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Efficacy of Cordyceps sinensis in long term treatment of renal transplant patients

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1. ABSTRACT

High doses of cyclosporin A (CsA) can not be used in the long term treatment of kidney allograft recipients primarily due to severe side effects. In the present study, we investigated the potential application of Cordyceps sinensis (CS) in the long term treatment of renal transplant patients. The renal function and survival rates of grafts and patients was not significantly different between the control group and the treatment group. With the exception of those showing acute rejection, the incidence of complications was significantly lower in the treatment group compared with that in the control group. Furthermore, the dosage and the concentration trough of CsA in whole blood were significantly lower in the treatment than control group. However, there was no significant difference in the serum level of IL-2 in the two groups. Interestingly, the serum level of IL-10 in the treatment group was higher than that in control group. These data demonstrat that CS may be used in combination with a low dose of CsA in the long term treatment of kideny transplant patients.

2. INTRODUCTION

Organ transplantation significantly prolongs the lives of patients with end-stage organ failure. However, this procedure is limited because of immunological rejection. Cyclosporine A (CsA), as an immunosuppressant, has led to a dramatic increase in early kidney graft and patient survivals (1). Early data have demonstrated that CsA improved 1-year survival rates after renal transplantation from 64% to 86 % (2). Despite the introduction of novel drugs, such as Mycophenolate mofetil (MMF), antithymocyte globulin (ATG), and anti-CD3 antibody (OKT3), CsA is still widely used in immunosuppressive management. However, the long term allograft survival rate has remained insignificantly changed due to CsA side effects (3, 4), the major side effects of CsA which mainly include nephrotoxicity, hepatotoxicity and infection. Nephrotoxicity has become one of the main reasons for graft loss with an overall frequency of 9% to 37% (5, 6). Thus there is an urgent need to find an immunoregulation drug adjuvant therapy with CsA to decrease the dosage and side effects.

Table 1. Demographic or immunological parameters of patients

Variables	Control (n=99)	Treatment (n= 83)	P
Male	80 (80.8%)	65 (78.3%)	0.82
Age (year)	38.3 ± 10.6	36.7 ± 11.7	0.34
Chronic glomerulonephritis	74 (74.7 %)	61 (73.5 %)	0.85
Polycystic kidney disease	3 (3.03 %)	2 (2.4 %)	0.84
Chronic interstitial nephritis	15(15.2 %)	14 (16.9 %)	0.75
Hypertensive nephrosclerosis	4 (4.04 %)	3 (3.6 %)	0.79
Diabetic nephropathy	3 (3.03 %)	3 (3.6 %)	0.84
Hematodialysis	76 (76.8 %)	64 (77.1 %)	0.96
Peritoneal dialysis	14 (14.1 %)	12 (14.5 %)	0.95
First transplantation	96 (96.7 %)	81 (97.6 %)	0.84
Second transplant	3 (3.03 %)	2 (2.4 %)	0.85
No. of HLA mismatches	2.4 ± 1.1	2.5 ± 0.8	0.48
Pretransplant PRA	1.0 ± 3.5	1.0 ± 3.9	0.94

Abbreviations: HLA: human leukocyte antigen PRA: Penel reactive antibody

Cordyceps sinensis (CS), a traditional Chinese herb, can efficiently improve the immune defense function and regulate the immune status (7). In recent years, as an immunoregulant, it has been widely used for post-transplantation patients in China. Some animal studies have demonstrated that CS has bidirectional immunoregulatory effects (8, 9). Studies have reported that, CS alone as immunosuppressive therapy could prolong the survival time of grafts(10), and another studies reported that the immunosuppressive effects of CS weaker but as an adjuvant drugs can be very good to reduce graft lesions, extending graft survival time and reduce the dosage of CsA (11,12). Therefore, we intend to study CS' immunoregulatory role in renal transplant recipients, and explore its mechanism of action

3. MATERIALS AND METHODS

3.1. Patients

This study was approved by the Ethics Committee of the Medical College of Xi'an Jiaotong University; all transplant recipients have signed an informed consent in preoperation. The 182 patients (145 men and 37 women) with the overall mean age of 37.8±11.1 years underwent renal transplantations from January 2005 to December 2007. They were randomly assigned into a treatment group (n = 83, Based immunosuppression program + CS) and a control group (n = 99, Based immunosuppression program). The two groups did not differ significantly in demographic or immunological parameters (Table 1).

