; (d) patients were treated with diltiazem, verapamil or felodipine (these agents may also interact with CNIs); and (e) animal experiments.

The baseline data of patients, SCr level, doses of CNIs and ketoconazole, follow-up duration, numbers of rejections, clinical parameters and adverse events were included in the extracted information.

2.3 | Risk of bias assessment

Two authors independently assessed the quality of the included studies. Disagreements were resolved through discussion among all authors. The quality of the included studies was assessed using the Cochrane risk of bias assessment tool for the following 6 aspects: random sequence generation, allocation concealment, blinding of participants and investigators, blinding of outcome assessors, incomplete outcome data and selective reporting.[7] When detailed data were not reported in the publications, the corresponding author was contacted, and *clinicaltrials.gov* was visited to obtain additional information. The GetData Graph Digitizer (Version 2.26) was used to capture the data from figures when necessary.

2.4 | Statistical analysis

Cochrane RevMan 5.3 was used to perform statistical analyses. The results were stated as odds ratios (ORs) for dichotomous outcomes

FIGURE 1 Flow diagram of studies identified, included and excluded
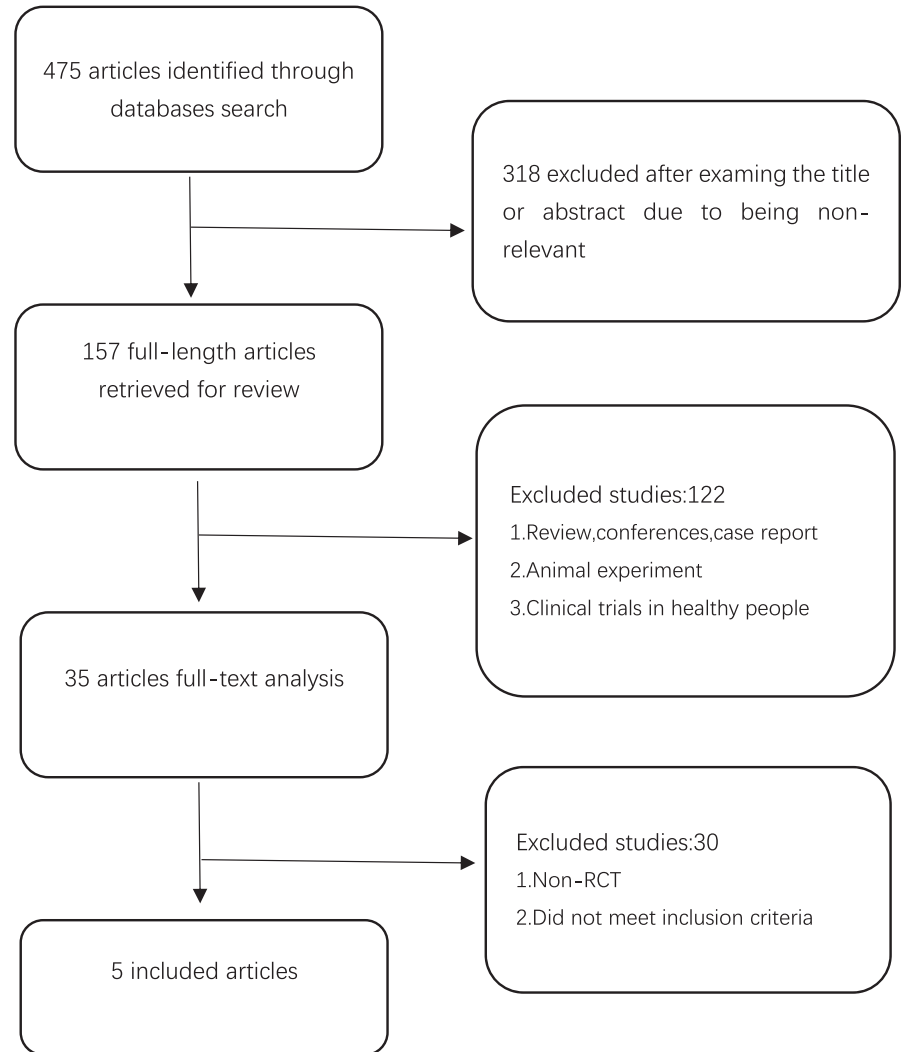
and weighted mean differences for continuous outcomes, with 95% confidence intervals (95% CIs). Heterogeneity was quantitatively assessed by the Q statistic and I^2 index (low heterogeneity: $I^2 \leq 25\%$; moderate: $25\% \leq I^2 \leq 50\%$; high: $I^2 > 75\%$). If $I^2 > 50\%$, which was considered a substantial heterogeneity, a random-effects model was implemented to solve the heterogeneity. If $I^2 < 50\%$, a fixed-effects model was adopted. Sensitivity analyses were employed when necessary. The PROSPERO registration number for this meta-analysis is CRD42019118796.