3.2. Immunosuppression therapy

All patients were given intraoperative and postoperative pulse therapy for 5 days after transplantation with Methylprednisolone (3.0 g) and Cyclophosphamide (0.7 g). Maintenance immunosuppression was Cyclosporine A (CsA; Sandimmun Neoral, Novartis, Basel, Switzerland) in combination with Mycophenolate mofetil (MMF; Cell Cept, Hofmann-La Roche, Grenzach-Wyhlen, Germany) and steroids. Recipients in the treatment group were plus oral CS (Bailing capsule; Hangzhou Huadong Pharmaceutical Co, Ltd□China) at a dosage of 1.0 g 3 times a day as an additional immunoregulant. All data of immunosuppressant were noted within 12 months.

3.3. Laboratory biochemistry examination

Fasting peripheral venous blood serum samples of patients were collected within 12 months posttransplantation. Alanine aminotransferase (ALT), Glutamic oxalacetic transaminase (AST), Serum total protein (TP), Serum albumin (ALB), Total bilirubin (TBIL), Direct bilirubin (DBIL), Serum creatinine (SCr), blood urea nitrogen □BUN□and serum uric acid (UA) were measured using an automated biochemistry detection equipment. Whole blood trough CsA concentrations were measured using an enzyme immunoassay method according to manufacturer's reagent and instrument (Emit 2000 Cyclosporine Specific Assay and Viva-ETM System, Dade Behring, Inc, United States).

3.4. Complication diagnosis

Acute renal allograft rejection episodes were suspected by an increased SCr level in the presence of clinical findings including reduced urine output, weight gain, increased blood pressure, and graft tenderness. All the cases suspected of acute rejection were confirmed by percutaneous renal transplant biopsy. The incidence, time, and therapy of acute rejection were noted within 12 months after transplantation. Hepatotoxicity was confirmed by 1 of 3 liver serum biochemical indices AST, ALT, TBIL, DBIL, or IBIL increasing above normal range and temporarily improved by decreasing or stopping CsA. The incidence of hepatotoxicity was noted within 12 months after the renal transplantation. SCr levels rising after an ineffective anti-rejection therapy and no obvious decrease in urine volume led to a suspicion of nephrotoxicity, which was confirmed by percutaneous renal transplant biopsy showing interstitial and tubular changes. The incidence of nephrotoxicity was noted within 12 months after renal transplantation. Pulmonary infections were diagnosticated based on clinical symptom**,** chest X-ray and CT examination.

3.5. Cytokine detection by enzyme-linked immunosorbent assay (ELISA)

IL-2 and IL-10 in the recipient serum were quantified by commercially available ELISA kits (R&D Systems, Minneapolis MN, USA) according to the manufacturer's instructions.

3.6. Statistics

Statistical analysis was performed using SPSS11.0. Data were presented as mean ± standard deviation. Student's unpaired t-test was used to analyze the differences between the two groups. Chisquare test was used to compare the incidence of the corresponding

Table 2. Renal function and survival rate of patients and grafts after 1 year

				Renal Function			
Group	**n**	**patients/grafts survival (%)**	**n**	**BUN (mmol/L)**	**SCr (μmol/L)**	**UA (μmol/L)**	**Proteinuria (g/24 h)**
Control	99	96.97/ 93.94	51	7.05 ± 2.07	114.15 ± 22.53	397.76 ± 132.17	0.21 ± 0.13
Treatment	83	97.59/ 95.18	58	6.78 ± 1.81	108.53 ± 26.58	313.57 ± 99.24	0.11 ± 0.09
P		0.84 / 0.79		0.36	0.14	0.00	0.00

Abbreviations: BUN: Blood urea nitrogen, SCr: Serum creatinine, UA: Serum uric acid

Table 3. Comparison of liver function between the two groups

Group	**n**	**AST(U/L)**	**ALT(U/L)**	**T.P(μmol/L)**	**ALB(μmol/L)**	**TBIL (g/L)**	**DBIL (g/L)**
Control	67	40.2 ± 14.3	34.3 ± 12.5	60.1 ± 14.7	37.7 ± 13.1	18.4 ± 3.1	6.2 ± 1.6
Treatment	69	34.5 ± 10.7	30.5 ± 10.1	72.8 ± 17.3	43.2 ± 13.4	14.3 ± 2.4	4.1 ± 1.2
P		0.0028	0.027	0.00	0.0066	0.00	0.00

Abbreviations: AST: Glutamic oxalacetic transaminase, ALT: Alanine aminotransferase, TP: Serum total protein, ALB: Serum albumin, TBIL: Total bilirubin, DBIL: Direct bilirubin.