3 | RESULTS

3.1 | Studies included in the meta-analysis

The comprehensive literature retrieval yielded 475 articles. Of these, five RCTs were identified as appropriate for inclusion in this meta-analysis (Figure 1). The included studies provided information on a total of 326 patients, and Table 1 summarizes the characteristics of the included studies. The dosage range of CNIs was reported in all the literature.[3,8-11] Changes in SCr values were reported in all five papers.[3,8-11] The incidence of rejection was reported in the five

papers,[3,8-11] but two articles did not report the actual number of rejections.[8,10]

3.2 | Rejection

The incidence of rejection was reported in the five papers,[3,8-11] but two articles did not report the actual number of rejections.[8,11] Three articles[3,9,11] included in the meta-analysis showed similar rates of graft rejection between the two study groups, with no statistically significant differences (OR = 0.58; 95% CI: 0.27 to 1.22, P = .15). The addition of ketoconazole did not significantly increase the incidence of graft rejection (Figure 2).

3.3 | Effect on SCr

Five studies reported changes in SCr values, and four were included in the meta-analysis.[8,10-12] The analysis showed that the addition of ketoconazole did not significantly affect SCr levels. There was no significant difference in the SCr levels between the two groups (weighted mean difference (WMD) = −0.19 mg/mL-1; 95% CI: −0.52 to 0.14, P = .26) (Figure 3).

TABLE 1 Characteristics of included studies

Studies	Published year	Patient	Sample Size (ket+/ket-)	Age (ket+/ket-)	CNIs group	CNIs level (ng/mL)	Ket dose	Follow-up (ket+/ket-)	Hepatotoxicity (n,%)
First, MR[9]	1993	Renal transplant recipients	45(17/28)	44.7/39.8	CsA	169/164	200 mg qd	15.3/15.6 mo	NA
Keogh, A[10]	1995	Cardiac transplant recipients	43(23/20)	46/47	CsA	120-180	200 mg qd	25 ± 4 mo	0, 0%
El-Agroudy, AE[3]	2004	Renal transplant recipients	100(51/49)	31.8/34.4	CsA	100-150	100 mg qd	125.3/128mo	0, 0%
El-Dahshan, KF[11]	2006	Renal transplant recipients	70(35/35)	30.5/30.5	Tac	3-7	100 mg qd	24 mo	0, 0%
Patton, PR[8]	1994	Renal transplant recipients	68(34/34)	NA	CsA	150-250	200 mg qd	12 mo	NA

Abbreviation: NA, not available.

3.4 | Dose of CNIs

In all the studies included, ketoconazole could significantly reduce the dose of CNIs in patients receiving solid organ transplantation while maintaining similar CNI blood levels in the experimental and control groups. After 12 months of ketoconazole addition, the dose of cyclosporine in the experimental group was significantly lower than that in the control group[3,8,10] (WMD = −203.04 mg/day-1; 95% CI: −310.51 to −95.57, P = .0002) (Figure 4).

4 | DISCUSSION

This meta-analysis included five RCT studies and 326 patients with solid organ transplants. We studied the efficacy and safety of CNIs combined with ketoconazole in patients with solid organ transplantation. The main findings indicated that CNIs combined with ketoconazole did not significantly increase the incidence of rejection or the value of SCr in patients with solid organ transplantation. In addition, CNIs combined with ketoconazole can significantly reduce the dose of CNIs in patients with solid organ transplantation.

Reducing medical expenses has become even more relevant as economic considerations have increasingly restrained medical

practice. The use of ketoconazole after solid organ transplantation can significantly reduce the need for CNIs, thereby reducing the cost of treatment. The mechanism of the interaction is not clear but is thought to be due to the strong binding of ketoconazole to the microsomal monooxygenase cytochrome P-450 enzyme system, which inhibits the metabolism of cyclosporine.[13] Other proposed mechanisms of the ketoconazole-cyclosporine interaction include altered absorption of cyclosporine, competition for excretion, change in the volume of distribution of cyclosporine and altered protein binding.[14]

Ketoconazole can significantly reduce the dose of CNIs (cyclosporin or tacrolimus) in patients receiving solid organ transplantation while maintaining similar CNI blood levels. This result was observed not only in the RCT studies included in the meta-analysis but also in several observational studies.[4] The reduction in the use of CNI significantly reduces the cost of treatment for patients with solid organ transplants.[2,5] However, due to its narrow therapeutic index, optimal dosing with therapeutic monitoring is necessary.

Regarding the incidence of rejection, in an observational study involving 348 people, the incidence of rejection in the ketoconazole group was greater than that in the control group. The 5-year Kaplan-Meier estimated graft survival and patient survival were not different between the 2 groups.[4] Another study suggests that the co-administration of ketoconazole and tacrolimus is associated with
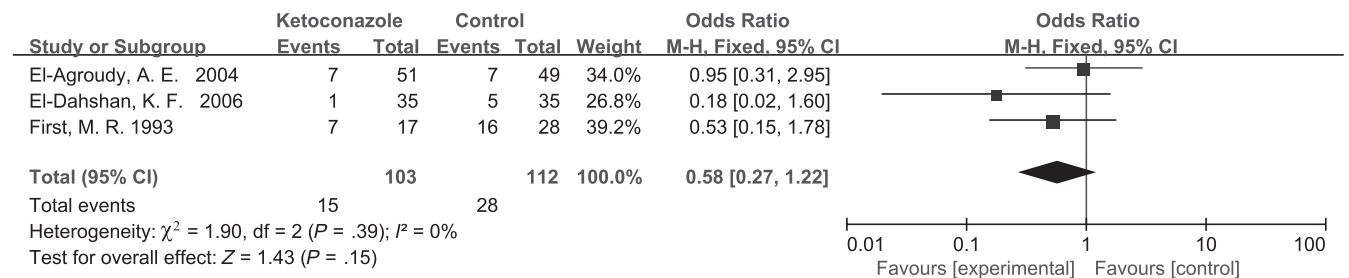
FIGURE 2 Forest plot and meta-analysis of the effect of ketoconazole group and control group on the number of rejections at the end of follow-up
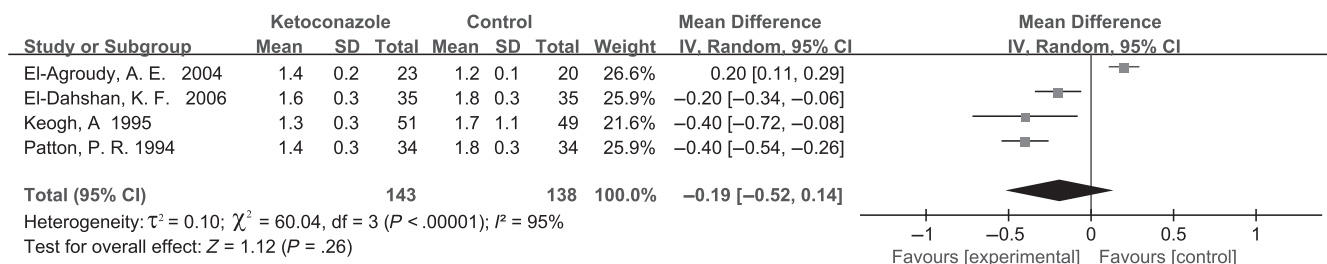
Study or Subgroup	Ketoconazole			Control			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
El-Agroudy, A. E. 2004	1.4	0.2	23	1.2	0.1	20	26.6%	0.20 [0.11, 0.29]	
El-Dahshan, K. F. 2006	1.6	0.3	35	1.8	0.3	35	25.9%	−0.20 [−0.34, −0.06]	
Keogh, A 1995	1.3	0.3	51	1.7	1.1	49	21.6%	−0.40 [−0.72, −0.08]	
Patton, P. R. 1994	1.4	0.3	34	1.8	0.3	34	25.9%	−0.40 [−0.54, −0.26]	
Total (95% CI)			143			138	100.0%	−0.19 [−0.52, 0.14]	

Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 60.04$, df = 3 ($P < .00001$); $I^2 = 95\%$
Test for overall effect: $Z = 1.12$ ($P = .26$)

Favours [experimental]   Favours [control]