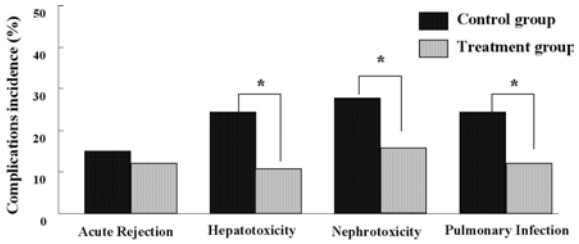

Figure 1. Complications incidence in the two groups, *P< 0.05 significant difference between the two groups.

indicators between the two groups. A level of significance of $P < 0.05$ was considered as sufficient in all the experimental groups.

4. RESULTS

4.1. The difference of renal function and survival rate of patients and grafts between the two groups

After the 1-year follow-up visit, no significant differences were found in the patient survive, the graft survival rate, BUN and SCr of the 2 groups (P >0 .05, Table 2). But UA and 24-hour UTP in the treatment group were significantly lower than those in the control group (P <0.05, Table 2). During the 12 months, 4 recipients in the control group died of postoperative complications and 2 recipients in the treatment group; 6 recipients in the control group suffered from the loss of allograft function and 4 recipients in the treatment group. To compare the renal function of the two groups, we excluded the recipients who have died, or suffered from allograft function loss and nephrotoxicity.

4.2. Complications incidence in the two groups

In the first year the post-transplantation complications mainly included acute rejection, hepatotoxicity, pulmonary infection and nephrotoxicity. The difference of those complications incidence in the treatment group was significantly lower than which that in the control group (P< 0.05, Figure 1) except the acute rejection. For acute rejection, there is no significantly difference between the two groups (P> 0.05, Figure 1).

4.3. Comparison of CsA dosages and concentrations in the two groups

The difference in CsA dosages between the 2 groups was not significant at 1 month after transplantation (P > 0.05, Figure 2A). However, from 2 to 12 months, the CsA dosage of the treated group was significantly lower than those in the control group (P < 0.01; Figure 2A). Similarly to CsA dosages no significant differences were observed in whole blood trough CsA concentrations at 1 to 2 months after transplantation (P>.05; Figure 2B). From 3 to 12 months, the whole blood trough CsA concentrations in the treated group were significantly lower than those in the control group (P <.05; Figure 2B). To compare the CsA dosages and Concentrations of the two groups, we excluded the recipients who have died, or suffered from allograft function loss and nephrotoxicity.

4.4. Comparison of the liver function between the two groups

The values of AST and ALT in the treatment group were significantly lower than those in the control group (P <0.01, Table 3); in the treatment group, the values of TP and ALB in the treatment group were significantly higher than those in the control group (P <0.01, Table 3); in treatment group, the values of TBIL and DBIL in the treatment group were significantly lower than those in the control group too (P <0.01, Table 3). To compare the liver function of the two groups, we excluded the recipients who have died, or suffered from allograft function loss and hepatotoxicity.

4.5. The levels of IL-2 and IL-10 cytokines in the sera of recipients

The immune responses were also determined by the cytokine production in the sera of recipients. At the 6 month and 12 month, the level of Th1 cytokines, IL-2, did not show significant difference between the two groups (P>0.05, Figure 3A). In contrast, the level of IL-10, a Th2 cytokine, in the treatment group was significantly higher than that in the control group (P<0.01, Figure 3B). To compare the level of IL-2 and IL-10 cytokines between the two groups, we excluded the recipients who have the unstable renal function.

5. DISCUSSION

CS, a kind of Chinese traditional medicine, which can regulate immune function, has been widely used in the clinical treatment of asthma, anti-tumor, chronic bronchitis, and chronic kidney failure (7, 14-15). Many researchers have recently focused on its effect of immunoregulation in the organ transplantation. Jordan *et al.* (11) and Ding *et al.*

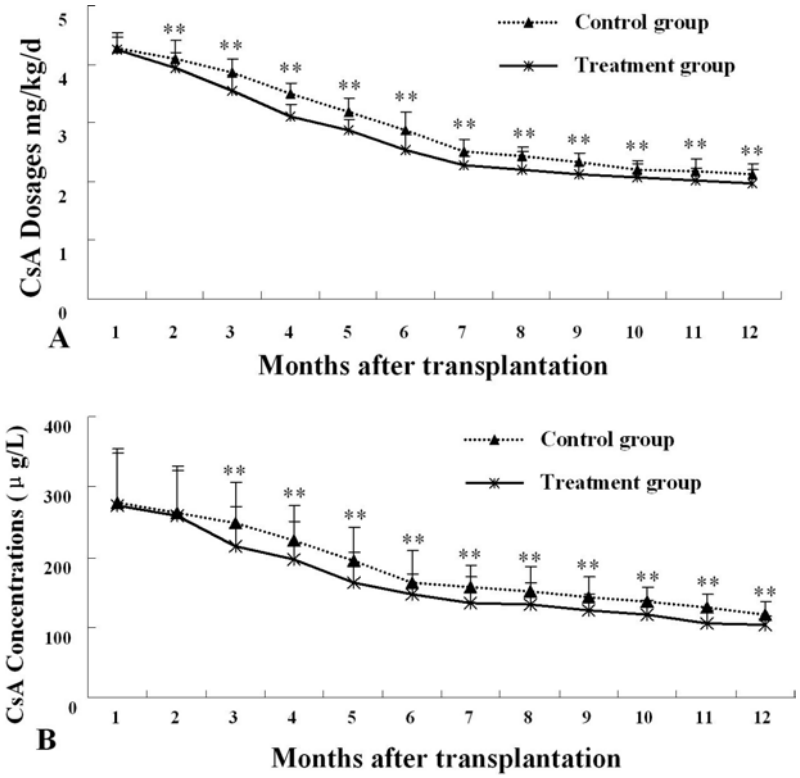

Figure 2. Comparison of CsA dosages and concentrations in the two groups, **P< 0.01 significantly difference between the two groups at the corresponding time.

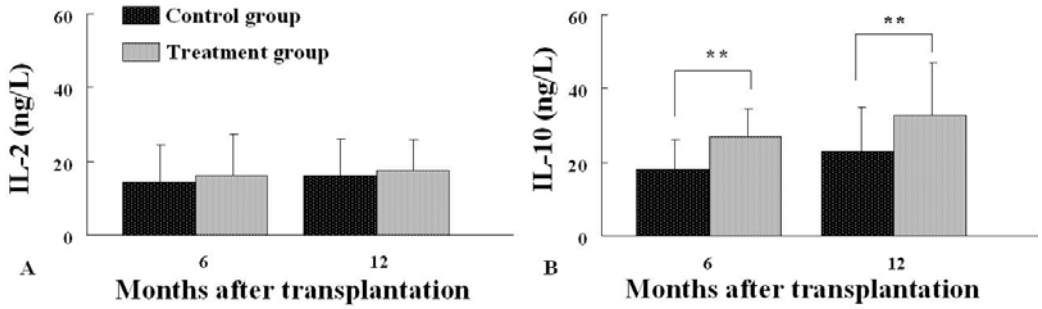

Figure 3. The level of IL-2, IL-10 cytokines in sera of recipients in the two groups, **P<0.01 significantly difference between the two groups at the corresponding time.

(12) both reported that CS has little immunosuppressive effects when used as a monotherapy in transplantation, whereas it possibly improve the grafts function and decrease the dosage of CsA when used with CsA. Their findings are in an agreement with our research results. We have found that the 2 groups show no significant difference with regard to the 1-year survival of transplant recipients and the graft, acute rejection incidence, and SCr and BUN after the renal transplantation. Fortunately, form 2 to 12 months, the CsA dosages in the treated group were significantly lower than those in the control group, Similarly to CsA dosages significant differences were observed in whole blood trough CsA concentrations from 3 to 12 months after transplantation. It was demonstrated that CS as an immunomodulator adjuvant with CsA, not only reduced the doses of CsA but also maintains stable renal function. The levels of TP and ALB in the control group which were significantly lower than that in the treatment group indicate that CS could inhibit the proteinuria and improve the hypoproteinemia. The treatment group showed a considerable reduction in UA than the control group, which suggests that CS has a potential role in reducing the incidence of gout after the renal transplantation. This may be related to the fact that CS can promote protein synthesis, correct the disorder of plasma amino acid, and transform macrophages and lymphocyte (16).