FIGURE 3 Forest plot and meta-analysis of the effect of ketoconazole group and control group on the serum creatinine value (mg/dL) during follow-up at 12 mo
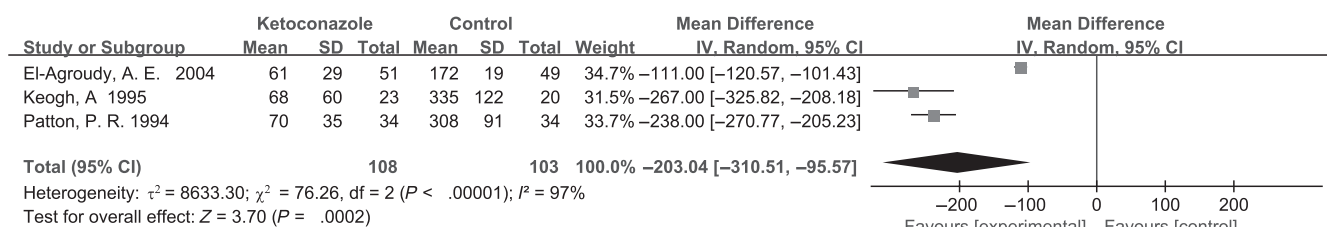
Study or Subgroup	Ketoconazole			Control			Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total			
El-Agroudy, A. E. 2004	61	29	51	172	19	49	34.7%	−111.00 [−120.57, −101.43]	
Keogh, A 1995	68	60	23	335	122	20	31.5%	−267.00 [−325.82, −208.18]	
Patton, P. R. 1994	70	35	34	308	91	34	33.7%	−238.00 [−270.77, −205.23]	
Total (95% CI)			108			103	100.0%	−203.04 [−310.51, −95.57]	

Heterogeneity: $\tau^2 = 8633.30$; $\chi^2 = 76.26$, df = 2 ($P < .00001$); $I^2 = 97\%$
Test for overall effect: $Z = 3.70$ ($P = .0002$)

Favours [experimental]   Favours [control]

FIGURE 4 Forest plot and meta-analysis of the effect of ketoconazole group and control group on the dose of cyclosporine(mg/day) during follow-up at 12 mo

a significantly higher incidence of acute rejection in kidney transplant recipients.[4] However, our meta-analysis revealed that there was no significant difference in the incidence of rejection between the ketoconazole group and the control group. In the ketoconazole group, the rejection rate was even lower than that in the control group in the first few months.[10,15] This result may be explained by the following: (a) increased prednisolone exposure and immunosuppressive effects[16]; (b) reduced toxicity of immunosuppressants at the low dose[17]; (c) low immunocompetence; and (d) the addition of ketoconazole resulted in an inhibition of cyclosporine metabolism, resulting in more parent compounds, which are known to be more immunosuppressive than cyclosporine metabolites as postulated by First et al.[9]

Graft function can be measured by SCr levels to some extent in kidney transplant patients. Our review found that there was no significant difference in the creatinine values between the two groups. Otherwise, most patients in the ketoconazole group had an SCr value <2 mg/dL at the end of follow-up. In addition, the SCr values of the ketoconazole group on all follow-up occasions became lower than the initial SCr value.[11] The addition of ketoconazole does not affect graft function in solid organ transplant patients and even promotes the stability of graft function to a certain extent.

Ketoconazole is effective for the prevention and treatment of skin fungal infections. It can also be used to prevent and treat patients who are prone to opportunistic fungal infections due to reduced immune function. This finding has also been demonstrated in many clinical studies. For patients with solid organ transplants, ketoconazole can significantly reduce the incidence of fungal infections. However, there have been reports of an increase in the incidence of adverse reactions in the ketoconazole group due to its hepatotoxicity.[15]

Although ketoconazole is known to be hepatotoxic, the adverse effects of ketoconazole on hepatotoxicity may be related to its dose. When used as a CNI-sparing agent, the dose of ketoconazole was relatively low, ranging from 50 mg/d to 200 mg/d. Thus, the incidence of adverse reactions caused by ketoconazole was greatly reduced.

There are possible limitations in the current meta-analysis. (a) Only five RCTs were included, and the sample sizes were small, which could reduce the reliability of the results. (b) The follow-up time and visit time of each study were inconsistent. (c) Important outcomes, such as CNI blood levels and survival, were not assessed because none of the eligible RCTs reported these outcomes.

5 | CONCLUSION

In solid organ transplant patients, CNIs (cyclosporin or tacrolimus) combined with ketoconazole can reduce the dose of CNIs and reduce the cost of medication. Treatment with CNIs plus ketoconazole was shown to be safe and efficient in this study, especially with low-dose ketoconazole. We need to adjust the dose of CNIs and monitor their concentration in the blood to achieve a better therapeutic effect in the future.

and TY performed the quantitative meta-analyses and drafted the manuscript with contributions from the other authors. YZ and YC helped with the interpretation of results. YC was responsible for the project and participated in its implementation. All authors read and approved the final manuscript.

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