Those side effects depend on the dosage and the concentration of CsA. Unfortunately, the decreased CsA is

associated with an increased risk for acute rejection episodes, especially at 4 to 6 months after transplantation (17). In order better to study the immunoregulation effect of CS in the renal transplantation, we investigated the post-transplantation complications incidence between the two groups. The treated group had much lower incidences of nephrotoxicity, hepatotoxicity and pulmonary infection than the control group, which demonstrates that CS plus lower-dose CsA could decrease the damage to the liver and the kidney. CS certainly improves the recovery of liver function and the secretion of bilirubin, and promotes excretion function after renal transplantation, which suggests that CS may play a role in the protection of liver cells. Studies have shown that the application of CS allows the infiltration of liver inflammatory cells, a lighter state of hepatic cell necrosis, a great enhancement of the function of Kupffer cells, and a considerably less deposition of immune complex in the liver (18). The incidence rate of infection after the renal transplantation in the treatment group was obviously lower than that in the control group, the incidence of infections lower due to comprehensive factors. CS has a two-way regulating effect on the body's immune system: while it is selectively immune to solid organs, may not lower the immune and defense role of the body system. Kuo *et al* (14) studied CS' regulation of bronchoalveolar lavage fluid vesicleson (BALF) and found that CS in a dose-dependent manner could inhibit the proliferation of LPS-activated BALF cells, reduce the generation of IL-β3, IL-6, IL-88, IL-10 of the LPS activated BALF cell cultures, and, in addition, increase the generation of IL-12 and IFN-γ of activated BALF cells. These results suggest us that CS have the effects of anti-inflammatory, anti-infection, to reduce the excessive inhibition of CsA on the immune system, and CS can make the recipients of lymphocyte recovery as soon as possible to the desired level (data not show). These effects of CS made the lower incidence of infection.

Furthermore, the immunoregulation effects of CS were also reflected by the inhibition on Th1 cytokine production. Our data showed that although the dosage and the concentration of CsA in the treatment group were decreased significantly compared with the control group, but the level of IL-2 in peripheral blood was no significant difference between the two groups. It is interesting that compared with the control group; the treatment group sees a considerable enhancement in IL-10, one of the Th2 cytokines, at 6 and 12 months after grafting. IL-10 is known to have an important role in limiting inflammation or autoimmunity (19–21). Several reports have shown that a particular subset of DC can induce IL-10 producing Terg cells (22, 23). Furthermore, many studies have proofed that CD4+D25+ regulatory T cells play a key role in the induction and maintenance of immune tolerance to grafts (24). However, recent data from *in vitro* studies have suggested that CsA might induce the suppression of naturally occurring CD4+CD25+ Treg cell function (25, 26). In addition, It was recently shown that liver-transplant patients with a high blood CsA level have a lower percentage of blood Treg cells than those with low blood CsA levels (27). These date indicate us that CS by decrease the CsA dosage and strengthen IL-10 expression ways to enhance the percentage of CD4+CD25+ Treg cell in transplantation recipients, then play its immunoregulatory effects after transplantation.

The research results have shown that CS, as an immunoregulant, has a good short- and mid- term effect after the renal transplantation with no obvious adverse effects and a low cost. It can be concluded that CS, as an immunoregulant, had its unique pharmacological advantages, and its potential effectiveness should be developed and long-term problems with clinical safety need to be clarified after the renal transplantation.

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Abbreviations: CsA: Cyclosporine A, MMF: Mycophenolate mofetil, ATG: Antithymocyte globulin, OKT3: Anti-CD3 antibody, CS: Cordyceps sinensis, ALT: Alanine aminotransferase, AST: Glutamic oxalacetic transaminase, TP: Serum total protein, ALB: Serum albumin, TBIL: Total bilirubin, DBIL: Direct bilirubin, SCr: Serum creatinine, BUN:Blood urea nitrogen, UA: Serum uric acid, ELISA: Enzyme-linked immunosorbent assay, BALF: Bronchoalveolar lavage fluid vesicleson, Treg cell: Regulation T cell, DC: Dendritic cell

Key Words: Transplantation, Renal, Cordyceps sinensis, Immunoregulation, Cyclosporine A

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